Physical Fitness Training for People with Stroke

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Abstract

INTRODUCTION: Impaired physical fitness may contribute to functional limitations and disability after stroke. Physical fitness (including cardiorespiratory fitness and muscle strength/power) can be improved by appropriate fitness training; this is of benefit to healthy people and patient groups but whether it is of benefit for people after stroke is unclear. The aim of this thesis was to determine whether physical fitness training is beneficial after stroke.

OBJECTIVES: (1) Develop a rationale for fitness training by determining whether physical fitness after stroke is a) impaired, and b) associated with functional limitations and disability. (2) Develop and evaluate randomized controlled trial (RCT) evidence by a) determining the feasibility of a definitive RCT, and b) evaluating the benefits of fitness training after stroke.

METHODS: (1) Systematic review of observational data and multiple linear regression of exploratory RCT baseline data determined the nature of fitness impairments and any associations with functional limitation and disability. (2) Systematic review and meta-analysis of RCTs established the effects of fitness training on disability, death and dependence. An exploratory RCT ('STARTER') compared the effects of a fitness training programme (cardiorespiratory plus strength training 3 days/week for 12 weeks) with an attention control (relaxation) on fitness, function, disability, mood and quality of life in 66 ambulatory people with stroke.

RESULTS: (1) Systematic review of observational data showed cardiorespiratory fitness (peak oxygen uptake and economy of walking) and muscle strength were low after stroke; the impairments predicted functional limitation but links to disability were unclear. STARTER baseline data showed little impairment in economy of walking but lower limb extensor power was impaired (42-54% of values expected in healthy age and gender matched people) and this predicted functional limitation and disability. (2) The systematic review identified 12 RCTs (n=289) in 2003, and 24 RCTs (n=1147) when updated in 2007. The systematic reviews showed death was uncommon, and effects on dependence and disability were unclear. However training did improve fitness and cardiorespiratory training during rehabilitation improved ambulation. Most benefits resulted from task-related training. The STARTER fitness training intervention was feasible, with good attendance (>90%) and good compliance with intervention content (94-99%). At the end of the fitness training intervention there were small improvements in some cardiorespiratory fitness, physical function and quality of life outcomes compared with the control group, but these differences had diminished four months later.

CONCLUSIONS: (1) Cardiorespiratory fitness, muscle strength and power are impaired after stroke, so there is scope to increase fitness, and there are plausible benefits. (2) Physical fitness training after stroke is feasible, it improves fitness and has some functional benefits, in particular for walking ability. Effects on disability, death and dependence are not known. Further research is required to determine the timing, mode, duration, frequency and intensity of fitness training for optimum benefits, and investigate how benefits can be retained in the long-term.

Table of Contents

List of Publications

Greig,C., **Saunders,D**., Renfree,A., Lewis,S., & Young,A. (2001) Reliability of oxygen uptake measured in very elderly women using the Metamax 3B system. 6th Annual Congress of the European College of Sports Medicine - Cologne.

Saunders,D.H., Greig,C., & Young,A. (2002) Concurrent validity and reliability of VO_2 measured using the Metamax 3B system during moderate intensity cycling. *British Journal of Sports Medicine*, 36.

Greig,C.A., Savaridas,T., **Saunders,D.,** Joseph,S., Young,A., & Mead,G.E. (2003) Lower limb muscle strength and power following 'recovery' from stroke. *Age and Ageing*, 32 (Suppl. 1), 34.

Saunders,D.H., Greig,C., Young,A., & Mead,G. (2004a) Physical fitness training for stroke patients. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD003316. DOI: 10.1002/14651858.CD003316.pub2.

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Mead,G.E., Greig,C.A., Cunningham,I., Lewis,S.J., Dinan,S., **Saunders,D.H.,** Fitzsimons,C., & Young,A. (2007) Stroke: a randomized trial of exercise or relaxation. *Journal of the American Geriatrics Society*, 55, 892-899.

Saunders,D.H., Greig,C.A., Young,A., & Mead,G.E. (2008) Association of Activity Limitations and Lower-Limb Explosive Extensor Power in Ambulatory People With Stroke. *Archives of Physical Medicine & Rehabilitation*, 89, 677-683.

Declaration and Ethical Approval

a) I declare this thesis has been composed by David H Saunders.

b) I declare that the work described in this thesis is original work and has been performed solely by David H Saunders with the exception of the following sections where the candidate made substantial contributions as part of a research group;

The systematic reviews (Chapters 9 and 11)

Candidate contribution detailed in Appendix 14.1

The STARTER trial (Chapter 10)

Candidate contribution detailed in Appendix 14.2

c) I declare that the work submitted in this thesis has not been submitted for any other degree or professional qualification.

d) I declare that all experimental work involving human participants had received prior ethical approval.

e) I declare that all participants shown in photographs had given written consent for the images to be used.

Signature: _____

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Part A

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PART A - Introductions

The ability to perform many important day-to-day physical activities is frequently impaired after stroke.

Physical fitness is important for the performance of all human physical activity; this includes the muscular work required to maintain posture, to walk, to perform activities of daily living and for occupational, leisure and sporting activities.

Physical fitness may be impaired in people who have had a stroke; this may reduce their ability to perform and tolerate everyday activities and exacerbate any stroke-related disability.

Physical fitness can be improved with fitness training. This results in benefits for healthy people of all ages and those with chronic diseases. However little is known about whether fitness training is beneficial for people with stroke.

1. Stroke

Stroke is defined as "*a clinical syndrome, of presumed vascular origin, typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death*" (World Health Organisation 1978). The WHO definition incorporates three main types of stroke, ischaemic stroke (~80%) intracerebral haemorrhage (~15%), and subarachnoid haemorrhage (~5%). The immediate and long term consequences of stroke are very diverse.

In the UK there are around 130,000 first strokes each year. In Scotland there are over 11,000, an incidence of around 2.8/1000 of the population. The majority (80%) of first strokes occur in people aged over 65 years, with the average age around 70 years (Syme et al. 2005). Over a period of 20 years (between 1981-84 and 2002-04) there has been a 29% reduction in the incidence of first strokes, even though the proportion of elderly people increased during this period (Rothwell et al. 2004). This may have occurred to improved primary prevention and reduction of risk factors.

1.1. Risk factors

There are many different risk factors for stroke (Hankey 2006): Randomized controlled trials show that hypertension, raised blood cholesterol, carotid stenosis, and atrial fibrillation are causal risk factors for ischemic stroke, and observational evidence suggests smoking, diabetes, and ischemic and valvular heart disease, are probable causal risk factors. In addition there are a range of other factors which may

be involved including obesity, psychosocial stress, low intake of fruit and vegetable and reduced physical activity.

The role of physical activity in stroke risk has been examined in recent reviews (Wannamethee and Shaper 1999; 5 studies) and meta-analyses (Lee et al. 2003; 23 studies; Wendel-Vos et al. 2004; 31 studies). Both meta-analyses show that the risk of total strokes, and its sub types, is reduced with moderate physical activity compared with low/inactivity. Lee et al. (2003) showed high levels of physical activity offer further benefit; this dose response relationship also implies a causal relationship (Brainin 2003). A more recent prospective study (Hu et al. 2005; n=4772; n=2863 strokes) indicates that physical activity during daily commuting, and especially leisure time are of greater importance than occupational activity.

1.2. Outcome of stroke

More than half of all stroke patients are either dead or dependent one year after stroke (Figure 1.1). Outcome varies after stroke and is influenced by both the severity and pathological type of stroke. For example worse outcome is associated with hemorrhagic strokes and some specific sub-types of ischaemic stroke (e.g. total anterior circulation infarct).

Stroke causes 5.54 million deaths worldwide every year. Immediate mortality is high with approximately 20% of people dying within 30 days of having a stroke, 30% are dead within a year due to complications (Scottish Intercollegiate Guidelines Network (SIGN 64) 2002). Stroke accounts for 11% of deaths in the UK, 9% in men and 13%

in women. Stroke is the third commonest cause of death after myocardial infarction and cancer. One third of those who survive have residual disability after 1 year and are dependent as a consequence. Those surviving the immediate effects of stroke are faced with a vast array of clinical problems. These problems may improve with lengthy rehabilitation.

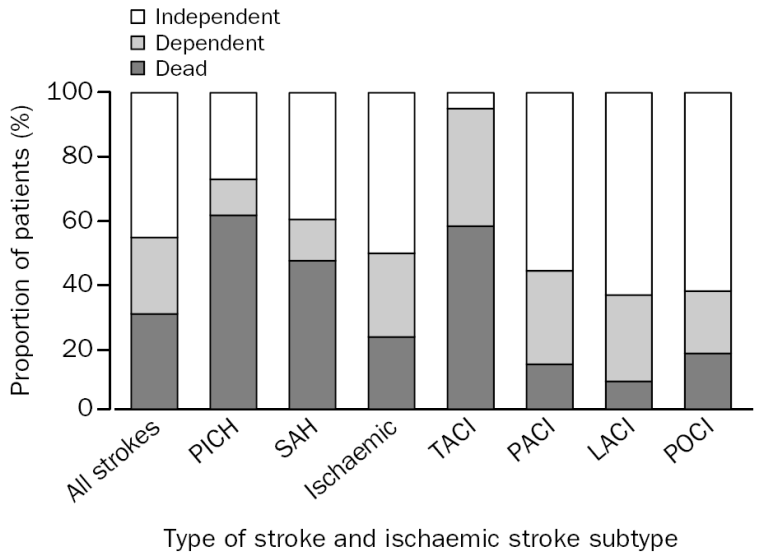


Figure 1.1 Prognosis one year after a first stroke in relation stroke pathology and ischaemic stroke subtype (PICH primary intracerebral haemorrhage; SAH subarachnoid haemorrhage TACI total anterior circulation infarct; PACI partial anterior circulation; LACI lacunar infarct; POCI posterior circulation infarct; Figure from Warlow et al. (1996).

1.3. Problems after stroke

There are a wide range of clinical problems which are common after stroke. These impairments, limitations and complications are summarized in Table 2.1 and Table 2.2. Post-stroke problems may occur as both direct neurological consequences of stroke (e.g. hemiparesis) and as indirect complications of stroke (Langhorne et al. 2000; Indredavik et al. 2008). Some problems may predate stroke such as comorbid diseases (e.g. cardiovascular disease).

Although the process of actually 'having a stroke' occurs in the brain Tables 1.1 and 1.2 illustrate that the consequences of stroke are extensive and complex, and can influence most areas of human function and behaviour.

Table 1.1 Compendium of impairments and limitations which are common after stroke. Information from the Scottish Intercollegiate Guidelines Network (SIGN 64; 2002) and http://www.EffectiveStrokeCare.org (accessed 04/09/2006).

Impairments	
Physical fitness impairments	Cardiorespiratory fitness Muscle strength (weakness)
Balance problems	Balance
Sensory impairments	Proprioception Vision
Musculoskeletal impairments	Oedema upper & lower limbs Shortening/contracture of soft tissue Shoulder subluxation Range of motion, active or passive
Neuromuscular impairments	General motor impairment Hemiparesis Ataxia Coordination Reaction times Altered muscle tone & associated reactions
Limitations	
Physical functions & movement	Walking & gait Wheelchair mobility Stair climbing Chair sitting & rising Rolling Transfers Dexterity & manipulation Quality and speed of movement
Activities of Daily Living	Dressing Feeding Personal hygiene Reaching Bathing Toileting Recreational/leisure activities

Table 1.2 Compendium of consequences and complications which are common after stroke. Information from the Scottish Intercollegiate Guidelines Network (SIGN 64; 2002) and http://www.EffectiveStrokeCare.org (accessed 04/09/2006).

Physical activity level	Immobility Physical Inactivity
Cardiovascular problems	Congestive heart failure Myocardial infarction Venous thromboembolism
Accidents and injuries	Falls & Fractures Pressure sores
Nutrition & digestion	Bowel function Gastrointestinal bleeding Salivation (excessive) Stress ulcers Dysphagia Nutrition, in Patients with/out dysphagia Oral Hygiene
Metabolic & endocrine problems	Dehydration Hyperglycaemia Hyper- & Hyponatraemia
Infection	UTI, chest, other
Involuntary abnormal movements	Chorea Dystonia (secondary) Parkinsonism Tremor
Psychological problems	Cognitive problems Executive functions Mood disturbance
Respiratory problems	Hiccups Hypoventilation Hypoxia Retention of respiratory secretions Sleep apnoea
Pain	Central post stroke pain Complex regional pain syndrome Headache Shoulder pain
Sensory function	General sensory loss Painful or uncomfortable sensations Sensitivity to pressure or temperature
Sleep and tiredness	Fatigue Hypersomnolescence Insomnia
Speech and language problems	Aphasia Apraxia of speech Dysarthria
Urinary problems	Urinary incontinence Urinary retention
Recurrent stroke	

1.3.1. Physical Inactivity

Physical inactivity is a premorbid risk factor for stroke and it can arise as a consequence of stroke. Most impairments and limitations in Table 1.1 relate to

physical activities which are rendered more difficult by the direct neurological effects of stroke (e.g. hemiparesis) resulting in reduced physical activity, and where this is more profound, immobility. Many of the secondary consequences of stroke listed in Table 1.2 are complications of immobility, and these have been shown to account for 51% of deaths in the first 30 days after stroke (Bamford et al. 1990).

Inactivity and immobility are often discussed in relation to people with stroke but few studies quantify physical activity. A number of studies have observed the nature and frequency of physical activities of people with stroke during inpatient care (Lincoln et al. 1989; Tinson 1989; Keith 1980; Keith 1988; Keith and Cowell 1987; Keith 1986). The more recent ones continue to show that a substantial percentage of the day is spent alone and physically inactive during inpatient rehabilitation (70%; Mackey et al. 1996; n=16; 34% Esmonde et al. 1997; n=17; 78% Bernhardt et al. 2004; n=64). Bernhardt et al. (2007; n=58) showed, not surprisingly, that those unable to walk were more inactive (98% of day) than those able to walk independently (40.5% of day). One study has recorded ambulatory activity in community dwelling people with stroke (Michael and Macko 2007; n=79) and showed low levels of walking activity which were associated with cardiorespiratory fitness.

Inactivity is known to cause in healthy people a deconditioning effect on the cardiorespiratory system (Saltin et al. 1968) and the musculoskeletal system (Degens and Alway 2006); for example inactivity causes disuse atrophy and an associated loss of muscle strength.

Muscle strength and cardiorespiratory fitness, two components of physical fitness, are identified as domains of impairment after stroke (Table 1.1). Subsequent sections will deal with these in detail and show how components of physical fitness are closely linked to functional limitation and disability (Section 2.3). Given that many post-stroke problems centre on limited physical activities it is plausible that impaired physical fitness could exacerbate (or even cause) some post-stroke problems.

1.4. Recovery from stroke

Most patients regain some motor function in the first days or weeks after having a stroke; recovery of function can continue for months or even years after stroke. The degree to which this occurs may depend upon many factors such as the severity and type of stroke, and location of the lesion. For example, 80% of patients achieve their best functional recovery 8.5 weeks (95% CI 8 to 9) after a mild stroke compared with 17 weeks (95% CI 15 to 19) after a severe stroke (Jørgensen et al. 1995).

Initial recovery during the acute phase arises from the plasticity of existing viable neurons which can reorganize and reinstate or compensate for lost tissue, and recovery of neurones in the penumbra. Neuro-functional recovery follows a logarithmic trend whereby around 50% of maximal motor recovery occurs after one week, reaching a plateau and becoming static after several months (Kreisel et al. 2006). Although neuro-functional recovery may cease in this chronic phase, stroke survivors may still benefit from improvements in day-to-day functioning through compensation for residual deficits and problems. Rehabilitation interventions may

influence the natural course of recovery during the acute phase (Kreisel et al. 2006), and promote compensatory strategies when provided during the chronic phase.

1.5. Stroke Rehabilitation

The goal of rehabilitation is to enable patients to preserve or reinstate their autonomy; it achieves this by limiting the impact of disease on physical, psychological and social functioning during daily life. Rehabilitation is a 'problem-solving' and educational approach usually delivered by multidisciplinary teams of health professionals. Many patients require rehabilitation after surviving a stroke, and a number of therapeutic options have been explored by systematic review (Young and Forster 2007).

1.5.1. Multidisciplinary stroke care

Systematic review evidence shows those who receive organised, multidisciplinary care in a specialised stroke unit are more likely to be alive or independent and living at home 1 year after stroke (Stroke Unit Trialists' Collaboration 2007) and the benefits are still evident 5 years after stroke. Stroke unit care is a complex intervention involving coordinated input from clinical and nursing staff specializing in stroke and therapists. Occupational therapy (OT) and physiotherapy (PT) are key components of multidisciplinary stroke care (Langhorne and Pollock 2002).

1.5.2. 'Black box' of rehabilitation

There remains uncertainty about which components of stroke rehabilitation are effective. If patients benefit from a package of rehabilitation therapies one is still left with the problem of identifying the principle 'active ingredient'(s), if any. As a consequence stroke rehabilitation, has been referred to as a 'black-box' (Ballinger and Ashburn 1999); this description still characterizes the problem of evaluating the therapeutic content of OT and PT. De Wit et al. (2006) identify that the therapeutic content of OT and PT are discrete; OT focused toward activities of daily living whilst PT focused on physical function and mobility (see *Limitations*; Table 2.1).

1.5.3. Physiotherapy

Recent Cochrane reviews indicate that PT interventions comprising 'mixed' therapeutic content are beneficial during inpatient and outpatient care after stroke. Pollock et al. (2007; 21 trials; n=1087) demonstrated that PT was significantly better than no intervention or placebo control in the recovery of functional independence following stroke. There was however inadequate evidence to distinguish the relative benefits (if any) of the individual component therapeutic approaches for lower limb function or postural control. Outpatient Service Trialists (2003; 14 trials; n=1617) showed that therapy-based rehabilitation services for stroke patients at home improved independence in activities of daily living. Again the interventions providing this evidence are heterogeneous with no indication of the value of the individual components of therapy.

A number of systematic reviews have examined various components of PT (summarised by Young and Forster 2007) and include acupuncture, electrical stimulation, force platform feedback for standing balance, constraint-induced movement therapy, treadmill training and body weight support for walking. There is also a review of physical fitness training (which forms Chapter 9 of the thesis).

Other general aspects of PT intervention delivery have been examined including the a) timing of interventions e.g early mobilization, b) whether training is 'task oriented' and c) the amount or 'intensity' of therapy. The intensity of therapy is an attempt to describe the overall 'dose' of rehabilitative training and this usually refers to the time dedicated to therapy (Kwakkel 2006). A recent systematic review (Kwakkel et al. 2004; 20 studies; n=2686) showed that ADL benefited from an increased (or 'augmented') therapy time during the first 6-months after stroke.

Most individual interventions show little benefit in terms of outcomes relating to the day to day functions valued by stroke patients. Although PT as a whole is a discipline containing a high content of repetitive physical activities very little is known about the benefits of exercise after stroke.

Stroke Summary

- Most stroke survivors are elderly and have comorbid disease
- Comorbid disease and physical inactivity may pre-date stroke
- There are limited data describing post-stroke physical inactivity, especially after discharge from rehabilitation
- Many stroke survivors experience functional limitation and disability linked to the reduced ability to perform physical activities
- Stroke unit care increases the chance of survival, return home and independence
- The optimal content of rehabilitation interventions remains unclear
- Guidance on the optimal types of physical therapies particularly within occupational therapy and physiotherapy is incomplete
- Many stroke survivors have residual disability after rehabilitation

2. Physical fitness

The ability to perform and tolerate physical activity is partly determined by ‘physical fitness’. 'Physical fitness' is the collective term for a set of physiological attributes, which people have or achieve, which relate to ability to perform physical activity (United States Department of Health and Human Services (USDHHS) 1996).

There are a number of separately defined components of physical fitness; the principal components include a) cardiorespiratory fitness, b) muscle strength and c) muscle power. Other parameters such as body composition, balance and agility can be defined as measures of physical fitness. All aspects of physical fitness show considerable variability due to a) genetic factors, b) increasing age, c) gender and d) presence of disease. Furthermore, physical fitness shows substantial adaptive plasticity; fitness improves in response to increased physical activity and becomes impaired by physical inactivity.

Those with higher levels of physical fitness exhibit greater capacity for physical activity and function. People with low physical fitness are less able to perform and tolerate physical activity and this may have undesirable functional consequences.

The following sections define the key components of physical fitness referred to in this thesis and will describe a) measurement and typical values of fitness, b) factors which influence the values of fitness and c) the functional importance of levels of fitness.

2.1. Cardiorespiratory Fitness

Cardiorespiratory fitness (sometimes termed 'aerobic fitness') is conferred by the central capacity of the circulatory and respiratory systems to supply oxygen (USDHHS 1996), and the peripheral capacity of skeletal muscle to utilise oxygen (Saltin and Rowell 1980). Cardiorespiratory fitness relates to an individual's ability to perform and tolerate continuous physical activity for an extended period of time (commonly referred to as 'endurance capacity' or 'stamina')

There are four physiological parameters which are commonly used to define cardiorespiratory fitness; these are a) maximal oxygen uptake, b) exercise economy, c) anaerobic threshold and d) oxygen uptake kinetics.

2.1.1. Maximal Oxygen uptake

2.1.1.1. Definition and measurement

Oxygen uptake ($\dot{V}O_2$) is defined as the amount of oxygen extracted from the inspired gas in a given period of time (Wasserman et al. 1999). $\dot{V}O_2$ is expressed either in absolute terms as litres of oxygen per kg body mass per minute ($l \cdot min^{-1}$) or scaled relative to body mass ($ml \cdot kg^{-1} \cdot min^{-1}$). $\dot{V}O_2$ is determined by means of respiratory gas analysis in conjunction with well established calculations.

The maximal oxygen uptake ($\dot{V}O_2$max) is defined as the highest possible oxygen uptake that a given individual can achieve for a given form of ergometry (Wasserman et al. 1999). $\dot{V}O_2$max occurs typically during maximal exercise at the

limit of tolerance. $\dot{V}O_2$ max is determined during repeated bouts of exercise of increasing intensity to identify the $\dot{V}O_2$ value which cannot be exceeded, alternatively the $\dot{V}O_2$ max is accepted when $\dot{V}O_2$ reaches a plateau during a single maximum work rate test (Wasserman et al. 1999). $\dot{V}O_2$ max is the most frequently reported physiological parameter of cardiorespiratory fitness, and is considered the 'gold standard' measure (American College of Sports Medicine 2006).

A closely related parameter to $\dot{V}O_2$ max is the peak oxygen uptake ($\dot{V}O_2$ peak); this is defined as the highest oxygen uptake achieved during a maximal work rate test (Wasserman et al. 1999). The values may be different from $\dot{V}O_2$ max since $\dot{V}O_2$ max is derived from repeated or plateaued measures of a $\dot{V}O_2$ which cannot be exceeded, whilst $\dot{V}O_2$ peak is simply the highest value obtained, and is often symptom limited.

2.1.1.2. Factors influencing maximal oxygen uptake

$\dot{V}O_2$ max is at its highest in the mid-late teens thereafter it declines progressively with increasing age. The data in Figure 2.1 demonstrate that healthy ageing is associated with loss of $\dot{V}O_2$ max at a fairly constant rate of 1-2% per year for men and women. These data also highlight the fact that women have a lower $\dot{V}O_2$ max across all ages ranging from 22-30% less than male values for ages 50-75yrs (Shvartz and Reibold 1990) to 35% less than those in their eighties (Malbut et al. 2002).

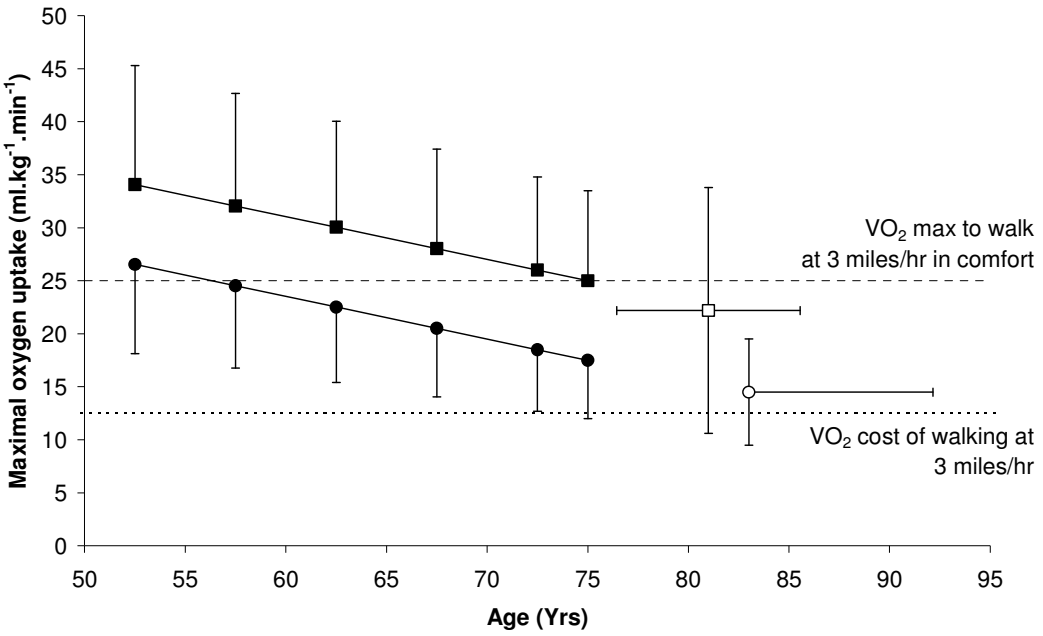


Figure 2.1 Influence of gender and age on $\dot{V}O_2$ max standardized for body mass in untrained men and women. Data are for men (■) and women (●) from a set of population norms (Shvartz and Reibold 1990) and a group of very elderly men (□) and women (○) from Malbut et al. (2002). The dashed lines represents an approximate $\dot{V}O_2$ for walking at 3 miles·h^{-1} and the $\dot{V}O_2$ max required to do so in comfort (Allied Dunbar National Fitness Survey 1992). Data points are means and error bars ±2SD.

Physical inactivity causes $\dot{V}O_2$ max to decline irrespective of age and gender. For example 3 weeks of bed rest in healthy young males caused $\dot{V}O_2$ max to decline by 25% (Saltin et al. 1968). Conversely appropriate physical fitness training can increase $\dot{V}O_2$ max in both young (Saltin et al. 1968), and very elderly people (Malbut et al. 2002). The unique 30 year follow-up of the Saltin et al. (1968) data by McGuire et al. (2001) shown in Figure 2.2 are an excellent example of the plasticity of $\dot{V}O_2$ max in relation to age and manipulating levels of physical activity. These data show that 3-weeks of inactivity causes a decline in $\dot{V}O_2$ max equivalent to 30-years of healthy ageing, and that the effects of physical inactivity and ageing on $\dot{V}O_2$ max can both be reversed by physical fitness training.

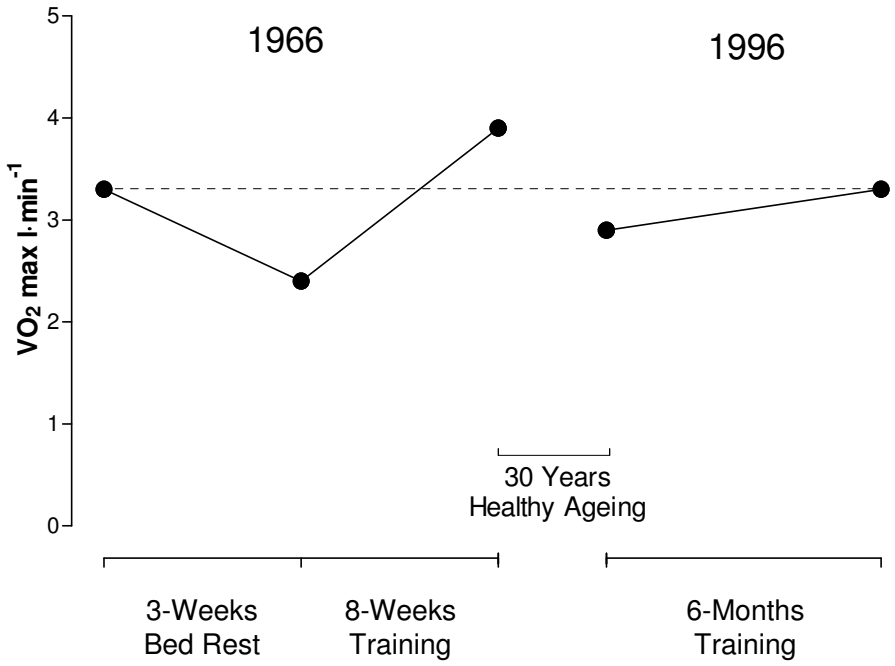


Figure 2.2 Response of $\dot{V}O_2$ to bed rest (inactivity) and high intensity training (activity) during the 'Dallas bed-rest study' (Saltin et al. 1968) and a 30-year follow-up of the same sample (n=5) showing the effects of healthy ageing and moderate intensity training (McGuire et al. 2001).

2.1.1.3. Functional importance

An individual's $\dot{V}O_2$ max represents their maximum achievable rate of aerobic metabolism. Although an element of anaerobic metabolism is always present any work in excess of $\dot{V}O_2$ max is met entirely by anaerobic metabolism. This means that due to fatigue physical activity will be either impossible or not tolerated. Different activity levels have different typical oxygen costs (Ainsworth et al. 2000). This means that people with low fitness may be able to comfortably tolerate gentle actvities (e.g. food shopping or washing dishes; $\dot{V}O_2$ ~7.6 ml·kg^{-1}·min^{-1}) but not more demanding activities with a higher $\dot{V}O_2$ which meets or exceed their $\dot{V}O_2$ max (e.g. walking at 3 miles·h^{-1}; $\dot{V}O_2$ ~11 ml·kg^{-1}·min^{-1}).

To be comfortable during exercise one must operate at a submaximal intensity. Fitzsimons et al. (2005) showed that elderly women asked to walk at their 'comfortable' pace utilized 55% of their $\dot{V}O_2$ peak. Waters et al. (1988) showed that elderly people (n=73; age range 60-80 years) walking at a 'normal' pace utilized 54% of the $\dot{V}O_2$ peak expected in untrained people (Shvartz and Reibold 1990). The examples demonstrate that the metabolic demands of comfortable, sustainable physical activity are some way below maximal capacity.

A low $\dot{V}O_2$ max for whatever reason has undesirable functional consequences because everyday activities may become impossible or fatiguing to perform. $\dot{V}O_2$ max declines with healthy ageing (and is lower in women); therefore performance of some day-to-day functions may be limited. These effects are intensified in people who are physically inactive, but can be ameliorated in those who are physically active.

2.1.2. Economy

2.1.2.1. Definition and measurement

Metabolic energy expenditure during submaximal exercise can be estimated from respiratory gas analysis, and approximates 20.1 $KJ \cdot min^{-1}$ per litre of oxygen utilized. This can be used to calculate the efficiency of exercise in which mechanical work can be determined. However most human physical activity does not occur in a form which allows direct determination of external mechanical work, for example floor walking has no vertical displacement and does not allow measurement of external

work. Therefore the metabolic cost (expressed as $\dot{V}O_2$ or energy) of a standardized physical activity is reported instead, in which case it is termed 'economy' rather than efficiency. The economy of walking is commonly reported as the $\dot{V}O_2$ utilized per unit distance covered ($\dot{V}O_2$ $ml \cdot m^{-1}$), higher values represent worse economy.

When economy is calculated using unadjusted $\dot{V}O_2$ values, gross economy is derived, however if resting values of $\dot{V}O_2$ are subtracted from the exercising values a net value for economy is calculated (Perrault 2006). This represents the metabolic cost and economy of the actual act of locomotion and is more reflective of the demands of the activity being performed (Waters et al. 1988).

2.1.2.2. Factors which influence walking economy

Speed - Economy of walking influenced by the velocity of walking. Slower walking speeds are less economical especially below 40 $m \cdot min^{-1}$ (Waters et al. 1988).

Age - Cross-sectional studies suggest a modest age-related deterioration in the economy of walking (Figure 2.3); the cost of preferred walking increases by 0.25-0.28% per year (Waters et al. 1988; n=260) and 0.35-0.72% per year (Malatesta et al. 2003; n=30). Worse economy of walking in healthy elderly people may arise from the age-related decline in self-selected walking speed (Waters et al. 1988), increased isometric activity and antagonist co-activation (Mian et al. 2006) and changes in the biomechanics of walking (Malatesta et al. 2003).

Gender - Davies and Dalsky (1997) showed the economy of walking in sedentary elderly men (n=47) age 71 years (SD 4) and elderly women (n=51) age 70 years (SD 3) was the same at 0.17 $ml \cdot kg^{-1} \cdot m^{-1}$ (SD 0.02). This agrees closely with Waters et al. (1988) to show that unlike other fitness parameters, economy of walking is unaffected by gender (Figure 2.3).

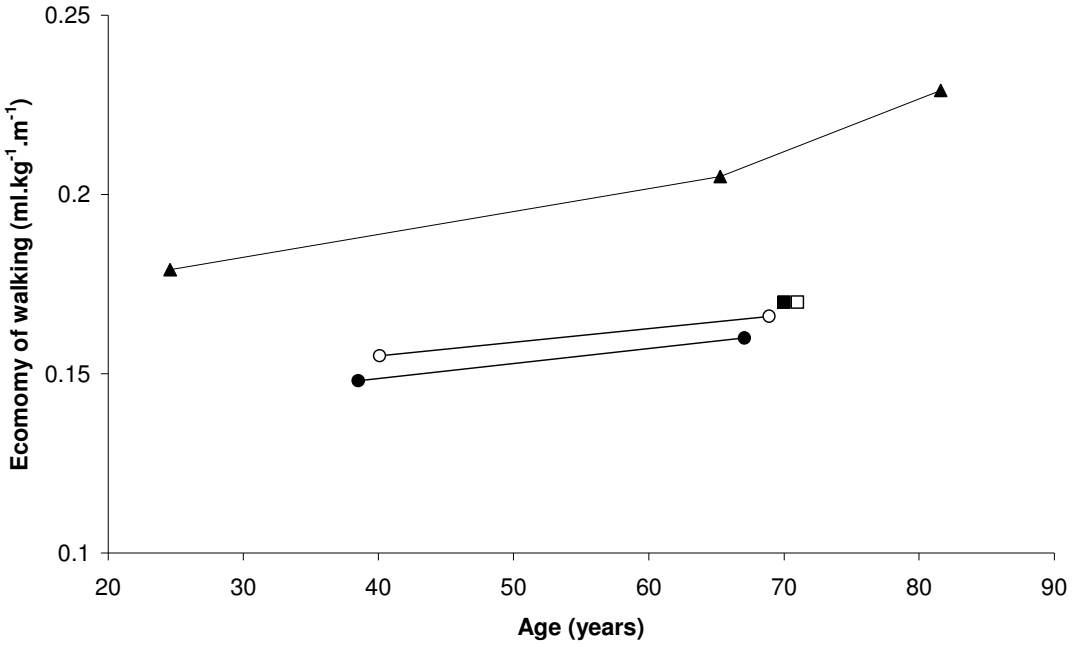


Figure 2.3 Influence of age and gender on the gross economy of walking at a customary 'normal' walking speed for 3-5 minutes. Data shown are the mean responses reported by Waters et al. (1988) for males (●) and females (○); Davies and Dalsky (1997) for males (■) and females (□) and Malatesta et al. (2003) for a mixed gender sample (▲).

Diseases - Any factors which cause abnormal patterns of gait can make walking less economical. For example pathologies such as spinal cord injury, hemiplegia, cerebral palsy, or use of prostheses and walking aids can worsen economy (Waters and Mulroy 1999).

Exercise - Thomas et al. (2007) showed that 12 weeks of treadmill training in healthy elderly women (n=22; age 75 to 85 years) reduced the net energy cost of walking by 18-21% at a range of walking speeds compared to a control group. Similar effects are seen in people with chronic diseases, for example chronic heart failure (18%; Beneke and Meyer 1997) and peripheral arterial occlusive disease (10%; Gardner et al. 2000).

Inactivity - There are currently no data to our knowledge showing that inactivity impairs economy. However given that economy is inversely related to $\dot{V}O_2$ max and muscle oxidative capacity (Hunter et al. 2005) and the fact that it is trainable, it is reasonable to suspect that economy of locomotion worsens with inactivity.

2.1.2.3. Functional importance

Impaired economy of walking dictates that walking will be performed more slowly and/or with more discomfort due to fatigue; this is in addition to any underlying biomechanical difficulties with gait. For people with a low $\dot{V}O_2$ max impairment to economy of walking means a high % of their $\dot{V}O_2$ max may be utilized in order to walk, leaving little in reserve. However people with a higher $\dot{V}O_2$ max are better able to tolerate, with less fatigue, the additional demands of a pathological gait as they have a greater 'fitness reserve', that is they utilize a smaller % of their $\dot{V}O_2$ max.

2.1.3. Anaerobic threshold

2.1.3.1. Definition and measurement

The anaerobic threshold (AT) is defined as the exercise $\dot{V}O_2$ above which anaerobic high-energy PO_4 production supplements aerobic high-energy PO_4 production causing a net increase in lactate production (Wasserman et al. 1999). Exercise intensities above AT are associated with lactate accumulation, metabolic acidosis and fatigue. AT is determined during progressive incremental exercise using blood lactate measures or non-invasively using measures of gas exchange (Beaver et al. 1986). The $\dot{V}O_2$ at the anaerobic threshold is always below the peak or maximum $\dot{V}O_2$ and is sometimes expressed as a % of the $\dot{V}O_2$ max. Measures such as $\dot{V}O_2$ max reflect centrally-limited aspects of cardiorespiratory fitness whilst the anaerobic threshold is more reflective of muscle oxidative capacity and is thus a peripherally limited aspect of cardiorespiratory fitness.

2.1.3.2. Factors affecting anaerobic threshold

Absolute values for AT are 13-21% lower in females than males of the same age (Figure 2.4). AT decreases by around 1% per year, one mechanism for this is the age-related decline in muscle oxidative capacity; Conley et al. (2000) showed that muscle oxidative capacity in a group aged 68.8 years was 50% lower than those aged 38.8 years; differences in physical activity could explain this. A meta-analysis by Londeree (1997; 34 studies) concluded that 8-12 weeks of endurance type training can improve AT especially in sedentary people and that detraining reduces AT.

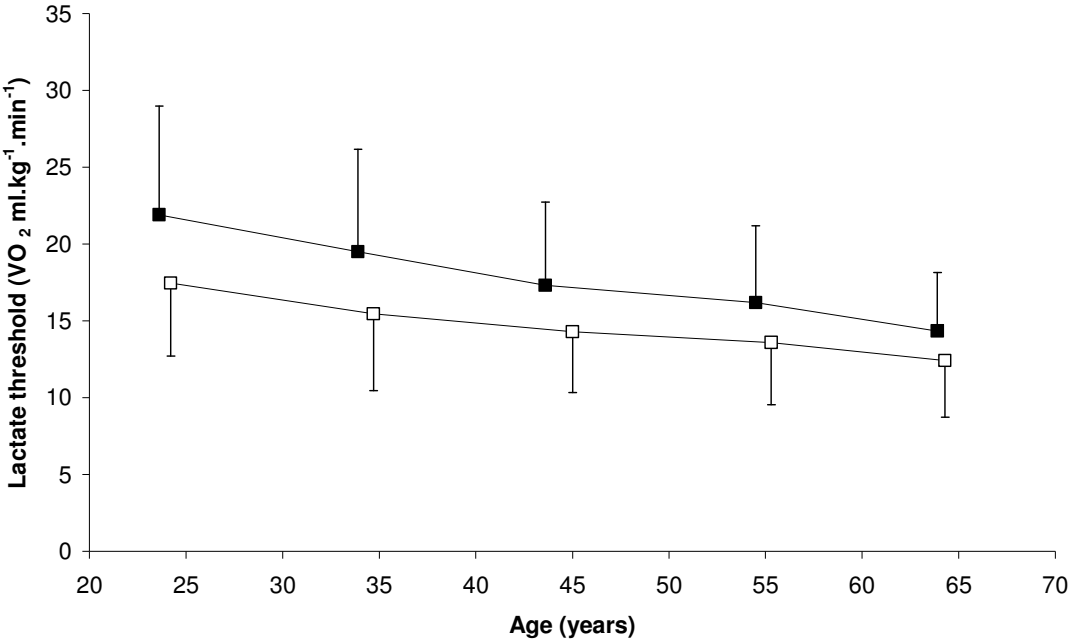


Figure 2.4 Influence of gender and age on the $\dot{V}O_2$ at which the lactate threshold (LT) occurs. The LT was determined via gas exchange in male (■; n=103) and female (□; n=101) sedentary non-smoking subjects during cycle ergometry (Davis et al. 1997). Data points are means and error bars ±2SD.

2.1.3.3. Functional importance of the anaerobic threshold

Exercise at an intensity below AT is associated with little lactate appearance and greater exercise tolerance, whilst intensities greater than AT are associated with fatigue due to lactate appearance. Impaired AT ($\dot{V}O_2$ <11 ml·kg^{-1}·m^{-1}) also has greater prognostic value than $\dot{V}O_2$ max in patients with chronic heart failure (Gitt et al. 2002).

2.1.4. Oxygen Uptake kinetics

2.1.4.1. Definition and measurement of oxygen uptake kinetics

The characteristics of the oxygen uptake response from rest at the onset of constant load exercise can be characterized mathematically. This response consists of three phases (Figure 2.5): Phase I a brief (15-20 sec) cardiodynamic period of increased pulmonary circulation preceding the arrival in the lungs of blood modified by exercise metabolism. Phase II is the true kinetic phase of the exercise response, a single exponential response which describes the increase in cell metabolism to a steady state value (Phase III), typically achieved in around 3 minutes after the onset of exercise (Wasserman et al. 1999).

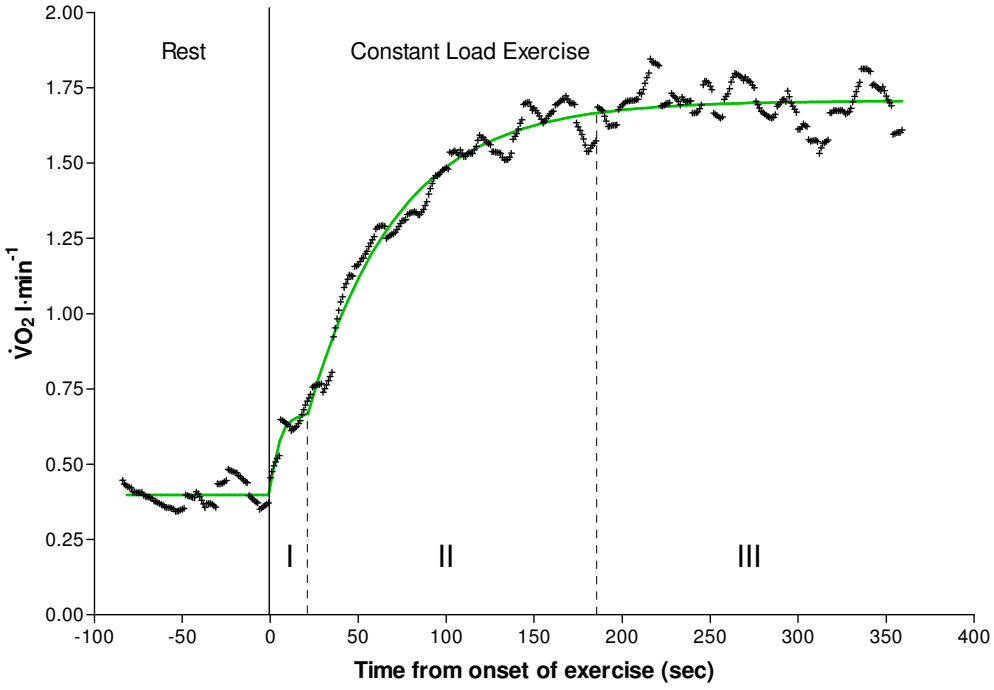


Figure 2.5 Example of the oxygen uptake response (Phase I and Phase II) after the transition from rest to constant load walking exercise during which a steady state is achieved (Phase III) typically after 180 sec in healthy people.

The rate constant for the phase II exponential increase in oxygen uptake ($\tau\dot{V}O_2$) is typically around 30 sec in healthy people; for individuals this remains remarkably constant across a range of workloads (Ozyener et al. 2001). A larger, therefore slower rate constant equates to a greater oxygen debt at onset of exercise. The consequences of this are increased fatigue and a longer period of recovery after exercise.

Not surprisingly different parameters measuring cardiorespiratory fitness are related to one another. The $\tau\dot{V}O_2$ shows a strong inverse relationship to $\dot{V}O_2$max (Chilibeck et al. 1996). In elderly people (68 – 91 years) those with lower values of $\dot{V}O_2$peak had correspondingly slower $\tau\dot{V}O_2$ values (Alexander et al. 2003).

2.1.4.2. Factors influencing oxygen uptake kinetics

Age - Cross-sectional studies of $\tau\dot{V}O_2$ in healthy untrained men (Harris et al. 2003; n=21), women (Cunningham et al. 1993; n=19; Chilibeck et al. 1996; n=unknown;Fitzsimons et al. 2007; n=10) and one undefined gender mix (DeLorey et al. 2004; n=12) suggest an age-related slowing in $\tau\dot{V}O_2$ of 1-4% per year (Figure 2.6). One small longitudinal study showed a more marked decline of 6.25% per year over 9 years (Bell et al. 1999; male n=6, female n=1).

Gender - These studies suggested that $\tau\dot{V}O_2$ in females is approximately ~38% slower than in males although similar to the gender difference in $\dot{V}O_2$max, but the data are very limited

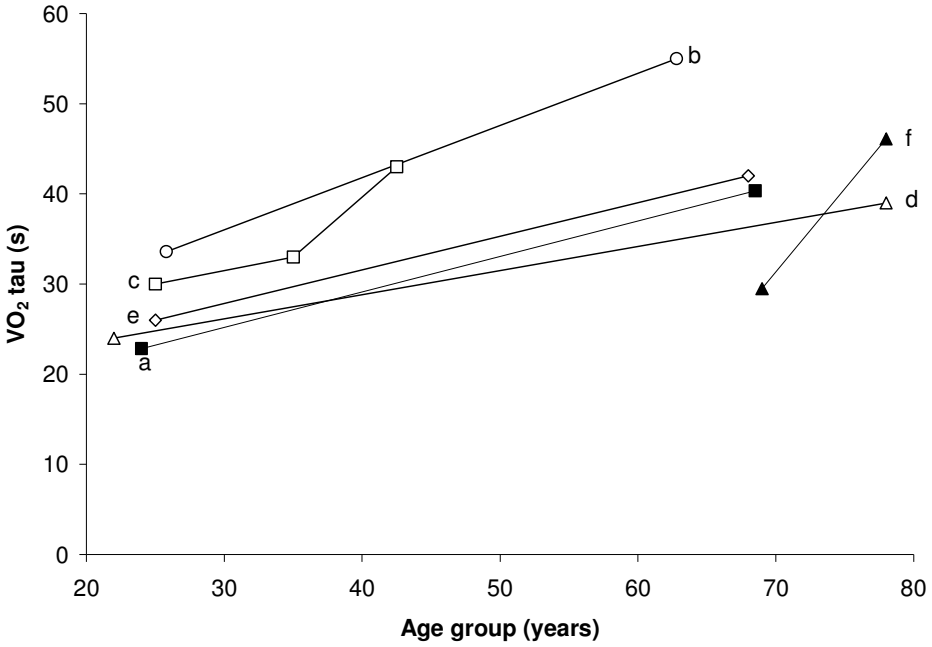


Figure 2.6 Influence of gender and age on the time constant for oxygen uptake kinetics ($\tau\dot{V}O_2$). Data are means from cross-sectional studies of male subjects (a. Harris et al. (2003 ■), female subjects b. Cunningham et al. (1993; □) c. Chilibeck et al. (1996; ○), d. Fitzsimons et al. (2007; Δ), unknown gender mix e. DeLorey et al. (2004; ◊) and one longitudinal study with a majority (6/7) of men f. Bell et al. (1999;▲).

Physical activity - $\tau\dot{V}O_2$ is trainable. Endurance training can improve $\tau\dot{V}O_2$ from 62.2sec (SD 15.5) to 31.9sec (SD 7.0) in elderly men age 72 years (Babcock et al. 1994). Little is known about the effects of physical inactivity on $\dot{V}O_2$ kinetics.

2.1.4.3. Functional importance

Smaller (faster) values of $\tau\dot{V}O_2$ are associated with greater mobility (6 minute walk distance) and physical function (timed up-and-go and carrying a weighted bag) in elderly people aged 68 to 91 years (Alexander et al. 2003). The predictive value was as good as, or significantly better than $\dot{V}O_2$ peak, but was limited to fitter people (24.4 vs. 14.2 $ml \cdot kg^{-1} \cdot min^{-1}$). In summary little is known about the functional importance of oxygen uptake kinetics.

2.2. Muscular strength and Power

Muscle force generation can be described in terms of strength and explosive power.

2.2.1. Muscle Strength

2.2.1.1. Definition and measurement

Muscle strength is defined as the maximum force or torque that can be generated by a specific muscle or muscle group (USDHHS 1996). The measures are reported in Newtons (N) for force and Newton metres ($N \cdot m^{-1}$) for torque and can be normalised to body mass (e.g. $N \cdot kg^{-1}$). Strength can be determined in a number of different ways. The force or torque may be measured in a static state (isometric), or dynamically throughout a range of joint motion (either concentrically or eccentrically). Modern dynamometry can also control rate of movement in which case the strength measure is termed isokinetic. The most common expressions of muscle strength in elderly or patient populations are a) isometric force or isometric torque, and b) isokinetic force or isokinetic torque.

2.2.1.2. Factors affecting muscle strength

Muscle strength deteriorates as a consequence of healthy ageing (~1-2% per year). The gender difference accompanying this means men have the equivalent of around a 20 year advantage (Figure 2.7). The loss of skeletal muscle mass due to inactivity during healthy ageing offers one mechanism to explain this. Muscle mass and strength are highly sensitive to disuse. For example cast immobilisation causes a

local reduction in muscle strength of 3-4% in healthy people within one week (Appell 1986), and is accompanied by muscular atrophy and changes in local muscle metabolism (MacDougall et al. 1977). However the 'quality' as well as quantity of muscle deteriorates with inactivity and increasing age. For example muscle fibre type transitions, neurological changes, and proportion of non-contractile material in muscle may also act to reduce neuromuscular function.

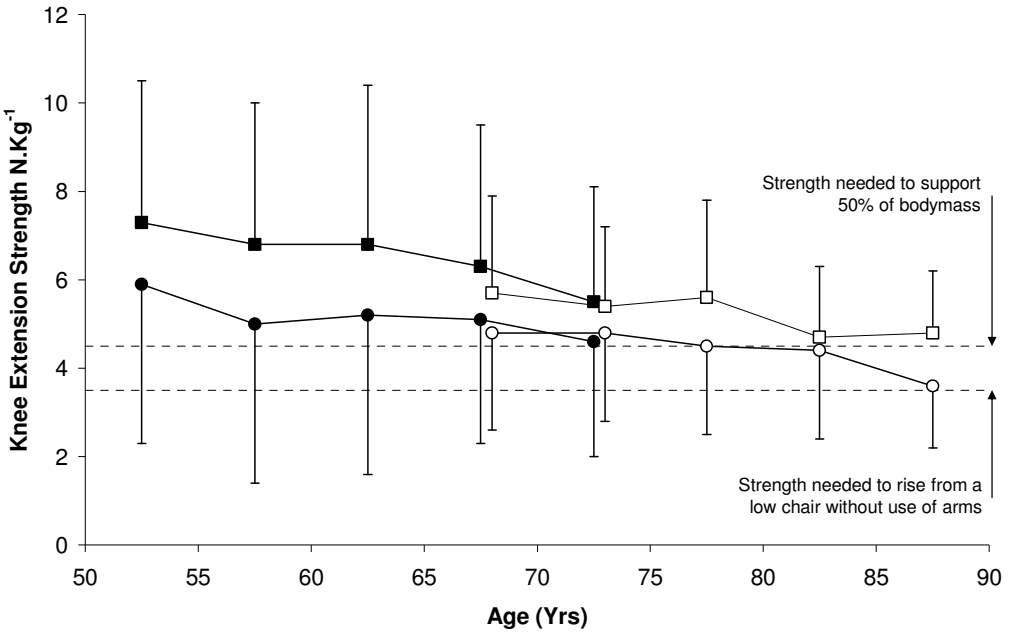


Figure 2.7 Isometric knee extensor strength of men (■) and women (●) from the general population (Skelton et al. 1999) and a sample of very elderly men (□) and women (○) from Skelton et al. (1994). Two functional thresholds are marked, strength required to a) support 50% of body mass and b) rise from a low chair without assistance (Allied Dunbar National Fitness Survey. 1992). Data are mean ± 2SD. Values at 67.5 and 72.5 years offset for clarity.

Chronic disease (e.g. chronic heart failure or chronic obstructive pulmonary disease) is also associated with loss of muscle mass and strength which may arise from disuse or systemic inflammation (Degens and Alway 2006). Local effects of disuse also occur; for example unilateral disuse due to hip-osteoarthritis in elderly people which

is associated with unilateral loss of muscle mass and strength (Suetta et al. 2007). In addition cigarette smoking is known to be associated with low muscle strength (Al Obaidi et al. 2004). Poor nutrition is linked to loss of muscle mass.

Muscle strength can be increased by strength training interventions (see Section 3) in people aged over 60 years (systematic review by Latham et al. 2004; 62 trials; n = 3674) and over 80 years (Skelton et al. 1995). This 'counteracts' the effects of age by the equivalent of 10-20 years (Young 2001).

In summary increased age, physical inactivity, chronic disease, poor nutrition and cigarette smoking are all associated with reduced muscle strength. Strength training increases muscle strength.

2.2.1.3. Functional importance of muscle strength

An immediate consequence of having low muscle strength can be functional limitation. Isometric knee extensor strength is associated with chair rise time in elderly men and women (Skelton et al. 1994). Leg extension strength is associated with habitual gait velocity, stair climbing speed and chair rise time (Cuoco et al. 2004). Knee extensor and hip flexor strength are associated with indices of lower extremity performance including walking, standing balance and chair rising (Ferrucci et al. 1997). A frequent observation is that the associations between muscle strength and functional limitation are not generally linear (see later Section 2.3.1).

Strength is also associated with self-reported indices of disability (Late Life Function and Disability Instrument; Puthoff and Nielsen 2007). Reduced strength (Skelton and Dinan 1999) muscle mass (Stewart et al. 2002) in the lower limbs are associated with increased risk of falls and fractures in elderly people. In addition to the immediate functional consequences, low strength also predicts future functional limitation and disability (Rantanen et al. 1999b) and mortality (Rantanen et al. 2000).

2.2.2. Explosive power

2.2.2.1. Definition and measurement

Explosive power output differs from strength in that it is a velocity-dependent characteristic defined as the greatest rate of work achieved during a single, resisted contraction (USDHHS 1996). Power output is the product of force and speed of movement usually reported in Watts as a power to body mass ratio ($W \cdot Kg^{-1}$).

There are several methods for measuring explosive power, e.g. vertical jumping on a force platform, use of isokinetic dynamometers or other equipment interfaced to concurrently measure force and velocity (Macaluso and De Vito 2004). Explosive activities like vertical jumping may be hazardous for elderly people. Isokinetic dynamometers restrict joint movement and velocity so although safer than jumping, the resulting pattern of movement and its measure of power have little functional relevance to everyday physical functions. Therefore specific pieces of apparatus have been produced which allow functional movement of the lower limb extensors in a safe seated position (Bassey and Short 1990).

2.2.2.2. Factors affecting muscle power

There is a gender-related decrement in explosive power with increasing age (Figure 2.8). Lower limb extensor power deteriorates more rapidly (3-4% per year) than knee extensor strength (1-2% per year) in the same cohort of subjects (Figure 2.7 vs. Figure 2.8). Muscle power output also deteriorates with physical inactivity, due to the sarcopenia which undermines muscle strength, selective atrophy of type II muscle fibres (and therefore loss of type IIX myosin heavy chain (MHC IIX), and adaptive shortening of muscle which occurs during inactivity (Harridge and Young 1998).

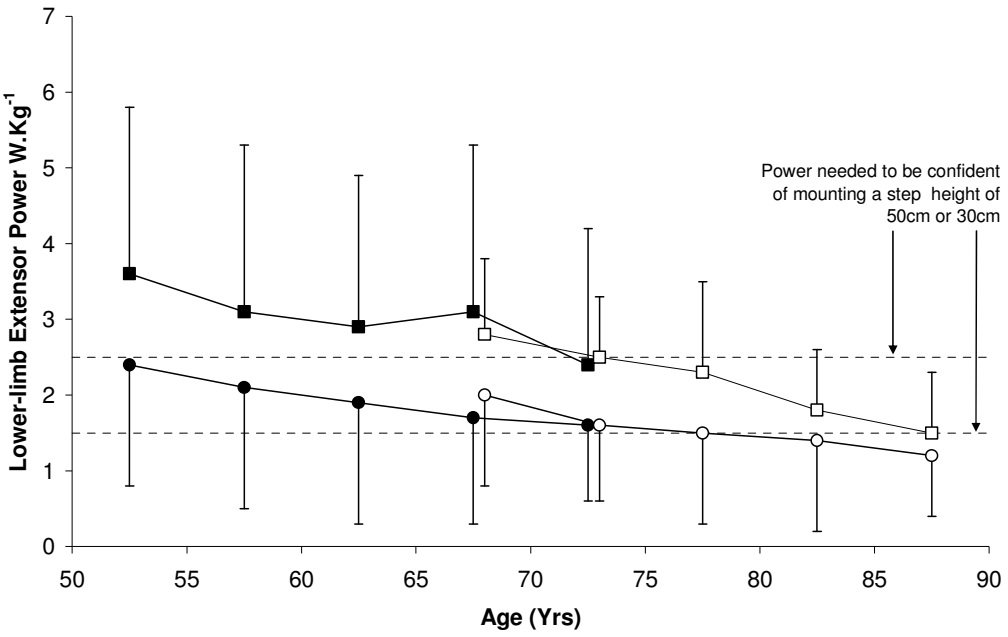


Figure 2.8 Lower-limb extensor power of men (■) and women (●) from the general population (Skelton et al. 1999) and a sample of very elderly men (□) and women (○) (Skelton et al. 1994). Two functional thresholds in power are marked below which some people are not able to mount a step of 30 or 50cm (Allied Dunbar national Fitness Survey. 1992). Values are mean ± 2SD. Data points at 67.5 and 72.5 years offset for clarity.

Leg extensor power in very elderly people does not, as expected, respond to cardiorespiratory training (e.g. Malbut et al. 2002) but it does respond specifically to resistance training (e.g. Skelton et al. 1995). In addition resistance training involving

rapid movements is proving to be more effective at improving muscle power than traditional strength training (Porter 2006;Sayers 2007).

2.2.2.3. Functional importance of explosive power

Low strength and low explosive power have very similar undesirable functional consequences (Young 2001). In elderly people with functional impairments, power output during leg-press exercise is associated with stair climbing ability, chair rise time and habitual gait velocity (Cuoco et al. 2004), and with self-reported functional status (Foldvari et al. 2000).

However explosive power output is more closely associated with ability to perform physical functions (e.g. stair climbing, chair rising and walking; Foldvari et al. 2000;Suzuki et al. 2001;Bean et al. 2002;Puthoff and Nielsen 2007) and with indices of disability (Puthoff and Nielsen 2007) than muscle strength. Also when impairment of explosive power in the lower limbs is not symmetrical, it is a better predictor of the frequency of falling than strength alone (Skelton et al. 2002).

Dynamic resistance training interventions are more beneficial than traditional strength training for function and disability in older people (Porter 2006; Sayers 2007; Hazell et al. 2007).

2.3. The relationships between physical fitness impairments, limitations, disability and autonomy

Even in the absence of disease, poor physical fitness can limit function, irrespective of whether this occurs due to the effects of inactivity, gender or ageing. This section discusses how impaired fitness is linked to function, disability and autonomy.

2.3.1. Complex Relationships between fitness and function

When physical fitness is limited, physical activities may become fatiguing, uncomfortable, or even impossible to perform. However the relationships between fitness and function are complex.

Cardiorespiratory fitness (Cress and Meyer 2003) and muscle strength (Buchner and De Lateur 1991) show non-linear associations with function in elderly people (Figure 2.9). At the lower end of the spectrum, limited function improves with increased fitness (‘*Limitation’*; Figure 2.9), after this, further increases provide no functional advantage (‘*Reserve Capacity’*; Figure 2.9). However, ‘reserve’ fitness capacity may still be beneficial by a) making activity less fatiguing and more comfortable, and b) acting as a ‘buffer’ against future loss of fitness. Where the minimum energy requirement of a task exceeds the maximum capacity of that individual (as defined by fitness) the task becomes impossible without some external assistance or modification. Where the activity in question is one of daily living the boundary is termed a ‘*Threshold for independence’* (Figure 2.9).

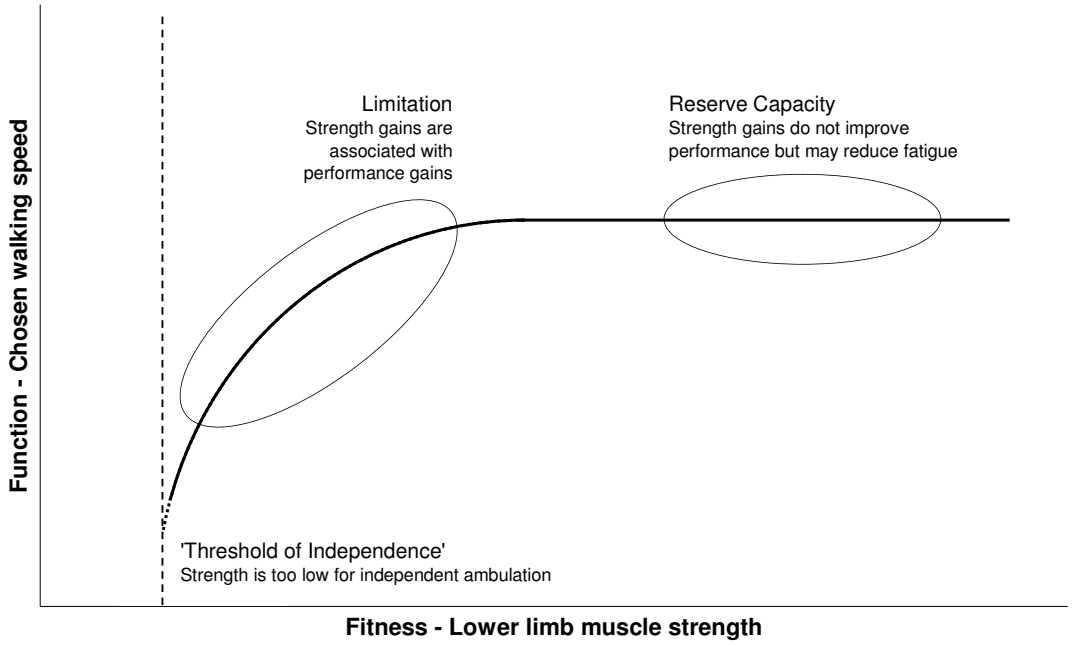


Figure 2.9 Graph to show the relationship between a physical fitness variable and function. This is a hypothetical representation of the data of Buchner & De Lateur (1991) who showed such a relationship between leg strength and mobility. The graph also includes the concept of a '*Threshold of Independence'* (Young 1986); in this example leg strength is so low that independent ambulation becomes impossible

The effects of healthy ageing mean that many disease-free elderly people live close to 'thresholds of independence'; those who are inactive, especially females, are vulnerable to subsequent functional limitation (defined as *'frail'*; Fried et al. 2001). Gender-related differences in fitness dictate that thresholds of independence are reached around 20 years earlier in women; this observation helps explain to why disability, falls and restricted independent mobility are more prevalent amongst elderly women.

Fitness-function relationships are multifactorial. For example muscle strength and balance act synergistically to predict the presence of severe walking disability in

elderly women (Rantanen et al. 1999a), and the onset of new severe walking disability after 3-year follow up (Rantanen et al. 2001). These studies show that one impairment can be compensated for by another with less of a deficit; for example good balance can offset the otherwise detrimental effects of low muscle strength on walking.

2.3.2. Relationship between functional limitation and disability

Disability defines the difference between an individual's functional capabilities and the requirements imposed by their environment. Disability is usually explored by asking individuals whether they find activities of daily living difficult. This self-reporting may underestimate 'pre-clinical' disability since elderly individuals may not report (or perceive) difficulties yet have functional limitations (Fried et al. 1996). For example individuals may deny walking difficulty despite slower indoor walking or use of a walking aid (Pine et al. 2000;Pine et al. 2002) or be independently mobile but describe tiredness in daily activities (Avlund et al. 2003).

Functional decline is linked to the process of disablement. For example walking speed, chair rising, and balance predict subsequent disability and hospitalization in non-disabled older people (Guralnik et al. 1995; Penninx et al. 2000).

2.3.3. Physical fitness plasticity

The previous sections have shown how age, gender, inactivity and exercise can affect physical fitness. Physical inactivity may have a rapid deleterious effect whilst the

effects of ageing which occur at slower rate. Across most of the parameters women are at a disadvantage, equivalent to approximately 20 years of healthy ageing.

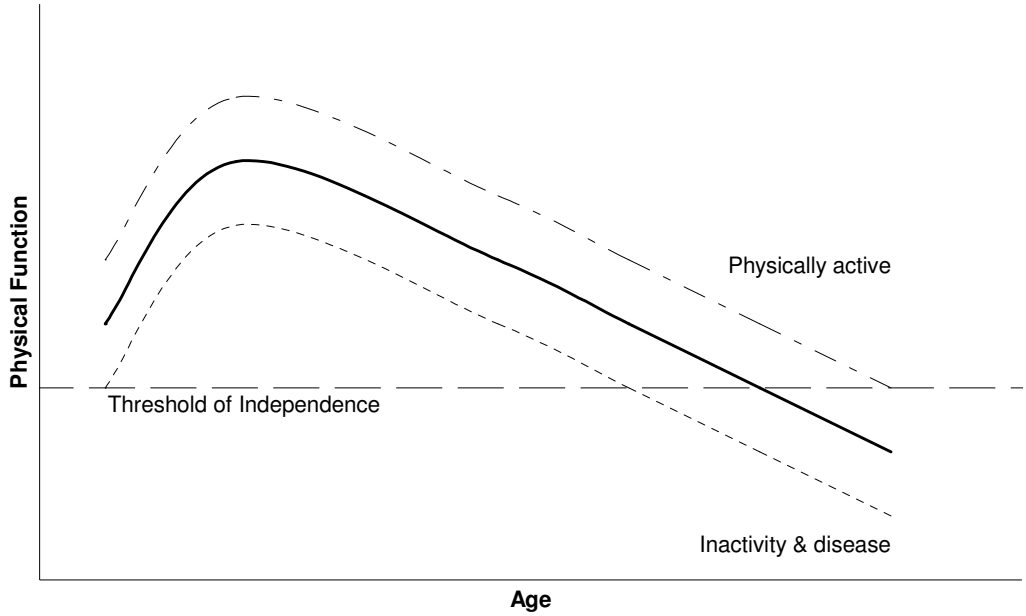


Figure 2.10 Illustration of how the improvements (due to exercise or activity) and impairments (due to physical inactivity or disease) in physical fitness could interact with the process of healthy ageing to influence physical function and the crossing of thresholds of independence (Young 1986).

In summary, the plasticity of physical fitness has implications for exacerbating disability but it also provides an opportunity to ameliorate it. For example if physical fitness can be improved there may be beneficial functional consequences. The next section of the thesis describes how exercise can be utilized as an intervention to improve physical fitness.

Physical Fitness Summary

- Cardiorespiratory fitness, muscle strength and muscle power define the capacity to perform, and comfortably tolerate, physical activity
- Physical fitness is lower in women than men
- Physical fitness deteriorates with increasing age
- Physical fitness is impaired by physical inactivity
- Physical fitness impairments are associated with chronic diseases and smoking
- Low physical fitness has undesirable functional consequences and contributes to disability
- Physical fitness can be improved with physical activity or exercise

3. Physical Fitness Training

'Exercise' is a subset of '*physical activity*' which is deliberately performed to improve one or more components of physical fitness. *'Physical fitness training'* (or training) is a slightly more specific term defining a planned, structured regimen of regular exercise (USDHHS 1996).

3.1. Benefits of physical activity and exercise for healthy people

The recent ACSM & AHA Physical Activity Recommendation (Nelson et al. 2007) stated that physical activity (including exercise) has extensive preventive benefits for older adults: Participation in physical activity reduces the risk of cardiovascular disease, stroke, hypertension, type II diabetes, osteoporosis, obesity, colon and breast cancer, anxiety and depression. In addition, the risk of falls and injury from falls is reduced and functional limitations are either prevented or compensated for. Regular physical activity, including exercise, can enhance quality of life and improve the low physical fitness associated with old age (Young 2001).

3.2. Basic structure of training

The structured regimen of fitness training is defined by several key variables a) *type of activity*, which describes the mode of exercise, b) *frequency* of training sessions, in days per week, c) *duration* of each training session, and d) *intensity* of training. Intensity is an important variable describing the degree of effort made and is related

to metabolic rate or magnitude of muscle force generation[1]. Frequency, duration and intensity of training together define the overall 'dose' of fitness training.

Training interventions are typically targeted at the improvement or maintenance of either cardiorespiratory fitness, or muscle strength (ACSM 1998b). Table 3.1 summarises the '*cardiorespiratory training'* and '*strength training'* aspects of a widely accepted model of physical fitness training intended for improving the fitness of healthy people (ACSM 1998b). Both types of training intervention can be used concurrently in which case the training is termed '*mixed training'*.

3.3. Basic principles of training

There are a number of basic principles underpinning all types of fitness training which can influence adaptations in components of physical fitness; the adaptations are collectively termed '*training effects'*.

3.3.1.1. Progressive overload

The training prescription in Table 3.1 provides a sufficient stimulus to cause a training effect in most people – it provides a tolerable degree of overload. Training effects increase exercise tolerance (making training less stressful) so the dose of training must progressively increase in order to maintain a sufficient stimulus. The intensity, frequency and/or duration of training can be increased throughout the programme to achieve this. This concept is termed *progressive overload* and this is a defining feature of a physical fitness training intervention.

[1] The term 'intensity' is used in rehabilitation literature to describe the amount of time spent receiving therapies. In this thesis intensity is used to describe metabolic rate or magnitude of force generation.

Table 3.1 Summary of the American College of Sports Medicine (ACSM) position stand guidelines (1998b) for developing and maintaining fitness in healthy adults.

Variable	Cardiorespiratory training	Strength training
Type of activity	Any activity that uses large muscle groups, which can be maintained continuously, and is rhythmical and aerobic in nature.	Most persons should complete 8-10 different exercises which each involve consecutive, repeated resisted muscle contractions which collectively activate all the major muscle groups.
	Examples: walking, swimming or group activities such as exercise classes either singly or in some combination.	Example of resistance: weights, elastic devices or body mass, and exercise machines.
Frequency	3-5 $d \cdot wk^{-1}$.	2-3 $d \cdot wk^{-1}$ is recommended
Intensity	55/65%-90% of maximum heart rate or 40/50%-85% of maximum $\dot{V}O_2$ reserve or maximum heart rate reserve.	The maximum degree of resistance which allows completion of one set of 8-12 repetitions (consecutive contractions) of each exercise is recommended.
	For unfit individuals the lower intensity values, i.e. 40-49% of $\dot{V}O_2$ reserve or maximum heart rate reserve and 55-64% of maximum heart rate are most applicable.	For elderly or frail people a lower resistance allowing 10-15 repetitions is recommended.
Duration	20-60 min of continuous or intermittent (minimum of 10-min bouts accumulated throughout the day) aerobic activity.	This is not an important variable in strength training
	Duration is dependent on the intensity of the activity; thus, lower-intensity activity should be conducted over a longer period of time (30 min or more). Moderate-intensity activity of longer duration is recommended for adults not training for athletic competition.	Multiple-sets of the regimens described above may provide greater benefits if time allows.

3.3.1.2. Specificity

Different types of training give specific adaptations in terms of; i) physiological adaptation (i.e. cardiorespiratory training improves cardiorespiratory fitness), ii) body segment activated (i.e. lower limb training benefits the lower limbs), and iii) neuromuscular adaptations to pattern of movement (i.e. walking not cycling improves gait performance). Therefore mode of exercise must also reflect the desired functional outcome - in a rehabilitation context this is often termed 'task-related' training.

3.3.1.3. Reversibility

Improvements gained from fitness training are transient and reversible i.e. unless training is maintained physical fitness, along with any associated functional gains, deteriorate to pre-training levels (ACSM 1998b).

3.4. Recommendations for training patient groups

Elderly people with a variety of existing diseases may benefit from training which forms part of their rehabilitation (Young and Harries 2001). The recent ACSM & AHA Physical Activity Recommendation (Nelson et al. 2007) summarises the wide-ranging therapeutic and management roles that physical activity (including exercise) plays in clinical practice. Physical activity has a therapeutic role in CHD, hypertention, PVD, type II diabetes, obesity, elevated cholesterol, osteoporosis, arthritis, claudication and COPD. Physical activity has a role in the management of depression and anxiety disorders, dementia, pain, congestive heart failure, syncope, prophylaxis of venous thromboembolism, back pain, constipation and stroke (Section

3.4.1). Physical activity may also improve sleep and it may prevent or delay cognitive impairment and disability.

3.4.1. Recommendations for Stroke

ACSM & AHA has previously made a physical activity and exercise recommendation (including cardiorespiratory and strength training) for people with stroke (Gordon et al. 2004). This is incorporated in the more recent guideline for elderly people (Nelson et al. 2007).

The recommendation for stroke is not based on systematic review of the evidence. The recommendation is supported by a small number of studies including some which are uncontrolled (Whitall et al. 2000), non-randomized (Rimmer et al. 2000) and use non-training interventions (Whitall et al. 2000). Other aspects are based on recommendations for healthy people (ACSM 1998b) and non-stroke patient groups (Fletcher et al. 2001). Therefore the quality of the evidence is low and there is a lack of generalizability.

There are numerous plausible benefits for people with stroke associated with participation in, and adaptations from, fitness training but the evidence is incomplete and current recommendations are not based on randomized controlled trials and systematic review.

Physical Fitness Training Summary

- Physical fitness training is a planned, structured regimen of regular physical exercise deliberately performed to improve physical fitness
- Cardiorespiratory training improves cardiorespiratory fitness
- Strength (or resistance) training improves indices of muscle force production (strength, power and muscular endurance)
- Fitness improvements arise in response to *overload,* are *specific* to the mode of training and are *reversible*
- Fitness training is beneficial for healthy people and those with a variety of chronic diseases
- Clinical practice guidelines for fitness training after stroke do exist but these are weakly supported in terms of amount and quality of evidence

4. Aim and Objectives of Thesis

Physical fitness training is known to be beneficial for healthy elderly people (Section 3.1) and for different patient groups (Section 3.4). Therefore it is plausible that physical fitness training may be beneficial for people with stroke.

The primary benefit may be that increased physical fitness reduces functional limitation and disability after stroke.

Secondary benefits may arise simply from participation in fitness training (even without fitness gains) and include social benefits which may improve quality of life and mood, secondary prevention of stroke, and other therapeutic benefits relevent to stroke (e.g. practice of gait).

It is not known whether physical fitness training is beneficial after stroke. Therefore the following aim and objectives can be stated.

Aim

Determine whether physical fitness training interventions are beneficial for people with stroke.

Objective 1

Develop the rationale for physical fitness training after stroke

Employ observational studies and systematic review of observational data in order to;

- Determine the nature and extent of fitness impairments in people with stroke.
- Determine the nature and strength of associations between physical fitness, and both functional limitation and disability in people with stroke.

Objective 2

Develop and evaluate Randomized Controlled Trial evidence for physical fitness training after stroke

Employ an exploratory RCT, and systematic review and meta-analyses of RCT data in order to;

- Evaluate whether a trial of fitness training is feasible for people with stroke.
- Evaluate whether fitness training is beneficial for people with stroke.

Part B

The Rationale for Fitness Training after Stroke

Cardiorespiratory Fitness after Stroke

- **Systematic review**
- **Observational study**

Muscle Strength & Power after Stroke

- **Systematic review**
- **Observational study**

PART B - THE RATIONALE FOR FITNESS TRAINING AFTER STROKE

Objective 1

Develop the rationale for fitness training after stroke;

- Determine the nature and extent of fitness impairments in people with stroke.
- Determine the nature and strength of associations between physical fitness, and both functional limitation and disability in people with stroke.

A model to test

In healthy elderly people physical fitness is known to be low and the low values associated with functional limitation and increased disability (Section 2.3). In people with stroke, physical fitness may be low due not only to the effects of age but also physical inactivity (Section 1.3), comorbid diseases and smoking before and after stroke. Motor impairments arising from the direct neurological effects of the stroke (e.g. hemiparesis) are central to functional limitation and the disability common after stroke, therefore low fitness may exacerbate this, and have greater impact in women compared with men.

Therefore a model is proposed which links the direct effects of stroke and other factors indirectly associated with stroke (i.e. age, cigarette smoking, comorbid disease and physical inactivity) to the cycle of detraining and the process of disablement after stroke (*Fitness-Function-Disability*; Figure 4.1). This suggests that

indices of physical fitness will be low after stroke and associated with functional limitation and disability. Part B of the thesis will test this model using systematic review of observational data (Chapters 5 and 6), and performing observational studies (Chapters 7 and 8) to determine whether there is scope to improve fitness, and postulate what the benefits of specific training might be.

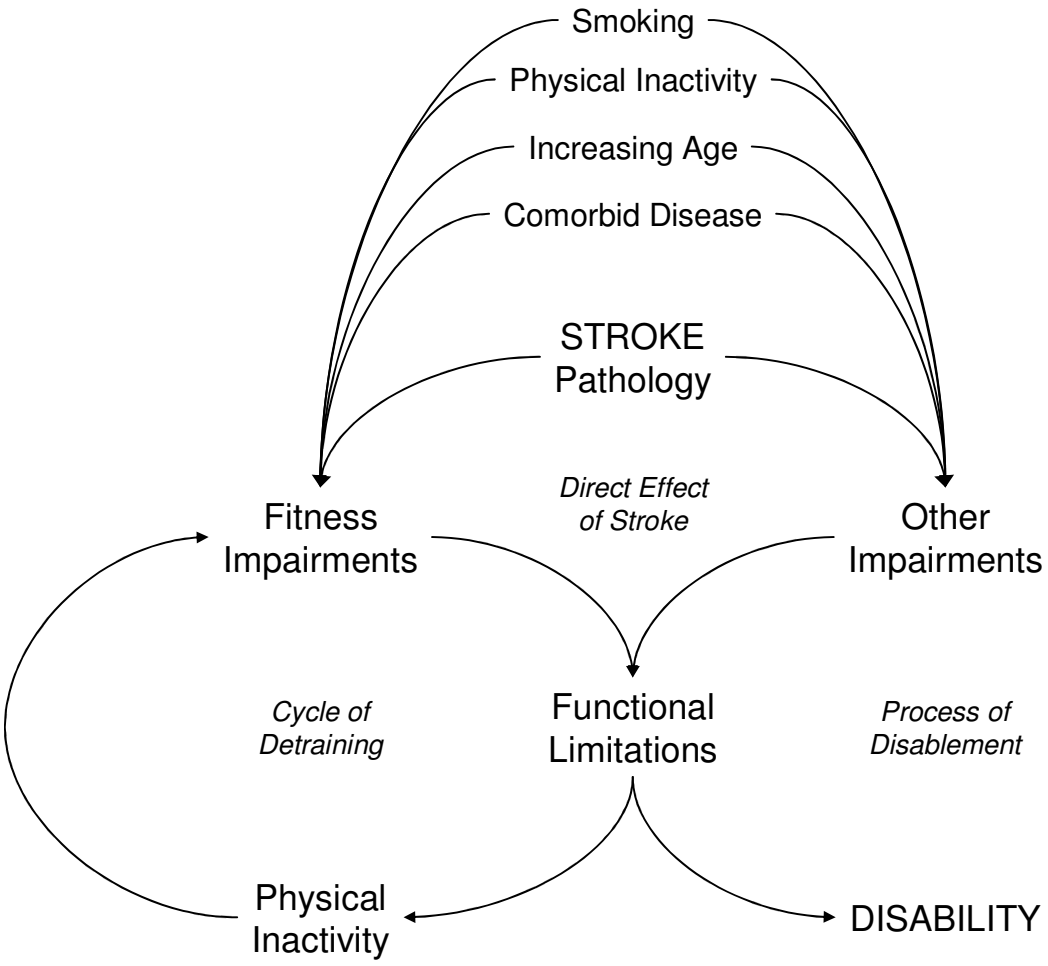


Figure 4.1 Fitness–Function–Disability model showing how the process of post-stroke disablement could be exacerbated by the cycle of detraining. Functional limitation and disability may be present before stroke due to the combined effects of age, inactivity, comorbid disease on physical fitness; pre-existing problems are increased by the immediate, direct neurological effects of stroke. Post-stroke physical inactivity may erode fitness further and exacerbate disability.

5. Cardiorespiratory fitness after stroke – systematic review of observational data

5.1. Abstract

OBJECTIVE: Determine the nature and extent of cardiorespiratory fitness impairments after stroke and determine the nature and strength of associations between cardiorespiratory fitness, and functional limitation and disability.

DESIGN: Systematic review of published observational data.

METHODS: Literature databases (MEDLINE, EMBASE, CINAHL and SportDiscus) were searched for studies reporting indices of cardiorespiratory fitness in people with stroke. Indices included a) maximal oxygen uptake, b) economy of gait, c) anaerobic threshold or d) kinetics of oxygen uptake. Indices of cardiorespiratory fitness were compared with healthy control values observed in control groups and/or predicted from normative data. Indices of correlation between cardiorespiratory fitness and both functional limitation and disability were recorded.

RESULTS: $\dot{V}O_2$ peak was reported in 19 studies and is 50-60% of values expected in healthy people of the same age and gender. Economy of gait was reported in 10 studies, and was lower than expected in healthy people, especially soon after stroke. Little data were available for anaerobic threshold (3 studies) and oxygen uptake kinetics (2 studies). Few data examine associations between cardiorespiratory fitness and function or disability.

CONCLUSIONS: $\dot{V}O_2$ peak is impaired after stroke and this may arise due to the direct effects of stroke and indirectly due to inactivity, comorbid disease and smoking. Since gait is also less economical the relative cost of walking is likely to be increased. However the relevance of impaired cardiorespiratory fitness for function and especially disability after stroke remains unclear.

5.2. Background

There have been no published systematic reviews of observational data which quantify cardiorespiratory fitness impairments after stroke, or determine whether impairments are linked to post-stroke problems. This means there is a limited basis on which to generate hypotheses about the benefits of physical fitness training interventions which contain cardiorespiratory training.

A systematic review is a useful approach, firstly because it aims to maximize inclusion of data, and secondly because it can restrict cardiorespiratory fitness measures to forms which are easily compared across studies, and easily compared with normative values established in healthy people. Therefore a systematic review of observational data was proposed with the following hypotheses.

5.2.1. Hypotheses

Hypothesis 1 - Measures of cardiorespiratory fitness ($\dot{V}O_2$ peak, economy, anaerobic threshold and $\dot{V}O_2$ kinetics) in people with stroke are impaired when compared with healthy people of a similar age and gender.

Hypothesis 2 - Impaired cardiorespiratory fitness ($\dot{V}O_2$ peak, economy, anaerobic threshold and $\dot{V}O_2$ kinetics) in people with stroke is associated with functional limitation and increased disability.

5.3. Methods

Search Strategy

A search strategy was constructed to identify publications relating to 'stroke' and parameters of 'cardiorespiratory fitness' within the following databases MEDLINE, EMBASE, CINAHL and SportDiscus. The strategy was based on the Cochrane Stroke Group strategy for 'stroke' (Appendix 14.15; Part A) in combination with search terms relating to cardiorespiratory fitness. These consisted of plain text searches of the following terms $\dot{V}O_2$ economy, efficiency, and anaerobic threshold, lactate threshold and ventilatory threshold. The plain text searches were also used to identify controlled vocabulary specific to each database and included 'oxygen consumption', 'aerobic capacity', 'anaerobic threshold' and 'physical fitness', 'aerobic fitness', 'cardiorespiratory fitness' and 'cardiovascular fitness'. The strategy was applied on 13/03/2007 and was supplemented by recursive searching and citation tracking.

Eligibility criteria

Studies of people with stroke were screened by one author (DS) and were eligible if they reported any indices of cardiorespiratory fitness a) $\dot{V}O_2$ peak/max, b) economy, c) anaerobic threshold or d) oxygen uptake kinetics. Observational or RCT studies were included. Multiple publications of data from the same participants were not included.

a) Studies examining $\dot{V}O_2$ peak or $\dot{V}O_2$ max were included if determined by respiratory gas exchange (not indirect prediction i.e. based on heart rate) measured

during progressive incremental or ramped exercise, and where the exercise continued until the limit of tolerance, or until termination for safety or clinical reasons.

b) Studies examining economy of gait were included if they reported economy directly or measures of submaximal $\dot{V}O_2$ recorded during steady-state walking efforts for which the velocity was reported or could be estimated from other data (i.e. distance covered during a 6-minute walking test).

c) Studies examining the anaerobic threshold were included if AT was determined during incremental exercise using either respiratory gas analysis or measurement of blood lactate concentration.

d) Studies examining $\dot{V}O_2$ kinetics were included if exponential models were used to determine the time constant for $\dot{V}O_2$ kinetics during the onset of constant intensity exercise.

Data extraction

Data was extracted from each study describing a) participants (sample size, age, gender, time since stroke, ambulatory status), b) cardiorespiratory fitness ($\dot{V}O_2$ peak/max $ml \cdot kg^{-1} \cdot min^{-1}$, economy of walking $ml \cdot kg^{-1} \cdot m^{-1}$, anaerobic threshold $\dot{V}O_2$ at AT $ml \cdot kg^{-1} \cdot min^{-1}$, time constant for $\dot{V}O_2$ kinetics in seconds) and c) parameters describing the exercise protocol used for fitness measurement (e.g. mode, intensity, termination criteria). Any indices of association between cardiorespiratory fitness and either physical functional or disability scales were extracted (e.g correlation coefficients). Data from RCTs were extracted only from the baseline assessments.

Analysis

For each included stroke cohort the mean values of cardiorespiratory fitness were expressed as a percentage of that observed or expected in healthy, untrained people of similar age and gender. Healthy control values were a) obtained from healthy control groups if included, and b) estimated from published age- and gender-related normative values (Section 2.1.1).

Suitable sources for the normative data were a) $\dot{V}O_2$ peak (Shvartz and Reibold 1990; synthesis of 62 studies) b) economy (Waters et al. 1988; n=260), c) AT (Davis et al. 1997; n=204); few data exist for $\dot{V}O_2$ kinetics in healthy elderly people (Section 2.1.4). These sources were selected because the data were a) derived from reasonably large samples of healthy, untrained people, b) reported separately for men and women across a range of ages, and c) other than being a non-stroke population the studies met the eligibility criteria applied to stroke studies in this review.

The normative data were used to generate a weighted average value for a comparison group of similar age and gender balance as each stroke cohort.

5.4. Results

Figure 5.1 shows that the majority of data describing the cardiorespiratory fitness of people with stroke relates to $\dot{V}O_2$ max or $\dot{V}O_2$ peak. Few data are available for the other parameters of cardiorespiratory fitness.

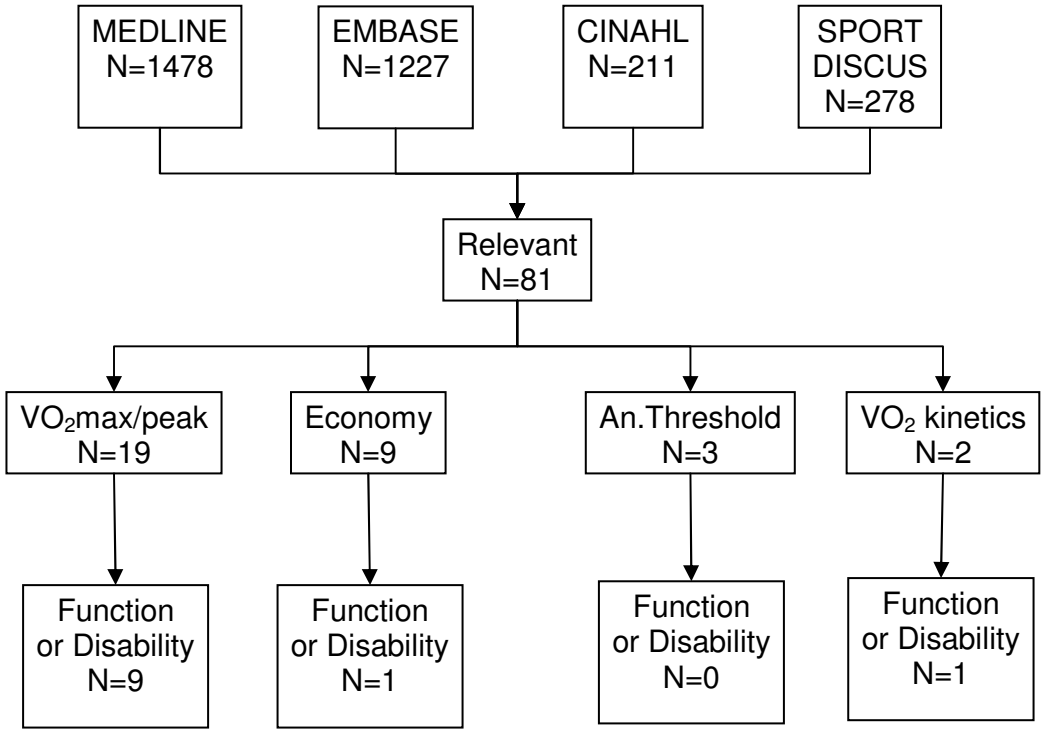


Figure 5.1 Distribution of potentially relevant (based on title and abstract) publications retrieved by the search databases, and the N=81 relevant full papers which reported a) cardiorespiratory fitness variables for stroke patients and b) their associations with physical function and disability.

5.5. Is cardiorespiratory fitness low after stroke?

5.5.1. Maximum oxygen uptake

Nineteen relevant studies (n=714) were identified and summarised in Table 5.1. The data of Yates et al. (2004) had two secondary publications (Duncan et al. 2003; Pohl et al. 2004), and Eng et al. (2004) had one (Chu et al. 2004), and Courbon et al. (2006b) had one (Courbon et al. 2006a); these secondary publications were excluded.

There were 468 (66%) male and 246 (34%) female participants. The mean age was around 62.9 years and time since stroke ranged from a few days (da Cunha Filho et al. 2001) to several years (Pang et al. 2005b). Some investigated convenience samples (Pang et al. 2005b) and indicated self-selection influenced recruitment (Eng et al. 2004). Most participants were classified as independently ambulatory (with or without standby aid) by a number of distance criteria ranging from 1 step (da Cunha Filho et al. 2001) to 25 feet (Yates et al. 2004).

The average $\dot{V}O_2$ reported was approximately 15 ml·kg^{-1}·min^{-1}. These values ranged from 8 ml.kg^{-1}.min^{-1} soon after stroke (~15 days; da Cunha Filho et al. 2001) to 22 ml·kg^{-1}·min^{-1} several years after stroke (5.5 years; Pang et al. 2005b). Only Fujitani et al. (1999) included age and gender matched controls who had not had a stroke. The $\dot{V}O_2$ peak of the stroke participants was ~72% of that (24.7 ml·kg^{-1}·min^{-1}) reported for the controls; they were however all male and unusually young for stroke (54.5 years).

Table 5.1 Studies reporting $\dot{V}O_2$ peak measured during progressive graded maximal exercise

	Participant				Exercise		Oxygen uptake	
Study	Age	n (m/f)	Days post stroke	Ambulatory	Mode	Termination criteria	VO_2 peak ml·kg·min^{-1}	% Healthy
(Bachynski-Cole and Cumming 1985)	52.4 (9.9)	8 (8/0)*	116 (76.1)	UN	Cycle ergometer	Not described	16.1 (4.2)	47%
(Potempa et al. 1995)	57 median	19 (8/11)† 23 (15/8)	216 (261)	UN	Cycle ergometer	Voluntary exhaustion; RER > 1.15; cardiac signs or symptoms	16.6 (6.48) † 15.1 (6.48)	55%
(Fujitani et al. 1999)	53.6 median Range 35-76	30 (30/0)	313 2-49 mths	Independent	Cycle ergometer	Cadence < 40 rev.min^{-1}; SBP > 200mmHg; arrhythmia or ischaemic signs on ECG	17.7 (4.2)	53% 72% ‡
(Ryan et al. 2000)	66 (9)	26 (22/4)	1169 (1717)	Independent	Treadmill	Patients request, gait instability, ACSM criteria	15.6 (4.4)	57%
(Rimmer et al. 2000)	52.3 (8.28)	35 (9/26)	182.5		Cycle ergometer	RER ≥ 1.1; peak HR within 10 beats.min^{-1} of age-predicted maximum; abnormal BP or ECG; cadence < 50 rev.min^{-1}	13.3 (4.22)† 14.1 (2.96)	49%
(da Cunha Filho et al. 2001)	59.7 (13.6) 57.8 (5.56)	6 (6/0) 6 (6/0)	14.3 (6.06) 15.7 (7.66)	Independent ≥ 1 steps	Cycle ergometer	Volitional fatigue; request to stop; RER > 1.0; peak HR within 10 beats.min^{-1} of age related maximum	8.02 (2.05)† 8.57 (2.09)	26%
(Macko et al. 2001)	67 (8)	23 (19/4)	852 (792)	Independent +standby aid	Treadmill	Patients request, gait instability, ACSM criteria	15.2 (3)	56%
(Murakami et al. 2002)	55 (13)	29 (23/6)	76 (65)	Independent	Cycle ergometer	Not stated	16.3 (4.4)	52%
(Katoh et al. 2002)	64 (9)	20 (16/4)	670 (365)	Independent	Cycle ergometer	Not stated other than 'maximal effort exercise'	16.6 (4.8)	59%
(Mackay-Lyons and Makrides 2002)	64.9 (13.5)	29 (22/7)	26.0 (6.6)	Dependent	Treadmill Supported 15% Body mass	ACSM criteria;; increase in VO_2 <100ml in last 1-min of exercise, peak HR within 10 beats.min^{-1} of age related maximum, RER > 1.10	14.4 (5.1)	53%
(Ryan et al. 2002)	65 (9)	60 (47/13)	1096 (1351)		Treadmill	Patients request, ACSM criteria	14.9 (3.9)	54%
(Dobrovolny et al. 2003)	64.8 (8)	53 (44/9)	1126 (1400)	Independent	Treadmill	Patients request, gait instability, ACSM criteria	14.6 (4.1)	52%
(Kelly et al. 2003)	60.8 (16.4)	17 (13/4)	29.2 (11.0)	Independent	Cycle ergometer Semi-recumbent	ACSM criteria Medical supervision	15.0 (4.26)	52%
(Yates et al. 2004)	69.8 (10.3)	100 (56/44)	70 (27.8)	Independent for 25 ft	Cycle ergometer	90% predicted maximal heart rate; angina, dyspnoea, voluntary exhaustion; cadence < 40 rev.min^{-1}. Various clinical criteria	11.4 (3.7)	50%
(Eng et al. 2004)	62.5 (8.6)	12 (11/1)	1278 (731)	Independent	Cycle erometer	ACSM criteria; other criteria	17.2 (3)	58%
(Pang et al. 2005b)	65.3 (8.7)	63 (36/27)	2009 (1790)	Independent	Cycle ergometer	RER ≥1.0; plateau in VO_2 of < 150 ml.min^{-1}; volitional fatigue	22.0 (4.8)	86%
(Courbon et al. 2006b)	53.5 (7.65) Range 18-70	21 (18/3)	746 (852)	Independent +/- aids	Cycle ergometer	Astrand guidelines followed	17.98 (4.24)	55%
(Michael and Macko 2007)	65 Range 45-84	50 (28/22)	314	Independent +standby aid	Treadmill	Volitional fatigue	11.7 (2.8)	45%
(Patterson et al. 2007)	64 (10)	74 (43/31)	1146 (1796)	Independent +/- aids	Treadmill	Volitional fatigue, gait instability, ACSM criteria	13.1 (4)	50%

Data are mean (SD) unless otherwise stated; Abbreviations: M male; F female; UN unknown; RER respiratory exchange ratio; ACSM termination criteria from (American College of Sports Medicine 2000); Healthy normative data interpolated from (Shvartz and Reibold 1990). * missing subjects noted in $\dot{V}O_2$ data; † data from control and intervention groups of an RCT; ‡ healthy control group comparison included by study authors (Fujitani et al. 1999).

The majority of the data are around 50 to 60% of that expected in a healthy age- and gender matched normative data (Table 5.1 and Figure 5.2). The data in Figure 5.2 suggest that low values of $\dot{V}O_2$ peak observed soon after stroke may persist several years after stroke. Although plotted against time longitudinal trends should be interpreted with caution.

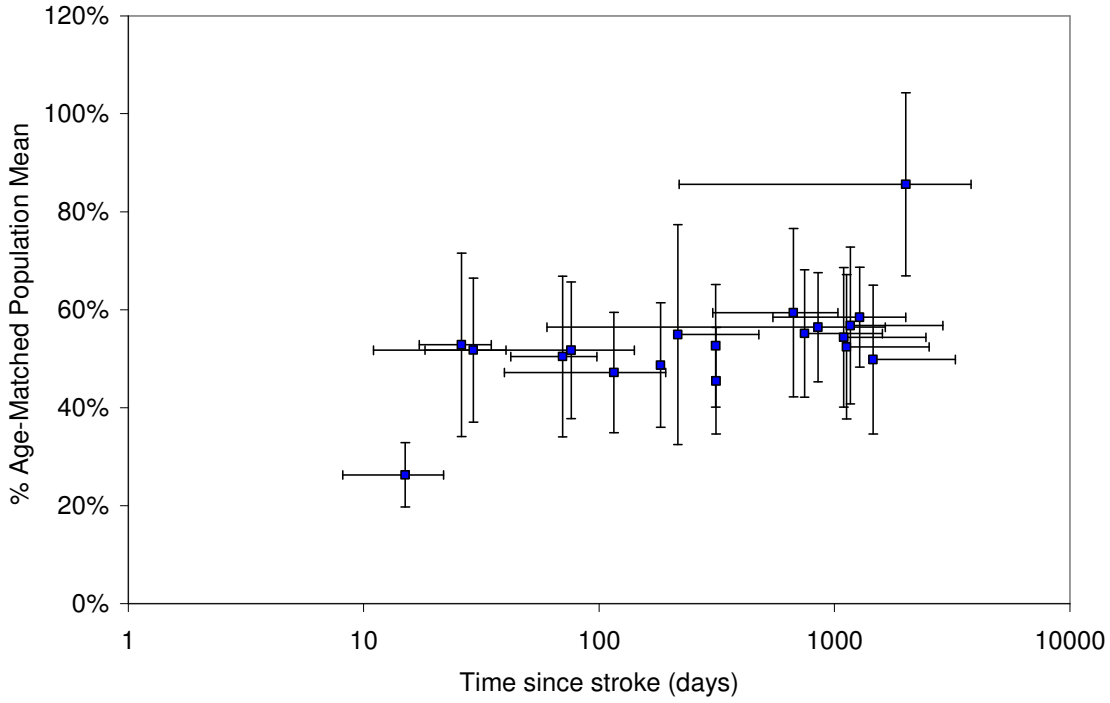


Figure 5.2 The $\dot{V}O_2$ peak of stroke patients reported in the 19 studies in Table 5.1 in relation to time since their stroke, expressed relative to body mass and as a percentage of that expected the healthy, untrained age- and gender-matched population (Shvartz and Reibold 1990). The data are expressed as mean ±SD.

Few studies examine longitudinal changes in $\dot{V}O_2$ peak after stroke. The Mackay-Lyons and Makrides (2002) data was followed up (MacKay-Lyons and Makrides 2004) to show that $\dot{V}O_2$ peak increased from 14.8 to 17.3 ml·kg^{-1}·min^{-1} (17%) between 1 and 6-months after stroke. There were 3/25 losses to follow-up which may bias this measure. Fujitani et al. (1999) showed $\dot{V}O_2$ peak to increased from 17.7 to

21.1 ml·kg^{-1}·min^{-1} (19%) when followed up after 9.4 months; however this follow-up period appears highly variable (3-22 months) and the participants received exercise advice within this period. The data of Yates et al. (2004) was followed up after 3 months (Pohl et al. 2004). The $\dot{V}O_2$ peak of participants initially classified as slower walkers (<213m/6-min walking) increased from 10.5 to 11.4 ml·kg^{-1}·min^{-1} (9%), and the $\dot{V}O_2$ peak of faster walkers (≥213m/6-min walking) increased from 12.4 to 12.8 ml·kg^{-1}·min^{-1} (3%). The general pattern of these longitudinal increases reflects the direction of the trend seen among studies in the summary of observational data (Figure 5.2), the magnitudes of some may be exaggerated.

The data of da Cunha Filho et al. (2001) are much lower than the remainder of the studies perhaps due to neurological rather than cardiorespiratory factors limiting performance of exercise, and the adoption of a criterion of a single independent step to define independently ambulatory. Conversely the data of Pang et al. (2005b) are higher than the other studies, maybe because the participants were a convenience sample and thus vulnerable to bias through self-selection of fitter participants. These two studies tend to exaggerate the impression of an upward trend. There are a number of potential limitations affecting the $\dot{V}O_2$ data;

Participants - The participants were ambulatory and typically younger than usual after stroke. Those who were habitually more physically active may have been more likely to participate. Therefore measures of cardiorespiratory fitness may be uncharacteristically high.

Mode of exercise - Six included studies used treadmill walking, the remainder used cycle ergometry. Treadmill walking tends to elicit higher $\dot{V}O_2$ values than cycle ergometry in healthy people (Åstrand and Saltin 1961). In people with stroke gait difficulties and balance may interfere with the measures, the partial body weight support used by Mackay-Lyons and Makrides (2002) to counteract this has been shown not to affect measures of $\dot{V}O_2$ peak, at least in healthy people (MacKay-Lyons et al. 2001).

Gas analysis - Most of the systems used to measure $\dot{V}O_2$ peak have been reviewed as valid and reliable (Macfarlane 2001); one used a non-standard system configuration without CO_2 measures (Bachynski-Cole and Cumming 1985). Measures of $\dot{V}O_2$ peak in people with stroke have good repeatability with intraclass correlation coefficients (ICC) of 0.92 to 0.94 (Potempa et al. 1995; Mackay-Lyons and Makrides 2002; Dobrovolny et al. 2003; Eng et al. 2004).

Termination of exercise – Variation between studies in the criteria for terminating exercise could result differing intensities of exercise and hence values of $\dot{V}O_2$ peak or max. For example the intensity of exercise terminated at RER >1.15 (Potempa et al. 1995) would probably be higher than studies terminating at lower values (RER 1.1; Rimmer et al. 2000; RER > 1.0; da Cunha Filho et al. 2001). This is a plausible explanation for the small differences in $\dot{V}O_2$ peak observed in these studies. Bachynski-Cole and Cumming (1985) reported $\dot{V}O_2$ peak was influenced by missing data and that 1/8 participants had mitral valve surgery; these factors along with the small sample size (n=8) and the equipment issues weaken this study.

In summary $\dot{V}O_2$ peak after stroke is substantially lower than expected in age- and gender-matched healthy people, importantly these studies may have underestimated values in the general stroke population due to selection bias and methodological issues. Impairment to $\dot{V}O_2$ peak is evident both soon after stroke and this seems to persist long into the acute phase of recovery.

5.5.2. Economy

Ten relevant studies (n=209) were included (Table 5.2). Only four (n=53) included measures of oxygen cost per unit distance covered reported as gross (da Cunha et al. 2002; da Cunha-Filho et al. 2003; Platts et al. 2006) and net economy (Dawes et al. 2005). In the remaining studies gross economy was calculated from concurrent $\dot{V}O_2$ and walking velocity measures and thus lacked measures of variance. The baseline data from the control group of one RCT (da Cunha et al. 2002) was excluded as this was skewed by non-ambulatory participant's economy (5.15 $ml \cdot kg^{-1} \cdot m^{-1}$).

Three studies included age- and gender-matched healthy controls (Corcoran et al. 1970a; da Cunha-Filho et al. 2003; Platts et al. 2006). The economy of these control groups agreed closely with the normative data (Waters et al. 1988) used as a comparison for the remainder of the studies.

Table 5.2 Table of studies which directly report economy of walking as oxygen cost per unit distance walked or data from which this can be estimated indirectly (i.e. submaximal $\dot{V}O_2$ values during walking of known velocity). Data are expressed as a percentage of values expected in healthy people walking at either a comfortable speed, and at the same average speed as the stroke cohort in each study.

Study	Participant				Walking				Economy of walking				
Author	Age	n (m/f)	Days post stroke	Ambulatory status	Mode of walking	Intensity Descriptor	Distance m	Time (min)	Velocity ($m \cdot sec^{-1}$)	VO_2 $ml \cdot kg^{-1} \cdot min^{-1}$	Economy $ml \cdot kg^{-1} \cdot m^{-1}$	% Healthy Norms	
												CWS	Same speed
(Corcoran et al. 1970)	45.1 (11.4)	12 (11/1)	1238 (1249)	Independent	Floor	CWS	4x100ft	-	0.692	12.89	0.310	202% 164%†	162%
(Hash 1978)	54	12 (UN)*	42	UN	UN	CWS	30	-	-	-	0.70 (0.475)	437 to 453%*	-
(da Cunha et al. 2002)	57.8 (5.5)	6 (6/0)‡	15.7 (7.7)	Independent	Floor 5-m shuttle	As fast & far as possible	81.6 (60.2)	5	0.36 (0.25)	8.15 (0.78)	0.85 (0.66)‡	545%	341%
(da Cunha-Filho et al. 2003)	59.3 (11.4)	20 (19/1)	<6 Mth	Dependent + assistance; (n=7) Independent + walker (n=6)	Floor 5-m shuttle	PWS	148.8 (64.30)	5	0.67 (0.32)	10.2 (2.14)	0.40 (0.52)	255% 222%†	207%
(Eng et al. 2004)	62.5 (8.6)	12 (11/1)	1278 (731)	Independent	Floor 6-MWT	As far as possible	378 (123)	6	1.05	12.0 (3.3)	0.190	120%	112%
(Michael and Macko 2007)	65 Range 45-84	50 (28/22)	314 Range 6-166	Independent +/- devices & standby assistance	Treadmill	75% floor PWS	-	-	0.315§	8.7 (1.7)	0.460	285%	-
(Pang et al. 2005b)	65.3 (8.7)	63 (36/27)	2009 (1790)	Independent for 25ft	Floor 6-MWT 42m track	As far as possible	316.3 (133.7)	6	0.879	14.7 (3.3)	0.279	173%	156%
(Dawes et al. 2005)	46.4 (8.4)	14 (8/6)	UN	Independent >4-min	Floor 40m track	PWS	-	4	0.70 (0.32)	-	0.35 (0.22)¶	N/A	-
(Platts et al. 2006)	40.7 (10.0)	13 (9/4)	110	Independent >5-min +aids (n=9) -aids (n=4)	Floor 10m track	PWS	120 (57.8)	5	0.39 (0.2)	11.1 (3.1)	0.63 (0.41)	418% 394%†	262%
(David et al. 2006)	46 (11)	7 (2/5)	84 (63)	Independent minimal assistance	Floor 30m corridor +rail	PWS	30	-	0.529 (0.231)	6.7#	0.761	489%	361%

Data are mean (SD) unless otherwise specified. Healthy normative data interpolated from (Waters et al. 1988).
Abbreviations: m male; f female; CWS comfortable walking speed; PWS preferred walking speed; 6-MWT six minute walking test;
* Gender mix unknown hence range of healthy values compared, all male to all female.
† Comparison with a healthy control group included in study.
‡ Only the baseline data from experimental group included – control group data biased as contained some non-ambulatory participants.
§ 75% of each participant's self-selected walking velocity (mean 0.42 $m \cdot sec^{-1}$).
¶ Presented as a net value (resting – walking energy expenditure).
# Data read from graph in publication.

The gait of ambulatory people with stroke is less economical than healthy people of similar age and gender (Waters et al. 1988). For some the energy cost of walking was several fold (394% to 545%) greater than healthy people (Hash 1978; da Cunha et al. 2002; Platts et al. 2006; David et al. 2006); these participants were assessed relatively soon after stroke. Others assessed well into chronic phase of recovery show that the energy cost of walking after stroke is remains typically double that of healthy people. The data in Figure 5.3 (Panel A) suggests the economy of walking might improve with increasing time since stroke.

All the samples of participants walked substantially slower than healthy people. Walking speed is known to influence economy expressed in energy cost per unit distance.

Figure 5.3 (Panel B) shows that the energy cost of walking in people with stroke exceeds that predicted by a speed-based model of the energy cost of walking in healthy people (Waters et al. 1988). This suggests apparent impairment to economy is not simply due to the effect of slow walking speed. Accounting for slow gait, the cost of comfortable/preferred walking remains 162% to 361% of healthy people (Table 5.2)

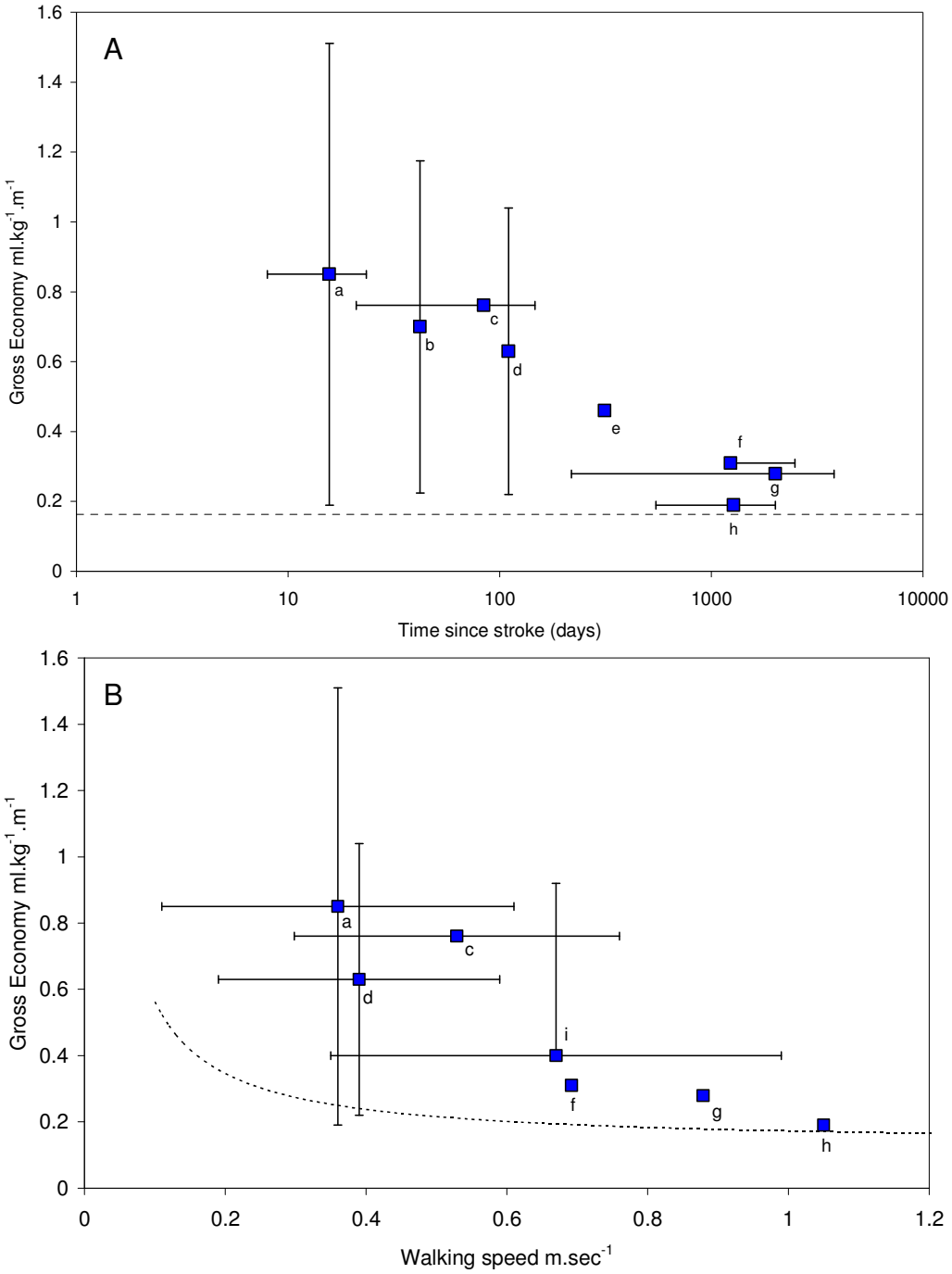


Figure 5.3 The gross economy of walking of people with stroke in relation to time since stroke and speed of comfortable or preferred walking. The data are expressed as the oxygen cost per unit distance walked relative to body mass ($ml \cdot kg^{-1} \cdot m^{-1}$) The data are expressed as mean (± SD where possible) synthesised from a) da Cunha et al. (2002), b) Hash (1978), c) David et al. (2006), d) Platts et al. (2006), e) Michael and Macko (2007), f) Corcoran et al. (1970), g) Pang et al. (2005b), h) Eng et al. (2004) and i) da Cunha-Filho et al. (2003). The dashed line (---) is the economy of walking typical of healthy elderly people at their comfortable speed (Panel A; Waters et al. 1988) and over a range of speeds (Panel B; Waters and Mulroy 1999).

There are some limitations affecting these economy data. Firstly the way in which walking was performed could influence economy measures: Treadmill walking, non-habitual speed of walking and use of support or handrails could influence energy expenditure, and walking interrupted by the need to make frequent turns or repeated stops could influence the measure relative to distance covered. Only two studies (Dawes et al. 2005; Platts et al. 2006) appear to not be affected by one of more of the above factors but have very small samples of uncharacteristically young participants. Secondly, selection bias affecting the data of Eng et al. (2004) may explain why these data show the smallest impairment of economy (about 112% of healthy speed-based values).

Although gait problems and the efficiency of walking after stroke are often discussed there are actually limited data describing the energetics of walking after stroke. These included studies suggest that the demands of walking, even when performed independently, are substantially greater after a stroke and (similar to $\dot{V}O_2$ peak) the residual impairment persists long into the chronic phase of recovery.

An important implication of poor economy arises from the interaction with impaired $\dot{V}O_2$ peak. The maximal oxygen utilisation ($\dot{V}O_2$ peak) is half, of that expected in age- and gender-matched healthy people, yet the oxygen cost of walking is typically double that expected in age- and gender-matched healthy people. Therefore these impairments are additive meaning the cost of submaximal walking requires a high proportion of maximal capacity, leaving little in reserve. The functional consequences are reduced walking performance and risk from further deterioration.

5.5.3. Anaerobic threshold

Three studies have examined the anaerobic threshold (AT) after stroke (Table 5.3). The data suggest that the AT is crossed at a lower workload than that expected in healthy age- and gender-matched people during cycle ergometry (Davis et al. 1997).

Table 5.3 Studies reporting $\dot{V}O_2$ values at the anaerobic threshold during cycle ergometry exercise in stroke survivors, and its comparison with healthy age- and gender matched people.

Study	Participant				Anaerobic Threshold (AT)		
	Age	N (m/f)	Days post stroke	Ambulatory status	AT % of $\dot{V}O_2$ peak	$\dot{V}O_2$ AT $ml \cdot kg^{-1} \cdot min^{-1}$	% of Healthy *
(Fujitani et al. 1999)	53.6	30 (30/0)	313 2-49 mths	Independent	64%	11.4 (3.5)	46%
(Yates et al. 2004)	69.8 (10.3)	100 (66/44)	70 (27.8)	Independent for 25 ft	75%	8.6 (1.7)	69%
(Okada 2005)	55.7 (12.3)	15 (UN)	37.3 (18.8)	Not known mild impairment	-	12.5 (2.41)	80%

Data are mean (SD) unless otherwise specified.
Abbreviations: m male; f female; AT anaerobic threshold; UN unknown
* Healthy normative data interpolated from (Davis et al. 1997)

A limitation affecting these few data is the use of cycle ergometry since this lacks functional relevance, and only the participants of Yates et al. (2004) are of typical age for stroke. Reduced AT after stroke suggests muscle oxidative capacity is lower meaning that peripheral cardiorespiratory fitness may be impaired. Paresis is known to cause reduced capillarization and a shift from slow to fast isoforms of the myosin heavy chain isoform (MHC; Pontén and Stål 2007); both of these changes are associated with a reduction in muscle oxidative capacity.

5.5.4. Oxygen uptake kinetics

Only two small studies characterise oxygen uptake kinetics in people with stroke (Katoh et al. 2002; Murakami et al. 2002). The characteristics are described in Table 5.1. The $\tau\dot{V}O_2$ measured by Katoh et al. (2002) was 29 sec (SD 6) and Murakami (2002) was 38.3 sec (SD 11.9). Both fall within the range of available data reported for age and gender matched healthy people (Section 2.1.4) and are 63% and 95% respectively of the values reported by Harris et al. (2003) and Cunningham et al. (1993) for male and female subjects.

One of the studies reported providing physical assistance with pedalling at the onset of square-wave exercise (Murakami et al. 2002). This would temporarily reduce workload and oxygen consumption meaning $\tau\dot{V}O_2$ would be biased toward slower (larger) values and exaggerate any impairment.

5.5.5. Discussion

This is the first systematic review to quantify cardiorespiratory fitness impairment after stroke. The main findings suggests cardiorespiratory fitness is impaired after stroke, being lower than expected when compared with age- and gender matched sedentary people who have not had a stroke.

Most available data report peak $\dot{V}O_2$ peak and show that this is impaired, consistently being 50-60% of that expected in age- and gender-matched healthy people. Economy of walking is also impaired such that the oxygen cost per unit distance walked is

several-fold higher than healthy people within the first 4-months post stroke, a a lesser degree of impairment is still evident several years after stroke. These impairments are not simply an artefact of the slow gait speeds common after stroke.

$\dot{V}O_2$ peak and economy data suggest an exercise capacity reduced by around half, whilst the energy cost of performing it has almost doubled. This means the fitness 'reserve' is greatly diminished; one consequence might be that ambulation is fatiguing and uncomfortable and there is little allowance for further deterioration in fitness. $\dot{V}O_2$ kinetics and AT data are lacking. The few data suggest impairments in both central and peripheral aspects of cardiorespiratory fitness.

In general observational data cannot be used to infer a causal link between stroke and low cardiorespiratory fitness. This is because in addition to the direct neurological effects of stroke there are a number of indirect effects present both before and after stroke which could also explain low cardiorespiratory fitness.

5.5.5.1. Indirect factors pre-dating stroke

Two prospective studies show people with low $\dot{V}O_2$ peak are more likely to have a stroke (Kurl et al. 2003; n=2011) and die from a stroke (Lee and Blair 2002; n=16878). This suggests low cardiorespiratory fitness may simply predate stroke. This could occur not only because of a) increasing age and b) physical inactivity, but also c) comorbid disease or d) cigarette smoking.

Various pathologies common after stroke affect the coupling of ventilatory, cardiovascular and metabolic organ systems (Wasserman et al. 1999), and these can influence the acquisition, transport and utilization of oxygen (Figure 5.4). The effect is that both central and peripheral components of cardiorespiratory fitness can be impaired. Several of these diseases and factors are associated with stroke.

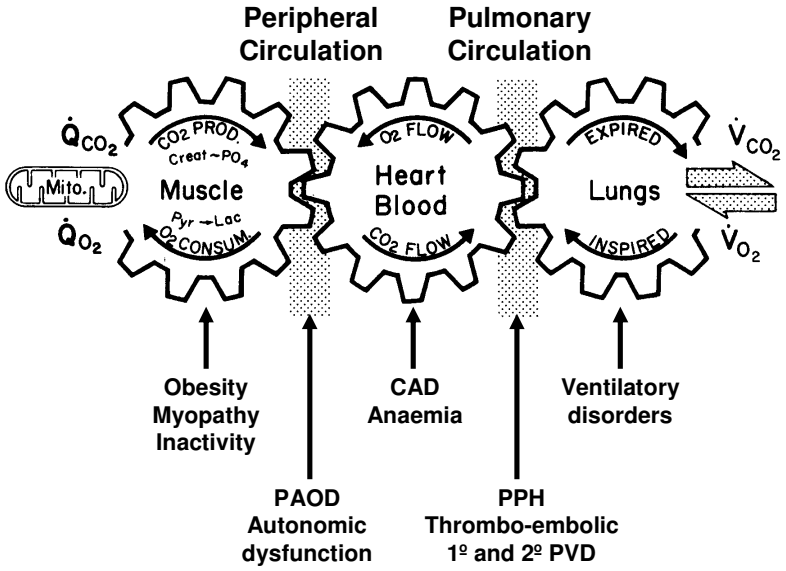


Figure 5.4 Figure to show the coupling of metabolic, cardiovascular and ventilatory systems which define cardiorespiratory fitness and the sites of interference of various diseases states and inactivity ('Gears Analogy' modified from Wasserman et al. 1999). Abbreviations; CAD coronary artery disease; PAOD peripheral artery occlusive disease; PPH primary pulmonary hypertension.

Central (e.g. $\dot{V}O_2$ peak) and peripheral (e.g. AT) indices of cardiorespiratory fitness are impaired in people with heart diseases compared with age- and gender-matched healthy people (Table 5.4); the values are similar to those for people with stroke. Mackay-Lyons and Makrides (2002) showed $\dot{V}O_2$ peak was significantly lower in stroke patients with CAD compared with those who did not (12.9 [SD 3.1] versus 16.0 [SD 5.2] $ml \cdot kg^{-1} \cdot min^{-1}$). The $\tau\dot{V}O_2$ of those with CAD is slower than expected in healthy people but comparisons with stroke are difficult to make due to too few data.

Table 5.4 Indices of cardiorespiratory fitness ($\dot{V}O_2$ peak, anaerobic threshold and oxygen uptake kinetics) in people with heart diseases compared with values expected in age- and gender-matched healthy people.

	Participant			Cardiorespiratory fitness	
Study	Disease	Age	n (m/f)	Parameter	% of healthy
a) $\dot{V}O_2$ peak					
(Gitt et al. 2002)	CHF	62.9 (10.7)	223 (192/31)	15.8 (5.3) ml·kg^{-1}·min^{-1}	55% †
(Barmeyer and Meinertz 2002)	CAD	66 (6.5)	25 (23/2)	13.3 (3.3) ml·kg^{-1}·min^{-1}	47% †
(Adachi et al. 2000)	CAD	55.2 (8.1)	14 (14/0)*	23.1 (3.5) ml·kg^{-1}·min^{-1}	70% †
b) Anaerobic threshold - $\dot{V}O_2$ AT					
(Gitt et al. 2002)	CHF	62.9 (10.7)	223 (192/31)	11.3 (3.5) ml·kg^{-1}·min^{-1}	80% ‡
(Barmeyer and Meinertz 2002)	CAD	66 (6.5)	25 (23/2)	9.4 (1.5) ml·kg^{-1}·min^{-1}	68% ‡
c) Oxygen uptake kinetics - $\tau\dot{V}O_2$					
(Adachi et al. 2000)	CAD	55.2 (8.1)	14 (14/0)*	57.4 (12.6) sec	142% §
(Koike et al. 1998)	CAD	59.0 (9.0)	14 (13/1)	44.5 (10.9) sec	104% §

Data are mean (SD) unless otherwise specified
Abbreviations: m male; f female; CHF chronic heart failure; CAD coronary artery disease; AT anaerobic threshold;
* Excludes n=3 patients with restenosis
† Healthy normative data (Shvartz and Reibold 1990)
‡ Healthy normative data (Davis et al. 1997)
§ Healthy normative data (Harris et al. 2003;Cunningham et al. 1993)

Cigarette smoking is a complicating factor as it has both immediate effects on the blood (carboxyhaemoglobinaemia), the cardiovascular system and ventilation, and longer term consequences due to its association with ventilatory disorders such as COPD; together or in isolation these factors reduce $\dot{V}O_2$ peak and AT and hence exercise tolerance (Wasserman et al. 1999).

5.5.5.2. 'Direct' effect of stroke/hemiparesis

Hemiparesis is common after stroke. Firstly this can reduce the amount of muscle mass available for contraction during physical activity thus imposing an immediate impairment in physical fitness. Secondly, hemiparesis can increase the difficulty of everyday tasks such as walking. The slower speeds of locomotion seen in patients with hemiparesis are associated with reduced economy. However factors such as abnormal patterns of movement, the use of walking aids, hemiparesis, poor flexibility, contractures, abnormal muscle tone, antagonist coactivation and poor balance may result in extra muscular work beyond that required for walking. This would cause an increase in energy expenditure (and $\dot{V}O_2$) which did not contribute to locomotion and would therefore reduce economy.

5.5.5.3. Indirect factors – after stroke

Physical inactivity may be common after stroke however there are limited data (Section 1.2). Post-stroke inactivity could be habitual or be imposed due to stroke-related neurological deficits which can reduce mobility such as motor weakness, ataxia, apraxia, impaired conscious level, and sensory and visuospatial effects (Warlow et al. 1996). Therefore post-stroke physical inactivity may cause fitness to deteriorate or may hinder its restoration. The problems associated with comorbid diseases and smoking present before stroke may continue after stroke.

A major limitation of these fitness data are that the majority were measured during exercise which is not typical of everyday human activities in terms of either mode (e.g. cycling), or intensity (e.g. to limit of tolerance), and therefore can be criticized

as not being functionally relevant. Few data were compared with a concurrent control group forcing reliance on normative data, and there are few longitudinal data available. The majority of participants were independently ambulatory, this may present problems of generalizability soon after stroke, however the majority (64%) of stroke survivors recover independent ambulation after rehabilitation (Jørgensen et al. 1995).

One limitation of this review is that the study selection and data extraction were performed by only one researcher (DS).

Although the study designs weaken the strength of the evidence there are sufficient data to accept the hypothesis that cardiorespiratory fitness in stroke survivors is impaired when compared with healthy people of a similar age and gender.

Since low cardiorespiratory fitness is associated with functional limitation and disability in healthy elderly people, one can postulate that it may have a role in causing or exacerbating some common post-stroke problems.

5.6. Is cardiorespiratory fitness associated with functional limitation and disability after stroke?

Eight studies (n=317) report associations between cardiorespiratory fitness and functional limitations, mostly restricted to measures of $\dot{V}O_2$ peak and walking performance (Table 5.5). These data show no consistent pattern of association between fitness and walking, even in sustained continuous efforts like the 6 minute walk which logically rely on cardiorespiratory fitness. Also the majority of studies attempt to relate a cycle ergometry measure to an ambulatory one.

Three studies incorporated multivariate analyses. Pang et al. (2005b) shows that $\dot{V}O_2$ peak is removed as a predictor variable when other stroke-specific impairments of balance, muscle strength and muscle tone were included. Michael and Macko (2007) support this, and suggest the influence of $\dot{V}O_2$ is swamped by the effects of balance impairment. Patterson et al. (2007) showed that $\dot{V}O_2$ peak, balance and leg strength were independently predictive of 6-MWT performance. For the slowest walkers only balance predicted walking, and for the fastest, only $\dot{V}O_2$ peak.

Katoh et al. (2002) was the only study to examine a cardiorespiratory fitness variable other than $\dot{V}O_2$ peak and showed that $\tau\dot{V}O_2$ was inversely associated with number of daily steps taken during walking, an index of physical activity ($r= -0.52$, $P<0.05$). Only Mackay-Lyons and Makrides (2002; n=29) explored disability showing patients with a Barthel Index score <90 had a lower $\dot{V}O_2$ peak than those >90; in multivariate analysis Barthel Index predicted absolute and relative values of $\dot{V}O_2$ peak.

Table 5.5 Eight studies (n=317) reporting bivariate associations between $\dot{V}O_2$ peak and measures of physical function after stroke.

Study	Participants				Exercise mode for $\dot{V}O_2$ peak	Association between $\dot{V}O_2$ and function
	Age	n m/f	Time post stroke	Ambulatory		
a) Walking Speed - Comfortable or Chosen						
(Kelly et al. 2003)	60.8 (16.4)	17 (13/4)	29.2 (11.0)	Independent	Cycle ergometer	r = 0.736
(Ryan et al. 2002)	65 (9)	60 (47/13)	1096 (1351)		Treadmill	r = 0.53, P<0.01
(Eng et al. 2004)	62.5 (8.6)	12 (11/1)	1278 (731)	Independent	Cycle ergometer	r = 0.32, NS
(Michael and Macko 2007)	65 (Range 45-84)	50 (28/22)	314	Independent +standby aid	Treadmill	r = 0.290; NS
(Patterson et al. 2007)	64 (10)	74 (43/31)	1146 (1796)	Independent +/- walking aids	Treadmill	r = 0.54;<0.001
b) Walking Speed - Maximum						
(Kelly et al. 2003)	60.8 (16.4)	17 (13/4)	29.2 (11.0)	Independent	Cycle ergometer	r = 0.68
c) Walking Endurance – Six Minute Walking Test (6-MWT)						
(Kelly et al. 2003)	60.8 (16.4)	17 (13/4)	29.2 (11.0)	Independent	Cycle ergometer	r = 0.84
(Courbon et al. 2006b)	53.5 (7.65) Range 18-70	21 (18/3)	746 (852)	Independent +/- walking aids	Cycle ergometer	r = 0.602; P<0.0032
(Pang et al. 2005b)	65.3 (8.7)	63 (36/27)	2009 (1790)	Independent	Cycle ergometer	r = 0.402; P<0.005
(Eng et al. 2004)	62.5 (8.6)	12 (11/1)	1278 (731)	Independent	Cycle ergometer	r = 0.37, NS
(Patterson et al. 2007)	64 (10)	74 (43/31)	1146 (1796)	Independent +/- walking aids	Treadmill	r = 0.64;<0.001
d) Walking Activity - Total Daily Steps						
(Katoh et al. 2002)	64 (9)	20 (16/4)	670 (365)	Independent	Cycle ergometer	r = 0.61, P<0.01
(Michael and Macko 2007)	65 (Range 45-84)	50 (28/22)	314	Independent +standby aid	Treadmill	r = 0.058; NS

Data are mean (SD) unless otherwise specified.
Abbreviations: m male; f female

5.6.1. Discussion

Few data link cardiorespiratory fitness to physical function and disability. Some studies show $\dot{V}O_2$ peak is associated positively, and moderately, with a number of indices of walking performance but these data do not allow a causal link to be established. The conclusions are also limited due to conflicting findings; these may arise for several reasons. Firstly, all the limitations surrounding use of $\dot{V}O_2$ peak data discussed previously (Section 5.5) are relevant here since this is relied on as the independent predictor variable. Secondly equating $\dot{V}O_2$ peak during cycling to ambulatory outcomes is problematic due to the lack of specificity.

There are strong theoretical reasons why impaired cardiorespiratory fitness might be associated with functional limitation and disability after stroke. Since cardiorespiratory fitness influences the performance and tolerance of physical activities in healthy people the same basic limitation will exist in people with stroke. A $\dot{V}O_2$ peak of 15 ml·kg^{-1}·min^{-1} has been suggested as the minimum to support independent living (Shephard 1986). Figure 5.5 shows the data for $\dot{V}O_2$ peak in people with stroke from Table 5.1 in relation to the energy requirements some basic activities of daily living in healthy people; this shows a substantial proportion of the $\dot{V}O_2$ peak of stroke patients is required. The added burden for stroke survivors is that neurological impairments increase the energy cost of walking (Section 5.5.2) and probably other ADL too (Bjuro et al. 1975).

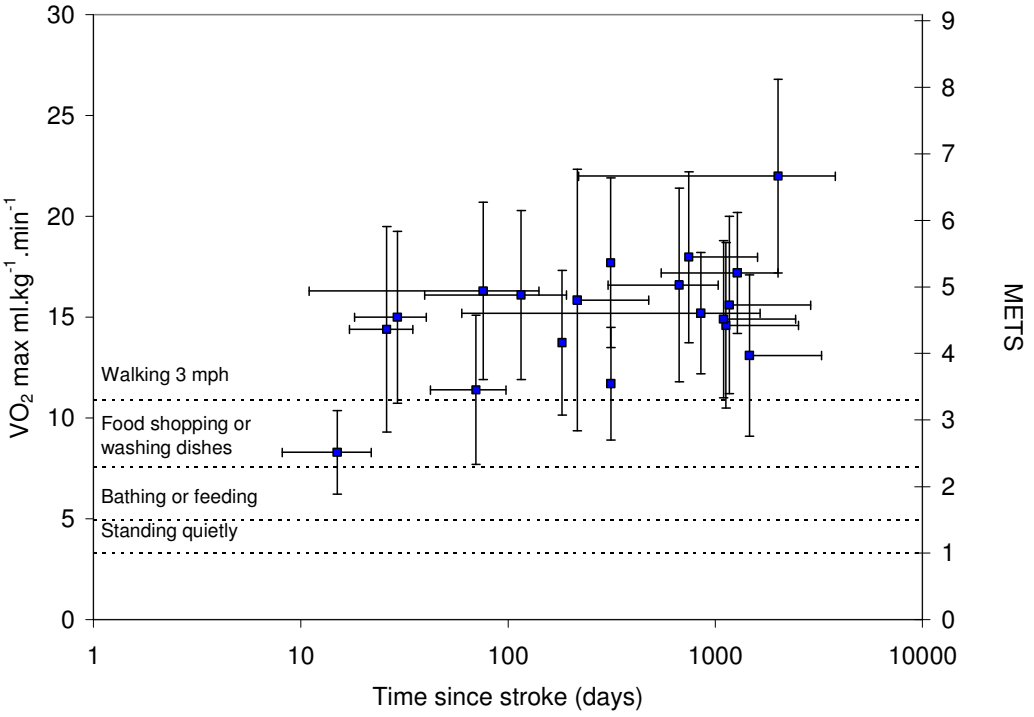


Figure 5.5 The $\dot{V}O_2$ peak in people with stroke reported in the studies in Table 5.1 in relation to time since stroke and the metabolic cost (in METS) of selected physical activities from the '*Compendium of Physical Activities'* (Ainsworth et al. 2000). Data are mean ±SD.

Relationships between fitness and function in elderly people can be non-linear and multifactorial (Section 2.3.1). Few studies have investigated the presence of non-normal data or have gone beyond beyond univariate analyses of $\dot{V}O_2$ peak. It is plausible that other post-stroke (co)impairments could influence function and the multivariate analyses support this (Pang et al. 2005b; Michael and Macko 2007).

In summary there are some potential links between cardiorespiratory fitness and ambulation; one can therefore postulate that improving cardiorespiratory fitness might improve ambulation after stroke. More research is needed to explore the links between cardiorespiratory fitness measured under functionally relevant conditions, and measures of functional limitation and disability after stroke.

Cardiorespiratory fitness after stroke - Summary

Impairment

- Cardiorespiratory fitness after stroke is substantially lower than healthy people of the same age and gender
- $\dot{V}O_2$peak is 50-60% of that in healthy people
- Economy of walking appears lower than healthy people - especially soon after stroke
- Cardiorespiratory fitness 'reserve' is low
- Impairments may be due to direct neurological effects of stroke, plus physical inactivity, comorbid disease and smoking
- Impairments persist into the chronic stage of recovery
- There are few data exploring anaerobic threshold, economy or oxygen uptake kinetics

Functional Consequences of Impairment

- The links between low cardiorespiratory fitness and both functional limitation and disability after stroke are unclear
- Associations between $\dot{V}O_2$ measured during cycling with functional assessment of gait are problematic as the mode of exercise testing is not specific.
- Virtually no data explore the links between cardiorespiratory fitness and disability

6. Muscle strength and power after stroke – systematic review of observational data

6.1. Abstract

OBJECTIVE: Determine the nature and extent of impairments in muscle strength and power after stroke and determine the nature and strength of their associations with functional limitation and disability.

DESIGN: Systematic review of published observational data.

METHODS: Literature databases (MEDLINE, EMBASE, CINAHL and SportDiscus) were searched for studies reporting indices of muscle force production (muscle strength and muscle power output) in people with stroke, along with data from healthy age- and gender-matched control groups and/or indices of correlation between muscle force production and both functional limitation and/or disability.

RESULTS: Eight studies (n=166) compared muscle strength in people with stroke and healthy control groups. Isometric strength was lower in those with stroke and although limb weakness was greater on the side affected by stroke, bilateral impairment was evident. Univariate associations (15 studies; n=422) between strength and functional limitation suggested low muscle strength was associated with functional limitation, especially walking performance. Multivariate analyses (7 studies; n=422) indicated additional involvement of factors such as balance and sensation. Limited data (3 univariate studies, n=168; 1 multivariate study, n=31) suggest and that strength may predict indices of disability.

No controlled studies directly compare explosive power measures in people who are healthy with people with stroke. Only 3 studies (n=55) examine associations with function and disability with mixed findings.

CONCLUSIONS: Muscle strength is low after stroke. Bilateral weakness suggests factors indirectly associated with stroke such as inactivity. Low strength along with other stroke-related impairments (e.g. balance) may contribute to functional limitations. These observational data suggest there is scope to improve muscle strength via strength training after stroke, and that although improvements may benefit specific physical functions the implications for disability are unclear. Little is known about whether explosive power is impaired after stroke or its relevance to function and disability.

6.2. Background

There is one systematic review of observational studies reporting relationships between muscle strength and gait after stroke (Bohannon and Andrews 1995; 24 studies). A similar, but non-systematic review (Bohannon 2007; 8 studies) summarizes relationships between lower limb muscle strength and a range of functional activities, including gait. Both reviews focus on univariate associations which may overlook co-impairments which interact with strength. Secondly, muscle strength data from handheld dynamometers[2] was included, this may be biased because these devices record force against resistance applied by another person against a variety of body segment movements.

6.2.1. Hypotheses

Hypothesis 1 - Muscle strength and muscle explosive power in people with stroke are impaired when compared with healthy people of a similar age and gender.

Hypothesis 2 - Impaired muscle strength and muscle explosive power are associated with functional limitation and increased disability after stroke.

[2] 'Hand-held' dynamometry should not be confused with 'hand-grip' dynamometry which measures hand-grip strength of an individual independent of the investigator.

6.3. Methods

Search Strategy

A search strategy was constructed with similar architecture as the previous chapter (Section 5.3). This included terms for 'stroke' combined with terms relating to muscle force production (e.g. muscle strength, torque, force and power).

Searches were then limited using terms to detect either a) inclusion of healthy control group data (e.g. healthy, matched, control) for hypothesis 1, and b) inclusion of data relating to association (e.g. correlation, association, regression) for hypothesis 2. Plain text searches were also used to identify controlled vocabulary specific to each database (e.g. 'Muscle strength/'). The strategy was applied on 29th August 2007.

Eligibility criteria

Studies of people with stroke were eligible if they reported any indices of muscle force production in terms of a) muscle strength (maximal force or torque production) or b) muscle power output measured using dynamometry such as strain gauges, isokinetic dynamometers, hand-grip dynamometers. Studies were excluded if 'hand-held' dynamometers were employed (e.g. Bohannon et al. 1995) or indices such as the MRC scale (e.g. Minana-Climent et al. 2005). Although simple and rapid for clinical purposes, these are conceptually weak as a physiological measure of muscle strength (Section 2.2) and will be more susceptible to investigator bias. Observational studies or RCT studies (baseline data used) were included. Multiple publications of data from the same participants were excluded.

For hypothesis 1 the included studies were limited to those including both a stroke cohort and an age- and gender-matched cohort of healthy people. This is particularly important for studies measuring strength since the modes of testing and types of measurement and equipment vary greatly (Macaluso and De Vito 2004). Normative values published elsewhere would usually be difficult to equate consistently and thus would not be a satisfactory approach.

For hypothesis 2 eligible studies were included if they reported bivariate or multivariate associations between muscle strength or power and concurrent measures of physical function and/or disability scales.

Data extraction

From all included studies the following data was extracted;

a) Participant data

i) sample size, ii) age, iii) gender, iv) time since stroke, v) stage of recovery (inpatient/community dwelling)

b) Muscle force production data

i) type of muscle force production (strength or power), ii) magnitude of strength (torque or force) or power (Watts), iii) type of resistance (Isometric/Isokinetic), iv) velocity of movement and v) location including body segment/joint, and side of body (affected/unaffected side).

Relevant participant data and muscle force data of healthy control groups were extracted where these were included (Hypothesis 1).

Measures of association (e.g. correlation coefficients) between indices of muscle force production and either physical function or disability scales were extracted where these were included (Hypothesis 2)

Analysis

For each included stroke cohort mean values of indices of muscle force production were expressed as a percentage of that reported recorded in the control group.

6.4. Is muscle strength or power low after stroke?

The search strategy for hypothesis 1 yielded 71 potentially relevant studies of which 8 met the inclusion criteria.

6.4.1. Muscle Strength

Eight studies were identified which compared the strength of people with stroke (n=166 participants) with healthy control participants (Table 6.1). Although the studies covered a number of body segments, all except one of the studies (Tanaka et al. 1998) were limited to static, isometric measures. Two studies reported data from the same participants (Ada et al. 2000; Canning et al. 2000) therefore only the first is included (Ada et al. 2000).

All measures of strength in the trunk and the affected arms and legs of people with stroke were lower than the matched control groups. On the unaffected side strength was less than the controls in the acute phase, tending to approach or exceed the controls in the chronic phase (>1 year; Boissy et al. 1999; Maeda et al. 2000; Ng and Hui-Chan 2005). Trunk muscle strength remained lower than the control in both the acute and chronic phase.

Longitudinal data were reported by two studies. One showed a decrease in strength during inpatient care between 2 and 9 days after stroke (Harris et al. 2001), and the other an increase between 3 weeks (inpatient) and 6 months (discharged) after stroke (Newham and Hsiao 2001).

Table 6.1 Eight studies reporting measures of muscle strength in stroke patients and matched healthy control groups.

	Stroke Participants				Strength Measure		% of healthy control group	
Study	Age	n (m/f)	Time post stroke	Stage of Recovery	Data	Muscle Group + velocity	Affected side	Unaffected side
a) Upper Limb Strength								
(Ada et al. 2000)	67	15 (8/7)	4.4 y	COMM	Isometric Torque	Elbow flex 30, 60, 90º Elbow ext 30, 60, 90º	81, 75, 67% 63, 79, 93%	- -
(Boissy et al. 1999)	47 (14)	15 (10/5)	> 1 y	COMM	Isometric Force	Handgrip	35 to 40%	107 to 115%
b) Lower Limb Strength								
(Maeda et al. 2000)	69.9	40 (21/19)	3.5 y (~1.0)	COMM	Isometric Force	Knee ext	63% (m) 72% (f)	103% (m) 108% (f)
(Harris et al. 2001)	73.6 (11)	10 (6/4)	2 d	INP	Isometric Torque	Knee ext	-	33%
			9 d	INP	Isometric Torque	Knee ext	-	19%
(Newham and Hsiao 2001)	61 (5)	12 (5/7)	21d (1)	INP	Isometric Force	Knee flex Knee ext	43% 56%	79% 92%
			6 m	COMM	Isometric Force	Knee ext Knee flex	70% 82%	90% 96%
(Ng and Hui-Chan 2005)	61.7 (7.2)	11 (6/5)	5.6 y (3.3)	COMM	Isometric Torque	Ankle dorsiflexion Ankle plantarflexion	51% 49%	99% 95%
c) Trunk Strength								
(Tanaka et al. 1998)	61.3 (6.7)	25 (25/0)	27.2 m (28.5)	COMM	Isometric Torque	Trunk flex Trunk ext	88% 64%	
					Isokinetic Torque	Trunk flex 60, 120, 150º/sec Trunk ext 60, 120, 150º/sec	80, 65, 58% 57, 55, 53%	
(Karatas et al. 2004)	59.1 (10.2)	38 (25/13)	39 d (37)	INP	Isometric Torque	Trunk flex Trunk ext	93% 88%	
					Isokinetic Torque	Trunk flex 60, 90, 120 º/sec Trunk ext 60, 90, 120 º/sec	72, 60, 50% 72, 62, 71%	

Data are mean (SD) unless otherwise stated
Abbreviations: m male; f female; UN unknown; y year; m month; d day; COMM community dwelling; INP inpatient; ext extension; flex flexion

6.4.2. Explosive power output

Explosive power output is reported by just two studies (Table 6.2) both of these (Dawes et al. 2005; Greig et al. 2003) used the same a specific piece of equipment, a Nottingham Power Rig (Medical Engineering Unit, University of Nottingham, Nottingham NG7 2UH, UK); this is described by Bassey and Short (1990) and shown in a later section (Figure 8.1). Although neither study included a healthy control group there are substantial normative data available for this device across a wide age range for both genders (Allied Dunbar National Fitness Survey 1992; Skelton et al. 1999; Skelton et al. 1994). Compared with these norms both studies suggest substantial impairment in the explosive power output of both lower limbs.

Table 6.2 Table of studies reporting muscle power in stroke patients and their comparison with healthy control data.

	Stroke Participants				Power Measure		% of healthy norms*	
Study	Age	n (m/f)	Time post stroke	Stage of Recovery	Data	Muscle group	Affected side	Unaffected side
(Dawes et al. 2005)	46.8 (8)	14 (8/6)	> 6 m	COMM	Power $W \cdot kg^{-1}$	Extensors of whole lower limb (knee + hip)	31%†	57%†
(Greig et al. 2003)	73.5 (8.7)	11 (9/2)	14 m (median)	COMM	Power $W \cdot kg^{-1}$	Extensors of whole lower limb (knee + hip)	48%	51%

Data are mean (SD) unless otherwise stated.
Abbreviations: m male; f female; UN unknown; m month; COMM community dwelling
* Age- and gender-matched norms reported in (Allied Dunbar National Fitness Survey 1992; Skelton et al. 1999; Skelton et al. 1994) using same equipment.
† Stronger side assumed to be 'unaffected'

6.4.3. Discussion

These results show that isometric strength in a variety of muscle groups is lower than expected when compared to age- and gender matched people who have not had a stroke. These data also hint that power output is impaired after stroke, and that this may be at least as much as for strength. Unsurprisingly the strength and power impairments were usually greatest on the side most affected by stroke. However bilateral measures suggest that force production by the unaffected side is also low. There are a number of factors relating to the amount, the quality and the recruitment of muscle which may explain the patterns of strength and power impairment.

6.4.3.1. Indirect factors pre-dating stroke

Longitudinal measures of hand grip strength in a 27 year follow-up of 3741 men showed deterioration in strength of -1.0% per year (Rantanen et al. 1998). A steeper deterioration (-1.5% p.a.) was observed in people who developed chronic diseases such as diabetes, arthritis, CHD, COPD and stroke. These data hint that low strength may pre-date stroke.

Strength may be impaired before stroke for similar reasons to cardiorespiratory fitness i.e. the effects of a) age, b) physical inactivity, c) comorbid disease and d) cigarette smoking. Increasing age and especially physical inactivity are associated with muscle atrophy and loss of muscle strength. The secondary consequences of comorbid chronic diseases, especially inflammation, are linked to muscle wasting (Degens and Alway 2006), and cigarette smoking is associated with impaired muscle

strength (Al Obaidi et al. 2004). Since these factors could act bilaterally or systemically they could contribute to strength impairments on the 'unaffected' side.

6.4.3.2. 'Direct' effect of stroke

The direct neurological effect of a unilateral stroke explains the contralateral motor impairments which are one defining feature of stroke. However there is evidence that the direct neurological effects may have bilateral motor effects (Colebatch and Gandevia 1989). The reasons for impairment may relate to impaired activation, reflex inhibition of the agonist and coactivation of the antagonists.

6.4.3.3. Indirect factors – after stroke

After stroke it is plausible that physical inactivity, comorbid disease and smoking may continue to affect muscle mass and force production. There are a few small longitudinal studies examining post-stroke changes in muscle strength, and these findings are conflicting reporting no change (Carin-Levy et al. 2006; n=17; <72hrs to 6 months), a decrease (Harris et al. 2001; n=10; admission to 1 week) and an increase (Newham and Hsiao 2001; n=12; 21 days to 6 months).

After stroke atrophy of type II muscle fibres occurs in both lower limbs (Hachisuka et al. 1997), and there is reduction in muscle cross sectional area, and the presence of increased intramuscular fat in the affected limbs (Ryan et al. 2002). These observations are indicative of inactivity and disuse either before and/or after stroke and are associated with reduced muscle force production.

Newham and Hsiao (2001) noted that bilateral impairment of muscle strength arose from failure of voluntary activation and that this was not contributed to by antagonist coactivation or disuse atrophy; this suggests bilateral motor effects or bilateral effects which predate the stroke. However the tendency for strength in the unaffected side to exceed the control data late after stroke may arise due to patients compensating for deficits by relying more on the unaffected side. The increased use may generate a local training effect.

Conclusions about the nature and extent of strength and power impairment after stroke are limited. A particular limitation is the lack of data describing time- or velocity-dependent characteristics. Only one study (Karatas et al. 2004) included a dynamic strength measure through a range of motion. Likewise explosive power data are very limited and lack matched control data. This type of study may be exposed to bias due to self selection by volunteers, and generalization may be limited. A strength of this systematic review is that it is currently the only synthesis of age and gender-matched data, and these are confined to rigorous measures of force production.

In healthy elderly people impaired muscle strength and power are associated with functional limitations and clinical and pre-clinical disability (Section 2.3). Therefore it is plausible that low muscle strength and power after stroke may be directly linked to some common post-stroke problems (Section 1.3) which involve physical activity.

6.5. Are muscle strength and power associated with function and disability?

The search strategy yielded a total of 472 potentially relevant studies of which 21 met the inclusion criteria.

6.5.1. Strength

Fifteen studies (n=422) reported bivariate associations between muscle strength measures and a) indices of walking speed and endurance (Table 6.3) and b) lower limb activities such as stair climbing and chair rising (Table 6.4). Most participants were community dwelling and below the age typical of a first stroke. Measures of strength were usually reported for both affected and unaffected sides and were confined to the lower limbs. Studies reported strength as isometric (static) force or torque, and isokinetic (dynamic) torque at a range of angular velocities.

Walking performance was categorised as comfortable walking speed (CWS), maximum walking speed (MWS), and walking endurance (6-minute walking test; 6-MWT). All studies examining gait showed significant medium ($r > 0.3$) or large ($r > 0.5$; Cohen 1992) associations with one or more indices of strength of the affected knee, hip and/or ankle. Associations with strength of the unaffected side tended to be weaker and, and more often statistically non-significant. Gait performance tended to be more strongly associated with dynamic rather than static indices of strength. Fewer studies examined physical functions such as chair rising and stair climbing but the pattern of observations corresponds to those made for gait performance.

Table 6.3 Bivariate associations between measures of muscle strength and categories of physical function.

	Participants				Strength measure		Association between muscle strength and function.	
Study	Age	n (m/f)	Time post stroke	Stage of Recovery	Data	Muscle group (+ velocity)	Affected side	Unaffected side
a) Walking Speed - Comfortable or Chosen								
(Bohannon and Andrews 1990)	59.0 (11.4)	17 (11/6)	51 d (41.8)	UC	Isometric Torque Nm	Knee ext	r = 0.539 - 0.605 p<0.05	-
(Bohannon 1991)	58.4 (11.7)	26 (13/13)	69.5 d (70.6)	INP/UC	Isometric Torque Nm & Nm/kg	Knee ext (Nm/kg) Knee ext (Nm)	r = 0.677 p<0.001 r = 0.645 p<0.001	r = 0.2 NS r = 0.245 NS
(Bohannon 1992)	63.7 (14.9)	20 (10/10)	70 d (109)	INP + COMM	Isometric Torque Nm	Knee ext	r = 0.747 p<0.0001	r = 0.524 p=0.018
(Lindmark and Hamrin 1995)	71 Median	34 (22/12)	3 m	COMM	Isokinetic Torque Nm	Knee ext (12/90º/sec) Knee flex (12/90º/sec)	r = 0.21 to 0.69*; p<0.05 r = 0.43 to 0.72*; p<0.05	- -
(Nadeau et al. 1999)	47.9 (15.6)	16 (12/4)	43.9 m (36.5)	COMM	Isokinetic Torque Nm/kg	Hip flex (30º/sec) Ankle P.flex (30º/sec)	r = 0.827; p<0.001 r = 0.337; NS	- -
(Hsu et al. 2003)	54.2 (10.9)	26 (19/7)	10.3 m (12)	COMM	Isokinetic Torque Nm/kg	Hip flex (30º/sec) Knee ext (90º/sec) Ankle P.flex (30º/sec)	r = 0.49 p<0.05 r = 0.52 p<0.01 r = 0.42 p<0.05	- - -
(Kim and Eng 2003)	61.2 (8.4)	20 (14/6)	4.0 y (2.6)	COMM	Isokinetic Torque Nm/kg	Hip ext/flex (60º/sec) Knee ext/flex (60º/sec) Ankle P/D.flex (60º/sec)	r = 0.351/0.574*; p<0.01 r = 0.408/0.555*; p<0.05 r = 0.845*/0.329; p<0.01	r = 0.346/0.380; NS r = 0.331/0.615*; p<0.01 r = 0.486*/0.294; p<0.05
(Flansbjer et al. 2006)	58 (6.4)	50 (38/12)	6 - 46 m	COMM	Isokinetic Torque Nm	knee ext/flex (60º/sec)	r = 0.61 / 0.61 p<0.01	r = 0.12 / 0.09 NS
(Patterson et al. 2007)	64 (10)	74 (43/31)	48 m (59)	COMM	Isokinetic Torque (eccentric) Nm	Knee ext (average of 30/90/120 º/sec)	r = 0.60 p<0.001	r = 0.38 p<0.05

Cont./

Table 6.3 Cont./

	Participants				Strength measure		Association between muscle strength and function.	
Study	Age	n (m/f)	Time post stroke	Stage of Recovery	Data	Muscle group (+ velocity)	Affected side	Unaffected side
b) Walking Speed - Maximum								
(Nakamura et al. 1985)	53.5 Range 27-72	11 (10/1)	4.0 m 0.5-22.5	UC	Isometric Torque Isokinetic Torque Nm	Knee ext (30/60/90º) Knee ext (30/90/180º/sec)	r = 0.595 to 0.759 p<0.01 r = 0.794 to 0.870 p<0.05	r = 0.175 to 0.436 NS r = -0.064 to 0.111 NS
(Bohannon 1992)	63.7 (14.9)	20 (10/10)	70 d (109)	INP + COMM	Isometric Torque Nm	Knee ext	r = 0.744 p<0.0001	r = 0.448 p=0.048
(Lindmark and Hamrin 1995)	71 Median	34 (22/12)	3 m	COMM	Isokinetic Torque Nm	Knee ext (12/90º/sec) Knee flex (12/90º/sec)	r = 0.31 to 0.63* p<0.05 r = 0.47* to 0.70* p<0.01	- -
(Nadeau et al. 1999)	47.9 (15.6)	16 (12/4)	43.9 m (36.5)	COMM	Isokinetic Torque Nm/kg	Hip flex (30 º/sec) Ankle P.flex (30 º/sec)	r = 0.887; p<0.001 r = 0.405; NS	- -
(Suzuki et al. 1999)	54.2 (12.3)	34 (34/0)	8.6 w (3.0)	INP UC	Isokinetic torque Nm	Knee ext (30 º/sec)	r = 0.644 (p<0.01)	r = 0.417 (p<0.05)
(Maeda et al. 2000)	69.9	40 (21/19)	3.5 y (~1.0)	COMM	Isometric Force N	Knee ext	r = -0.42 (m); p<0.01 r = -0.33 (f); NS	r = -0.41 (m); p<0.01 r = -0.43 (f); p<0.01
(Hsu et al. 2003)	54.2 (10.9)	26 (19/7)	10.3 m (12)	COMM	Isokinetic Torque Nm/kg	Hip flex (30º/sec) Knee ext (90º/sec) Ankle P.flex (30º/sec)	r = 0.59 p<0.05 r = 0.68 p<0.01 r = 0.40 p<0.05	- - -
(Flansbjer et al. 2006)	58 (6.4)	50 (38/12)	6 - 46 m	COMM	Isokinetic Torque Nm	knee ext/flex (60º/sec)	r = 0.67 / 0.65 p<0.01	r = 0.19 / 0.15 NS
c) Walking Endurance – 6 Minute Walking Test								
(Flansbjer et al. 2006)	58 (6.4)	50 (38/12)	6 - 46 m	COMM	Isokinetic Torque Nm	knee ext/flex (60º/sec)	r = 0.70 / 0.71 p<0.01	r = 0.26 / 0.25 NS
(Patterson et al. 2007)	64 (10)	74 (43/31)	48 m (59)	COMM	Isokinetic Torque (eccentric) Nm	Knee ext (average of 30/90/120 º/sec)	r = 0.57 p<0.001	r = 0.41 p<0.001

Data are mean (SD) or range.
Abbreviations: m male; f female; UN unknown; y year; m month; d day; COMM community dwelling; INP inpatient; ext extension; flex flexion; P.flex plantar flexion; D.flex dorsi-flexion; r Pearson correlation coefficient; NS not significant
* Significant variable

Table 6.4 Bivariate associations between measures of muscle strength and categories of physical function.

	Participants				Strength measure		Association between muscle strength and function.	
Study	Age	n (m/f)	Time post stroke	Stage of Recovery	Data	Muscle group (+ velocity)	Affected side	Unaffected side
a) Chair Rising Time								
(Maeda et al. 2000)	69.9	36 (17/19)	3.5 y (~1.0)	COMM	Isometric Force N	Knee ext	r = -0.02 (m); NS r = -0.03 (f); NS	r = -0.20 (m); NS r = -0.33 (f); NS
(Lomaglio and Eng 2005)	67.0 (8.8)	22 (19/3)	5.3 y (2.1)	COMM	Isokinetic Torque Nm/kg	Ankle P/D.flex (30º/sec) Knee ext/flex (60º/sec) Hip ext/flex (60º/sec)	r = -0.355/-0.616*; p<0.05 r = -0.232/-0.736*; p<0.01 r = -0.420/0.025; NS	r = -0.323 to 0.111 NS r = 0.005 to 0.250 NS r = -0.237 to 0.250 NS
b) Timed Up-and-Go								
(Ng and Hui-Chan 2005)	61.7 (7.2)	11 (6/5)	5.6 y (3.3)	COMM	Isometric Torque Nm	Ankle D.flex Ankle P.flex	σ = -0.1; NS σ = -0.86 p<0.05	σ = -0.21; NS σ = -0.24; NS
(Flansbjer et al. 2006)	58 (6.4)	50 (38/12)	6 - 46 m	COMM	Isokinetic Torque Nm	knee ext/flex (60º/sec)	r = -0.65 / -0.64 p<0.01	r = -0.14 / -0.15 NS
c) Stair Climbing								
(Kim and Eng 2003)	61.2 (8.4)	20 (14/6)	4.0 y (2.6)	COMM	Isokinetic Torque Nm/kg	Hip ext/flex (60º/sec) Knee ext/flex (60º/sec) Ankle P/D.flex (60º/sec)	r = 0.273/0.544*; p<0.05 r = 0.337/0.482*; p<0.05 r = 0.709*/0.328; p<0.01	r = 0.324/0.289; NS r = 0.443/0.477*; p<0.05 r = 0.450*/0.367; p<0.05
(Flansbjer et al. 2006)	58 (6.4)	50 (38/12)	6 - 46 m	COMM	Isokinetic Torque Nm	knee ext/flex (60º/sec)	r = -0.58 / -0.61 p<0.01 r = -0.61 / -0.61 p<0.01 †	r = -0.07 / -0.06 NS r = -0.13 / -0.10 NS

Data are mean (SD) unless otherwise stated.
Abbreviations: m male; f female; UN unknown; y year; m month; d day; COMM community dwelling; INP inpatient; ext extension; flex flexion; P.flex plantar flexion; D.flex dorsiflexion; r Pearson corellation coefficient; NS not significant; σ Spearman correlation coefficient
* Significant variable
† Descending stairs

Seven studies (n=314) report multivariate analyses which examine the predictive value of both muscle strength and confounding variables of measures of gait and mobility (Table 6.5). These include five studies from Tables 6.3 and 6.4 along with multivariate data from two other studies (LeBrasseur et al. (2006); n=31, age 66.2 years, time since stroke 17.5 months) and (Pohl et al. (2002a); n=83, age 70.3 y, time since stroke 78.6 (SD 27.4) days). All studies examined the effect of dynamic strength. The data suggest that the muscle strength, particularly of the affected leg, was linked to post-stroke mobility. Strength of the unaffected side, where measured, also had an influence in some studies (Flansbjer et al. 2006). When the rate of force production (Pohl et al. 2002a) and the amount of work completed in Joules (Hsu et al. 2003) were included as independent variables their predictive value exceeded that of strength measured using torque.

The only two prediction models to include more than one muscle group gave the strongest predictions of (maximum) walking speed. Both included hip flexor strength plus one other muscle group i.e. ankle plantarflexors (Nadeau et al. 1999) and the knee extensors (Hsu et al. 2003); both of these models also included sensation at the lower limb (a domain of Fugl-Meyer scale).

Most of the multivariate models included factors such age and gender, or impairments including balance, sensation, motor function and muscle tone which were independently predictive of walking performance.

Table 6.5 Seven studies (n=314) using multiple linear regression to predict indices of physical function in people with stroke from muscle strength and other confounding variables.

	Included predictor (independent) variables		Physical function (Dependent) variable	Significant predictor variables			
Study	Strength measures	Other		Strength affected side	Strength unaffected side	Other	Multiple linear regression model R^2
(Nadeau et al. 1999)	Hip flex Ankle P.flex	Fugl-Meyer (lower limb, balance, sensation), spasticity	CWS MWS	Hip flex* Hip flex* Ankle P.flex	Not examined Not examined	NS Sensation	R^2 = 0.685 (p<0.001) R^2 = 0.845 (p<0.001)
(Suzuki et al. 1999)	Knee ext	Age, height, body mass, time since stroke, balance	MWS	NS	NS	Balance	R^2 = 0.454
(Pohl et al. 2002a)	Knee ext	Rate of torque development, gender , age	CWS	NS	NS	Age, rate of torque development	R^2 = 0.12 aff R^2 = 0.10 unaff
(Hsu et al. 2003)	Hip flex † Knee ext † Ankle P.flex †	Fugl-Meyer (motor function, sensation), spasticity	CWS MWS	Hip flex work* Hip flex work* Knee ext work	Not examined Not examined	Spasticity, sensation Motor, sensation	R^2 = 0.57 (p<0.001) R^2 = 0.72 (p<0.001)
(Flansbjer et al. 2006)	Knee ext/flex	Gender, age, time since stroke, stroke type, side of weakness.	TUG CWS MWS 6-MWT Stair climb Stair descend	Knee ext* Knee flex* Knee ext/flex * Knee ext/flex* Knee ext/flex* Knee ext/flex * Knee ext/flex *	Knee ext Knee flex Knee ext/flex NS Knee ext/flex Knee ext/flex Knee ext/flex	Age Right weakness NS NS NS NS NS	R^2 = 0.57 R^2 = 0.47 R^2 = 0.46 / 0.42 R^2 = 0.50 / 0.42 R^2 = 0.49 / 0.50 R^2 = 0.45 / 0.44 R^2 = 0.46 / 0.42
(LeBrasseur et al. 2006)	Knee ext	Gender, cognition, depression, self efficacy	CWS Stair climb StS	Knee ext * Knee ext NS	NS NS NS	Self efficacy, gender Self efficacy Self efficacy	R^2 = 0.71 R^2 = 0.66 R^2 = 0.43
(Patterson et al. 2007)	Knee ext	$\dot{V}O_2$ peak, Berg Balance, body composition	6-MWT	Knee ext	NS	$\dot{V}O_2$ peak*, balance	R^2 = 0.60 (p<0.001)

Data are mean (SD) unless otherwise stated.
Abbreviations: ext extension; flex flexion; P.flex plantar flexion; CWS comfortable walking speed; MWS maximum walking speed; 6-MWT six minute walking test; StS sit to stand time; r Pearson correlation coefficient; NS not significant;
* Principal predictor of regression model;
† Torque ($Nm \cdot kg^{-1}$) and work ($J \cdot kg^{-1}$) included

6.5.2. Strength and disability

Three studies (n=168) reported bivariate associations between measures of muscle strength and disability (Table 6.6). A mixture of strength measures were examined, including static and dynamic strength of the trunk, and the upper and lower limbs. Hamrin et al. (1982) was the only study to present data for limbs of the unaffected side and the comparison suggested this was less predictive of ADL performance than the affected side. Only Karatas et al. (2004) used inpatients (39d post-stroke) and reported motor and locomotion subsets in addition to the overall FIM score, these showed a similar pattern of association; these data hint that more faster, more dynamic expressions of muscle force production are more closely associated with disability.

Few data explore the multivariate association between strength and disability (Table 6.7). The dependent variable used by Lebrasseur et al. (2006), the Late Life Function and Disability Instrument, and its principal predicative factor (Ewart Self-Efficacy Scale) have not been validated or reliability tested in people with stroke. Also these participants were recruited via media advertisement and therefore are vulnerable to (self) selection bias.

Table 6.6 Bivariate associations between measures of muscle strength and global indices of disability (n=168).

	Participants				Strength measure			Association between muscle strength & disability	
Study	Age	n (m/f)	Time post stroke	Stage of Recovery	Data	Muscle group	Disability measure	Affected side	Unaffected side
(Hamrin et al. 1982)	68 to 71	37 (21/16)	1 y	INP + COMM	Isokinetic Torque Nm	Elbow ext/flex (90, 30 °/sec)	Hygiene † Dressing † Household †	σ = 0.45-0.59 p<0.05* σ = 0.31-0.55 p<0.05* σ = 0.17-0.77 p<0.01*	σ = 0.12-0.53 NS σ = 0.03-0.53 NS σ = 0.09-0.68 p<0.05*
						Knee ext/flex (90, 30 °/sec)	Locomotion †	σ = 0.71-0.90 p<0.001	σ = 0.38-0.67 p<0.01-5
(Karatas et al. 2004)	59.1 (10.2)	38 (25/13)	39 d (37)	INP	Isometric Torque lb/ft	Trunk ext/flex	FIM FIM Motor FIM-LT	r = 0.15 / 0.21 NS r=0.14/0.28 NS r=0.01/0.23 NS	
					Isokinetic Torque lb/ft	Trunk ext/flex (60, 90, 120 °/sec)	FIM FIM Motor FIM-LT	r = 0.10 to 0.40* / 0.18 to 0.37* p<0.05 r = 0.20 to 0.51* / 0.18 to 0.41* p<0.05 r = 0.25 to 0.50* / 0.19 to 0.39* p<0.05	
(Harris and Eng 2007)	68.7 (9.4)	93 (60/33)	5.1 y (4.1)	COMM	Isometric Force Units UN	Handgrip	Chedoke AHAI Motor Activity Log Reintegration into normal living Index	r = 0.69 p<0.01 r = 0.61 p<0.01 r = 0.10 NS	- - -

Data are mean (SD) unless otherwise stated. Abbreviations m male; f female; UN unknown; y year; d day; COMM community dwelling; INP inpatient; ext extension; flex flexion; σ Spearman correlation coefficient; r Pearson correlation coefficient; NS not significant; * significant variable; † ADL index domains

Table 6.7 One study (n=31) using multiple linear regression to predict disability after stroke from muscle strength and confounding variables.

	Included predictor (independent) variables		Disability measure (Dependent) variable	Significant predictor variables			Multiple linear regression model R^2
Study	Strength measures	Other		Strength affected side	Strength unaffected side	Other	
(LeBrasseur et al. 2006)	Knee ext	Gender, cognition, depression, self efficacy	Limitation†	NS	NS	Self efficacy*, depression	R^2 = 0.70 (p<0.001)
			Instrumental†	NS	NS	Self efficacy*	R^2 = 0.63 (p<0.001)
			Management†	NS	NS	Self efficacy*, depression	R^2 = 0.53 (p<0.001)

NS not significant; * principal predictive factor; † domain of Late Life Function and Disability Instrument

6.5.3. Power

Only three studies (n=65) report bivariate or multivariate associations between muscle power with either function or disability in people with stroke (Tables 6.7 and 6.8). The studies suggest power of the lower limbs has some involvement in mobility although interpretation is problematic. The data of Dawes et al. (2005) showed power of both lower limb extensors were not significantly associated with comfortable walking speed, but asymmetry in power between limbs was predictive of comfortable walking speed. However, the sample was small (n=14) with a mean age of 46.8 years (SD 8) which is unusually low for stroke.

The multivariate analyses of LeBrasseur et al. (2006) showed that power of the knee extensors, particularly of the affected side, was the principal predictor of comfortable walking speed and stair climbing performance, but not measures of disability. But this study used unvalidated outcome measures and there was self-selection bias of participants.

LeBrasseur et al. (2006) and Bohannon (1992) directly compare strength and power and show comfortable walking speed is similarly predicted by both variables of muscle force production. However LeBrasseur et al. (2006) showed that power explained more than double the variation in stair climbing time than strength (Tables 6.7 and 6.8)

Table 6.7 Bivariate associations between muscle power and function.

Study	Participants				Power measure	Function measure	Association between power and function	
	Age	n (m/f)	Time post stroke	Stage of Recovery			Affected side	Unaffected side
(Bohannon 1992b)	63.7 (14.9)	20 (10/10)	70 d (109)	INP + COMM	Knee ext	CWS	r=0.752; p<0.0001	r=0.613; p=0.004
						MWS	r=0.735; p<0.0001	r=0.507; p=0.023
(Dawes et al. 2005)	46.8 (8)	14 (8/6)	> 6 m	COMM	Extensors of whole lower limb (knee + hip)	CWS	σ = 0.37; NS	σ = -0.28; NS

Data are mean (SD) unless otherwise stated.
Abbreviations: m male; f female; m month; d day; COMM community dwelling; INP inpatient; ext extension; r Pearson corellation coefficient; σ Spearman correlation coefficient; CWS comfortable walking speed; MWS maximum walking speed; NS not significant

Table 6.8 One study (n=31) using multiple linear regression to predict function and disability after stroke from muscle power and confounding variables.

Study	Included predictor (independent) variables		Dependent variables		Significant predictor variables			Multiple linear regression model R^2
	Power measures	Other			Power affected side	Power unaffected side	Other	
(LeBrasseur et al. 2006)	Knee ext	Gender		CWS	Knee ext*	NS	Self efficacy, gender	R^2 = 0.70 (p<0.001)
		Cognition (MMSE)	Function	Stair climb	Knee ext *	Knee ext	Self efficacy	R^2 = 0.78 (p<0.001)
		Depression (Geriatric Depression Scale)		StS	NS	NS	Self efficacy	R^2 = 0.43 (p<0.001)
				Limitation	NS	NS	Self efficacy*, depression	R^2 = 0.70 (p<0.001)
		Self efficacy (Ewart self efficacy scale)	Disability†	Instrumental	NS	NS	Self efficacy*	R^2 = 0.63 (p<0.001)
				Management	NS	NS	Self efficacy*, depression	R^2 = 0.43 (p<0.001)

NS not significant; * principal predictive factor; † domain of Late Life Function and Disability Instrument

6.5.4. Discussion

This systematic review shows that low muscle strength is associated with reduced mobility after stroke, and that the strongest associations exist with dynamic muscle strength, that is those expressed through a range of motion. There are few data showing associations with global measures of disability but the data reinforce the potential importance of dynamic rather than static measures of muscle force production. Few data are available examining the role of explosive power in function or disability.

Walking, rising from a chair, negotiating stairs all represent physical functions which are dynamic and require varying degrees of muscle force production. Therefore after stroke it is not surprising that impaired strength and power might reduce performance in just the same way as it can healthy elderly people.

When fitness is very low in people of any age some physical functions may become impossible to perform (‘*Threshold of Independence’*; Section 2.3.2). There are no data showing such a threshold in people with stroke in the included studies.

The relationships between variables of muscle force production (strength, power) and both function and disability in people with stroke are multifactorial, just as for elderly people (‘*Co-impairments*’; Section 2.3.1). The multivariate analyses identified a number of confounding factors (e.g. sensation, rate of force development, muscle tone, balance, age, side of weakness, gender, self efficacy, depression and $\dot{V}O_2$ peak).

There are few data to determine whether strength, power or cardiorespiratory fitness is of greatest relative importance for function and disability. Patterson et al. (2007) showed that both strength (knee extension), cardiorespiratory fitness ($\dot{V}O_2$ peak) along with balance, were independent predictors of 6-MWT performance, but $\dot{V}O_2$ peak emerged as the most important factor.

There are experimental and procedural factors which may introduce variation in the reviewed findings including for example whether measures of strength were absolute or normalized to body mass, and whether gravity correction on isokinetic devices was used, and whether walking aids are used for ambulation.

The studies exploring the role that muscle strength play in post stroke function and disability have some limitations. These include i) the general lack of more global indices of disability, ii) few data relating to force production in more complex, multi-joint patterns of movement

The studies exploring explosive power output and its role also have limitations, which include i) few published data, ii) use of equipment not ideal for explosive power movements, ii) unusually young participants and iii) few disability measures previously validated for stroke.

Muscle strength and muscle power both show non-linear associations with functional measures (Section 2.3.1). Therefore it is surprising that so few of the studies report tests of normality and data transformations (or non-parametric statistics). Also many of the studies use only bivariate analyses and thus ignore potentially confounding 'coimpairments'. Finally, the principle limitation affecting all the data discussed is that it is observational which means that causal effects cannot be inferred.

The implications of the link between muscle force production (strength and power) and both function and disability suggests that improving strength and power may offer a means of improving function in activities commonly impaired after stroke, and also provide a strength 'reserve' to protect from the functional consequences of the gradual reduction of strength and power which inevitably occurs with increasing age.

Muscle strength and power after stroke - Summary

Impairments

- After stroke isometric muscle strength is lower than healthy people of the same age and gender
- Muscle strength impairments
  - occur bilaterally
  - are greater on affected side
  - are highly variable in magnitude
- Little is known about impairments in muscle power – possibly impaired at least as much as strength

Functional Consequences of Impairment

- Lower limb strength is predictive of functional limitations – especially walking
- Muscle strength measures are more predictive of function when they are;
  - on the affected side
  - dynamic rather than static
  - complex multi-joint movements rather than about a single joint
- Confounding factors such as balance and sensation (coimpairments) are involved in functional limitation – not just strength
- Some data show strength is predictive of disability – but the data are limited
- Little is known about the associations between muscle power and both function and disability
- Not clear whether muscle power or muscle strength is more predictive of functional consequences

7. Cardiorespiratory fitness after stroke – an observational study

7.1. Abstract

OBJECTIVE: To determine whether the economy of walking and the kinetics of oxygen uptake are impaired in people with stroke, and whether the impairments, if any, are associated with functional limitation and disability after stroke.

DESIGN: Cross sectional observational study of baseline data from a randomized controlled trial.

SETTING: Hospital clinical research facility.

PARTICIPANTS: Independently ambulatory community-dwelling people with stroke (n=66), mean age 72 yrs (SD 10).

MEASURMENTS: Cardiorespiratory fitness measures were gross and net economy of walking expressed as the oxygen cost per unit distance walked ($\dot{V}O_2$ ml·kg^{-1}·m^{-1}), and the time constant for oxygen uptake kinetics ($\tau\,\dot{V}O_2$ sec) determined during self-paced comfortable walking, and global indices of disability (FIM Instrument, Rivermead Mobility Index, and Nottingham Extended ADL).

RESULTS: During comfortable walking the gross oxygen cost per unit distance walked was greater (116%, IQR 98% to 164%; $p<0.001$) than expected in healthy elderly people walking at a comfortable speed. Comfortable walking speed was slower than expected in healthy people (~50%). The gross oxygen cost per unit distance walked was similar (99%, IQR 87% to 131.5%; NS) to values expected in healthy elderly people adopting the same slow pace of walking observed in the stroke patients. Normative data for net economy were not available. Net and gross economy were associated with indices of disability, however multivariate analyses showed these effects were not independent of walking speed. It was not feasible to reliably determine $\tau\dot{V}O_2$ in this study because the $\dot{V}O_2$ response could not be modelled in >30% of cases. Analysis of available cases suggests $\tau\dot{V}O_2$ after stroke may be slower than but no associations with either walking speed or disability were evident.

CONCLUSIONS: In high-functioning ambulatory people with stroke, walking economy was impaired compared with healthy elderly people. These observed impairments in economy arise largely as a consequence of the slow walking speeds typical after stroke. Self-paced walking may be slow due to low fitness or other factors associated with stroke.

7.2. Introduction

7.2.1. Rationale

7.2.1.1. Impairments

Measures of $\dot{V}O_2$ peak suggest that after stroke cardiorespiratory fitness is lower than age- and gender-matched healthy people (Section 5.5). This may be due to the direct effects of stroke and indirect effects of factors such as physical inactivity, comorbid disease and cigarette smoking, both before and/or after stroke. The other indices of cardiorespiratory fitness (anaerobic threshold, economy and $\dot{V}O_2$ kinetics) may be impaired but few data are available.

Measurement of anaerobic threshold, like $\dot{V}O_2$ peak, requires exercise of progressively higher intensity on treadmills or cycle ergometers. This represents uncomfortable activity which is not functionally relevant for elderly frail patients (Greig 2002), in particular those with gait disorders. Conversely, walking economy and $\dot{V}O_2$ kinetics can be determined during constant intensity, submaximal floor walking, using modern lightweight respiratory gas analysis systems. This approach allows both parameters to be determined in a single procedure, avoids use of ergometry and allows comfortable levels of effort in an activity that is functionally relevant and more feasible for people with stroke who may be frail but ambulatory.

7.2.1.2. Consequences of impairments

Gait problems are very common after stroke; the principal reason is motor impairments on the affected side (Lamontagne et al. 2007). The hemiparetic gait is associated with slow walking speed and reduced walking economy. Poor walking economy coupled with low $\dot{V}O_2$ peak results in a diminished cardiorespiratory 'fitness reserve' (Section 2.1.2). A limited fitness reserve means that walking, if it is to be achieved comfortably, must be performed at a slower speed since this reduces energy expenditure. Therefore it is plausible that poor walking economy causes self-selection of slow walking speeds after stroke. Unfortunately, since speed of walking is known to affect economy an association is highly likely, meaning cause and effect become difficult to separate. However, if poor walking economy is indicative of a general 'non-productive' energy expenditure arising from stroke-related impairments, then one might reasonably expect a range of day-to-day physical activities (including walking) to be similarly constrained by a limited fitness reserve. There are currently no data available which examine the link between economy of walking and global measures of disability after stroke.

If $\dot{V}O_2$ kinetics are impaired (slowed), there is increased anaerobic metabolism with any increase in exercise intensity; this is associated with muscle lactate production and reduced exercise tolerance due to fatigue (Section 2.1.4). This has theoretical implications for the tolerance of many day-to-day activities including both intermittent activities and more 'steady state' activities such as walking. Therefore slowed $\dot{V}O_2$ kinetics may be associated with the limitation of walking and other functional activities

after stroke. Only one small study (Katoh et al. 2002) examined the association between $\dot{V}O_2$ kinetics and function after stroke (Section 2.1.4).

This study will examine walking economy and $\dot{V}O_2$ kinetics in people with stroke, and determine whether they are associated with functional limitation and disability.

7.2.2. Hypotheses

Hypothesis – Walking economy and $\tau\dot{V}O_2$ in people with stroke are impaired when compared with data from healthy people of a similar age and gender.

Hypothesis - Walking economy and $\tau\dot{V}O_2$ are associated with global indices of disability (FIM Instrument, Nottingham Extended ADL and Rivermead Mobility Index).

7.3. Methods

In this observational study a subset of baseline measures from the RCT reported later (Chapter 10).

7.3.1. Participants

The participant recruitment, eligibility and characteristics are described in detail in a later section (*Participants* Section 10.3.2). In brief, 66 individuals with stroke

participated; they were community-dwelling with a mean age of 72 yrs (SD 10). Inclusion criteria were i) independently ambulatory (with or without walking aids), ii) living within the recruitment catchment area, iii) completion of inpatient and outpatient stroke rehabilitation, iv) absence of dysphasia or confusion judged severe enough to prevent safe participation in exercise or relaxation classes or to preclude informed consent. A modified version of absolute contraindications to exercise in elderly people (Dinan 2001) was applied as exclusion criteria. Approval was obtained from the local research ethics committee.

7.3.2. Measurements

Cardiorespiratory fitness variables - The indices of cardiorespiratory fitness (economy of walking and $\dot{V}O_2$ kinetics) were determined during the same procedure. Participants wore a portable metabolic measurement system during three 3-min bouts of self-paced walking around an elliptical 17-m circuit with 5-min break between each walk. Participants were instructed to walk at their 'comfortable pace' (Fitzsimons et al. 2005). Intermediate times for each lap of the circuit were recorded with a stopwatch in order to determine whether each participant adopted an even walking speed.

Before and during each 3-min walk, respiratory gas analysis variables were recorded to determine the economy walking and characterize oxygen uptake kinetics. Respiratory gas analysis was performed using a portable breath-by-breath metabolic measurement system (Metamax 3B, Cortex Biophysik). The Metamax system is worn on the torso and

is interfaced to a facemask enclosing the nose and mouth. The system continuously monitors O_2 and CO_2 concentrations (%) in respired gas, and determines minute ventilation (volume inspired and expired in one minute) via a bi-directional turbine volume transducer (low-flow VTR, Cortex Medical) in the facemask (Figure 7.1)

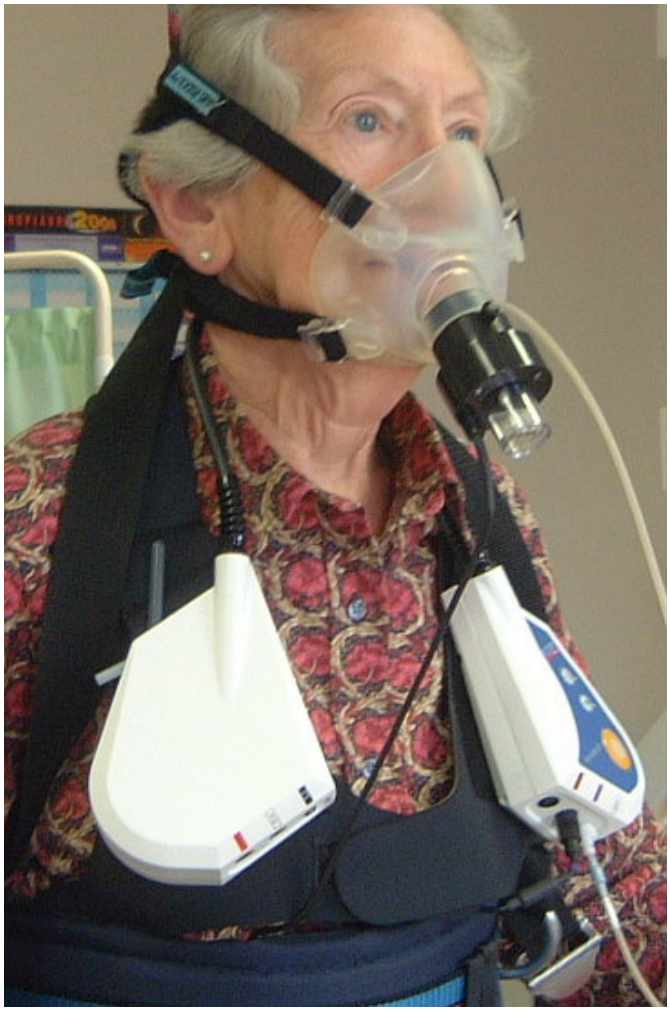


Figure 7.1 Metamax 3B metabolic measurement system as worn by a participant. The facemask houses a turbine to determine minute ventilation and a sample tube through which respired gases are continuously drawn The system on the chest analyses performs breath-by-breath respiratory gas analysis, including calculation of $\dot{V}O_2$. These data can be viewed in real-time on a remote computer via telemetry.

The measures allowed $\dot{V}O_2$ in ml·kg^{-1}·min^{-1} to be determined breath-by-breath throughout standing and walking using the Metasoft software (Cortex Biophysik). The volume transducer of the Metamax system was calibrated with a 3L syringe, and the O_2 and CO_2 sensors calibrated with room air and a certified gas mixture (O_2 15% and CO_2 5%; BOC) immediately prior to each participant's measures.

Any very high or very low $\dot{V}O_2$ data points that were associated with coughing or speech were excluded because these data would not reflect the underlying rate of energy expenditure. Unexplained outliers located more than 4 standard deviations from the local mean (4 sequential breaths) were also excluded since these would not reflect the underlying physiological response. The $\dot{V}O_2$ response during standing and walking were interpolated to provide $\dot{V}O_2$ values every 1 sec. This allowed the data from all three walks to be superimposed by time-aligning the data to the onset of exercise (t = 0 sec). Finally the average $\dot{V}O_2$ for each second was calculated to provide a single set of $\dot{V}O_2$ data summarizing the three walks which were then analyzed.

The $\dot{V}O_2$ on-response to the commencement of walking was characterised for each participant by fitting an exponential model where τ^1 is $\tau\dot{V}O_2$, the rate constant for the primary component of $\dot{V}O_2$ kinetics (Equation 7.1). This was achieved using the least squares method and was performed with non-linear regression software (Graphpad Prizm, Version 4, 11452 El Camino Real, #215 San Diego, CA 92130, USA) to derive the model fitting parameters and generate a curve (Figure 7.2).

$$\dot{V}O_2(t) = \dot{V}O_2(b) + A_0 \cdot (1 - e^{-t/\tau 0}) + A_1 \cdot (1 - e^{-(t-\delta 1)-\tau 1})$$

Equation 7.1 Double Exponential Model ("Cardiodynamic component + Primary Component"). $\dot{V}O_2$(t) represents the $\dot{V}O_2$ at any time t. $\dot{V}O_2$(b) describes the baseline value whilst standing prior to the onset of exercise t=0 sec. The amplitude of each component is denoted A^0 and A^1; τ^0 and τ^1 are the rate constants; δ is the time delay of the primary component.

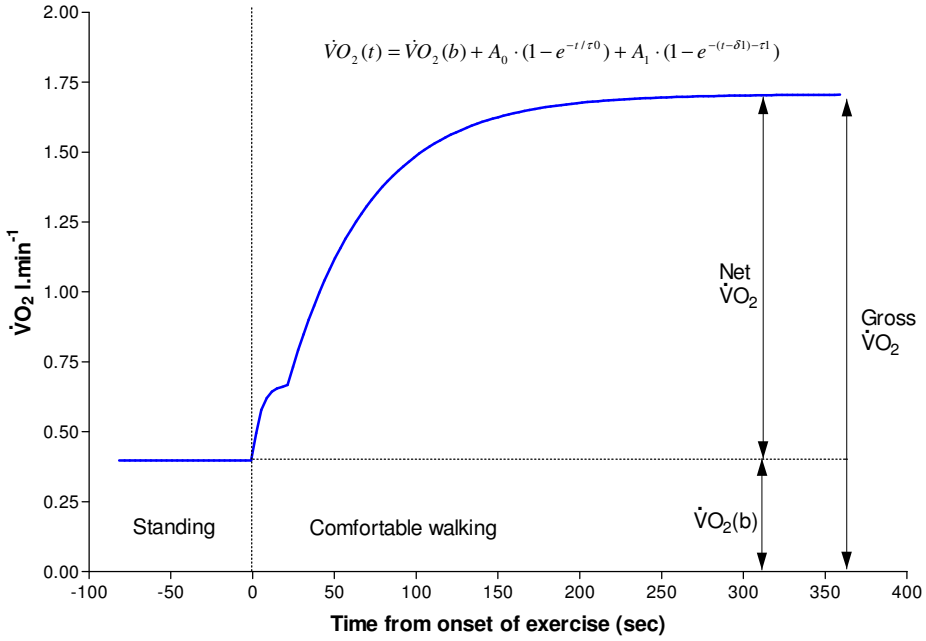


Figure 7.2 Double exponential model fitted to $\dot{V}O_2$ data during the transition between standing and comfortable walking, showing how net and gross values of $\dot{V}O_2$ are estimated from baseline $\dot{V}O_2$(b) values and asymptotic values.

Asymptotic values for each participant at the end each 3-min walk (gross $\dot{V}O_2$) were used to calculate gross economy. Values of $\dot{V}O_2$ after subtraction of baseline values were used to calculate the net economy (Figure 7.2; Equation 7.2).

$$\text{GROSS Walking Economy}\,(\text{ml}\cdot\text{m}^{-1}) = \left(\frac{\dot{V}\text{O}_2 \text{ walking}}{\text{Walking Velocity}\,(\text{m}\cdot\text{min}^{-1})}\right)$$

$$\text{NET Walking Economy}\,(\text{ml}\cdot\text{m}^{-1}) = \left(\frac{\dot{V}\text{O}_2 \text{ walking - } \dot{V}\text{O}_2 \text{ standing}}{\text{Walking Velocity}\,(\text{m}\cdot\text{min}^{-1})}\right)$$

Equation 7.2 Formulae for gross and net economy of walking in terms of the oxygen cost per unit distance walked, calculated from $\dot{V}O_2$ in ml·kg^{-1}·min^{-1} and walking velocity in m·min^{-1}.

Compared with gross economy, net values are a more direct measure of the cost of locomotion, are influenced little by gait speed and reduce the age-related variation associated with basal metabolic rate (Baker et al. 2001; McDowell et al. 2008). However in patients with locomotor disorders the reproducibility of net economy may be less than gross economy. However this can be minimized with protocol features such as repeated measures which were adopted in this study (Schwartz 2007; Brehm et al. 2008). Furthermore, calculating net economy using energy expenditure measured during standing rather than sitting corrects for some of the energy expenditure associated with maintaining balance (Malatesta et al. 2003).

Previous pilot work has characterized the Metamax 3B (Saunders et al. 2002; Greig et al. 2001). In young healthy people measures of $\dot{V}O_2$ using the Metamax up to ~1.5 l·min^{-1} demonstrated high concurrent validity with the criterion Douglas Bag method and showed acceptable repeatability (similar to Douglas Bags) during rest (Coefficient of variation CV < 10%) and low-intensity cycling (CV < 5%; Appendix 14.4). In healthy

elderly people we have also shown that the $\dot{V}O_2$ measures are repeatable ($\bar{d}$ = -0.80 ml·kg^{-1}·min^{-1}) during submaximal treadmill walking (Appendix 14.5).

Dependent variables - The following global indices of disability were recorded during face-to-face interview: FIM Instrument (Guide for the uniform data set for medical rehabilitation (Adult FIM) 1993), Rivermead Mobility Index (Collen et al. 1991) and Nottingham Extended ADL (Nouri and Lincoln 1987).

Confounding factors - Age, gender, time since stroke, stature, smoking history, use of walking aids, the incidence of key comorbid diseases and the total number of comorbid diseases were recorded (see Chapter 10; Table 11.8) as potential confounding factors (Skelton et al. 1999; Harris et al. 2001; Al Obaidi et al. 2004).

7.3.3. Analysis

Normally distributed data were reported as mean and standard deviation (SD). Non-normal data were expressed as median and inter-quartile range (IQR) and transformed to a normal distribution prior to any statistical analysis.

Gross values of walking economy were compared with a) normative data for the economy of walking at a comfortable speed in healthy elderly people (0.17 ml·kg·m^{-1}) aged ~70 years (Davies and Dalsky 1997), and b) an established model which predicts the economy of walking from walking speed (Waters and Mulroy 1999), where gross

economy ml·kg·m^{-1} = 0.129 + (2.6/m·min^{-1}). Suitable normative data for $\tau\dot{V}O_2$ are not available therefore studies reporting $\tau\dot{V}O_2$ in elderly men and women were used for comparison (Harris et al. 2003; Chilibeck et al. 1996; Cunningham et al. 1993; Fitzsimons et al. 2007; DeLorey et al. 2004; Bell et al. 1999).

Stepwise multiple linear regression analysis was used to identify whether walking economy and $\dot{V}O_2$ kinetics, plus confounding factors, predicted disability. Analyses were performed with SPSS (Version 12; SPSS, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606, USA) and a P value of <0.05 was considered statistically significant.

7.4. Results

The cardiorespiratory predictor variables and the dependent variables are summarised in Table 7.1. The repeated comfortable walking was completed by 64/66 participants at a velocity of 0.67 m·sec^{-1} (SD 0.24). Of these, 62/64 measures of $\dot{V}O_2$ were obtained (8.06 ml·kg^{-1}·min^{-1} [SD 1.95]) allowing calculation of gross and net economy for most (62/64) participants, but $\tau\dot{V}O_2$ could be only determined in only 43/64 cases with $\dot{V}O_2$ data.

7.4.1. Values of Cardiorespiratory Fitness

Economy - In people with stroke, walking at a comfortable speed was less economical than expected in healthy people (Figure 7.3; Panel A) because the median energy cost was elevated, 116% (IQR 98 to 164%; p<0.001) of healthy values (Davies and Dalsky

1997). A multivariate analysis showed the only factor predictive of gross economy was comfortable walking speed (R^2=0.601; P<0.0001).

Table 7.1. Indices of cardiorespiratory fitness established during self-paced comfortable walking, physical functions, and disability.

Variable	n	Mean(SD)	Median(IQR)
a) Comfortable Walking			
Speed ($m \cdot sec^{-1}$)	64	0.67 (0.24)	-
$\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	62	8.06 (1.95)	-
b) Cardiorespiratory fitness			
Economy Gross ($ml \cdot kg \cdot m^{-1}$)	62	-	0.1985 (0.167 to 0.2785) †
Economy Net ($ml \cdot kg \cdot m^{-1}$)	62	-	0.115 (0.971 to 0.155) †
Oxygen uptake kinetics $\tau\dot{V}O_2$ (sec)	43	-	49.0 (36.9 to 56.0) †
c) Global Indices of Disability			
FIM Instrument	66	-	117.5 (114 to 122) §
Nottingham Extended ADL	66	-	13.0 (11 to 14) §
Rivermead Mobility Index	65	-	17.0 (12 to 19) §

Abbreviations: SD standard deviation; IQR inter-quartile range
† Transformed using Log^{10}
§ Transformed using square root of reflected data

The median cost of slow walking after stroke was 99% (IQR 87% to 131.5%; P=0.097) of values predicted for similarly slow walking in healthy people (Figure 7.3; Panel B). However at very low walking speeds (<0.5 $m \cdot sec^{-1}$) economy impairments tended to exceed those expected simply from a slow gait speed. When the model was fitted to these data the curve generated (economy = 0.06098 + (3.436 / $m \cdot min^{-1}$)) agreed with the model of Waters and Mulroy (1999) at faster speeds, and deviated at the slow speeds.

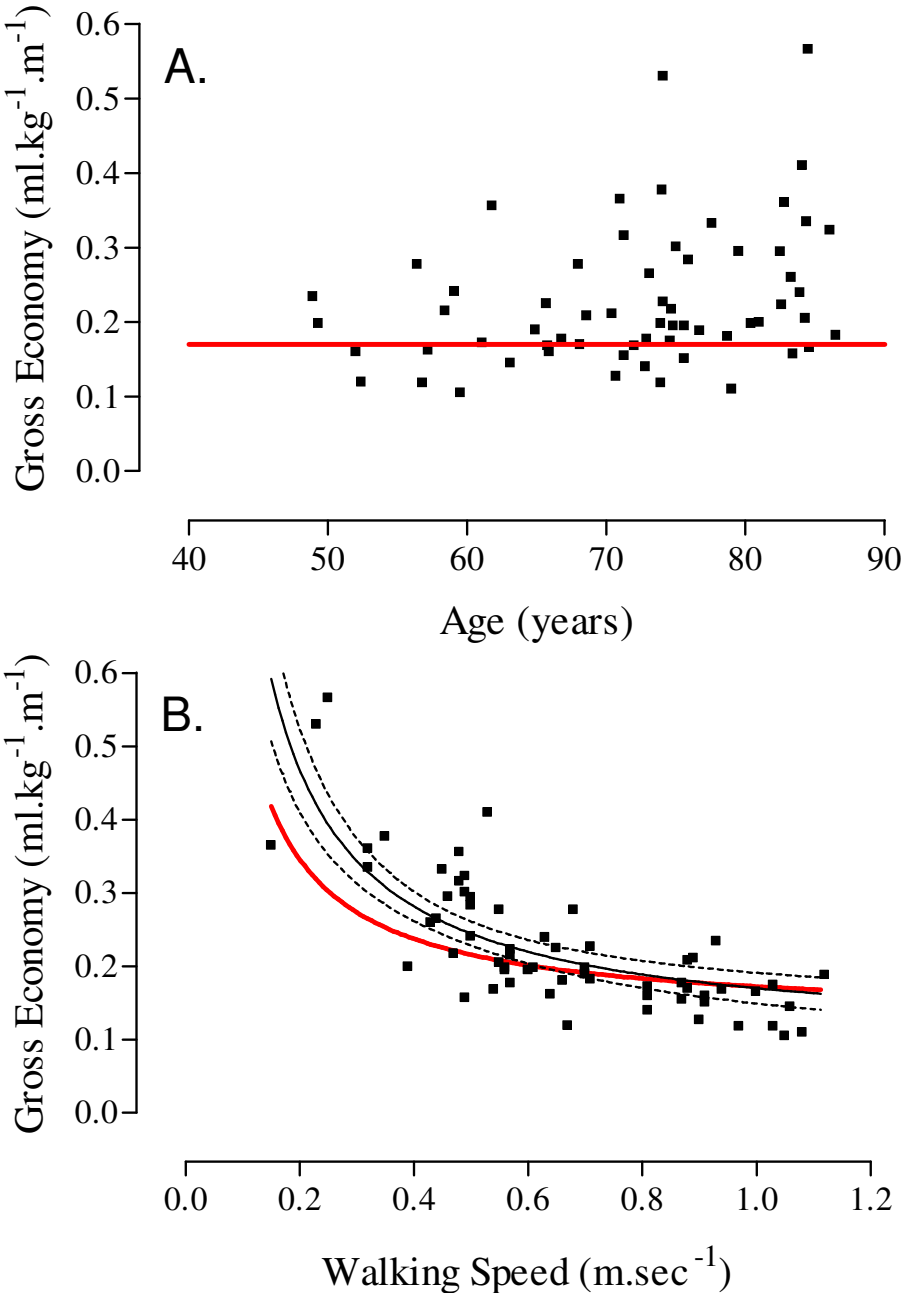


Figure 7.3 The gross economy of walking at a comfortable speed individuals with stroke. Panel A shows economy in relation to age, and the value typical (—) for comfortable walking in healthy people (Davies and Dalsky 1997). Panel B shows economy in relation to speed of walking and the values from a model predicting economy of walking (—) where economy = 0.129 + (2.6 / m·min^{-1}) in healthy people over a range of speeds (Waters and Mulroy 1999). A similar regression model) is fitted to the stroke data (— ± 95% CI) where economy = 0.06098 + (3.436 / m·min^{-1}).

Oxygen uptake kinetics – Although $\dot{V}O_2$ data were collected for 64/66 participants during walking, the iteration procedure applying the model to the $\dot{V}O_2$ data could not converge on a satisfactory solution. The available values for $\tau\dot{V}O_2$ are shown in Figure 7.4 in relation to age and gender and contrasted with the limited data available for healthy people (Section 2.1.4). The $\tau\dot{V}O_2$ was greater (slower) than the average values reported in three healthy cohorts of similar age, 68 to 69 years (i.e. Bell et al. 1999, 66.5% (IQR 25 to 90.5); Harris et al. 2003, 21.5% (IQR -9 to 39); DeLorey et al. 2004, 16.5% IQR (-12 to 33.5)).

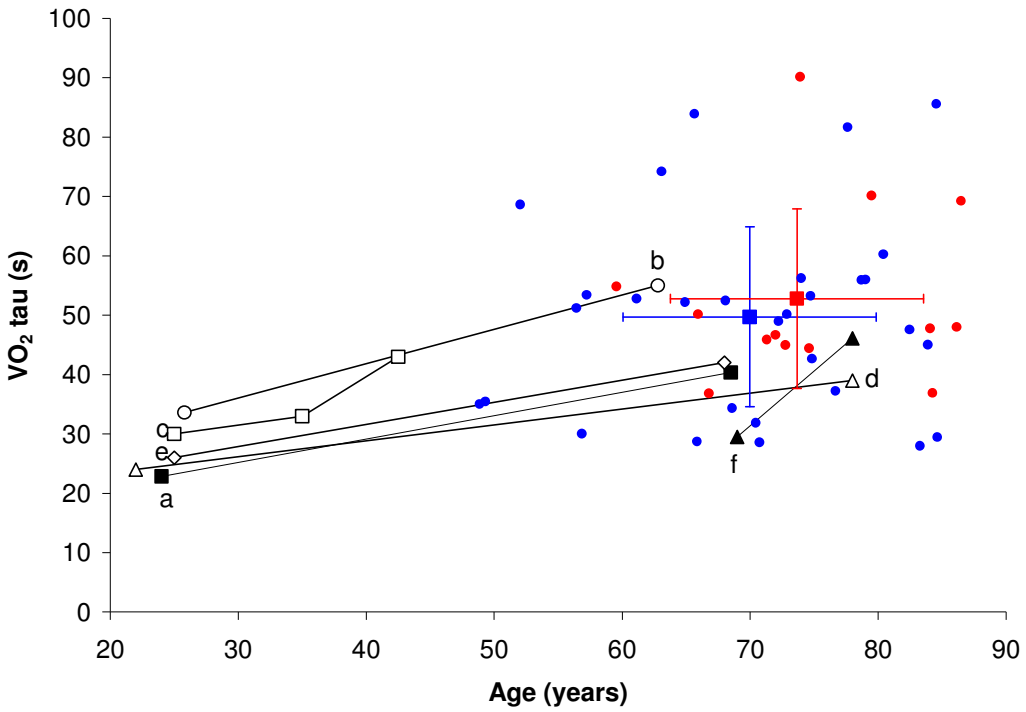


Figure 7.4 The time constant for the kinetics of the oxygen uptake response in individuals with stroke in relation to age and gender (male ● female ●; mean values ■ and ■; error bars ± SD). Data are shown in relation to data (mean values) from cross-sectional studies of healthy people including male subjects; Harris et al. (2003; ■), female subjects; Chilibeck et al. (1996; □), Cunningham et al. (1993; ○) and Fitzsimons et al. (2007; Δ); unknown gender mix; DeLorey et al. (2004; ◊) and one longitudinal study containing a majority (6/7) of men (Bell et al. (1999) ▲).

7.4.2. Association of cardiorespiratory fitness with function and disability

Economy – Multiple linear regression analysis showed that the global scale measures of disability were not predicted by walking economy (gross or net values; Table 7.2). Comfortable walking speed emerged as the only predictor of the FIM Instrument, and the strongest predictor of both Rivermead Mobility Index and Nottingham Extended ADL) from amongst the confounding factors included (age, gender, stature, time since stroke, use of walking aids, number of comorbid diseases (N) and smoking history).

Oxygen uptake kinetics – There were no univariate or multivariate associations between $\tau\dot{V}O_2$ and either comfortable walking speed or indices of disability.

Table 7.2. Stepwise multiple linear regression analysis of the economy of walking (gross and net values) and potential confounding predictor variables (comfortable walking speed (CWS), age, gender, stature, time since stroke, use of walking aids, number of comorbid diseases (N) and smoking history) on global indices of disability (FIM Instrument, Rivermead Mobility Index and Nottingham Extended ADL). Standardized β coefficients are reported for each independent variable having significant predictive value, and adjusted R^2 values for each overall model.

	Included Independent Variables			Model	
Dependent Variable	Variable	β	P=	R^2	P=
FIM Instrument	CWS	-0.625	P<0.0001	0.380	P<0.0001
Rivermead Mobility Index	CWS	-0.611	P<0.0001	0.523	P<0.0001
	Diseases (N)	0.273	P=0.004		
Nottingham Extended ADL	CWS	-0.601	P<0.0001	0.469	P<0.0001
	Diseases (N)	0.226	P=0.024		

Abbreviations: β Standardized beta coefficient; R^2 adjusted correlation coefficient; CWS comfortable walking speed; ADL activities of daily living.

7.5. Discussion

This observational study examined two under-investigated parameters of cardiorespiratory fitness in people with stroke, walking economy and $\dot{V}O_2$ kinetics, by monitoring the $\dot{V}O_2$ response during self-paced level indoor walking. The procedures to achieve constant speed self-paced walking and ambulatory $\dot{V}O_2$ measures were feasible and allowed calculation of walking economy but oxygen uptake kinetics could not be reliably characterised.

Gross Economy - This is the largest study to assess economy of gait during floor walking in people with stroke. This study shows that in high-functioning people several months after stroke comfortable walking is half that typical of healthy elderly people. Walking is also less economical, incurring median oxygen cost per unit distance of 117% (IQR 89% to 165%) of that expected in healthy elderly people. This impairment is modest compared with that estimated in all 10 studies reviewed in Section 5.5.2. The data were closest to those of Eng et al. (2004; 120% of healthy people) and studies performed several years after stroke (Corcoran et al. 1970; Pang et al. 2005b). The few studies reporting measures of walking economy after stroke tend to include small samples and involve participants below the age typical for a first stroke (Section 5.5.2).

Slow walking speed may explain impaired economy of comfortable walking. The mean preferred gait speed in healthy elderly people is 1.23 $m \cdot sec^{-1}$ (Waters et al. 1988; age 60-80 years) twice as fast as the stroke patients in this study (0.667 $m \cdot sec^{-1}$). When elderly

people slow their gait speed to 0.815 m·sec^{-1} the economy is reduced from 0.164 to 0.185 ml·kg^{-1}·m^{-1}, a value similar to the stroke patients in this study (0.1985 ml·kg^{-1}·m^{-1}). Therefore it is plausible that at least part of the observed deficit in economy after stroke is simply a consequence of slow gait speed.

The mean $\dot{V}O_2$ of comfortable walking was 8.06 ml·kg^{-1}·min^{-1}(SD 1.95), this is 54% of the $\dot{V}O_2$ peak typically observed in people with stroke (~15 ml·kg^{-1}·min^{-1}; Section 5.5.1). Section 2.1.1 has previously shown that healthy elderly people utilize 54% $\dot{V}O_2$ peak walking at a 'comfortable' speed (Fitzsimons et al. 2005), and 55% $\dot{V}O_2$ peak walking at a 'normal' speed (Waters et al. 1988). This suggests low fitness after stroke may dictate that a slower (less economical) walking speed must be adopted if comfort is to be achieved. Furthermore, people with stroke may deliberately adopt a slower walking speed as a compensatory strategy, for example due to pain or fear of falling.

Our data hint that those walking at the slower speeds (<0.5 m·sec^{-1}) may incur an extra $\dot{V}O_2$ demand beyond that expected from slow walking alone. Other mechanisms may be involved. Platts et al. (2006) measured gait economy in healthy people when they adopted the same preferred gait speed (~0.39 m·sec^{-1}) as a group of younger stroke patients; economy was still significantly worse in the stroke group (0.63 vs. 0.36 ml·kg^{-1}·m^{-1}). A similar finding reported by Zamparo et al. (1995) showed that the energy expenditure of people with hemiplegia is greater than healthy people when walking at the same speed. These findings suggest there may be other physiological and

biomechanical factors directly and indirectly associated with stroke which are responsible for additional non-productive energy expenditure. Potential factors include impairments to balance, cognitive function and sensory perception, abnormal muscle tone and antagonist co-activation (Lamontagne et al. 2007) and impaired mitochondrial and muscle fibre efficiency associated with loss of oxidative muscle fibres (Perrault 2006).

Net economy - The net oxygen cost of comfortable walking (0.115 $ml \cdot kg^{-1} \cdot m^{-1}$) is similar to the baseline data (~0.12 to 0.14 $ml \cdot kg^{-1} \cdot m^{-1}$) obtained[3] from randomized trial of gait training in n=22 elderly women (Thomas et al. 2007). The participants were older (age 75 to 85 years) but the data were collected using similar techniques of test (floor walking circuit), measurement (ambulatory gas analysis) and calculation ($\dot{V}O_2$ walking minus $\dot{V}O_2$ standing). This comparison (as for gross economy), suggests little impairment in our high-functioning group of people with stroke. Only one other study (Dawes et al. 2005) reported the net economy of walking after stroke as 0.35 $ml \cdot kg^{-1} \cdot m^{-1}$ (SD 0.22); this was performed at a self-selected speed similar to our participants (0.70 $m \cdot sec^{-1}$) however the cohort was small (n=14) and unusually young for stroke (mean 46.4 years). Although net economy may offer more of an insight into the cost of locomotion little is known about net economy in people with stroke.

[3] Data interpolated from graphs and transformed from $J \cdot kg^{-1} \cdot m^{-1}$ to $ml \cdot kg^{-1} \cdot m^{-1}$ assuming 1 ml = 20.9J

Kinetics of oxygen uptake - Substantial missing data biases observations about $\dot{V}O_2$ kinetics; this is not a reliable method for assessing cardiorespiratory fitness in people with stroke during floor-walking at a self-selected pace. One likely reason was a low signal to noise ratio, a consequence of low gain in $\dot{V}O_2$ response due to slow walking in relation to degree of fluctuation in the breath-by-breath data. The $\tau\dot{V}O_2$ in this study showed greater impairment than that reported by Katoh et al. (2002), 29 sec (SD 6) and Murakami (2002), 38.3 sec (SD 11.9) in people with stroke: Taken together these three studies suggest there may be some central and/or peripheral impairment of cardiorespiratory fitness after stroke.

Associations with function

A logical consequence of an uneconomical gait is a reduced walking speed. However since economy itself is speed-dependent it is impossible to separate cause and effect within these data. Furthermore, people with a higher $\dot{V}O_2$ peak may be able to comfortably tolerate a faster chosen gait speed despite poor economy as they have a larger 'fitness reserve'. Therefore, hypotheses about the influence of impaired economy on walking speed are difficult.

Walking economy (gross and net) was inversely associated with all three global indices of disability. However these associations were not independent of walking speed, the effects of which swamped those of economy. Therefore it is not possible to draw conclusions about associations between economy of movement and disability. But it

does remain plausible that poor economy of gait (and other physical activities) results in slowing down and fatigue during day-to-day physical activities.

This is the largest study to directly measure the economy of gait during self-paced floor walking in people with stroke who are of typical age for a first stroke. The limitations include the lack of a matched control group and confounded associations which limit conclusions about functional importance.

Very little is known about oxygen uptake kinetics and economy of walking after stroke. Training may have functional benefits but further research should include submaximal, functional measures of economy in conjunction with measures of maximal capacity such as $\dot{V}O_2$ peak in order to clarify the role of the 'fitness reserve' in mediating any changes in function.

Economy of walking and oxygen uptake kinetics - Summary

Impairment

- Speed of comfortable walking after stroke
  – comfortable walking speed is 50% slower than healthy people
- Economy of comfortable walking after stroke
  – gross oxygen cost is 116% of that seen in healthy people walking at a comfortable speed
  – gross oxygen cost is 99% of that seen in healthy people walking at the same absolute speed
  – impairment in gross economy may be partly due to slow walking speed
  – little is known about net economy of walking
- Oxygen uptake kinetics
  – biased due to missing data (>30%)
  – difficult to characterize
  – may be impaired (slower) compared with healthy elderly people

Consequences of Impairment

- Economy of walking
  – uneconomical gait (gross or net) is associated with increased disability
  – low walking speed is associated with increased disability
  – influence of economy not independent of comfortable walking speed
  – role of economy is unclear
- Oxygen uptake kinetics
  – biased due to missing data (>30%)
  – no association with walking speed or indices of disability

8. Lower limb extensor power after stroke - an observational study

8.1. Abstract

OBJECTIVE: To determine whether the explosive lower limb extensor power (LLEP) is impaired in people with stroke, and whether LLEP of the affected and unaffected sides, and any asymmetry, are associated with functional limitation and disability after stroke.

DESIGN: Cross sectional observational study of baseline data from a randomized controlled trial.

SETTING: Hospital clinical research facility.

PARTICIPANTS: Independently ambulatory community-dwelling people with stroke (n=66), mean age 72 yrs (SD 10).

MEASUREMENTS: The LLEP of each lower limb ($W \cdot kg^{-1}$), performance of specific functional activities (comfortable walking velocity, functional reach, chair rise time, 3-m timed up-and-go), and global indices of disability (FIM Instrument, Rivermead Mobility Index, and Nottingham Extended ADL).

RESULTS: The LLEP of both lower limbs is less (affected side 42%; unaffected side 54%) than expected in age and gender-matched population data. Low LLEP in either lower limb was the only factor from amongst the confounders recorded that significantly ($P<0.001$) predicted the limitation of dynamic functional activities (walking, chair rising, and timed up-and-go), and low LLEP in either lower limb was the principal predictive factor for global indices of activity limitation ($P<0.001$-0.003). The degree of asymmetry of LLEP between legs was low and had little or no predictive value.

CONCLUSIONS: In ambulatory individuals with stroke, functional limitation and disability are associated with deficits in LLEP of both lower limbs, and not the severity of any residual asymmetry. These findings suggest that interventions to increase LLEP in both lower limbs might reduce functional limitations and disability after stroke.

8.2. Introduction

Data from this section has been published as an abstract (Saunders et al. 2006; Appendix 14.6) and a full paper (Saunders et al. 2008; Appendix 14.7).

8.2.1. Rationale

8.2.1.1. Impairment

Little is known about whether explosive power is impaired after stroke. The few data available suggest power impairment like strength is bilateral but greater on the affected side, and occurs to at least the same degree as strength impairment (Section 6.4). Bilateral impairment in muscle power or muscle strength observed after stroke could arise directly from bilateral motor effects of the stroke, and indirectly from reduced physical inactivity, smoking, comorbid disease, cigarette smoking and poor nutrition before and/or after stroke (Section 6.4.3).

8.2.1.2. Consequences of impairment

In healthy people lower limb extensor power (LLEP) may be of relevance to important functional activities, disability and risk of falling (Section 2.2.2.3). However little is known about the whether impaired muscle power is associated with functional limitation or disability after stroke (Section 6.5.3). Available studies are problematic because i) there are few data, ii) use of unsuitable equipment for power measurement, ii) unusually young participants, iii) no disability measures validated for stroke, iv) bivariate analyses

ignore confounding ‘coimpairments’ and v) little consideration for non-linear associations (Section 6.5.4).

By extrapolating what is known about explosive power in elderly people (Section 2.2.2), and muscle strength in people with stroke (Section 6.4 and 6.5.1), it is plausible that i) muscle power will be impaired bilaterally (but more on the affected side) after stroke, and ii) that measures of power (and any asymmetry) will be associated with functional limitations and global measures of disability.

The relationship of power with function and disability should be examined to explore the potential benefits which might result from attempts to improve explosive power after stroke. This is important because fitness training can be presented in such a way as to specifically improve explosive power and this might improve function and reduce disability after stroke.

8.2.2. Hypotheses

Hypothesis – LLEP in people with stroke is impaired when compared with healthy people of a similar age and gender.

Hypothesis - LLEP of the affected and unaffected sides and any asymmetry is associated with performance of specific functional activities (reaching, walking, and chair rising).

Hypothesis - LLEP of the affected and unaffected sides and any asymmetry is associated with global indices of disability (FIM Instrument, Nottingham Extended ADL and Rivermead Mobility Index).

8.3. Methods

In this observational study a subset of baseline measures were used from all participants in the RCT reported later in Chapter 10.

8.3.1. Participants

The same participants and eligibility criteria were used as in the previous chapter.

8.3.2. Measures

Muscle explosive power - LLEP during hip and knee extension was measured whilst seated on a Nottingham Power Rig (Medical Engineering Unit, University of Nottingham, Nottingham NG7 2UH, UK. The apparatus is described by Bassey and Short (1990) and shown in Figure 8.1. Ten maximal pushes were encouraged using each lower limb (Mitchell et al. 2001) with a rest (minimum 30-sec) between each push. The limb most affected by the stroke was tested first. Power to body mass ratio ($W \cdot kg^{-1}$ body mass) was recorded for each push and the highest value achieved was recorded for the affected ($LLEP_{aff}$) and unaffected lower limbs ($LLEP_{unaff}$).

Figure 8.1 Healthy volunteer in the 'start position' prior to having the explosive power output of their right leg measured using the Nottingham Power Rig.

In addition to LLEP for the affected ($LLEP_{aff}$) and unaffected lower limbs ($LLEP_{unaff}$), asymmetry in LLEP was expressed as a ratio ($LLEP_{aff}/LLEP_{unaff}$) and used to indicate hemiparesis. This would allow some insight into whether LLEP impairment was simply related to hemiparesis or whether 'indirect' factors (e.g. inactivity, disease, smoking; Section 6.4.3) acting bilaterally were involved. For participants who presented with no lateralising signs but had relevant stroke lesions evident on brain imaging, we considered the affected side to be ipsilateral to the side of posterior circulation lesions,

and contralateral for all others. The effects of this assumption did not influence the statistical analyses.

Our pilot work had established the repeatability of the LLEP technique with 11 ambulatory stroke patients: Left leg (ICC = 0.84; R^2 = 0.88; mean difference ($\bar{d}$) and reliability coefficient $\bar{d}$ = -0.265 ± 0.374 W·kg^{-1} and the right ICC = 0.74; R^2 = 0.79; $\bar{d}$ = -0.103 ± 0.480 W·kg^{-1}.

Physical function – a) Functional reach was determined in triplicate, and the data from the best attempt retained (Duncan et al. 1990). Participants were asked not to use walking aids during the measure of functional reach. b) Comfortable walking speed was determined during three 3-min bouts of self-paced walking around an elliptical 17-m circuit with 5-min break between each walk; participants were instructed to walk at their 'comfortable pace' (Fitzsimons et al. 2005). Intermediate times for each lap of the circuit were recorded in order to determine whether each participant adopted an even walking speed. The mean value from the three walks was calculated. c) The timed 3-m up-and-go measure (Podsiadlo and Richardson 1991) began with participants seated, and resting back, in a chair. The measurement involved rising from the chair, walking 3 metres, turning through 180º around a second chair, returning to the start point and resuming a seated position in the chair. Participants were instructed to do this procedure quickly, but safely. Participants were asked not to use their arms or walking aids during the chair rising, but walking aids could be used during the 3-metres of walking. The whole procedure was timed (in seconds). d) Chair rising performance (Skelton 1995) was

determined from the intermediate time taken to rise from being seated, to standing vertically was also recorded during the timed up-and-go procedure (in seconds). The timed up-and-go including chair rise was performed 3 times and the fastest times retained for analysis.

Disability - The following global indices of disability were recorded during face-to-face interview; FIM Instrument (Guide for the uniform data set for medical rehabilitation (Adult FIM) 1993), Rivermead Mobility Index (Collen et al. 1991) and Nottingham Extended ADL (Nouri and Lincoln 1987).

Confounding factors - Age, gender, time since stroke, stature, smoking, use of walking aids, the incidence of key comorbid diseases and the total number of comorbid diseases were recorded as potential confounding factors (Skelton et al. 1999; Harris et al. 2001; Al Obaidi et al. 2004).

8.3.3. Analysis

Normally distributed data were reported as mean and standard deviation (SD). Non-normal data were expressed as median and inter-quartile range (IQR) and transformed to a normal distribution prior to any statistical analysis. Affected and unaffected legs were compared using a paired *t* test.

The $LLEP_{aff}$ and $LLEP_{unaff}$ were compared with age- and sex-matched normative data from the general population (Skelton et al. 1999) and a sample of very elderly men and women (Skelton et al. 1994), both produced using the same equipment as this study.

Stepwise multiple linear regression was used to identify a) whether any of the confounders predicted LLEP, and b) whether LLEP and confounders predicted functional limitation or disability. Analyses were performed with SPSS (Version 12; SPSS, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606, USA) and a P value of <0.05 was considered statistically significant.

When LLEP was the only significant predictor of activity limitation the regression coefficients were used to generate non-linear models (and 95% CI) of the untransformed graphed data using Graphpad Prizm (Version 4, Graphpad, 11452 El Camino Real, #215 San Diego, CA 92130, USA).

8.4. Results

The data for LLEP, along with specific functional activities and global indices of disability are summarised in Table 8.1.

Table 8.1 Untransformed data for lower limb extensor power (LLEP), measures of performance of specific functional activities, and global indices of disability.

Variable	n	Mean(SD)	Median(IQR)
a) Lower Limb Extensor Power			
Affected side $LLEP_{aff}$ ($W \cdot kg^{-1}$)	64	-	0.92 (0.53 to 1.49)*†
Unaffected side $LLEP_{unaff}$ ($W \cdot kg^{-1}$)	61	-	1.05 (0.73 to 1.56) †
Asymmetry ratio $LLEP_{aff}$ / $LLEP_{unaff}$	60	0.89 (0.24)	-
b) Specific Functional Activities			
Functional reach (cm)	63	26.53 (6.65)	-
Comfortable walking velocity ($m \cdot sec^{-1}$)	64	0.67 (0.24)	-
Timed up-and-go (sec)	61	-	11.68 (8.17 to 16.09) ‡
Chair rise time (sec)	60	-	1.28 (0.83 to 1.70) ‡
c) Global Indices of Disability			
FIM Instrument	66	-	117.5 (114 to 122) §
Rivermead Mobility Index	66	-	13 (11 to 14) §
Nottingham Extended ADL	65	-	17 (12 to 19) §

Abbreviations: SD standard deviation; IQR inter-quartile range; $LLEP_{aff}$ affected side lower limb extensor power; $LLEP_{unaff}$ unaffected side lower limb extensor power.
* $LLEP_{aff}$ lower than $LLEP_{unaff}$ (t=3.77; P<0.001)
† transformed to a normal distribution using square root
‡ transformed to a normal distribution using reciprocal
§ transformed to a normal distribution using square root of reflected data

8.4.1. Values of LLEP

A successful measure of LLEP was achieved in both legs of 60/66 (91%) participants; measures of at least one limb were achieved in 65/66 (98%) participants. The reasons preventing data collection were leg pain (n=4) and equipment and/or software failure (n=2).

The average $LLEP_{aff}$ increased by 76% and $LLEP_{unaff}$ by 55% throughout the 10 repetitions with around 50% of participants achieving peak values of LLEP after 8 to 10 repetitions, and many doing so on the final effort. LLEP approached asymptotic values between repetitions 8 and 10 during which the increases were trivial (2.3% affected leg, 0.3% unaffected leg). These data are summarized in Appendix 14.8.

Median $LLEP_{aff}$ was 42% (IQR 27 to 66) and $LLEP_{unaff}$ was 54% (IQR 37 to 71) of that expected in age- and gender-matched individuals (Skelton et al. 1999; Skelton et al. 1994; Figure 8.2).

$LLEP_{aff}$ was significantly lower than $LLEP_{unaff}$ (t=3.77; P<0.001) but the difference was small (~10%; median 0.14 $W \cdot kg^{-1}$ (IQR -0.09 to 0.26) and the LLEP of each lower limb were highly correlated (R^2=0.68; P<0.001).

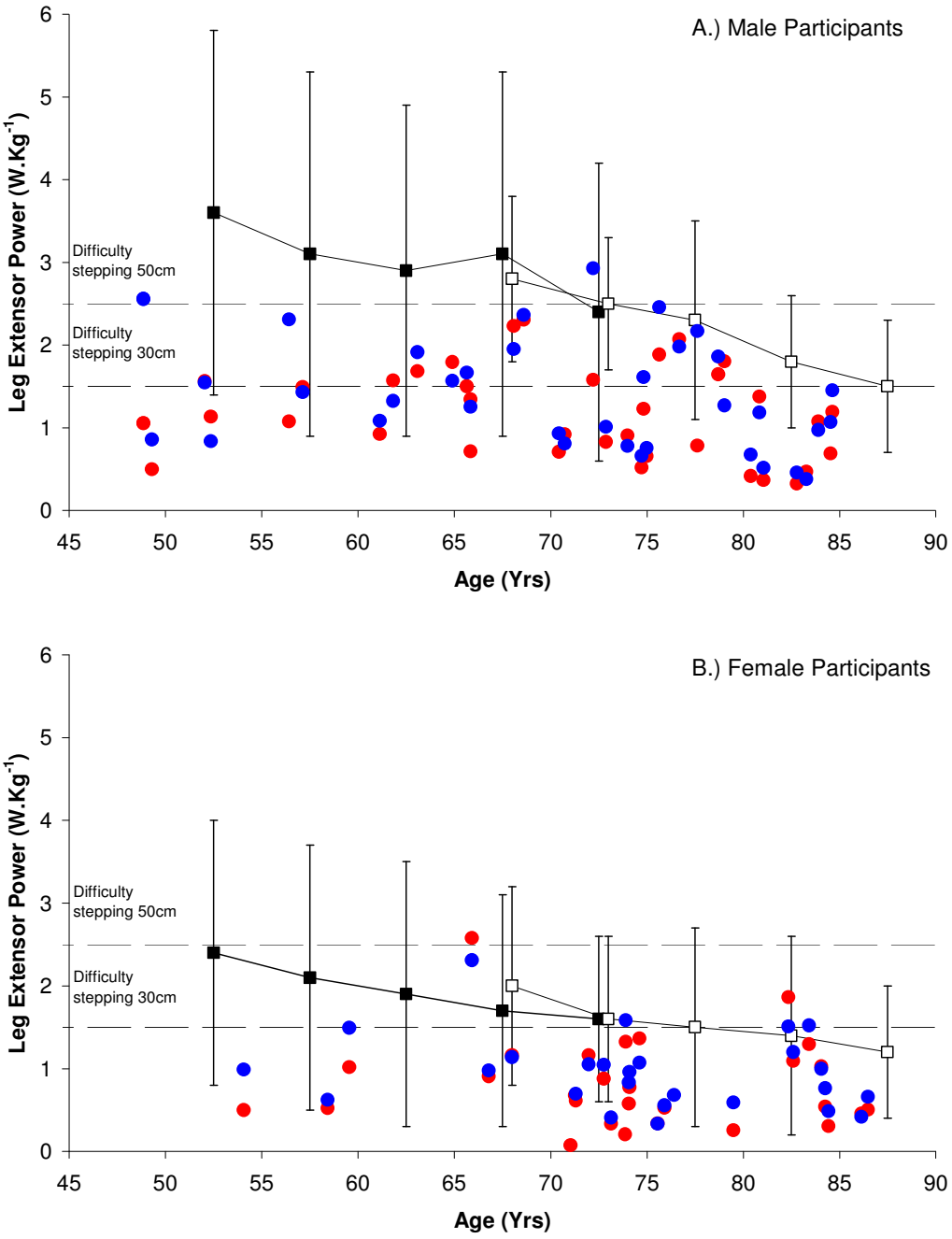


Figure 8.2 Explosive Lower limb extensor power of the affected (●) and unaffected (●) legs of male (Panel A), and female (Panel B) stroke patients in relation to age- and sex-matched values (Mean ± 2SD) from the general population (■; Skelton et al. 1999) and a sample of very elderly men and women (□; Skelton et al. 1994)). The two thresholds indicated at 1.5 and 2.5 W·kg^{-1} indicate the minimum power to body mass ratio required to mount a step of height 30cm and 50cm respectively (Skelton et al. 1999).

8.4.2. Associations between LLEP and function

Low values of $LLEP_{aff}$ or $LLEP_{unaff}$ were associated with limitation in each specific functional activity (Figure 8.3). LLEP showed pronounced curvilinear associations with chair rising time, and timed up-and-go. When walking speed ($m \cdot sec^{-1}$) was instead expressed as a function of time ($sec \cdot m^{-1}$) the same curvilinear association was observed with all three dynamic physical functions (chair rising, walking, timed up-and-go) showing reduced performance when LLEP was below ~1.0 $W \cdot kg^{-1}$ but with no increase in performance above this value.

Both $LLEP_{aff}$ and $LLEP_{unaff}$ were significant predictors of performance in each functional activity (Table 8.2). Comfortable walking velocity, chair rise time and timed up-and-go performance were predicted by $LLEP_{aff}$ and $LLEP_{unaff}$, with each leg having similar influence; these predictions were exclusive with no contribution from the included confounders. Five participants with low LLEP values (<1.0 $W \cdot kg^{-1}$) found chair rising impossible without using their arms; their data were excluded from the regression analysis of timed up-and-go and chair rising. Functional reach was predicted by LLEP, but not exclusively nor as strongly as were other activities. The ratio of $LLEP_{aff}/LLEP_{unaff}$ had no predictive importance for performance of specific functional activities.

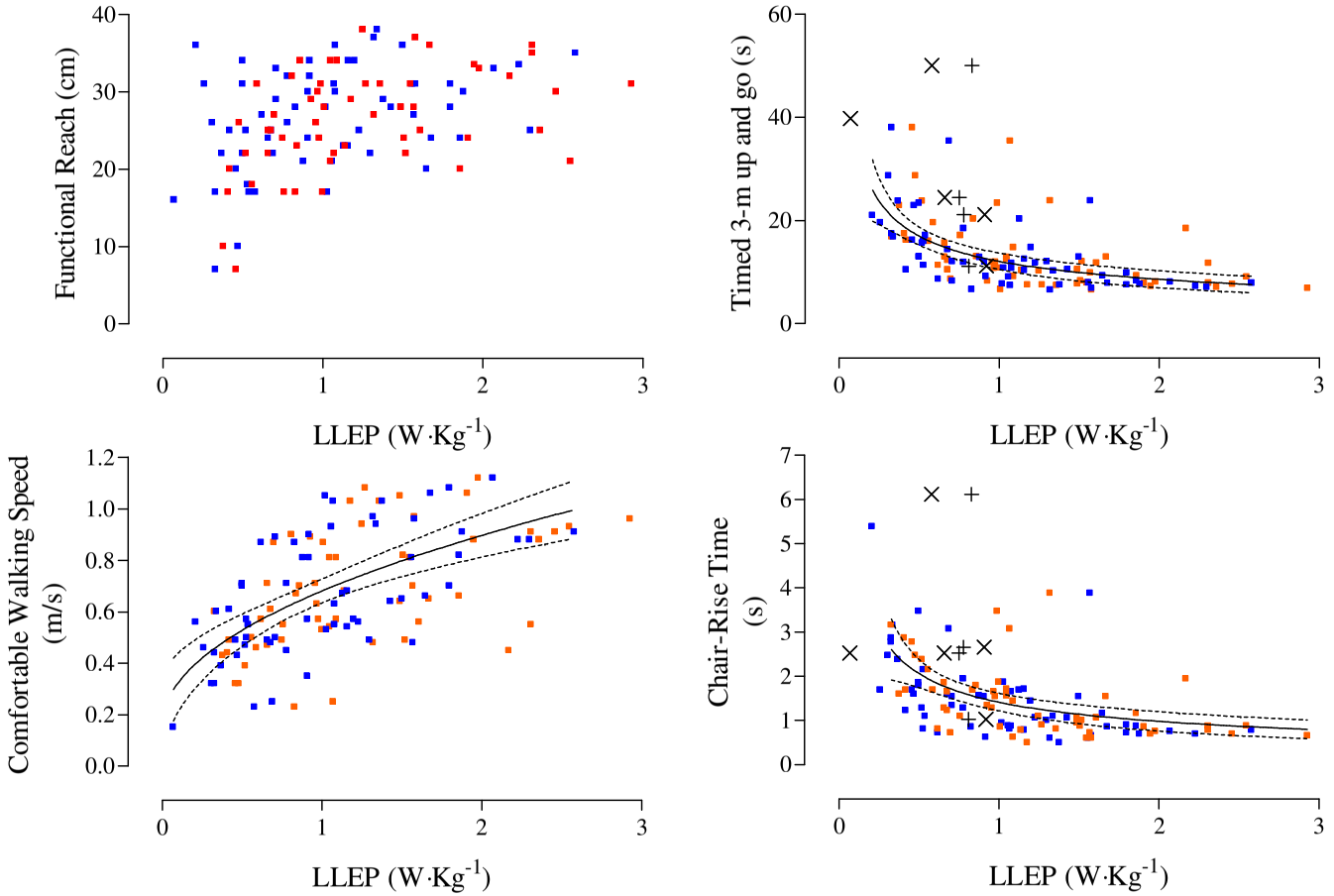


Figure 8.3 The relationships between the explosive lower limb extensor power (LLEP) in $W \cdot kg^{-1}$, of the affected (■) and unaffected (■) lower limbs and performance of specific functional activities assessed using functional reach, 3-m timed up-and-go, chair rising time and comfortable walking velocity. When arms were used for assistance during chair rising and 3-m timed up-and-go the data are marked differently (× affected, and + unaffected). For clarity the lines of best fit (—) with 95% confidence intervals (---) are included only for the unaffected LLEP data.

Table 8.2 The results of stepwise multiple linear regression analysis of the LLEP (affected side, unaffected side and their ratio) and potential confounding predictor variables (age, gender, stature, time since stroke, use of walking aids, comorbid disease and smoking history) on a) performance of specific physical functions, and b) global indices of disability. Standardized β coefficients are reported for each individual independent variable having significant predictive value, and adjusted R^2 values for each overall model where this could be fitted.

	Affected Side $LLEP_{aff}$					Unaffected Side $LLEP_{unaff}$					Asymmetry ratio $LLEP_{aff}$ / $LLEP_{unaff}$				
	Included variable			Model		Included variable			Model		Included variable			Model	
Dependent Variable	Variable	β	P=	R^2	P=	Variable	β	P=	R^2	P=	Variable	β	P=	R^2	P=
a) Specific Physical Functions															
Functional Reach*	LLEP Stature	0.32 0.28	P<0.01 P<0.023	0.21	P<0.001	LLEP Stature Gender	0.48 0.54 0.39	P<0.001 P<0.001 P<0.019	0.33	P<0.001	Stature	0.38	P<0.003	0.13	P<0.003
Comfortable Walking Speed	LLEP	0.54	P<0.001	0.28	P<0.001	LLEP	0.65	P<0.001	0.41	P<0.001	Age	-0.31	P<0.020	0.08	P<0.020
Timed up-and-go	LLEP	0.68	P<0.001	0.46	P<0.001	LLEP	0.60	P<0.001	0.35	P<0.001	-	-	-	-	NS
Chair Rise Time*	LLEP	0.63	P<0.001	0.38	P<0.001	LLEP	0.56	P<0.001	0.30	P<0.001	Age	-0.30	P<0.026	0.07	P<0.026
b) Global Indices of Disability															
FIM Instrument	LLEP Stature	-0.64 0.23	P<0.001 P<0.039	0.35	P<0.001	LLEP	-0.38	P<0.003	0.13	P<0.003	-	-	-	-	NS
Rivermead Mobility Index	LLEP	-0.58	P<0.001	0.33	P<0.001	LLEP	-0.53	P<0.001	0.27	P<0.001	-	-	-	-	NS
Nottingham Extended ADL	LLEP Smoking	-0.64 0.21	P<0.001 P<0.045	0.38	P<0.001	LLEP	-0.41	P<0.001	0.16	P<0.001	LLEP	-0.29	P<0.027	0.07	P<0.027

Abbreviations: β Standardized beta coefficient; R^2 adjusted correlation coefficient; NS No significant regression model solution; LLEP Lower limb extensor power

* Use of walking aids omitted from models

8.4.3. Associations between LLEP and disability

LLEP was nearly exclusive as a predictor of global indices disability from amongst the variables included in the regression models (Table 8.2); the only exceptions being marginal contributions of stature to FIM, and smoking to Nottingham EADL scores. Associations tended to be stronger for $LLEP_{aff}$ than $LLEP_{unaff}$, but asymmetry in LLEP did not predict FIM or Rivermead scores and had only marginal predictive value for Nottingham EADL scores.

When statistical analyses were repeated after excluding individuals with prior stroke (11/66) the multivariate R^2 values increased slightly and marginal variables were dropped from the models leaving $LLEP_{aff}$ than $LLEP_{unaff}$ as the exclusive predictors of performance or limitation of activities.

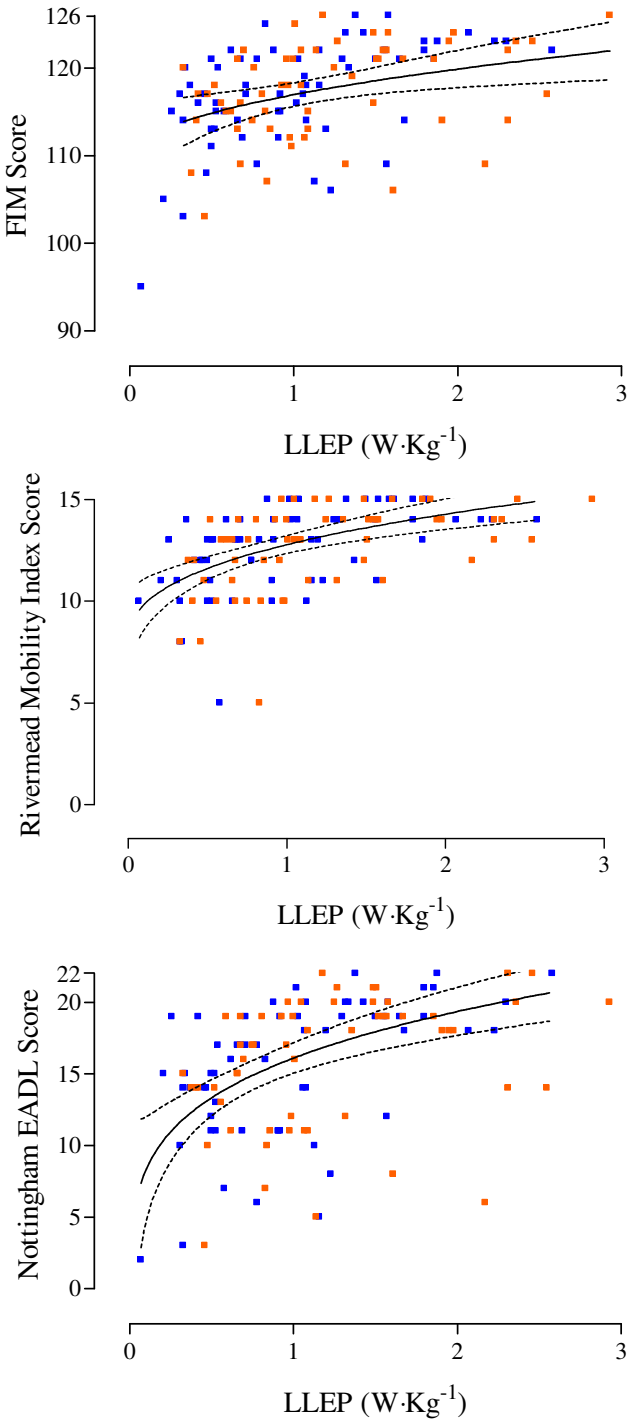


Figure 8.4 The relationship between the explosive lower limb extensor power (LLEP) measured in $W \cdot kg^{-1}$, of the affected (■) and unaffected (■) lower limbs and global indices of disability assessed using FIM Instrument, Rivermead Mobility Index and Nottingham Extended Activities of Daily Living (EADL). For clarity the lines of best fit (—) with 95% confidence intervals (---) are included are included only for the unaffected LLEP data.

8.5. Discussion

This study shows that amongst a sample of ambulatory individuals with stroke (mean age 72 years), the unaffected LLEP was lower than expected in age- and gender matched healthy people and that low LLEP in either leg was associated with a) reduced performance in some everyday dynamic functional activities which involve the legs, and b) disability as assessed using more global scale indices. Asymmetry in LLEP was small and not predictive of limitations.

Our data suggest LLEP is important for the performance of dynamic day-to-day lower limb activities which require rapid rates of muscle contraction. Associations were strongest with comfortable walking velocity, timed 3-m up-and-go and chair rising time. When LLEP is very low, performance of chair rising may be impossible for some people unless modified (e.g. use of arms); this is compatible with similar observations in healthy elderly individuals (Young 2001). As expected the weakest association between LLEP (of either leg) and physical function was with functional reach, probably because this is not limited by speed of movement.

Our data show a convincing association between low LLEP and increased global indices of disability even though not all questions within each scale (viz. FIM Instrument 5/18, Rivermead Mobility Index 11/15 and Nottingham EADL 5/22) directly addressed performance of activities involving the lower limb extensors.

In elderly individuals with functional impairments, power output during leg-press exercise, a procedure similar to LLEP determination, was found to be associated with stair climbing ability, chair rise time and habitual gait velocity (Cuoco et al. 2004) and with self-reported functional status (Foldvari et al. 2000) These observations resemble the types of association found in our study.

In a small study of unusually young (46 years) ambulatory individuals with stroke (Dawes et al. 2005) substantial asymmetry in LLEP was observed (mean 43%) and this was inversely associated with walking speed (Spearman Rho -0.76; $P<0.01$). These younger participants (Dawes et al. 2005) had mean a Rivermead Mobility Index score of 13 (SD 3.0) and a walking speed of 0.70 $m \cdot sec^{-1}$ (SD 0.32) which are similar to the present study (Table 8.1). It is plausible that the greater LLEP of their stronger side (1.99 $W \cdot kg^{-1}$ [SD 0.85]) allowed functional compensation. Asymmetry in our typically older participants (mean age 72 years) was not predictive of activity limitation to any important extent, probably because little asymmetry (10%) existed. This lack of asymmetry may have occurred because our participants had made a good neurological recovery. Secondly, substantial asymmetry may be unusual in the older ambulatory person with stroke simply because LLEP is already low prior to stroke, and a threshold effect limits the reduction in LLEP which can occur without rendering the participant non-ambulatory. The lack of asymmetry in our data suggests that the low values of LLEP could have arisen due to the influence of factors which act bilaterally (i.e. bilateral motors effects, comorbid disease and habitual physical inactivity) before and/or after stroke.

Longitudinal post-stroke deterioration could cause bilateral loss of LLEP. Although no longitudinal data of LLEP are available one small study has reported a ~30% loss of strength of the ipsilateral leg during the week after stroke (Harris et al. 2001). Another, however, found no post-stroke deterioration (Carin-Levy et al. 2006). In the present study neither time since stroke nor comorbid disease(s) were predictive of LLEP or activity limitations, perhaps because the sample was homogeneous due to restrictive eligibility criteria. Although it is not possible to identify the underlying cause for low LLEP and activity limitations, habitual physical inactivity before and/or after stroke remains a possible cause.

High-velocity resistance training improves power and provides functional benefits in healthy elderly individuals (Section 2.2.2.2 and 2.2.2.3). For example, it increases explosive power of the knee extensors and this is associated with significant improvements in chair rising, walking and reaching ability (aged 60-80 n=25; Henwood and Taaffe 2005). Extrapolating findings from studies of elderly individuals suggest that increasing $LLEP_{aff}$ and $LLEP_{unaff}$ might improve activity and independence after stroke. After stroke this type of training has not been studied.

LLEP was measured in most (>90%) participants (Section 10.4.2); this compares favourably with measurement in healthy elderly people (78%) using the same equipment (Skelton et al. 1999). This suggests that ambulatory people with stroke can perform the repeated, high-velocity, resisted muscle contractions needed to improve explosive power. In addition, if LLEP is impaired due to reduced habitual physical activity, there is no

reason why reversal through suitable training should not occur. Therefore training LLEP after stroke may be feasible.

The main limitation of this study was that we recruited a homogeneous sample of high functioning independently ambulatory individuals with stroke. Homogeneity may have limited the strength of the observed associations. The potential self-selection of fitter participants would also tend give rise to a higher functioning cohort. Participants had minimal hemiparesis so it is difficult to speculate on the functional importance of LLEP for those with more severe impairment. Future work should therefore include more impaired participants, and examine the role of other confounding factors, such as stage of motor recovery and pre- and post-stroke habitual physical activity levels.

8.6. Conclusion

In a sample of ambulatory individuals with stroke of mean age 72 years, activity limitations were associated with bilateral deficits in LLEP and not the severity of any residual asymmetry. These data suggest that the feasibility and effectiveness of training interventions to improve muscle explosive power after stroke should be explored since increases in LLEP may improve function and reduce disability.

Explosive Lower Limb Extensor Power (LLEP) - Summary

Impairment

- LLEP in ambulatory people with stroke is less than expected in healthy people of similar age and gender
  - affected side 42%
  - unaffected side 54%
- LLEP is impaired bilaterally suggesting factors indirectly associated with stroke such as physical inactivity

Consequences of Impairment

- Low values of LLEP are associated with
  - functional limitation
  - mild disability
- LLEP has a non-linear association with the performance of specific physical functions including chair rising and walking

Part B - summary

The Rationale for Fitness Training after Stroke

Although incomplete, the available data examining the impairment in physical fitness of stroke patients and some of its functional consequences agrees with the suggested elements of the proposed Fitness-Function-Disability model (Figure 4.1).

These observations validate the following rationale for fitness training in people with stroke:

- Values of physical fitness which are low suggest scope for improvement.
- Improvements in cardiorespiratory fitness and/or muscle strength, and possibly power, may be improve function and possibly reduce disability.
- There is no biological reason why physical fitness should not be increased by physical physical fitness training, providing the training is feasible.
- Cardiorespiratory training, strength training and mixed training interventions may improve physical fitness and this may improve function and possibly reduce disability.

The next chapters of the thesis (Section C) addresses the evidence for the benefits of physical fitness training in people with stroke.

Part C

Physical Fitness Training after Stroke; Developing and Evaluating RCTs

Evaluation of RCT evidence
- **Systematic review**
- **Exploratory RCT**
- **Updated systematic review**

Development of RCT evidence
- **Exploratory RCT**

PART C - PHYSICAL FITNESS TRAINING AFTER STROKE; DEVELOPING AND EVALUATING RCTs

Objective 2

Develop and evaluate RCT evidence for physical fitness training after stroke;

- Evaluate whether a trial of fitness training is feasible for people with stroke.
- Evaluate whether fitness training is beneficial for people with stroke.

8.6.1.1. Evaluating RCTs of fitness training

The best level of evidence to evaluate interventions usually involves randomized controlled trials (RCTs) and systematic reviews: a) RCTs are accepted as the most reliable experimental approach for determination of the effectiveness of many healthcare interventions (Sibbald and Roland 1998): b) Systematic review and meta-analysis of RCT data has a strong rationale based on reduction of bias, increased statistical power and more precise estimates of effect (Mulrow 1994). These approaches will be used in this Chapter; however RCTs of physical fitness training interventions after stroke may be difficult to perform and to evaluate.

8.6.1.2. Developing RCTs of fitness training

Physical fitness training is a '*complex intervention*' that is one which consists of several parts which interact or operate independently. For example, fitness training can involve different modes of exercise, different regions of the body, and utilize different

physiological systems. Unlike a drug, the 'dose' of training (i.e. frequency, intensity, duration) may vary and be difficult to control due to factors such as attendance at, and compliance with training, and individual tailoring of exercises. A well known example of a complex intervention is stroke unit care (Stroke Unit Trialists' Collaboration 2007).

Complex interventions are difficult to evaluate therefore the Medical Research Council proposed a stepwise framework (Figure 8.5) for the development and evaluation of RCTs of complex interventions to improve health care (Campbell et al. 2000; Medical Research Council 2000a). This thesis centres on the theory, modelling and exploratory trial steps).

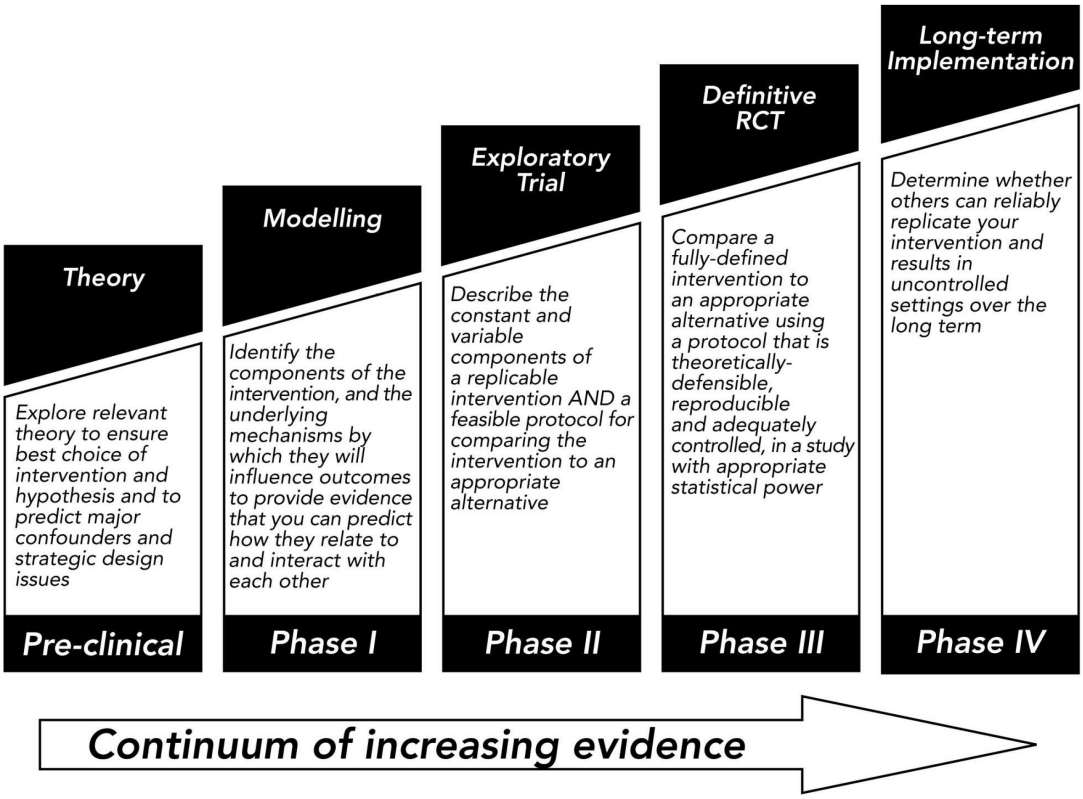


Figure 8.5 Sequential phases of developing randomized controlled trials of complex interventions (Medical Research Council 2000a).

9. Physical Fitness Training after Stroke - a systematic (Cochrane) review

9.1. Abstract

BACKGROUND: Physical fitness is impaired after stroke and this may exacerbate disability. It is not known whether improving physical fitness after stroke reduces disability.

OBJECTIVES: The primary aims of the review were to establish whether physical fitness training reduces death, dependence and disability after stroke. The secondary aims of the review included an investigation of the effects of fitness training on physical fitness, mobility, physical function, health related quality of life, mood and the incidence of adverse events.

SEARCH STRATEGY: We searched the Cochrane Stroke Group Trials Register (June 2003). The following databases were also searched (December 2002): Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, SPORTDiscus, Science Citation Index Expanded, Web of Science Proceedings, Physiotherapy Evidence Database, REHABDATA and Index to UK Theses. We hand searched relevant journals and conference proceedings and screened reference lists. To identify unpublished and ongoing trials we searched trials directories and contacted experts in the field.

SELECTION CRITERIA: Randomized controlled trials were included when an intervention represented a clear attempt to improve either muscle strength and/or cardiorespiratory fitness, and whose control groups comprised either usual care or a non-exercise intervention.

DATA COLLECTION & ANALYSIS: Data from eligible studies were independently extracted by two reviewers. The primary outcome measures were death, disability and dependence. Lack of common outcome measures prevented some intended analyses.

MAIN RESULTS: A total of twelve trials were included in the review. No trials reported death and dependence data. Two small trials reporting disability showed no evidence of benefit. The remaining available secondary outcome data suggest that cardiorespiratory training improves walking ability. Observed benefits appear to be associated with specific or 'task-related' training.

CONCLUSIONS: There are few data available to guide clinical practice at present with regard to fitness training interventions after stroke. More general research is needed to explore the efficacy and feasibility of training, particularly soon after stroke. In addition more specific studies are required to explore the effect of content and type of training. Further research will require careful planning to address a number of issues peculiar to this type of intervention.

9.2. Introduction

This section has been published as an abstract, see Appendix 14.9 (Saunders et al. 2004b). A full publication in the Cochrane Library (Saunders et al. 2004a) is not appended; instead this chapter preserves the structure and content of the published review as far as possible.

9.2.1. Rationale

Little is known about the effectiveness of interventions that are aimed at improving the physical fitness of stroke patients. Physical fitness in people with stroke is low due to the effects of ageing. It may be reduced further by the direct neurological effects of stroke (e.g. hemiparesis) and the risk factors and sequalae indirectly associated with stroke (e.g. physical inactivity, comorbid disease and smoking).

Impaired physical fitness is associated with functional limitation and disability in healthy elderly people (Section 2). After stroke, impaired fitness is associated with functional limitation, but the links to disability and dependence are unclear (Sections 5 and 6). Given that healthy people (Section 3.1) and those with different chronic diseases (Section 3.4) all benefit from physical activity and training (Section 3.1), it is plausible that stroke patients may also benefit.

Improvements in physical fitness may improve gait, balance, and motor control; which may, in turn, improve mobility, reduce the risk of falls and fractures, reduce disability and improve quality of life. For example, improvements in cardiorespiratory fitness may compensate for the increased energy requirement of the hemiparetic gait by conferring a smaller relative demand during ambulation (Macko et al. 1997; Waters and Mulroy 1999). Improvements in cardiorespiratory fitness might also reduce the risk of subsequent cardiovascular and cerebrovascular events (Goldberg and Berger 1988). However, physical activity and training in particular, may be associated with some adverse effects. Accordingly, the risks of training-induced soft tissue injuries, altered muscle tone, falls and vascular events will be investigated as part of this review.

9.2.2. Objective

This systematic review will aim to establish whether physical fitness training is beneficial to stroke patients when provided either during or after their rehabilitation or ward care, and in particular whether it is associated with a reduction in death, dependence and disability. The Cochrane reviews states the following 'Primary' and 'Secondary' objectives.

9.2.2.1. Primary objectives (Cochrane)

Determine whether stroke patients allocated training compared with controls, at any time after the onset of their stroke, were less likely to be a) dead, b) dead or dependent, or c) disabled, at the end of intervention.

9.2.2.2. Secondary objectives (Cochrane)

a) Determine the effect of training on secondary outcome measures (see *Types of Outcome Measure* - Section 9.3.4). Outcomes were assessed at the end of intervention or the scheduled end of follow-up. This may be at some defined point during the training and/or some weeks or months after the training is complete.

b) Determine the effect of factors which could influence the primary and secondary outcome measures (see *Subgroup Analyses* - Section 9.5.4.1).

c) Effect of the 'Dose' of training, including; i) whether the frequency, intensity and duration of training sessions exceeded or fell below recommended levels for development of fitness (ACSM 1998b); ii) degree of progression, iii) the duration of the training programme.

d) Effect of the 'Type' of training, including; i) type of training (e.g. cardiorespiratory and/or strength training), ii) mode of exercise (e.g. cycling, weight training), iii) upper and/or lower extremity or iv) affected and/or unaffected limb.

e) Effect of 'Timing' of training; i.e. during usual care vs. after usual care.

f) The degree to which benefits or effects were retained; i) duration of training effect, ii) effect of measures to facilitate continuation of exercise after the end of intervention.

g) Effect of initial patient status on outcome measures; i) effect of initial disability on outcome, ii) effect of training on ambulatory patients with mild, severe or no hemiparesis

h) Effect of physical activity performed by control groups.

i) Effect of trial quality.

9.3. Criteria for considering studies for this review

9.3.1.1. Types of studies

Randomized controlled trials (RCTs), single-blinded or open, were considered where studies made the following comparisons:

Comparison 1 - Cardiorespiratory training vs. control

Cardiorespiratory training plus usual care vs. usual care ..... (during usual care)
Cardiorespiratory training vs. no training ..... (after usual care)

Comparison 2 - Strength training vs. control

Strength training plus usual care vs. usual care ..... (during usual care)
Strength training vs. no training ..... (after usual care)

Comparison 3 - Mixed training (cardiorespiratory + strength) vs. control

Mixed training plus usual care vs. usual care ..... (during usual care)
Mixed training vs. no training ..... (after usual care)

Usual care included hospital or ward care. Control groups were exposed to either physical activity occurring during usual care or 'no training', comprising either no intervention or a non-exercise intervention (e.g. attention control groups); separate analyses were intended for each subgroup.

9.3.1.2. Types of participants

Stroke patients of any age were considered if they were considered medically stable enough for training by the trialists. It had been intended that the ambulatory patients be categorised further into subgroups with mild, severe or no hemiparesis. Patients were included irrespective of the time since the onset of the stroke.

9.3.1.3. Types of interventions

Training interventions included any of the following;

a) Cardiorespiratory Training

The aim of this type of training is to improve the cardiorespiratory component of fitness. It is typically performed for extended periods of time on devices or ergometers (e.g. treadmill, cycling, rowing), or utilising other modes of activity such as walking or stair climbing.

b) Strength Training

This is performed primarily to improve the strength and muscular endurance component of fitness. It is typically carried out by making repeated muscle contractions resisted by; body weight, elastic devices, masses, free-weights or specialised machine weights, or isokinetic devices. Concentric, isometric or eccentric contractions of any muscle groups were considered.

c) Mixed Training

Mixed training interventions comprise different activity components, some intended to improve cardiorespiratory fitness and others to improve strength and muscular endurance; e.g. a training programme comprising both cycling and weight training.

Training interventions were included only where clear evidence was described of an intention to train the participants, i.e. a systematic, progressive increase in the intensity or resistance, the frequency and/or the duration of exercise throughout the programme. The 'dose' of the cardiorespiratory and/or strength training components of a programme were individually categorised as falling within or below the ACSM (1998b) guidelines on developing and maintaining fitness. Measures of adherence to training were sought since this can modify the 'dose' of training. For the purposes of this review we defined adherence as both i) degree of attendance at training sessions, and ii) compliance with exercise instructions etc during training sessions.

Some training programmes may focus the training just on either the upper or lower extremities. Since this may influence some of the outcome measures subgroup analyses comparing upper body, lower body and whole body training interventions were included.

If any description of a training regimen was unclear, then the authors were contacted for further information.

9.3.2. Types of outcome measures

Studies that included any scale measuring relevant domains were included. Studies that incorporated any of the primary or secondary outcome measures were included.

9.3.3. Primary outcome measures

a) Case Fatality; numbers of deaths from all causes
b) Death or Dependence
c) Disability

9.3.4. Secondary outcome measures

a) *Adverse effects;* Recurrent non-fatal cardiovascular or cerebrovascular events; Altered muscle tone; Training-induced injury; Incidence of falls; Incidence of fractures.

b) *Physical fitness:* For example: Cardiorespiratory fitness; exercise duration, exercise heart-rate and oxygen consumption ($\dot{V}O_2$). Muscle strength and power output. Body composition; bone mineral density, body mass index (BMI), adiposity.

c) *Mobility:* For example, gait speed and walking ability.

d) *Physical function*; For example, task performance, balance and stair climbing

e) *Health-related quality of life*: Any relevant scale

f) *Mood*: Any relevant scale

Assessments of outcome occurred at the scheduled end of a training period (end of intervention), or at any other defined point either within the trial and/or some weeks or months after the training is complete (scheduled end of follow-up).

9.4. Search strategy for identification of studies

This review has drawn on the search strategy developed for the Stroke Group as a whole. Relevant trials were identified in the Stroke Group's specialised Trials Register. The last search for this review was carried out in June 2003. In addition the following electronic bibliographic databases were searched in December 2002.

- Cochrane Central Register of Controlled Trials. Cochrane Library, Issue 4 2002
- MEDLINE (OVID) 1966-December 2002
- EMBASE (OVID) 1980-December 2002
- CINAHL (OVID) 1982-December 2002
- SPORTDiscus (OVID) 1949-December 2002
- Science Citation Index Expanded 1981-December 2002
- Web of Science Proceedings 1982-December 2002
- Physiotherapy Evidence Database (PEDro) .....December 2002
- REHABDATA 1956-December 2002
- Index to UK Theses 1970-December 2002

The structure of the searches comprised a generic 'Stroke' component, supplemented with search terms for locating studies that related to exercise, physical fitness, cardiorespiratory training or strength training. Studies were limited to trials and intervention studies by a further subset of maximally sensitive search strings. The MEDLINE search strategy (see Appendix 14.10) comprised both MESH controlled vocabulary (/) and free text terms (.tw.). An equivalent search strategy was generated for the other databases using the same logic as the MEDLINE search strategy but modified to accommodate differences in indexing and syntax.

9.4.1. Additional measures

a) References from retrieved articles were examined to identify additional relevant trials that meet the inclusion criteria.

b) Examination of relevant conference proceedings to identify unpublished and/or ongoing trials. This comprised procedings listed on the Internet Stroke Centre's web site (http://www.strokecenter.org/) and included the European Stroke Conference (2000-02), International Stroke Conference 2000-02) and the World Stroke Conference (2000).

c) Liaison with authors of identified trials to identify unpublished or ongoing trials.

d) Liaison with investigators involved in relevant physiotherapy reviews for the Cochrane Collaboration.

e) National and international experts and organisations were contacted to identify unpublished and/or ongoing trials.

f) Hand-searching of journals, particularly those related to exercise and physical fitness which are currently excluded from the Cochrane Collaboration hand-searching. Those included were; Adapted Physical Activity Quarterly (1995-2002), British Journal of Sports Medicine (1974-2002), International Journal of Sports Medicine (1995-2002), Journal of Science and Medicine in Sport (1998-2002), Research Quarterly for Exercise and Sport (1985-2000), and Sports Medicine (1984-2002).

g) Citation tracking of all retrieved papers by Science Citation Index.

h) Ongoing trials were identified using the Internet Stroke Centre's Stroke Trials Directory database (http://www.strokecenter.org/trials/), the metaRegister of Controlled Trials (http://www.controlled-trials.com/mrct/) and by liaising with investigators.

9.5. Methods of the review

9.5.1. Study selection

The title and abstract (where available) of studies identified by the electronic search strategies, along with correspondence describing any unpublished trials, were independently screened for relevance by one reviewer (DS). Where the study was potentially relevant the full publication was obtained. Three reviewers (DS, plus CG or GM) independently applied the selection criteria to the full publications. A consensus discussion resolved disagreements on whether studies were included in the review. A fourth reviewer (AY) was consulted where disagreements persisted. For any relevant or potentially relevant trial identified, published in a language other than English, translation was available in collaboration with the Cochrane Stroke Group.

9.5.2. Methodological quality assessment

The methodological quality of the selected trials was assessed by two reviewers (DS plus CG or GM) using a validated quality scale (Jadad et al. 1996). This tool assesses randomization, blinding and a description of withdrawals and dropouts to give an overall score between 0 and 5. Scores of less than 3 are associated with 'Poor' trial quality, and 3 - 5 with 'good' trial quality. Additional information was obtained including an indication as to whether different trialists were involved in intervention, outcome assessment, and reporting. Assessments were made of the reliability and validity of any measurement tool, scale or method employed by trialists of included studies. Where the article did not

contain sufficient information for completion of the quality assessment the authors were contacted. Where missing information could not be retrieved the criteria were scored as 'unclear' or 'unknown'. The process was completed using a standard form and a fourth reviewer (AY) arbitrated where no agreement could be reached.

9.5.3. Data extraction

Data were independently extracted by two reviewers (DS plus CG or GM). The data extraction form included the methodological and quality information, and the following;

Participants; Number recruited, number randomized, number analysed; age; gender; stroke type, affected side; time from stroke to trial entry; first or recurrent stroke; whether ambulatory, non-ambulatory or initially non-ambulatory; walking aids.

Interventions; Type of training - cardiovascular/strength/mixed; exercise mode; training frequency; training duration; training intensity; programme duration; evidence of programme progression; upper and or lower body training; affected and/or unaffected side trained; evidence of training attendance and compliance; description of usual care.

Setting; Inpatient or outpatient; supervised or self-lead; home-based or hospital based.

Outcome measures; For continuous variables baseline values and measures of variability (mean and standard deviation (SD) or standard error (SE) were recorded. Where the SD

of the mean difference was not reported it was calculated from the baseline and follow-up data (Follmann et al. 1992).

9.5.4. Analysis of results

Statistical analysis was carried out using Review Manager[4] software. For dichotomous variables the individual and pooled statistics were calculated using a fixed effects model and reported as Peto ratios with 95% confidence intervals. For continuous data pooled weighted mean differences (WMD) with 95% confidence intervals were recorded. Where different scales were employed by different studies for the assessment of the same outcome (i.e. dependence and disability) standardised mean differences (SMD) with 95% confidence intervals were calculated. Where meta-analyses were included, tests of homogeneity (Chi^2 statistic) between comparable trials were carried out. In all meta-analyses both a fixed effects and a random effects model was applied; non-identical results were considered indicative of statistical heterogeneity, and the most conservative outcome was reported. Whenever this, and other evidence (Chi^2 $p>0.1$) of statistical heterogeneity was present, explanations were sought using the subgroups below. Funnel plots of pooled data were planned to investigate publication bias.

[4] Review Manager (RevMan) [Computer Program]. Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

9.5.4.1. Subgroup analyses

Some, but not all, of the secondary objectives could be fulfilled using the following subgroup analyses to compare the effects of;

a) Training programmes meeting ACSM (1998b) guidelines and those that did not.
b) Long duration (>12 weeks) or short duration (<12 weeks) training programmes.
c) Cardiorespiratory, strength or mixed training.
d) Different modes of exercise.
e) Training programmes concentrating on upper or lower extremity exercise.
f) Training programmes concentrating on affected or unaffected limbs.
g) Training during usual care or after usual care.
h) Inclusion of measures to facilitate continuation of exercise between the end of intervention and the scheduled end of follow-up.
i) Mild, severe or no hemiparesis.
j) Control groups utilising no intervention, a non-exercise intervention or other intervention.
k) 'Good' or 'poor' trial quality (Jadad et al. 1996).

9.5.4.2. Sensitivity analyses

Sensitivity analyses assessed the effect of;

a) Inclusion of trials in which the control condition or usual care was considered to contain elements which may provide an intentional or unintentional training effect.

b) Inclusion of trials examining mixed cardiorespiratory/strength training of which only one component met or exceeded the ACSM (1998b) guidelines.

c) Blinding, drop-outs and withdrawals.

9.6. Description of studies

The search strategy identified a number of relevant review articles (Andersen et al. 2001; Aagaard et al. 2001; Ernst 1990; Giuliani 1995; Potempa et al. 1996; Wagenaar and Meijer 1991) and a systematic review (van der Lee et al. 2001) and the bibliographies of these were screened for further studies. On the basis of information in the title and abstract, 42 studies were identified as being potentially relevant and full papers obtained. Of these, 31 studies did not meet the inclusion criteria. The studies and the reasons for exclusion are not catalogued in the thesis; see *Table of Excluded Studies* in Saunders et al. (2004a). The majority of these studies were excluded because the intervention could be not classified as fitness training.

A total of 11 published RCTs met the inclusion criteria and are discussed in the current review (Cuveillo-Palmer 1988 (thesis); da Cunha et al 2002; Dean et al. 2000; Duncan et al. 1998; Glasser 1986; Inaba et al. 1973; Kim et al. 2001; Pohl et al. 2002b; Potempa et al. 1995; Richards et al. 1993; Teixeira-Salmela et al. 1999). The studies took place in and involved participants from Australia (1), Canada (3), Germany (1) and USA (6). The trial by Pohl et al. (2002c) included two different treadmill training intervention groups sharing the same control group. The data are included in this review as two separate comparisons (Pohl et al. 2002c; 'A' and 'B') and referred to as separate 'trials'. The trial by Inaba et al. (1973) consisted of two intervention arms sharing the same control group, only one of which met the inclusion criteria. Therefore 12 trials are described in the review and the details are summarized as 12 separate entries in Appendix 14.17 (Characteristics of Included Studies). Additional information about some trials was

obtained from the authors (Dean et al. 2000; Kim et al. 2001; Richards et al. 1993) and additional data.

One RCT met the inclusion criteria (Bateman et al. 2001) but examined a mixed population of participants with different brain pathologies including stroke. The stroke-only data (control n=32/79; intervention group n=38/78) may be available for inclusion in a future version of this review therefore the trial is described in Appendix 14.11 (Characteristics of Ongoing Studies). In addition to the data of Bateman et al. (2001) there are 6 further trials described in Appendix 14.11 that are either ongoing or for which data are not yet available.

A recent potentially relevant systematic review of exercise therapy for arm function in stroke patients (van der Lee et al. 2001) included 13 RCTs. All 13 trials had already been identified by the search strategy employed in this review, but only one (Duncan et al. 1998) met the current inclusion criteria. Of the remaining 12 trials, two were identified as not relevant. Although the other 10 were identified as being potentially relevant they were excluded as none was found to include an intervention with a clear fitness training component as defined in this review.

9.6.1. Participants:

A total of 289 patients were randomized and attended baseline assessment in the 12 included trials. Six withdrawals occurred after randomization and baseline assessment

due to illness (2), transport costs (1), discharge (1), failure to complete training (1) and 1 unreported reason. Therefore 283 patients (male:female 3:2; precise numbers unclear) were available for outcome assessment at the end of training. The mean time since onset of stroke in participants in the trials ranged from 7.7 years in trials examining training in patients after discharge (Teixeira-Salmela et al. 1999) to 8.8 days in those examining training before discharge from hospital (Richards et al. 1993).

The mean age of the patients was approximately 63 years. 11/12 trials recruited patients who were ambulatory at baseline (n=271/289) and 1/12 (n=18/289) only recruited patients who were non-ambulatory at baseline (Richards et al. 1993).

9.6.2. Interventions:

A summary of the interventions is shown in Table 9.1. In four trials, comprising 60/289 patients, mixed cardiorespiratory and strength training was provided (Dean et al. 2000; Duncan et al. 1998; Richards et al. 1993; Teixeira-Salmela et al. 1999), Six trials (155/289 patients) examined the effect of cardiorespiratory training in isolation (Cuveillo-Palmer 1988; da Cunha et al. 2002; Glasser 1986; Pohl et al. 2002b ('A' and 'B'); Potempa et al. 1995), and two trials (74/289 patients) examined strength training in isolation (Inaba et al. 1973;Kim et al. 2001).

Table 9.1 Summary of the training intervention programmes, indicating whether they meet the ACSM (1998b) criteria.

Trial	Meet ACSM (1998b) criteria?	Training Mode	Duration $min \cdot d^{-1}$	Frequency $d \cdot wk^{-1}$	Programme Length wk	Usual Care
a) Cardiorespiratory Training						
(Cuveillo-Palmer 1988)	-	Body weight supported treadmill training	20	5	2-3	During
(da Cunha et al. 2002)	-	Kinetron*	7-17	6	3	During
(Glasser 1986)	-	Kinetron*	20-60†	5†	5	After
(Pohl et al. 2002b 'A')	-	Treadmill training	30	3	4	During
(Pohl et al. 2002b 'B')	-	Treadmill training	30	3	4	During
(Potempa et al. 1995)	Cardiorespiratory	Cycling	30	3	10	After
b) Strengh Training						
(Inaba et al. 1973)	Strength	Resistance training	UN	UC‡	4-8	During
(Kim et al. 2001)	Strength	Resistance training	30	3	6	After
c) Mixed Training						
(Dean et al. 2000g).	-	Walking, Circuit training	60	3	4	After
(Duncan et al. 1998)	Strength only	Walking or cycling Elastic resisted contractions	~90	3	12§	After
(Richards et al. 1993)	-	Treadmill, Kinetron*	104	5†	5	During
(Teixeira-Salmela et al. 1999)	Cardiorespiratory and strength	Walk and step or cycle Resistance training	60-90	3	10	After

Abbreviations: UN unknown; UC unclear
* Kinetron is an ergometer similar to a stair-stepping machine
† Two Sessions per day
‡ Frequency described as 'Daily'
§ 8 supervised weeks, 4 home-based weeks

9.6.3. Timing of intervention

The interventions of six trials (124/289 patients) occurred after usual care (Dean et al. 2000; Duncan et al. 1998; Glasser 1986; Kim et al. 2001; Potempa et al. 1995; Teixeira-Salmela et al. 1999). The interventions of the remaining six trials (165/289 patients) took place during usual care (Cuveillo-Palmer 1988; da Cunha et al. 2002; Inaba et al. 1973; Pohl et al. 2002b; 'A' and 'B'; Richards et al. 1993). Only three trials (Cuveillo-Palmer 1988; da Cunha et al. 2002; Richards et al. 1993) comprising 48/289 patients commenced interventions in the acute phase (<1 month) post-stroke. In all other trials the interventions commenced months or years after stroke.

9.6.4. Duration of intervention

The training programmes ranged from 2-3 weeks (da Cunha et al. 2002) up to 10 weeks (Potempa et al. 1995; Teixeira-Salmela et al. 1999), or 12 weeks including 4 weeks of unsupervised home-based training (Duncan et al. 1998). All included trials involved 3 or more days of training per week, sometimes with more than one session per day (Glasser 1986; Richards et al. 1993).

Individual training sessions ranged between 7 and 90 minutes of training on each occasion. The duration of training was approximately 50 minutes or less during usual care (Cuveillo-Palmer 1988; da Cunha et al. 2002; Pohl et al. 2002b; 'A' and 'B'; Richards et al. 1993) and 30 to 90 min after discharge (Dean et al. 2000; Duncan et al.

1998; Glasser 1986; Kim et al. 2001; Potempa et al. 1995; Teixeira-Salmela et al. 1999). The duration of training was not specified by Inaba et al. (1973).

9.6.5. Cardiorespiratory Training Interventions

All trials except Inaba et al. (1973) and Kim et al. (2001) included some component of cardiorespiratory training (n=215). The modes of cardiorespiratory training activated the large muscle groups of the lower limbs using equipment such as treadmills, cycle ergometers and isokinetic devices (Kinetron). In addition, walking, stepping and circuit training were used. The duration of this cardiorespiratory component commenced above or progressed to a minimum of 20 minutes per session. All cardiorespiratory training interventions showed some element of progression, usually an increase in duration of exercise. Only two trials (Potempa et al. 1995; Teixeira-Salmela et al. 1999; n=55/215) quantified the intensity of cardiorespiratory training, and its progression, in terms of a percentage of a participant's maximal capacity. Both studies met the ACSM (1998b) guidelines for the development of cardiorespiratory fitness in healthy individuals. In the other 10 studies (n=160/215) it was not possible to judge whether the intervention met the guidelines.

9.6.6. Strength Training Interventions

Five trials (n=134) included a component of strength training (Dean et al. 2000; Duncan et al. 1998; Inaba et al. 1973; Kim et al. 2001; Teixeira-Salmela et al. 1999). Two of the

trials (Inaba et al. 1973; Kim et al. 2001) included only strength training and this was confined to the affected lower limb only; the remaining trials included bilateral training of the lower or both upper and lower limbs. The modes of strength training comprised muscle contractions resisted by weights (Inaba et al. 1973; Teixeira-Salmela et al. 1999), elastic devices (Duncan et al. 1998; Teixeira-Salmela et al. 1999) or body weight (Teixeira-Salmela et al. 1999; Dean et al. 2000). An isokinetic dynamometer was used by Kim et al. (2001). The isokinetic Kinetron device was used by Richards et al. (1993) as a means of increasing muscle strength, although this has a more obvious role for cardiorespiratory training. The trials included evidence of progression and 4 quantified the intensity of muscle contraction either in relation to maximum strength (Inaba et al. 1973; Kim et al. 2001; Teixeira-Salmela et al. 1999) or number of resisted contractions that could be tolerated (Duncan et al. 1998). The interventions described by Duncan et al. (1998), Kim et al. (2001), Teixeira-Salmela et al. (1999) and possibly Inaba et al. (1973) meet the ACSM (1998b) guidelines for the development of strength and muscular endurance in healthy individuals (n=107/134).

9.6.7. Adherence to Training Interventions

Dean et al. (2000) reported 75% attendance at training after usual care, Pohl et al. (2002b; 'A' and 'B') report 100%, and Richards et al. (1993) 84% attendance at training during usual care. Teixeira-Salmela et al. (1999) did not report attendance but described attempts to make up missed sessions. da Cunha et al. (2002) excluded participants if they attended fewer than 9 training sessions.

Compliance during training sessions was difficult to fully quantify since measures of exercise intensity are frequently not reported. No trials described compliance to training during sessions.

Attendance at, and compliance during training were encouraged in one trial (Dean et al. 2000) through supervision of training, provision of transport and group exercise. Duncan et al. (1998) ensured attendance during 8-weeks of home-based training through one-to-one supervision; however compliance during a further 4-weeks of unsupervised training remained unknown.

9.7. Methodological quality of included studies

9.7.1. Randomization

All included trials were described as randomized. The participants of Duncan et al. (1998) were balanced into groups of similar size by randomizing in blocks of 10. Six trials balanced group size and baseline characteristics using the following approaches: Matched pairs (Dean et al. 2000), balanced blocks (Teixeira-Salmela et al. 1999), stratified based on initial disability (Barthel index; Richards et al. 1993), stratified using age, gender and time since stroke (Kim et al. 2001), and restricted randomization in blocks based on walking (Pohl et al. 2002b; 'A' and 'B').

9.7.2. Trial quality

Other indicators of trial methodological quality were poorly reported. 6/12 trials described blinding of the outcome assessor, 5/12 fully described dropouts and withdrawals, and 2/12 described randomization methods. No trials described how blinding was achieved. When a simple model of methodological quality (Jadad et al. 1996) was applied to these data 4/12 trials were classified as 'good' (Kim et al. 2001; Pohl et al. 2002b; ‘A’ and ‘B’; Richards et al. 1993). The remainder were classified as 'poor'. There were inadequate data to explore the effect of trial quality on outcome. Even though supplementary information relating to trial quality was obtained from authors (da Cunha et al. 2002; Dean et al. 2000) it generally remains unclear whether poor scores reflect trial methodology or arise from incomplete reporting.

9.7.3. Blinding

Other than concealing the hypothesis of a trial of exercise, the blinding of the patients is not possible in exercise intervention studies. Placebo responses may arise in comparisons with a non-exercise control intervention, and particularly where no intervention is used (after discharge and lag-control trials). However Kim et al. (2001) attempted to 'blind' by informing participants that they would be allocated one of two different leg-training interventions. In the Dean et al. (2000) trial the outcome assessor was reported to have accidentally observed a group training session thus potentially identifying the members of the intervention group.

9.7.4. Losses to follow-up

Loss of participants before randomization can influence the extrapolation and generalizability of the results (Schulz and Grimes 2002a). Three participants were lost from Potempa et al. (1995), and nine from Pohl et al. (Pohl et al. 2002b; 'A' and 'B').

Loss of participants after randomization may bias the comparison of the intervention and control groups. In da Cunha et al. (2002) 3/15 (20%) and Dean et al. (2000) 3/12 (25%) of the participants were lost to follow-up comprising two participants from each intervention group and one from each control group lost (n=6). Losses of 20% or more may seriously threaten the validity of trials (Schulz and Grimes 2002a). Where data from da Cunha et al. (2002) and Dean et al. (2000) are combined in meta-analyses their weighting was often small and sensitivity analyses of their exclusion did not influence the findings. Furthermore, although data for intention to treat analysis were not obtained, losses to follow-up of these small numbers are unlikely to bias the overall findings of this review. da Cunha et al. (2002) excluded those with poor attendance, this manner of exclusion after randomization removes the possibility of intention to treat analysis and threatens methodological quality.

A large proportion (101/177) of patients recruited to the Inaba et al. (1973) trial were lost both before and after randomization. The distribution of losses across excluded and included arms of the trial remain unknown. Data for 54 patients were analysed per protocol for Inaba et al. (1973). One reason given for dropouts was discharge before the end of the study.

9.7.5. Recruitment

The participants in the Teixeira-Salmela et al. (1999) trial were volunteers recruited from a stroke club and from media advertisements, and those in the Kim et al. (2001) trial were recruited on a volunteer basis from the surrounding community. This may render these studies susceptible to self-selection bias and thus affect the generalizability of the findings.

9.7.6. Reliability of outcome measures

The clinical scales used as outcome measures in this review are in common use in stroke trials. With regard to mobility outcomes, the repeatability of maximal walking speed has been demonstrated in stroke patients (intraclass correlation coefficient (ICC) 0.87 - 0.88; Green et al. 2002). With regard to measures of physical fitness in stroke patients, the methods are less well established. The reliability of measures of muscle strength in stroke patients has been explored, for example the test-retest reliability of muscle strength using an isokinetic dynamometer (ICC 0.62 - 0.94; Eng et al. 2002). However these measures were limited to the affected limb and utilised very specific equipment. Some reliability data are available for measurements of peak oxygen uptake ($\dot{V}O_2$ peak) in stroke patients (ICC 0.94; Potempa et al. 1995).

9.7.7. Types of comparison

The anticipated comparisons published a priori in this review protocol were a) training plus usual care vs. usual care, and b) training vs. no exercise or non-exercise intervention. Some data did not match the anticipated comparisons. The cardiorespiratory treadmill walking interventions of three trials (da Cunha et al. 2002; Pohl et al. 2002b; 'A' and 'B') substituted an equivalent duration of usual care gait training (training + % usual care vs. usual care). Similarly, in the fitness training intervention of Glasser (1986), training replaced part of the non-exercise intervention after usual care (training plus % control vs. control). These types of comparison ensure that experimental and control groups receive a similar amount of intervention. Time spent in therapy would otherwise be a confounding factor since it is known to influence rehabilitation outcomes similar to those sought in this review (Kwakkel et al. 1997; Kwakkel et al. 1999; Kwakkel et al. 2002; Langhorne 2002).

9.8. Results

Where data were combined in meta-analyses, the Chi-squared statistic did not indicate statistical heterogeneity (P>0.1). Unless stated otherwise the results of both fixed and random effects meta-analysis were identical. Funnel plots of data combined in meta-analyses were inconclusive because data for so few trials were combined. The small numbers of trials within each meta-analysis (maximum 3) limited the usefulness of any planned subgroup and sensitivity analyses.

9.8.1. Effect of training on primary outcome measures

9.8.1.1. Case fatality

None of the 289 included patients was reported to have died during the included trials.

9.8.1.2. Death or dependence

No measures of dependence were reported, and therefore neither was the composite outcome of death or dependence.

9.8.1.3. Disability

There were limited disability outcomes reported in the trials (Table 9.2). Disability data reported by Cuveillo-Palmer (1998) and Duncan et al. (1998) were combined in a meta-analysis (Figure 9.1) to show no significant effect of training (SMD -0.06, 95% CI -0.76,

0.65). Cuveillo-Palmer (1998) reported changes in the FIM Instrument scores and concluded that it was not beneficial to perform cardiorespiratory training on an isokinetic ergometer (Kinetron II) during 2-3 weeks of usual care. Duncan et al. (1998) showed no significant effect of mixed training on the changes observed in the Barthel Index ADL or the Lawton Instrumental ADL. Individual patient data for Duncan et al. (1998) showed Barthel Index scores reaching a ceiling of 100 in 5/20 participants at baseline and 10/20 at follow-up, therefore the Lawton Instrumental ADL data were adopted for the meta-analysis.

Table 9.2 Summary of the disability outcome measures from the included trials.

Trial	Disability outcome measure
(da Cunha et al. 2002)	Functional Independence Measure - incomplete scale used (lower extremity; NS)
(Cuveillo-Palmer 1988)	Functional Independence Measure (NS)
(Dean et al. 2000)	-
(Duncan et al. 1998)	Barthel Index (NS) Lawton instrumental activities of daily living (NS)
(Glasser 1986)	-
(Inaba et al. 1973)	Activities of daily living (*)
(Kim et al. 2001)	-
(Pohl et al. 2002b; 'A')	-
(Pohl et al. 2002b; 'B')	-
(Potempa et al. 1995)	-
(Richards et al. 1993)	Barthel Index - incomplete scale used (NS)
(Teixeira-Salmela et al. 1999)	-

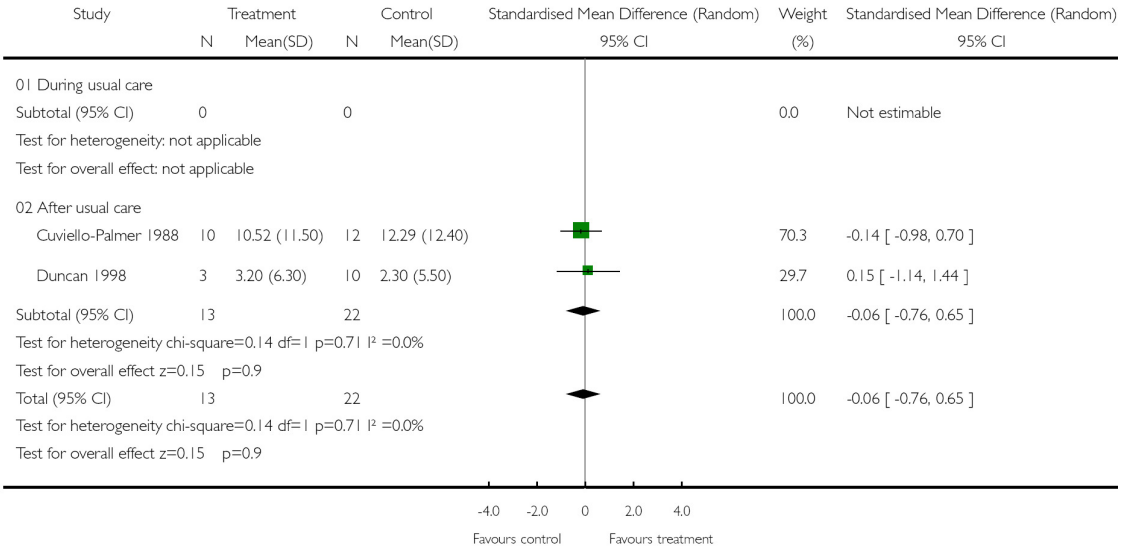
NS Outcomes reported by authors as not significant.

* Outcomes reported by authors as statistically significant (P<0.05)

Incomplete disability scales were reported by da Cunha et al. (2002; FIM; locomotor scale) and Richards et al. (1993; Barthel Index; ambulation) and were therefore excluded from the analysis. Inaba et al. (1973) reported that 18/28 patients receiving strength

training of the affected lower limb improved in 10 activities of daily living (no scale used) compared with only 10/26 of those receiving only ADL training ($p<0.05$). The authors of this trial state that little additional improvement occurred during a further month of training although these data are not presented.

Figure 9.1 Meta analysis of the effect of cardiorespiratory fitness versus a control on measures of disability.



The mixed brain lesion trial by Bateman et al. (2001) includes measures of disability and dependence using the Barthel Index, FIM and Nottingham Extended Activities of Daily Living (NEADL) but a subset of this data limited to stroke patients is not yet available.

Since few disability data were available it was not possible to examine the effect of initial disability on secondary outcome measures.

9.8.2. Effect of training on secondary outcomes

The secondary outcome measures from the included trials are summarized in Table 9.3.

9.8.2.1. Adverse effects

No trials reported the incidence of recurrent non-fatal cardiovascular or cerebrovascular events. In addition there were no data available describing altered muscle tone, or the incidence of falls, fractures or training induced injury.

9.8.2.2. Physical fitness

a) Cardiorespiratory Fitness

Potempa et al. (1995) and da Cunha et al. (2002) measured aspects of cardiorespiratory fitness during incremental cycling exercise. Both described a significantly higher $\dot{V}O_2$ peak following cardiorespiratory training compared with controls, Potempa et al. (1995) 18.8 (4.8) vs. 15.2 (4.32) $ml \cdot kg^{-1} \cdot min^{-1}$ and da Cunha et al. (2002) 11.6 (2.76) vs. 8.32 (2.05) $ml \cdot kg^{-1} \cdot min^{-1}$). However, meta-analysis of the pooled data showed no significant improvement in $\dot{V}O_2$ (Figure 9.2; WMD 2.51 $ml \cdot kg^{-1} \cdot min^{-1}$, 95% CI -0.20, 5.23), or maximal work rate (Figure 9.3; WMD 14.1 Watts, 95% CI -11.8, 40.0).

Table 9.3 Summary of the secondary outcome measures from the included trials.

Trial	Physical Fitness	Physical function		Health and Quality of Life
		Mobility domains	Other domains	
(da Cunha et al. 2002k)	Cycle data… workload (NS); time (NS); heart rate (NS); $\dot{V}O_2$ peak (*); blood pressure (NS)	FIM Instrument - Locomotor scale (NS) CWS 5-min (NS) MWS 5-metres (NS) FAC (*)		
(Cuveillo-Palmer 1988)		CWS (NS)		
(Dean et al. 2000)		CWS (*); MWS (*)	Timed up and go (NS) Sit to stand (*); Step Test (*)	
(Duncan et al. 1998)		CWS (NS); MWS (*)	Berg Balance Scale (NS); Jebsen hand test (NS); Fugl-Meyer Lower (*); Upper (NS)	MOS-36 (NS)
(Glasser 1986)		Functional Ambulation Profile (NS) MWS (*)		
(Inaba et al. 1973)	Muscle strength (*)			
(Kim et al. 2001)	Muscle strength (*)	CWS (NS); MWS (NS)	Stair climbing… comfortable speed (NS); maximum speed (NS)	SF-36 (NS)
(Pohl et al. 2002b; 'A')		MWS (*) FAC (*)		
(Pohl et al. 2002b; 'B')		MWS (*) FAC (*)		
(Potempa et al. 1995)	Maximal cycling… workload (*); time (*); heart rate (NS); $\dot{V}O_2$ peak (*); blood pressure (NS)		Fugl-Meyer score (NS)	
(Richards et al. 1993)		Barthel Index - ambulation scores (NS)	Fugl-Meyer - lower (NS); upper (NS); balance (NS)	
(Teixeira-Salmela et al. 1999)		CWS (*)	Human Activity Profile (*)	Nottingham Health Profile (*)

Abbreviations: CWS comfortable walking speed; FAC Functional Ambulation categories; MWS maximum walking speed; NS authors report not significant
* Outcomes reported by authors as statistically significant ($P < 0.05$)

da Cunha et al. (2002) assessed the economy of gait during 5-min of walking in terms of the oxygen cost per unit distance walked ($ml \cdot kg^{-1} \cdot m^{-1}$) and reported a moderate (but non-significant) effect size of 0.7 SD units. Potempa et al. (1995) also reported a post-training increase in maximal work rate and decreased maximal heart rate during incremental cycling exercise. da Cunha et al. (2002) reported no effect on heart rate or blood pressure during incremental cycling exercise.

Figure 9.2 Meta analysis of the effect of cardiorespiratory training versus a control on cardiorespiratory fitness ($\dot{V}O_2$ peak).

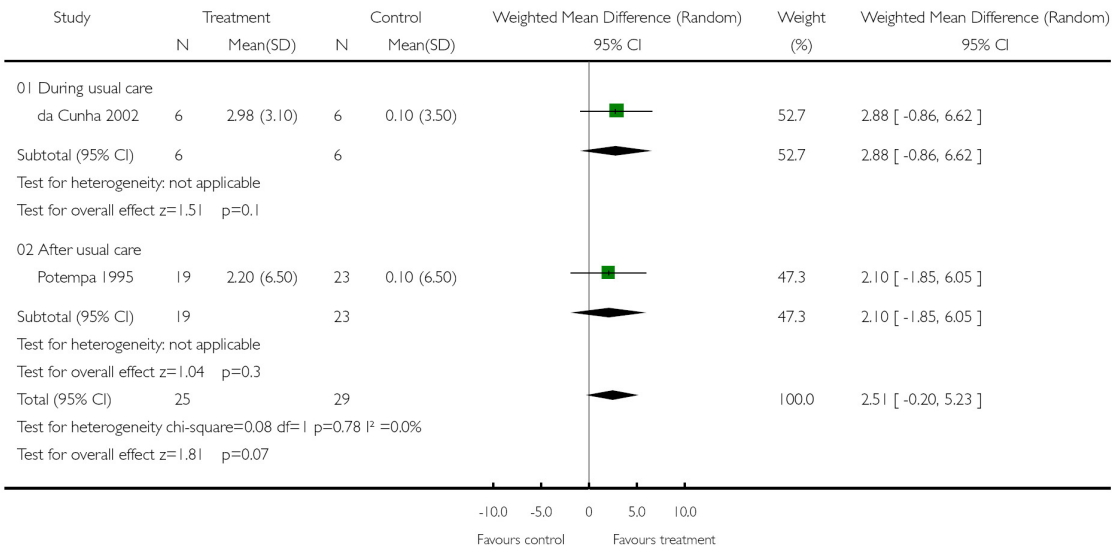
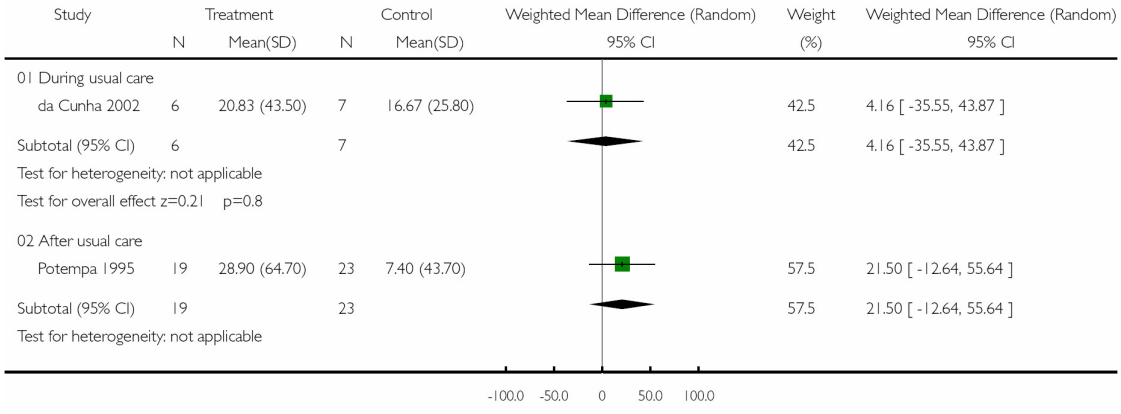


Figure 9.3 Meta analysis of cardiorespiratory training versus a control on maximum cycling workload.



b) Muscle Strength

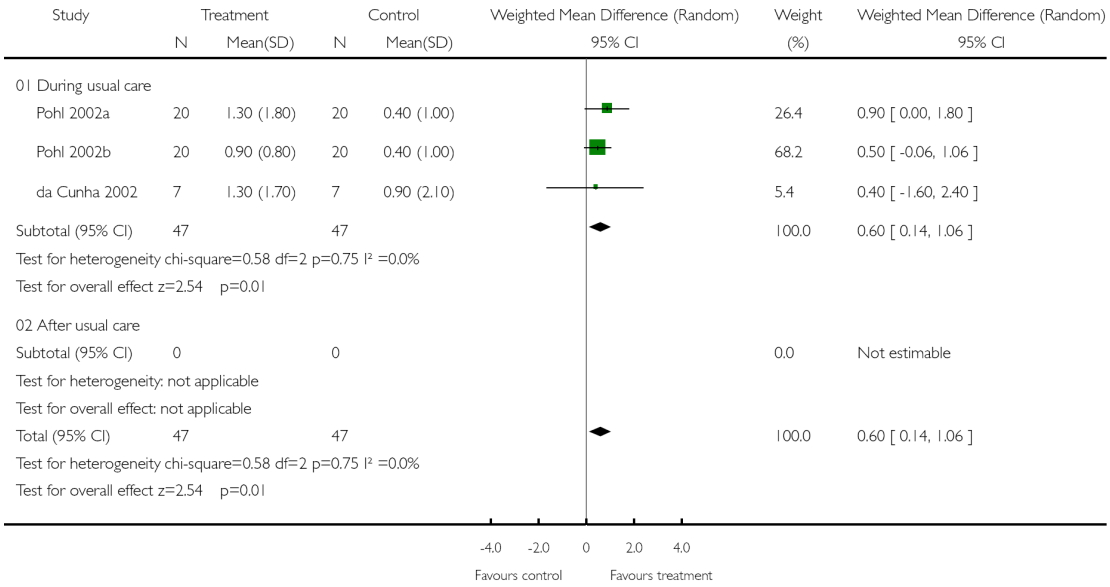
Only two trials measured muscle strength (Inaba et al. 1973; Kim et al. 2001). Inaba et al. (1973) showed that patients allocated strength training of the involved lower limb made significantly greater gains in the 10 repetition maximum compared with controls (12.18 vs. 8.58 kg, P<0.02) after 1 month of intervention. There were no differences between groups after 2 months of training. No standard deviations or standard error were included with these data. Kim et al. (2001) showed patients allocated strength training of the involved lower limb on an isokinetic dynamometer (Kin-Com) exhibited no significant (borderline) improvement in the strength of the trained leg compared with controls (sum % change in 6 muscle groups 507 (SD 559) vs. 142 (SD 193), P=0.06).

c) Mobility

Functional Ambulation Categories

Significant improvements in Functional Ambulation Category (FAC) scores were reported after treadmill training (Pohl et al. 2002b; 'A' and 'B'), and after treadmill training with partial body weight support (da Cunha et al. 2002); these cardiorespiratory training interventions took place during usual care. Meta-analysis of these trials (Figure 9.4) showed a significant improvement in FAC scores (WMD 0.60, 95% CI 0.14, 1.06). The trial of da Cunha et al. (2002) contributes only 5% of the weighting in this comparison.

Figure 9.4 Meta analysis of the effect of cardiorespiratory training versus a control on Functional Ambulation Category scores.



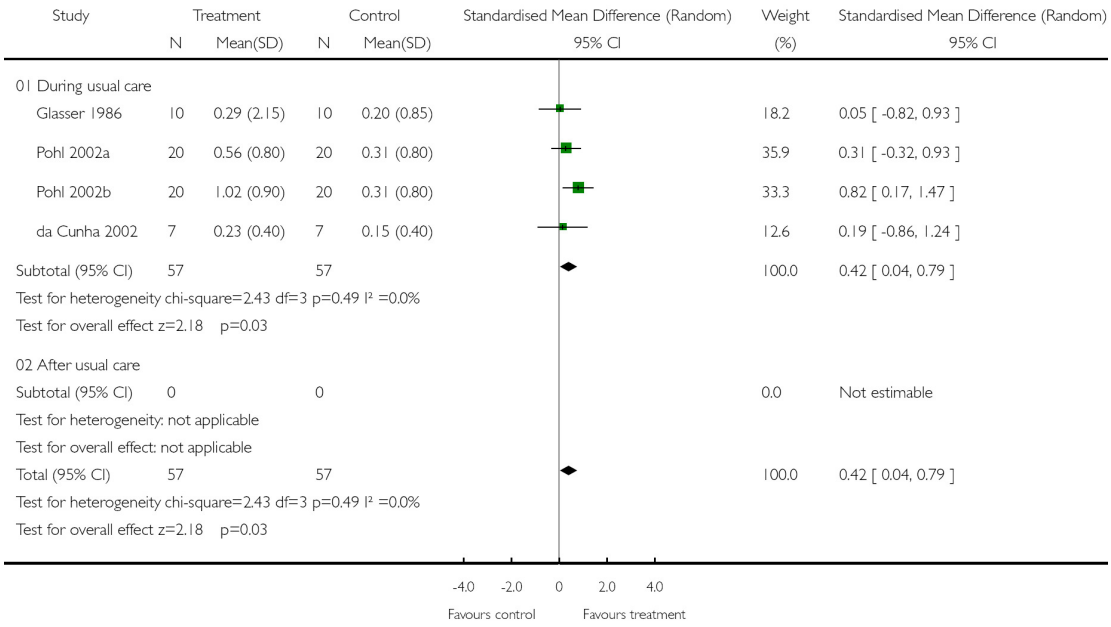
Maximal walking speed

Maximal walking speed was measured by Dean et al. (2000), Duncan et al. (1998) and Pohl et al. (2002b; 'A' and 'B') over 10-metres, by Glasser (1986) over 6-metres and da Cunha et al. (2002k) over 5-metres.

Meta-analysis (Figure 9.5) of the cardiorespiratory training interventions (da Cunha et al. 2002; Glasser 1986; Pohl et al. 2002b; 'A' and 'B') showed a significant overall improvement in maximal walking speed (SMD 0.42 $m \cdot sec^{-1}$, 95% CI 0.04, 0.79). Of these trials the greatest individual effect size (SMD 0.82 $m \cdot sec^{-1}$, 0.17, 1.47) was associated with the most intense and rapidly progressing training programme of Pohl et al. (Pohl et al. 2002b; 'B'). Excluding Glasser (1986) limits the analysis to treadmill training studies and increases the effect (SMD 0.50 $m \cdot sec^{-1}$, 95% CI 0.08, 0.91).

Improvements in maximum walking speed compared with controls after a mixed training intervention were reported by Duncan et al. (1998), mean change 0.25 vs. 0.09 m·sec^{-1}) and by Dean et al. (2000), mean change 0.13 vs. 0.02 m·sec^{-1}; P<0.05). The data could not be combined in a meta-analysis as standard deviation data were not available for Duncan et al. (1998). The benefits reported by Dean et al. (2000) were retained after a 2-month follow-up.

Figure 9.5 Meta analysis of the effect of cardiorespiratory training versus a control on maximum walking speed (m·sec^{-1} over 5-10 m).

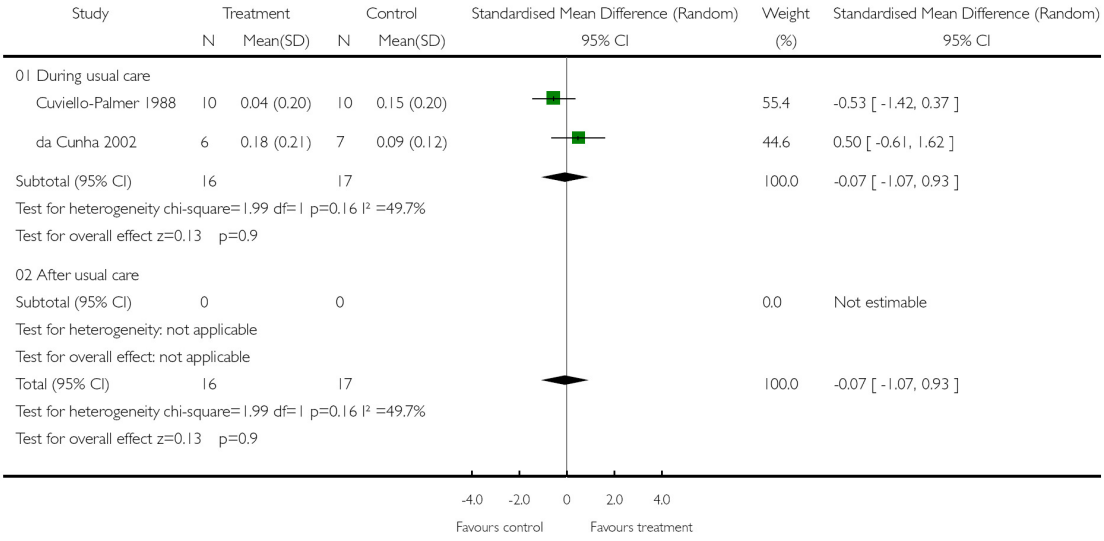


Comfortable or chosen walking speed

Comfortable or chosen walking speed was assessed using a number of different protocols; 5-min walk (da Cunha et al. 2002), 6-min walk (Dean et al. 2000; Duncan et al. 1998), 22-metre walk (Teixeira-Salmela et al. 1999), 8-metre walk (Kim et al. 2001) and a 7-sec walk (Cuveillo-Palmer 1988).

Meta-analysis of the cardiorespiratory training interventions of da Cunha et al. (2002) and Cuveillo-Palmer (1988) delivered during usual care (Figure 9.6) indicated no significant benefit of training (SMD Fixed 0.12 m·sec^{-1}, 95% CI -0.82, 0.57). The Cuveillo-Palmer (1988) intervention represented a very small 'dose' of training since it was of short duration (7-12 min) and of very low intensity (heart rate within 20 beats·min^{-1} of resting).

Figure 9.6 Meta analysis of the effect of cardiorespiratory training versus a control on chosen walking speed (m·sec^{-1}).

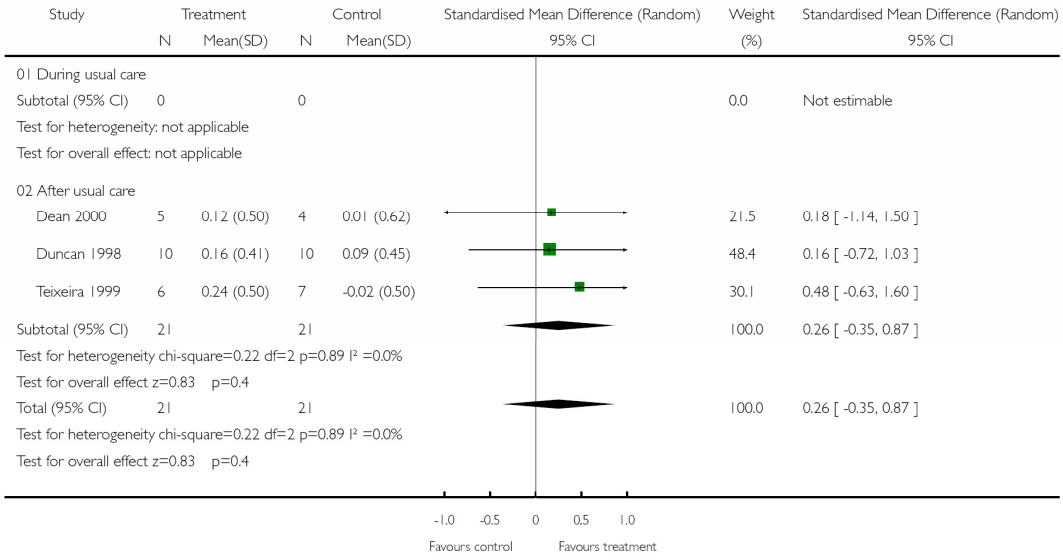


Only Kim et al. (2001) examined the effect of strength training in isolation on self selected walking speed and showed no significant benefit compared to control, mean change 0.04 m·sec^{-1} (SD 0.13) vs. 0.09 m·sec^{-1} (SD 0.07).

Dean et al. (2000), Duncan et al. (1998) and Teixeira-Salmela et al. (1999) examined the effect of a mixed training programme, including walking, delivered after usual care. Meta-analysis of these data (Figure 9.7) showed no significant benefit in chosen walking speed (SMD 0.13 m·sec^{-1}, 95% CI -0.16, 0.42). Dean et al. (2000) and

Teixeira-Salmela et al. (1999) reported significant benefits within their studies, and those of Dean et al. (2000) were retained after a 2-month follow-up. The matched pairs data of Dean et al. (2000) are assessed as unmatched data in the meta-analysis. This may bias the results for this trial; however exclusion did not alter the findings of the pooled data.

Figure 9.7 Meta analysis of mixed training (cardiorespiratory plus strength) versus a control on chosen walking speed.



Richards et al. (1993) reported faster chosen walking speed at the end of a mixed training intervention (including walking) delivered during usual care (effect size 0.58). These data are excluded from the above meta-analysis as the participants were non-ambulatory at baseline (walking velocity of 'zero'). The degree of benefit in this mixed training trial was associated with the amount of time spent on the gait training component (R^2=0.63). However, the increased comfortable walking speed reported by Richards et al. (1993) was not retained after a 3-6 month follow-up.

d) Physical Function

A variety of physical function and motor function outcomes were reported (Table 13.3). Global Fugl-Meyer (FM) scores were reported by Potempa et al. (1995) while other studies limited the measure to the upper extremity (FM-U; Duncan et al. 1998, Richards et al. 1993), lower extremity (FM-L; Duncan et al. 1998, Richards et al. 1993) and balance (FM-B Richards et al. 1993) subsets of the FM scale. The only significant improvement reported was in FM-L by Duncan et al. (1998).

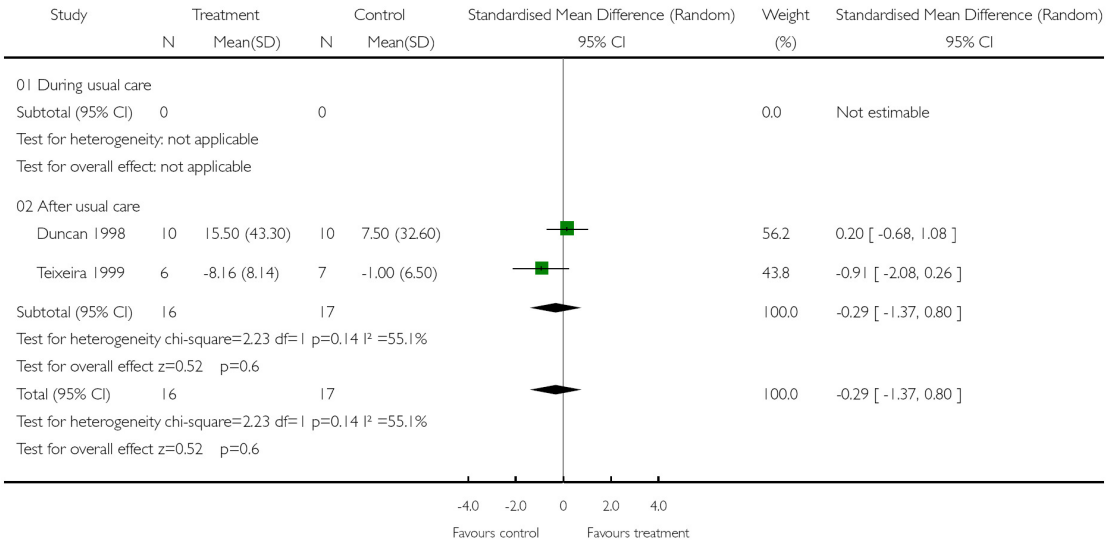
Significant improvements in simple physical tasks such as a timed step test and timed sit to stand were noted by Dean et al. (2000) to occur after specific (or task-related) circuit training. Kim et al. (2001) reported that strength training of the affected lower limb did not improve stair climbing ability. In addition to there being no significant strength gains, this intervention employed an isokinetic dynamometer to train only the affected lower limb, and was not considered specific or task related training.

e) Health Status and quality of life

Very few measures relating to this domain were reported. Meta-analysis of the mixed training trials (Duncan et al. 1998, SF-36; Teixeira-Salmela et al. 1999, Nottingham Health Profile) indicated no significant benefit of mixed training on health status and quality of life (Figure 9.8; SMD Random 0.29, 95% CI -1.37, 0.80).

Kim et al. (2001) showed no significant benefit of strength training compared with a control on the ‘physical health’ (mean change 0.74 vs. -0.73) and ‘mental health’ components (mean change 1.73 vs. -1.07) of the SF-36.

Figure 9.8 Meta analysis of the effect of mixed training (cardiorespiratory plus strength) on health related quality of life scores.



f) Mood

There were no data available relating to outcome measures of mood.

9.8.2.3. Subgroup Analyses

Since few data were available it was not possible to perform any of the planned subgroup analyses. However several observations relating factors influencing primary and secondary outcome measures are described in the discussion.

9.8.2.4. Sensitivity Analyses

The effect of loss to follow-up in Dean et al. (2000) and da Cunha et al. (2002) was assessed. Exclusion of these trials from the meta-analyses did not influence any of the conclusions of this review. There were too few data to perform other intended sensitivity analyses.

9.9. Discussion

The small number of relevant trials identified in this review and in particular their lack of primary outcome measures means that few conclusions can be drawn about the impact of physical fitness training or physical fitness on death, disability or dependence after stroke. The outcome measures described in the included trials were very diverse. This is typical of stroke rehabilitation trials and presents a problem when combining data in systematic reviews (Greener and Langhorne 2002).

9.9.1. Effect of training on primary outcome measures

9.9.1.1. Case fatality

It is not known whether training reduces the chance of death in patients with stroke. One possible reason for this is the training programmes in this review are all very short duration (≤12 weeks). A systematic (Cochrane) review of the effect of exercise-only interventions showed that exercise reduced deaths in people with coronary heart disease (Jolliffe et al. 2000) but the training programmes often lasted several years. Since many stroke patients have co-existing heart disease training might influence mortality post stroke provided it comprised cardiorespiratory training delivered over long periods of time. This requires investigation.

9.9.1.2. Death or Dependence

There are no data available to draw conclusions about the influence of training on the composite outcome of death or dependence after stroke.

9.9.1.3. Disability

Some disability outcome data were retrieved but individual studies reported no significant benefits arising from fitness training other than Inaba et al. (1973). Pooling data in a meta-analysis also showed no benefit but this approach was problematic: Incomplete subsets of outcomes scales, utilising different measurement tools were reported, making comparison of studies more difficult. In addition the measurement tools lacked sensitivity due to the recruitment of patients typically presenting with milder strokes. Therefore the common disability outcome measures such as the Barthel Index were rendered less useful than tools such as the FIM, due to ceiling effects (e.g. Duncan et al. 1998). However, the FIM may also be subject to ceiling effects, particularly in community living patients (Hall et al. 1996).

Several ongoing studies (Appendix 14.11) and the data of Bateman et al. (2001) include the FIM as an outcome so more disability data will become available for a greater number of patients (n=268).

There were insufficient data to investigate any secondary objectives or to perform any subgroup analyses on the primary outcome measures.

9.9.2. Effect of training on secondary outcome measures

9.9.2.1. Adverse events

No data were available to assess whether programmes of physical fitness training increase or decrease the incidence of adverse events such as vascular events falls, fractures and other injuries.

9.9.2.2. Physical Fitness

Cardiorespiratory fitness - Cardiorespiratory fitness was shown to be impaired after stroke. Baseline $\dot{V}O_2$ peak of the participants in da Cunha et al. (2002) and in Potempa et al. (1995) was 30% and 50-60% respectively, of the values expected in untrained age- and sex-matched healthy people (Shvartz and Reibold 1990). The functional significance of low peak $\dot{V}O_2$ is an impaired ability to perform sustained aerobic exercise.

Cardiorespiratory training did not significantly improve $\dot{V}O_2$ peak or cycling performance, however the studies were underpowered to detect a difference in $\dot{V}O_2$ peak of the magnitude observed. Low exercise economy, (i.e. a higher absolute oxygen cost of a given task or activity) has important consequences for stroke patients since this also impacts upon the ability to perform sustained activity. Only da Cunha et al. (2002) reported improved (walking) economy, but a small sample size and variable baseline data make interpretation of this outcome measure difficult.

Muscle strength - There were too few data available to ascertain whether muscle strength can be increased via programmes of fitness training, including strength training. Muscle strength is known to be associated with standing, stepping and walking ability, but it is not known whether there is any functional benefit associated with improved strength in patients with stroke.

The Inaba et al. (1973) and Kim et al. (2001) trials provided strength training of the involved lower limb only. Strength impairments post-stroke, although greater on the involved side, are known to occur bilaterally (Harris et al. 2001; Andrews and Bohannon 2000). Therefore functional benefits arising from improved strength may not be apparent if training occurs unilaterally.

Those studies which examined mixed cardiorespiratory and strength training (Dean et al. 2000; Duncan et al. 1998; Teixeira-Salmela et al. 1999) measured neither cardiorespiratory fitness nor muscle strength. Therefore it was not possible to identify whether any particular benefits were associated with strength (or cardiorespiratory) training.

Mobility - Treadmill walking (cardiorespiratory) training significantly improved the Functional Ambulation Category scores of patients with stroke. This is indicative of patients being less dependent on others for ambulation. This observation relies heavily on data from one trial (Pohl et al. 2002b; 'A' and 'B') however it is of high quality and is of a robust design.

Cardiorespiratory training significantly improved mobility by increasing maximum walking speed over short distances (5-10 metres). These observed benefits may have arisen due to improvements in motor function since improved cardiorespiratory fitness would logically provide little benefit to short duration effort. The contrast between the two comparisons of treadmill walking in Pohl et al. (2002b; 'A' and 'B') is a valuable one and suggests potential benefits of increasing the intensity of exercise. In Pohl et al. (2002b; 'B') the treadmill walking speed (exercise intensity) was increased as much as could be tolerated every session, whereas in Pohl et al. (2002b; 'A') the speed progressed by a fixed, more modest amount. The improvements in mobility when traditional gait training (control group) was substituted with more intense treadmill training occurred even though the patients received 20% less total intervention time (12 vs. 15hrs). Increased functional benefit was associated with the highest intensity and fastest progressing treadmill intervention Pohl et al. (2002b; 'B').

Neither cardiorespiratory training during usual care, nor mixed training after usual care, resulted in any improvement in comfortable or customary walking speed.

All trials which included walking as part or all of the training intervention reported one or more significant improvements in ambulation outcome measures. The two trials that did not report improvements in ambulation outcome measures (Cuveillo-Palmer 1988; Glasser 1986) both employed an isokinetic ergometer (Kinetron) as the mode of training. Training on devices like this (including cycle ergometers) in isolation may not provide relevant adaptations that translate into functional benefits.

Although planned subgroup analyses examining the effect of mode of exercise were not possible, this observation is compatible with the concept of 'task-related' or 'specific' training.

There were too few data (Richards et al. 1993) to examine the benefits of fitness training for non-ambulatory stroke patients. These data reinforced further the notion of specificity of training.

9.9.2.3. Physical function

There were too few data to comment on physical function. Benefits appeared to occur when task-related training was employed (Dean et al. 2000).

9.9.2.4. Health related quality of life

There were too few data relating to health related quality of life.

9.9.2.5. Mood

No conclusions could be drawn about the effect of training on mood as no outcome data were available.

9.9.3. Factors influencing primary & secondary outcome measures

There were too few data for subgroup analyses however a number of important observations can be made.

9.9.3.1. Dose of training

Although training has been shown to be of some benefit to patients after stroke there are too few data to establish a dose-response relationship between training and potential benefits for stroke patients.

The ACSM (1998b) criteria were used to define an effective overall 'dose' of fitness training as defined by the parameters of intensity, duration and frequency. The interventions of several trials (Duncan et al. 1998; Inaba et al. 1973; Potempa et al. 1995; Teixeira-Salmela et al. 1999) met the criteria and showed benefits. Benefits were also noted in trials whose interventions did not meet the ACSM (1998b) criteria. Other trials may have met these criteria but the interventions were not fully reported especially with regard exercise intensity.

Exercise intensity is probably one of the most important fitness training variables; rather confusingly it is also used to describe the frequency and duration of therapeutic interventions (e.g. Kwakkel et al. 2002). Only the data of Pohl et al. (2002b; 'A' and 'B') examined this and indicated that higher intensity walking training (‘B’) is more beneficial to maximal walking speed. However this

intervention was also the most rapidly progressing so this effect is difficult to separate the effect from that of intensity.

Poor adherence to a programme of training reduces the training dose and therefore the training stimulus. Attendance was reported in some studies and this was greatest during inpatient care. This review indicates stroke patients can complete a variety of different short-term training interventions.

9.9.3.2. Type of training

It is not known whether cardiorespiratory, strength or mixed training interventions are most beneficial. One ongoing trial (Kilbreath; Appendix 14.11) will determine the relative effects of cardiorespiratory, strength and mixed training.

Fitness, mobility and physical function data presented in the review demonstrate the specificity of the training response, and are supportive of the concept of 'task-related' training. Improvements in physical fitness were seen during exercise that mirrored that used during the intervention. All significant improvements in mobility outcomes reported within individual studies or meta-analyses were exclusively associated with interventions involving walking; no benefits occurred when walking was not included. The data of Richards et al. (1993) further supports specificity as time spent gait training was associated with mobility outcomes.

There were insufficient data to determine whether training limited to the upper or lower limbs, or the affected and unaffected limbs was beneficial.

9.9.3.3. Retention of benefits

Only two trials (Dean et al. 2000; Richards et al. 1993) included follow-up measures of outcome after completion of training. Little, if any, information can be concluded about retention of benefits. Functional improvements observed at the end of rehabilitation interventions (Kwakkel et al. 1999) have been shown to disappear at a later stage (Kwakkel et al. 2002), probably due to continued improvements in the control group rather than deterioration in function (Langhorne 2002). Increases in physical fitness are reversible, if training is reduced or stopped then cardiorespiratory and skeletal muscle adaptations will be lost. Therefore the benefits of fitness training interventions may be prone to being short-lived.

In summary functional benefits mediated by increased physical fitness may not be sustained unless some form of training stimulus is maintained. At present there are no data examining facilitation of continued exercise after the end of fitness training. Long-term follow-up measures should be incorporated into future fitness training trials.

9.9.3.4. Effect of initial patient status on outcome measures

There were not enough data to determine the effects of disability, ambulatory status or degree of hemiparesis.

9.9.3.5. Effect of physical activity performed by control groups

There are not enough data to draw conclusions about the effect of different control group conditions on outcome; in addition there are too many other factors that make it difficult to isolate any effect.

9.9.3.6. Effect of trial quality

Too few data prevent conclusions being drawn about the effect of trial quality on outcome. This was exacerbated by two other factors. First, one element of the validated quality scale used (Jadad et al. 1996) relies on trials being described as double blind or not. Exercise intervention trials can never be double-blind therefore modifying the scale to instead score trials as being outcome assessor-blinded or not may undermine the validity of the tool. Second the few trials that were scored as 'good' comprised very different types of intervention that spanned the whole range of types of exercise, e.g. cardiorespiratory training (Pohl et al. 2002b; 'A' and 'B'), strength training (Kim et al. 2001) and mixed training (Richards et al. 1993), which makes the effects of 'good' trial quality difficult to isolate.

9.9.3.7. Sensitivity analyses

Although one of the proposed sensitivity analyses was undertaken there were too few trials and highly variable interventions for these analyses to be of any value.

9.9.3.8. Summary of findings

a) Few of the data in this review relate to the acute (<1 month) phase post-stroke.

b) This review suggests that stroke patients can adhere to a variety of short term fitness training regimens during usual care or after usual care interventions.

c) The lack of primary outcome measures of disability, dependence and death do not allow any conclusions to be drawn at the present time. More disability data will be forthcoming from identified ongoing trials.

d) Cardiorespiratory training did not improve cardiorespiratory fitness. Several ongoing studies examine cardiorespiratory interventions.

e) Cardiorespiratory training, particularly using a treadmill, improved maximum walking speed and reduced the degree of dependence on others during ambulation.

f) Strength training data are few and inconclusive. One strength training study is ongoing (Lum; n=60), however this intervention is limited to the upper body.

g) Mixed training data are few and inconclusive. Several ongoing studies comprise mixed interventions.

h) Outcome data concerning physical function and health related quality of life are scant and inconclusive.

i) Outcome data regarding mood and adverse events were not available.

j) It was not possible to determine the effect of factors (e.g. 'dose' and type of training) that could influence the primary and secondary outcome measures.

k) Observations in this review support the idea that benefits may be greater when fitness training is specific or 'task-related'.

l) There were methodological issues with every included study that could undermine the generalisability and/or validity of the findings.

9.9.3.9. Issues for research

Generalizability - Future research should aim to establish the proportion of stroke patients with no contraindications to fitness training interventions, the proportion who typically become enrolled in training interventions and are available for follow-up, and the degree of adherence to training that can be achieved. Within the included trials most participants were recruited months or years after stroke and were typically those with milder strokes (e.g. most were ambulatory). Further research is needed to examine whether fitness training is beneficial soon after stroke and for those who are more disabled.

Types of training Intervention - In general, larger trials of combined cardiorespiratory and strength training are required to explore the extent of potential benefits to patients. The benefits associated with different modes of exercise (e.g. walking, cycling or circuit training) are not well understood nor are the potential costs of each. Delivery of training to individuals or groups has both cost and compliance issues. The effect of timing of fitness training, either early after stroke during usual care, or post-rehabilitation is not known. Where benefits are shown the dose-response relationship between post-stroke training and any benefits should be established in order to optimize interventions.

Randomization - Age and gender have a strong influence on physical fitness (Young 2001) and therefore should be balanced during randomization in small trials.

Researcher blinding - Those involved with outcome assessment in trials of fitness training are susceptible to being un-blinded. A test of blinding should be applied after each outcome assessment and reported statistically.

Outcome measures - Diverse outcome measures make pooling data from different studies difficult (Greener and Langhorne 2002). Therefore the concept of a 'core set' of outcome measures suitable for stroke patients (Tennant 2000) is attractive. In particular, disability and dependence should be considered primary outcome measures in trials of fitness training for stroke patients.

Long-term follow-up - Improvements in physical fitness following training are known to be transient therefore the long-term retention of any benefits should be examined routinely in training studies.

Patient Transport - Duncan et al. (1998) noted that only 3/20 patients could have participated if transport had not been provided. The study by Dean et al. (2000) reported that 1/12 patients were lost to follow-up because of transportation costs. This suggests that patient transport may be an important issue for patient recruitment and retention in trials.

Cochrane Review of Physical Fitness Training after Stroke - Summary

Implications for Practice (in 2004)

There is very little evidence available that can influence practice at the present time. Data suggesting that the fitness of some stroke patients can be improved with training suffers from methodological problems. The extent to which improved fitness might translate into other functional benefits is unclear. Benefits observed in fitness, mobility and physical function appear to be compatible with the concept of specific or 'task-related' training. This suggests that if training is provided after stroke it may be more beneficial if the form of exercise closely resembles the desired functional outcomes. However there are inadequate data to either encourage or discourage physical fitness training after stroke.

More exploratory research is required in this area. There are a number of important unanswered research questions and some important considerations for the design of such research.

Implications for Research (in 2004)

Fitness training after stroke is an under-researched area. Beyond improvements in some measures of ambulation little is known about the benefits of fitness training in stroke patients, or the optimal regimen for improving fitness. There is a need for larger trials addressing simple questions of effectiveness, particularly soon after stroke. In addition smaller detailed studies are warranted examining the effects of different types of training and the manner of their delivery after stoke.

10. Fitness training or relaxation after stroke? - an exploratory randomized controlled trial

10.1. Abstract

OBJECTIVES: To determine the feasibility and effect of physical fitness training after stroke.

DESIGN: Randomized controlled exploratory trial comparing physical fitness training (including progressive cardiorespiratory and strength training) with relaxation (non-exercise attention control).

SETTING: Interventions were performed in a rehabilitation hospital.

PARTICIPANTS: Sixty-six independently ambulatory patients (mean age 72 years, 36 men) without significant dysphasia, confusion, or medical contraindications to exercise training who had completed their usual rehabilitation and had been discharged from hospital.

INTERVENTION: Both interventions were held three times a week for 12 weeks. Up to seven patients attended each session.

MEASUREMENTS: The following measures were recorded at baseline, end of intervention (3 months), and 7 months after baseline: i) Physical fitness (walking economy, oxygen uptake kinetics and explosive lower-limb extensor power); ii) Physical function (comfortable walking speed, functional reach; sit-to-stand; timed up-and-go); iii) Global measures disability (FIM Instrument; Nottingham Extended ADL; Rivermead Mobility Index; elderly mobility score); iv) Quality of life (Medical Outcomes Study 36-Item Short Form Questionnaire, ver.2 [SF-36]; and v) Mood (Hospital Anxiety and Depression Score).

RESULTS: The median number of intervention sessions attended was 33.5 (IQR 27 to 36) for exercise and 34 (IQR 28 to 35) for relaxation, 92% and 92% respectively. Compliance with each individual fitness training exercise ranged from 94% to 99%. At 3 months, only walking economy, $\dot{V}O_2$ kinetics, timed up-and-go and SF-36 role-physical were significantly better in the exercise group (analysis of covariance). At 7 months, role-physical was the only remaining significant difference between groups.

CONCLUSION: All elements of this trial of physical fitness training for ambulatory stroke patients (recruitment, measurements, randomization and intervention) were feasible. The fitness training intervention led to significant but transient improvements in some aspects of cardiorespiratory fitness and physical function, and a longer lasting improvement in perceived effect of physical health on daily life. The intervention had no effect on disability or mood.

10.2. Introduction

This RCT is published (Mead et al. 2007b) and referred to as 'STARTER' (Stroke: A Randomized Trial of Exercise or Relaxation; Appendix 14.12).

10.2.1. Rationale

The Cochrane review (Chapter 9) identified the need for trials examining the effectiveness of fitness training after stroke. In addition to a general lack of trial data on effectiveness, the existing data has a number of problems. This included i) small sample size, ii) diverse forms of intervention, iii) non-specific (non task-related) interventions, iv) short periods of training, v) few clinical measures of global disability, vi) few fitness outcomes, vii) little feasibility data and viii) little follow-up data examining retention of benefits after the interventions have finished.

Therefore an exploratory RCT of fitness training after stroke was proposed with a sample size of 90. The training intervention would be 'mixed' (cardiorespiratory plus strength training) and 'task-related' (*Specificity*; 3.3) in order to maximize functional benefits. The programme would be long enough (12-weeks) to allow fitness to improve (*Programme duration*; 3.3). Outcome measures would include clinical scale measures of 'global disability', and measures of physical fitness to help elucidate the mechanism of any fitness training-mediated benefits. Outcome measures would be followed-up 4-months after the end of intervention since benefits of fitness training (*Reversibility*; 3.3) and rehabilitation (9.9.3.3) may be short-lived. Finally the feasibility of key aspects of trial design would be examined in order to guide possible future definitive trials of exercise after stroke.

10.2.2. Objectives and research questions

The purpose of this study related to the development of RCT evidence. The trial had two objectives which comprise a number of research questions. The data would also be suitable for inclusion in subsequent systematic review.

Objective 1

Quantify the effects of the intervention and the variability of outcome measures in order to guide power calculations for a definitive trial.

Research Question -

What is the effect of training versus a control intervention on physical fitness, physical function, disability, health related quality of life and mood?

Objective 2

Evaluate whether a trial of physical fitness training is feasible for people who have had a stroke by testing the feasibility of key components of the trial design.

Research questions -

Recruitment	-What proportion of stroke patients are eligible?
	-What proportion of stroke patients are enrolled?
Measurements	-What proportion of participants attend follow-up assessments?
	-Is the battery of outcome measures feasible and appropriate?
Randomization	-Is the proposed system feasible?
Intervention	-What proportion of participants drop out, and when?
	-What proportion of intervention sessions is attended?
	-What proportion of participants comply with the content of the intervention sessions?

10.3. Methods

The trial involved a group of people with varying roles, e.g. administration, intervention delivery and design, recruitment and randomization. My contributions are catalogued in Appendix 14.2.

10.3.1. Design

Randomized controlled trial (Figure 10.1) comparing mixed physical fitness training (cardiorespiratory plus strength training) with relaxation (attention control) with outcome assessed at baseline, at the end of intervention (3-month follow-up) and 3 months after the end of intervention (7-month follow-up).

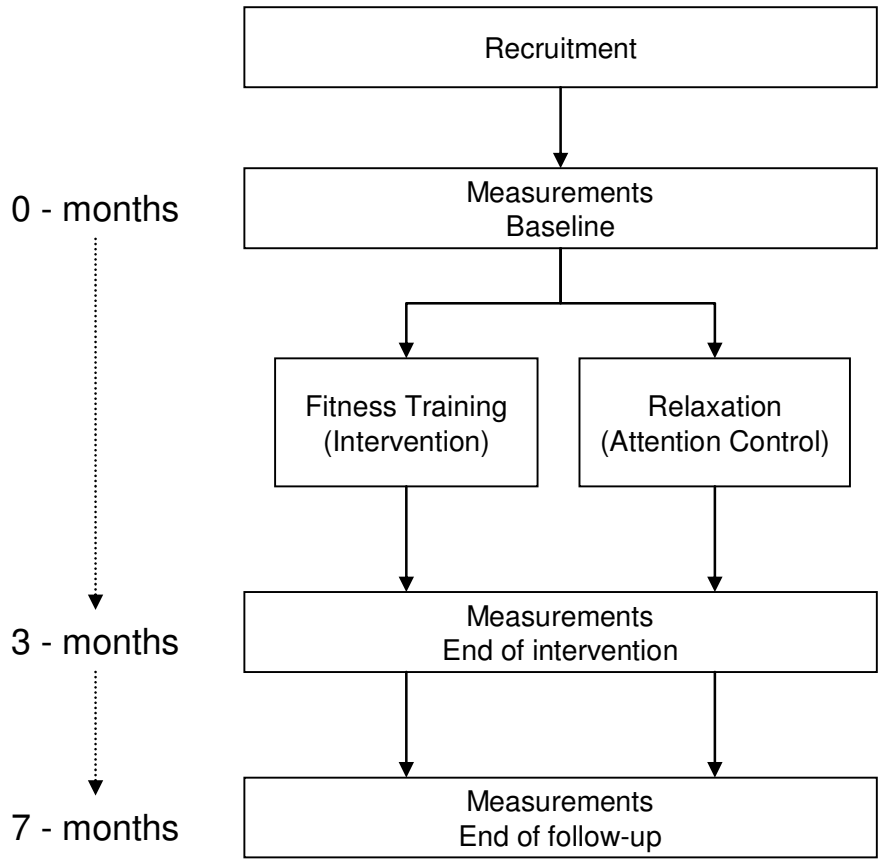


Figure 10.1 Summary of the RCT design

10.3.2. Participants

10.3.2.1. Recruitment

Between October 2002 and July 2004, the stroke wards at three hospitals were visited at least once a week; in addition stroke patients who were admitted and discharged from the medical assessment ward were screened when they attended the Royal Infirmary stroke clinic for follow-up. From August 2003, suitable patients who had been inpatients or who had attended the stroke clinic at the Western General Hospital were referred to the trial. All recruitment hospitals were part of the Lothian Managed Clinical Network for stroke and therefore adopted similar patterns of stroke care. Patients identified during inpatient care were approached directly and asked to participate; those identified on medical history were approached via their GP or consultant (Medical Research Council 2000b). Only patients able to give consent were recruited. Those with incapacity, as defined by the Adults with Incapacity (Scotland) Act (2000), were not eligible. Written informed consent was obtained by the investigator recruiting the patients (GM, AY, IC).

10.3.2.2. Eligibility criteria

Inclusion criteria - i) independently ambulatory and ii) due to complete both their inpatient and outpatient rehabilitation prior to the start of the next set of classes. *Exclusion criteria* - i) dysphasia or confusion severe enough to prevent informed consent or impair safety in exercise classes, ii) living outside our catchment area (i.e. central or south Edinburgh, suburbs south of Edinburgh) primarily to control transport costs and iii) medical contraindications to fitness training (Figure 10.2).

Figure 10.2 Absolute contraindications to fitness training (Dinan 2001).

Uncontrolled angina
Uncontrolled resting systolic blood pressure >180mmHg or resting diastolic blood pressure >100 mmHg
Uncontrolled resting tachycardia
Unstable or acute heart failure
Uncontrolled acute systemic illness (e.g. pneumonia)
Uncontrolled systemic disease (e.g. cancer, rheumatoid arthritis)*
Uncontrolled metabolic disease (e.g. diabetes, thyroid disease)
Uncontrolled visual or vestibular disturbances
Inability to walk without 'a lot of pain'*
Proven inability to comply with exercise instructions
Injurious fall without medical assessment

* Two contraindications additional to those summarised by (Dinan 2001).

10.3.2.3. Sample size

The purpose of this exploratory RCT was to establish feasibility and effect sizes to guide design and estimate sample size for a definitive trial, therefore sample size calculations were not necessary. Approximately 50 patients per month were admitted to the Royal Infirmary prior to the trial; assuming 10/50 met the eligibility criteria and that 50% provided consent, this would mean 5 patients per month could be recruited. Practical limitations of the intervention supervision and delivery also imposed a theoretical upper limit of ~15 new participants every 3-months, i.e. 8 per class. Therefore our recruitment target was n=90, with n=45 in each arm of the trial over 2 years.

10.3.3. Measurements

Measures were recorded on three occasions; at baseline within 2-weeks of the start of intervention (baseline assessment), as soon as possible (<2-weeks) after the end of intervention (3-month assessment) and as close as possible to the end of the 4-months follow-up period (7-month assessment).

Measurements were made in the Human Performance Laboratory, Ward 24, Royal Infirmary Edinburgh until May 2003, and thereafter in the Clinical Research Facility, New Royal Infirmary, Edinburgh.

One of four doctors (GM, AY, SS or AM) attended each baseline assessment where they reapplied the eligibility criteria, recorded clinical characteristics and performed a limited neurological assessment. All other measures were performed by one of four exercise physiologists (DS, CG, GC-L, CF). Where possible the same individual performed each participant's measures at baseline, 3-months and 7-months to minimize the influence of inter-individual error.

The exercise physiologists applied a battery of tests assessing a broad range of variables; these are summarized in Table 11.1. All measures were made in the same order and were determined during one session of around 2-hrs, which included time for a refreshment break.

Table 11.1 Measures used in the trial. Superscripted numbers identify the order in which the measures were made.

1 Physical fitness	
Economy of walking[10]	Section 7.3.2
Oxygen uptake kinetics[10]	Section 7.3.2
Lower limb extensor power (LLEP)[4]	Section 8.3.2
2 Specific measures of physical function	
Functional reach [5]	(Duncan et al. 1990)
Timed 3-m up-and-go [8]	(Podsiadlo and Richardson 1991)
Chair rising time [8]	(Skelton 1995)
Comfortable walking speed[10]	(Fitzsimons et al. 2005)
3 Global measures of disability and function	
FIM Instrument[1]	(FIM; 1993)
Nottingham Extended ADL (NEADL)[2]	(Nouri and Lincoln 1987)
Rivermead Mobility Index (RMI) [3]	(Collen et al. 1991a)
Elderly Mobility Score (EMS) [9]	(Smith 1994)
4 Health-related quality of life	
MOS Short Form Questionnaire (SF-36v2) [6]	(Ware et al. 2000)
5 Mood	
Hospital Anxiety and Depression Score (HADS)[7]	(Zigmond and Snaith 1983)

10.3.3.1. Physical fitness

Physical fitness variables were determined as described in Section 7.3 & 8.3.

10.3.3.2. Specific measures of physical function

Functional reach, comfortable walking velocity, timed 3-m up-and-go and chair rise time were determined as previously described (Section 8.3).

10.3.3.3. Global measures of disability and function

The following global indices of disability were recorded during face-to-face interview as previously described (Section 8.3); FIM Instrument (Guide for the uniform data set for medical rehabilitation 1993), Rivermead Mobility Index (Collen et al. 1991) and Nottingham Extended ADL (Nouri and Lincoln 1987). In addition the Elderly Mobility Scale (Smith 1994) was scored by including data from the measures of function (chair rising, walking speed and functional reach).

10.3.3.4. Health related quality of life

The SF-36 is the most widely used instrument for measurement of health related quality of life (Ware et al. 2000), and it has been widely used in people with stroke. The SF-36 was completed during a face-to-face interview. Eight domains of health and well-being were scored from the patient perspective (Physical functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health). Scores were normalized from 0 up to 100.

10.3.3.5. Mood

The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983) consists of one anxiety and one depression subscale, each consisting of seven items. Each item has four responses scored from 0 to 3. During face-to-face interview participants selected responses which best described how they felt during the previous week. Totalled item scores gave responses from 0 to 21 for each subscale, with higher values indicating mood problems. HADS is widely used after stroke, is

validated, and is appropriate for use in community-dwelling patients and those with no communication difficulties (Bennett and Lincoln 2006).

10.3.3.6. Suitability of the measures

Apart from physical fitness, all measures have all been previously used in studies of people with stroke so the measures are feasible. The same outcome assessors were used (where possible) for each participant therefore the repeatability of each outcome measure was investigated. The reliability of disability, quality of life and mood measures has been established (Ottenbacher et al. 1996; Daving et al. 2001; Green et al. 2001; Dorman et al. 1998; Bennett and Lincoln 2006). Some of the few studies reporting reliability of the physical fitness and physical function measures, preferably in people with stroke, are summarised in Appendix 14.13.

10.3.4. Randomization

After baseline assessment each participant was allocated either a programme of physical fitness training or relaxation using a bespoke internet-based software programme (David Perry; Department of Clinical Neurosciences, University of Edinburgh). The software applied a 'minimisation algorithm' (Treasure and MacRae 1998), this generates groups of a) similar size and b) similar selected characteristics. Three dichotomised variables were chosen to categorise important characteristics of the participants, these were age (<75 or ≥75 years), gender and baseline disability (FIM Instrument score, <115 or ≥115). The frequency of each characteristic within each of the two groups previously allocated influences each subsequent allocation.

New participants would be allocated to a group which results in the smallest overall between group differences; an example is shown in Appendix 14.14.

10.3.5. Blinding

Participant blinding - Where physical interventions such as exercise are employed true participant blinding cannot be achieved simply because the participants will be aware that they are performing movements involving a degree of physical exertion. This is a potential source of bias. However we attempted to achieve a degree of 'participant blinding' by explaining that both interventions may have benefits.

Investigator blinding - Investigators involved in outcome assessment in trials of physical interventions such as exercise, are vulnerable to being un-blinded. For example, this can occur if the intervention is inadvertently observed (Dean et al. 2000) or the participant reveals their intervention allocation to the outcome assessor (Kwakkel et al. 1999). Therefore we aimed to reduce the possibility of accidental unblinding in the trial. Firstly the exercise and relaxation classes were held in a hospital at a different geographical location (Liberton Hospital, Edinburgh) than the rest of the trial team. Secondly, prior to the 3-month and 7-month follow-up assessments all participants were instructed not to discuss the content of their classes or the time of day which these occurred.

The allocation software was password protected and access limited to trial administrators (SQ, CR) and principal investigator (GM) none of whom who were involved in either delivering the interventions or assessing outcome.

During the 3- and 7-month assessments any explicit accidental un-blinding of group allocation was recorded along with the reason for this occurring. Where no explicit un-blinding occurred the outcome assessor recorded a 'guess' of treatment allocation.

10.3.6. Intervention programmes

One advanced exercise instructor (IC) delivered both the exercise and relaxation interventions throughout the trial. Both interventions took place within the same venue, The Old Function Hall, Liberton Hospital, Edinburgh.

The trial interventions began in October 2002 and continued until September 2004. Each participant attended an intervention programme for 3 days per week (Monday, Wednesday and Friday) for 12 weeks; adjustment was made for any public holidays ensuring all participants could complete 36 sessions. Where individual absence occurred (due to illness or other reason) up to 3 additional sessions could be added to make up lost sessions. If total absence exceeded 3-days the participant would complete less than 36 sessions.

Both interventions were delivered to small groups of participants (ranging from 3 to 9). The maximum group size was constrained by i) equipment availability, and ii) the need for safe supervision by a single instructor. During week 1 the instructor familiarized the participants in both arms of the trial with the protocol, techniques and any equipment. Once a week blood pressure was measured. Participants were asked if they had fallen since the previous session. Each session lasted a total of 1

hour and 15 min, this allowed time for refreshments and socializing with fellow participants in the classes.

In total there were six, sequential, 12 week 'iterations' each containing both interventions one delivered in the morning and one in the afternoon.
Allocation of interventions to morning or afternoon was randomized for two reasons. Firstly, an intervention (exercise or relaxation) delivered in the morning or afternoon may influence physical activity levels during other parts of the day. For example, exercise in the morning may cause fatigue in the afternoon resulting in an overall reduction in habitual physical activity. Secondly, randomization prevented participants accidentally unblinding the outcome assessors by revealing the time of day of their sessions. A restricted randomization (Schulz and Grimes 2002b) was employed to allocate the exercise and relaxation group of each of the six iterations to morning or afternoon. This ensured random allocation but preserved an equal number of exercise and relaxation classes in both morning and afternoon.

10.3.7. Exercise Intervention

a) Rationale for content

The Cochrane review indicated the importance of 'task-related' training with the available data showing benefits to mobility were exclusively associated with training interventions involving walking (Section 9.9.3.2). Since ambulation is of key importance to stroke patients, this mode of training was included in the programme. There was little other information to guide the formulation of training. Therefore other sources were drawn upon as a guide to a programme most suitable for stroke.

Community exercise sessions designed for the UK charity *Different Strokes* were used as guide. *Different Strokes* have provided supervised group circuit training programmes aimed at younger stroke patients. The mode of training is mixed, incorporating both cardiorespiratory training (usually cycle ergometry), and strength training. The programme includes functionally relevant exercises and systematic progression of exercise intensity. This programme was perceived as very successful; the participants enjoyed the social contact, felt better, and reported being more able to complete day-to-day activities.

The *Different Strokes* intervention was designed for younger people with stroke. However it was anticipated that older people with stroke would be recruited so the exercise modes, initial intensity and progression were based on an intervention to reduce falls in older frailer people (Skelton and Dinan 1999). This intervention was evaluated in the *Falls and Exercise Management Study* (FAME; Skelton et al. 2005) with participants aged 72.7 years (SD 5.8). The FAME intervention addressed all the basic components of physical fitness important for the general population (ACSM 1998b) and older people (ACSM 1998a), along with specific and progressive fall management exercises aimed at improving postural stability. There are a number of risk factors for falls including impaired muscle strength, poor balance and gait problems. These risk factors can all be influenced by exercise and, along with falls, are all common post-stroke problems (Section 1.3).

Since cardiorespiratory fitness and muscle strength are both associated with functional limitation (Section 2.3.1) and both clinical and pre-clinical disability

(Section 2.3.2), it is plausible that improving both of these is most likely to be of benefit than improving just one.

Each exercise session started with a gentle warm-up for 15 to 20 minutes to increase circulation (e.g. marching), mobility (e.g. shoulders) and flexibility (e.g. seated hamstring stretches). The exercise training comprised cardiorespiratory training and resistance training components; together these were allocated 15 minutes in week one, increasing to 40 minutes by week 12.

b) Cardiorespiratory training

The cardiorespiratory training was delivered in a 'circuit training' format. A 'circuit' refers to a group of different exercises which are each performed at 'stations' located adjacent to one another in a room or gym; this is to facilitate rapid transition between exercises. 'Circuit training' involves performing the exercises at each station in a predefined sequence, with minimal or no rest between each. A group of participants thus can all exercise together, distributed between the stations, all rotating between stations, possibly completing more than one 'circuit' of all the different exercises.

Circuit training offers a number of benefits: i) The format reduces competition within a group encouraging each to work at their own pace, ii) few participants at each station allow the instructor to supervise stations requiring more technical attention than others, iii) encourages social interaction and a relaxed environment, iv) facilitates easy control of individual and group progression via manipulation of duration, exercise number and type etc, v) allows an 'interval training' approach, that

is alternating more demanding exercises with those using different muscle groups and/or requiring less effort; this maximizes potential training effects and reduces fatigue.

The cardiorespiratory training began in week 1 as a circuit of four exercise stations, i) cycle ergometry, ii) ball raising exercise, iii) shuttle walking, iv) standing chest press, with v) stair climbing and descending was added from week 4 onwards. Any delay between the exercise stations was filled with 'marching on the spot' thus the total duration of the circuit comprised continuous exercise.

Throughout the cardiorespiratory training programme, progression was achieved by increasing i) the total duration (from 9 min in Week 1 to 21 min in Week 12), ii) the number of stations from 4 to 5, and iii) the intensity and technical difficulty of the exercises. Brisker efforts were encouraged during all exercises as the participants became more familiar with the training session.

The endurance training ended with a gentle cool down and stretches whilst standing to keep participants mobile prior to the resistance training component. The form of each cardiorespiratory exercise is summarised in Figure 10.3 and the structure of the progression in Table 14.3.

Figure 10.3 The cardiorespiratory training components of the fitness training intervention.

a) Cycle ergometry

Technique
Continuous, submaximal steady-state cycling

Intensity
Small weekly increases in pedal cadence and/or resistance whilst maintaining an Rating of Perceived Exertion (6-20 scale) of 13-16

Modifications
Reduced workload
Walking substituted
Physical support by instructor during exercise
Limbs secured to pedals or handlebars

b) Ball raise

Technique
Raising and lowering an exercise ball (diameter 55-cm) using both arms

Intensity
Mass of ball 1.5 kg

Modifications
Physical assistance by instructor holding the exercise ball

c) Chest Press

Technique
Same concept as press-ups

Intensity
Use of chair back = less intense
Use of wall = more intense (shown)

Modifications
Physical assistance by instructor

Cont./

d) Shuttle walking

Technique
Shuttle walking back and forth.
Walking aids permitted

Intensity
'Brisk' or 'with energy' in one direction and 'comfortable but not slow' in the other

Modifications
Physical assistance by instructor

e) Stair ascending and descending

Technique
Repeated climbing and descending of flights of 4 stairs.

Intensity
Comfortable safe speed

Modifications
Physical assistance by instructor

c) Resistance training

The resistance training included; i) an upper back strengthener, ii) a triceps extension exercise, iii) lifting a weighted pole and iv) a sit-to-stand exercise. The upper back and the tricep exercises were both performed seated using elastic resistance training bands (Thera-Band™, The Hygenic Corporation, 1245 Home Avenue, Akron, Ohio 44310 USA). Four types of Thera-Band™ were used offering progressively greater degrees of resistance relative quantified as force requiring 100% elongation: These were 19N ('red'), 22N ('green'), 31N ('blue') and 65N ('grey') per 100% elongation (Scottish Intercollegiate Guidelines Network (SIGN) 2002b). Training progressed from 4 repetitions using a red band to 10 repetitions using a grey band by week 12. Participants were allowed to progress at the scheduled increase in band resistance only after demonstrating they could complete a performance test involving 16 repetitions without a rest. The pole lifting exercise was performed whilst standing and progressed from 4 repetitions with a light pole (mass 0.22 kg) to 15 repetitions with a heavier pole (mass 3.6 kg) by week 12. The sit-to-stand exercise was resisted by body mass. This progressed from 4 to 10 repetitions by week 12, and became more difficult though introduction of pauses during rising from the chair, and/or changing posture to limit upper body involvement thus further isolating and overloading the lower limb extensor muscles. After the resistance training there was a gentle cool down and some flexibility exercises lasting 10 to 15 minutes. The form of each resistance training exercise is summarised in Figure 10.4 and the structure of the progression in Table 10.3.

Figure 10.4 The strength training components of the intervention

a) Upper back strengthener

Technique
Thera-Band resisted repeated contraction

Intensity
Four grades of Thera-Band offering progressively higher resistance
19N ('red'),
22N ('green')
31N ('blue')
65N ('grey') per 100% elongation

Modifications
Reduced work
Instructor assistance
Limb secured to band

b) Tricep extension

Technique
Thera-Band resisted repeated contraction

Intensity
Four grades of Thera-Band offering progressively higher resistance
19N ('red'),
22N ('green')
31N ('blue')
65N ('grey') per 100% elongation

Modifications
Reduced work
Instructor assistance
Limb secured to band

c) Pole lifting

Technique
Lifting a weighted pole involving legs and lower back

Intensity
Light pole (0.22 kg)
Heavier pole (3.6 kg)

Modifications
Reduced work
Instructor assistance

Cont./

d) Sit to stand exercise

Technique
Rising from and sitting in a chair to isolate and overload the lower limb extensor muscles

Intensity
Four progressively more difficult approaches to isolate legs and minimise upper body involvement
i) Basic
ii) Pause
iii) Arms folded (shown)
iv) Pause + arms folded

Modifications
Reduced work
Instructor assistance

d) 'Tailoring' of the programme

Post-stroke problems are very diverse and some may render certain exercise tasks difficult or impossible. Therefore each exercise could be individually 'tailored' (shortened, modified or replaced with an alternative) appropriate to individual impairments in order that the programme was as inclusive as possible and to maximize compliance. The modifications for each exercise are included in Figure 10.3 (Cardiorespiratory training) and Figure 10.4 (Strength training).

Table 10.3 The STARTER exercise intervention and the planned weekly progression of training quantity and intensity.

Training		Week of fitness training intervention											
Mode	Load and volume	1	2	3	4	5	6	7	8	9	10	11	12
a) Cardiorespiratory Training Circuit													
Cycle	min	2	3	3	4	4	5	5	6	6	6	6	6
Ball raise	min	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1
Shuttle Walk	min	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1
Chest Press	load	Chair					Wall						
	min	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1
Stairs*	min	*	*	*	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1	2 x 1
TOTAL	min	9	12	12	15	15	18	18	21	21	21	21	21
b) Strength Training Circuit													
Upper back strengthener	load†	Red (19N)			Green (22N)		Blue (31N)			Grey (65N)			
	sets x reps	1 x 4	1 x 8	1 x 8	2 x 6	2 x 6	1 x 6	1 x 6	2 x 6	1 x 6	1 x 8	1 x 10	1 x 10
Tricep extension	load†	Red (19N)			Green (22N)		Blue (31N)			Grey (65N)			
	sets x reps	1 x 4	1 x 8	1 x 8	2 x 6	2 x 6	1 x 6	1 x 6	2 x 6	1 x 6	1 x 8	1 x 10	1 x 10
Pole lift	load	Stick (0.22 kg)				Mixed‡		Pole (3.6 kg)					
	sets x reps	1 x 4	1 x 8	1 x 8	1 x 8	1 x 8	1 x 8	1 x 3	1 x 6	1 x 10	1 x 15	1 x 15	1 x 15
Sit-to-stand	load§	Basic			Hold	Fold		Hold plus Fold					
	sets x reps	1 x 4	1 x 8	1 x 8	1 x 8	1 x 8	1 x 8	1 x 8	1 x 8	1 x 10	1 x 10	1 x 10	1 x 10

Abbreviations: Reps repetitions; N Newtons

* Stair ascending and descending not introduced until week 4

† Thera-Band elastic resistance reported as Newtons per 100% elongation

‡ Use of a stick and pole during transition from Weeks 4 to 7

§ Difficulty of the basic sit-to-stand (basic) increased by introducing pauses (hold), folded arms (fold), or both (hold plus fold).

e) Exercise intervention measures

For each participant, attendance at, and compliance with the exercise interventions were recorded on a daily basis. Reporting of these data will be limited to the first 36 consecutive sessions of each participants intervention programme regardless of whether any of the three catch-up days were used: This allows simple evaluation of the exact incidence of problems which may interrupt the delivery of a regular programme of exercise or relaxation after stroke.

Compliance with the intended protocol (form, quantity, intensity and progression) for each individual exercise component (Figure 10.3 and Figure 10.4) was recorded for every participant on each occasion they attended. Compliance with the intended protocol was recorded as i) completed, ii) modified ('tailored'), or iii) not completed. Any 'tailored' modifications to the exercises were recorded, along with the reasons for modification. The reason for each non-attendance was also recorded.

During cycling pedalling cadence ($rev \cdot min^{-1}$) and the resistance applied to the ergometer flywheel (kg) were recorded. On the Monark cycle ergometers used the product of these variables allows calculation of the average rate of work (Watts), and hence the total amount work completed (Joules).

Exercise intensity was also monitored using perceived exertion and pulse monitors. These approaches are recommended for the exercise component of cardiac rehabilitation to enable regulation of exercise intensity by both instructor and participant (Scottish Intercollegiate Guidelines Network (SIGN 57) 2002).

Rating of perceived exertion (RPE; 6 to 20 scale; Borg 1982) was monitored by the exercise instructor during cycling to guide intensity, and recorded at the end of cycling. This RPE tool provides a subjective measure of the intensity of exercise and effort and is scored by the participant between 6 ('no exertion at all') to 20 ('maximal exertion'). RPE measured using this instrument increases as a linear function of exercise intensity and thus closely correlates with physiological variables such as $\dot{V}O_2$ and heart rate which also increase linearly.

Each participant had their heart rate monitored and recorded every 5 seconds throughout one of their three weekly sessions using telemetric heart rate monitors (Polar Electro, Finland).

Exercise Summary	
Programme	12 weeks
Frequency	3 days per week
Intensity	Rating of perceived exertion 13-16
Duration	15 min (week 1) increasing to 40 min (week 12)
Training Type	Mixed cardiorespiratory and strength group circuit
Specificity	Task related components; stair ascending/descending, chair rising and walking
Progression	Cycling intensity, exercise duration, repetition number, task complexity

10.3.8. Relaxation Intervention

a) Rationale for content

Relaxation was selected as non-exercise 'attention control' to balance social contact time between groups and control for the physical activity involved in travel to and from the intervention location. Exercise and relaxation invoke opposite physiological responses; exercise is hypermetabolic whilst relaxation is hypometabolic. This means no physiological training effect can occur in either cardiorespiratory fitness, or muscle strength and power. Therefore relaxation may be a good control for RCTs examining the effects of fitness training after stroke. Relaxation has been used as the attention control in an RCT of cardiorespiratory training for people with brain injuries, including stroke (Bateman et al. 2001). Although relaxation has been employed for many years in cardiac rehabilitation little is known about relaxation for people with stroke.

b) Relaxation techniques

Relaxation is a psychosocial intervention which can be defined as '*teaching the individual to induce a reduction in tension within themselves, without using any external means*' (van Dixhoorn and White 2005). The usual content of relaxation therapy varies and involves techniques such as imagery, postural changes, breathing and muscle relaxation; some methods also include muscle contraction. Three relaxation techniques were selected for the attention control, i) diaphragmatic breathing, ii) progressive muscle relaxation, and iii) visualization and imagery, followed by a rest and review period. Techniques involving muscular contraction

were omitted to avoid unintentional fitness training. The duration of the three relaxation components increased from 20 minutes at Week 1 to 49 minutes at Week 12. Each session also began with a 10 minute 'warm-up' (welcome, settle in, feedback), and finished with a 5-min 'warm-down' (informal feedback, tea, social interaction).

To facilitate relaxation the intervention was performed seated, cushions were available and seating posture was monitored (Figure 10.5). The environment was also adjusted; lighting was dimmed, room temperature was warm (and blankets available), and instrumental background music was used during the three intervention components.

Figure 10.5 Typical view of the group relaxation sessions.

The relaxation intervention was made progressive by increasing the length of the relaxation periods, and the number of body parts focussed on, and by reducing the review periods.

c) Relaxation intervention measures

Attendance was recorded in the same way as for the exercise group. Instead of compliance we recorded any 'threats to relaxation', for example those arising from i) noise, ii) discomfort, iii) health issues, iv) the facility or v) anxiety.

Relaxation Summary	
Duration	12 weeks
Frequency	3 days per week
Time	20 min (week 1) increasing to 49 min (week 12)
Type	Deep breathing & muscular relaxation

10.3.9. Data preparation

The raw data were recorded in a booklet intended for data collection by interview, not self completion. The data were then transcribed into a spreadsheet (Microsoft Excel) file with a data structure corresponding to the forms which also calculated any summary variables derived from the raw data (e.g. scale totals, economy).

We decided not to double enter any data sets; instead an independent person checked entered data from a random 10% sample of data collection forms across all iterations. These showed transcription errors in 0.4% of the entered fields.

All entered raw data and calculated variables were checked for any unlikely, impossible or missing values; this included range checking of continuous variables and scales, validity and correct order of dates. Anomalies were checked against the data collection forms. If missing data could not be retrieved the reasons for the missing data were recorded where possible.

Outcome data were assessed graphically and statistically for normality. Data with skewed distributions were appropriately transformed to a normal or near-normal distribution when possible. Outcome measures with large ceiling or floor effects (i.e. a large proportion of measures reached the maximum or minimum possible score) could not be transformed and so were omitted from the main analyses.

10.3.10. Data analysis

The primary statistical analyses were performed by the trial statistician (SL). The exercise and relaxation groups were compared by applying the intention to treat (ITT) principle (Montori and Guyatt 2001). All randomized participants were encouraged to attend the 3- and 7-month assessment irrespective of level of attendance and compliance, or whether they dropped out of the interventions.

Missing data items at the 3- and 7-month assessments, including those arising from loss to follow-up, were replaced using the last observation carried forward (LOCF) method (Shao and Zhong 2003). Missing data items during baseline assessments occurred occasionally for different reasons (e.g. pain, dizziness in the patient, equipment failure); this affected 2.7% of these data points. Where possible, these missing data were imputed using the first observation carried backward to preserve the ITT design as closely as possible (Doraiswamy et al. 2001). The LOCF approach has been validated for two-group, balanced designs like STARTER (Shao and Zhong 2003). Imputation of data items missing at follow-up is superior to the elimination of the participants (Streiner and Geddes 2001), whilst imputation of data for those lost to follow-up remains controversial (Montori and Guyatt 2001). Imputation encourages conservative intervention effects but introduces a degree of uncertainty; this may be acceptable with few missing data/participants but when losses reach 20% this is a major threat to the validity of studies (Schulz and Grimes 2002a; Streiner and Geddes 2001). Sensitivity analyses were performed to compare the results of the available case analysis and ITT analysis; both produced similar results.

Between group differences - Analysis of covariance (ANCOVA) was used to test whether, and by how much, the outcome measures at the 3- and at 7-month assessments differed between the groups, controlling for their baseline levels. Adjustment was also made for age, gender, and time from stroke to baseline. Other participant characteristics were considered for inclusion as independent variables, including hospital of origin, but none was sufficiently influential. Possible reasons for outliers were investigated, but none was excluded. All models used the Type III sum-of-squares method. All two-way interactions were tested for significance.

Results are expressed as means of the outcome measures, adjusted for the influence of independent variables, and the significance of the difference between the exercise and relaxation groups. Effect size is also given as a standardized measure of the size of the treatment effect, independent of sample size. For this unbalanced ANCOVA design, partial eta-squared (η^2) is the appropriate effect size index; η^2 is small at 0.01, medium at 0.09, and large at 0.25 (Cohen 1977).

Within group changes - For each intervention, baseline assessments were also compared with the 3- and 7-month assessments using univariate analysis to determine the degree of within group change (paired t tests for normally distributed and transformed data and sign tests for non-normal data).

Frequency data were assessed using relative risk (RR) and the significance assessed using either Fishers Exact test or Chi squared analysis.

10.4. Results I - Feasibility of the trial design

10.4.1. Recruitment

Of those assessed and referred 68/313 (22%) were unable to participate due to medical contraindications and 98/313 (31%) lived too far away to participate (Figure 10.6). Of the 147/313 (47%) remaining who met the eligibility criteria (i.e. no contraindications and feasible to participate) 81/147 (55%) were unwilling, and 66/147 (45%) were willing to participate, 21% of the total. We recruited 66/90 (73%) of our target sample size.

10.4.2. Measures

Sixty four (97%) participants attended the 3-month assessment and 62 (94%) attended the 4-month follow-up. Each assessment lasted approximately two hours. In total, there were 192 assessment sessions.

During the 192 assessment visits data were obtained for most outcome measurements. For the questionnaire-based measures (disability, health related quality of life and mood) less than 3% of data were missing. For measures involving activity (physical fitness, specific physical function and Elderly Mobility Scale) missing data were more frequent; Timed up-and-go 8/192 (5%); chair rising 9/192 (5%); functional reach 10/192 (5%); Elderly Mobility Scale 12/192 (5%); LLEP 15/192 (8%); walking speed 14/192 (7%); walking economy 21/192 (11%); and $\tau\dot{V}O_2$ 68/192 (35%).

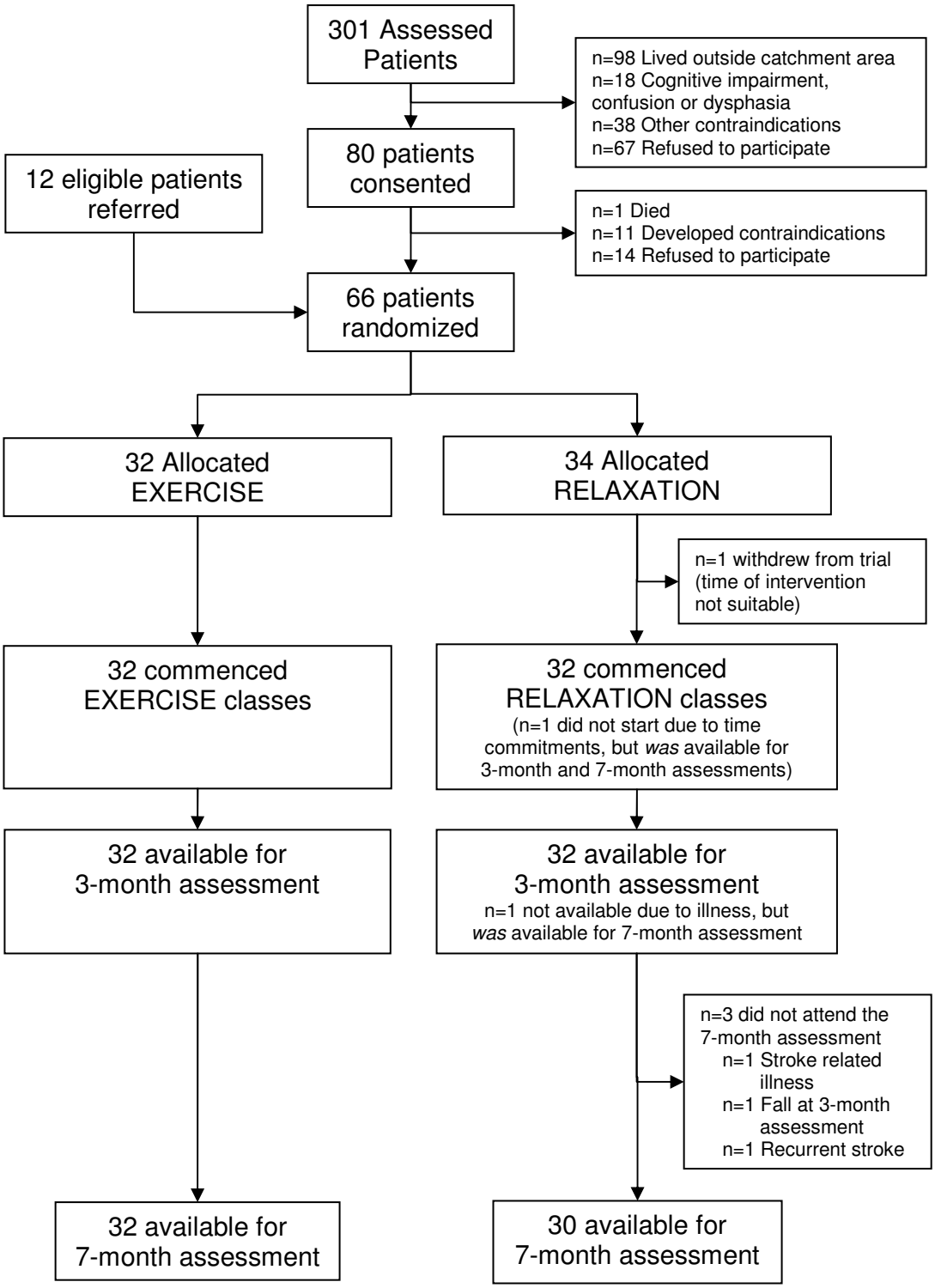


Figure 10.6 Flow of participants through the trial; 301 patients were assessed at the Royal Infirmary, Liberton and Astley Ainslie Hospitals, Edinburgh, and the 12 additional patients were referred from the Western General Hospital, Edinburgh 301 screened and 12 referred).

The reasons for non-completion of the individual tests included illness or limb pain (affecting, for example, the timed up-and-go), inadequate time, or because the assessors decided that the assessments would have excessively tired or upset patients. Those who were unable to perform the walking test were also unable to provide $\tau\dot{V}O_2$ data. However most missing $\tau\dot{V}O_2$ data occurred because the model-fitting iteration procedure could not converge on a satisfactory solution.

In several of the scales used a high proportion of the baseline data reached the maximum achievable score, this included the Elderly Mobility Scale (77%), and several domains of the SF-36; social function (54%), bodily pain (46%), and role emotional (43%). This prevented transformation to a normal distribution and analysis of the data affected.

10.4.3. Group allocation

The allocation software generated exercise and relaxation groups that were similar in size (n=32, n=34) and in characteristics of initial disability (FIM), age, and gender balance upon which the algorithm was based. The system was simple and fast to use.

10.4.4. Interventions

10.4.4.1. Attendance

During the first 36 consecutive sessions 11/32 (34%) in the exercise group and 4/34 (12%) in the relaxation group attended every session, thus achieving the full

prescribed ‘dose’. Inclusion of 3 catch up days increased this to 19/32 (59%) and 17/34 (50%) respectively.

The rates of attendance and absence are summarised in Table 10.4. The median % attendance is high; the majority of absences were due to pre-arranged personal commitments and medical reasons. The high rate of absence in the ‘other’ category for relaxation is elevated by two participants who did not commence the intervention.

Table 10.4 Rates of attendance and absence at 36 scheduled exercise and relaxation classes.

	Sessions Scheduled	Sessions Attended			Sessions Absent							
		Number		%	Number		Reasons for absence Total sessions lost (d) and participants affected (n)					
Group	Total n	Total n	Median (IQR)	Median (IQR)	Total n	Median (IQR)	Personal*	Medical†	Excluded‡	Trial§	Other¶	UN
Exercise (n=32)	1152	933	33.5 (27 to 36)	93% (75 to 100)	219	2.5(0 to 9)	53d (n=11)	96d (n=11)	26d (n=2)	1d (n=1)	35d (n=1)	8d (n=2)
Relaxation (n=34)	1224	998	34 (28 to 35)	92% (78 - 97)	226	3 (1 to 8)	48d (n=17)	76d (n=17)	0d (n=0)	2d (n=2)	96d (n=5)	4d (n=2)

Data; total number of sessions = 36 x n participants
Abbreviations; IQR inter-quartile range; d days; UN unknown
* includes holidays, domestic commitments, family commitments
† includes absence due to illness, GP and hospital appointments
‡ trial exclusion criteria prevented participation
§ includes transport problems
¶ includes people who did not want to continue

10.4.4.2. Compliance

Compliance with each individual exercise component was recorded for each participant on every occasion they attended the exercise class. The reason for any protocol deviation, and any tailored alternative offered, was recorded.

a) Cardiorespiratory circuit

The data in Table 10.5 show the five exercises of the cardiorespiratory circuit were completed per protocol, without modification (tailoring), on most occasions ranging from 83% (cycling) to 98% (chest press).

Tailoring of cardiorespiratory exercises was required by few of the participants, mostly relating to the use of cycle ergometers. Compliance improved when tailoring of exercises was incorporated, ranging from 94% (cycling) to 98% (chest press).

Where suitable tailoring could not be achieved the exercise was omitted. This was a rare occurrence in those attending classes affecting only 2 – 6% of the total instances of each cardiorespiratory exercise, and involving few participants.

Table 10.5 Compliance with cardiorespiratory training shown as the frequency (f; and %) of attended sessions which were completed per protocol, completed with modifications or not completed. Numbers in parentheses are participants affected (n).

Exercise	Total Attended Sessions containing exercise	Per-Protocol		Modified Protocol					Protocol Not Completed			
		f	%	f	%	Modifications	f (n)	Reason	f (n)	f (n)	%	Reason	f (n)
Cycling	933	778	83%	99	11%	Reduced workload	31 (6)	Recent fall	1 (1)	56 (4)	6%	High BP	1 (1)
								Pain	18 (3)			Could not use bike	4 (1)
								Depression	2 (1)			Various medical	9 (1)
								Fatigue	2 (2)			Leg discomfort	1 (1)
								Infection	3 (2)				
								Nausea	1 (1)				
								Unknown	4 (2)				
								Other (tooth extraction)	1 (1)				
						Walking substituted	65 (2)	Hip arthritis	33 (1)				
								Hip discomfort	32 (1)				
						Instructor Support	1 (1)	Impaired balance	1 (1)				
						Limbs Secured	38 (1)	Poor limb function	38 (1)				
Ball Raise	933	883	95%	36	4%	Instructor Assistance	38 (1)	Poor Right function	38 (1)	14 (7)	2%	High BP	2 (2)
												Hip Pain	1 (1)
												Various medical	7 (1)
												Numb legs	1 (1)
												Late	1 (1)
												Unknown	1 (1)
Walking	933	888	95%	31	3%	Instructor Assistance	32 (2)	Balance	21 (1)	14 (7)	2%	High BP	2 (2)
								Frail	11 (1)			Hip Pain	1 (1)
												Various medical	7 (1)
												Numb legs	1 (1)
												Late	1 (1)
												Unknown	1 (1)
Chest press	933	918	98%	0	0%					15 (7)	2%	High BP	2 (2)
												Hip Pain	1 (1)
												Various medical	9 (1)
												Numb legs	1 (1)
												Late	1 (1)
												Unknown	1 (1)
Stair Climbing	715 (from week 4 only)	696	97%	2	0.3%	Instructor Assistance	1 (1)	Balance	1 (1)	17 (2)	2%	High BP	1 (1)
						Other	1 (1)	Hip pain/arthritis	1 (1)			Hip Pain	9 (2)
												Various medical	8 (1)
												Numb legs	1 (1)
												Unable to step	4 (1)
												Unknown	1 (1)

During the cycling exercise the average amount of work completed (Joules), and the rate of work performed (intensity; Watts) increased progressively throughout the 12 weeks of training (Figure 10.7; Panel A and B). This was the consequence of i) increased duration of cycling, and ii) incremental increases in resistance applied to the ergometer flywheel.

The RPE measures did not change after week 5 of the programme (Figure 10.7; Panel C) even though continued increases of both the amount (+123%) and intensity (+49%) of exercise during this same period. After the initial 3 weeks the RPE values lay consistently within the range recommended (13-16) for continuous aerobic exercise which is intended to improve cardiorespiratory fitness in healthy people (ACSM 1998b).

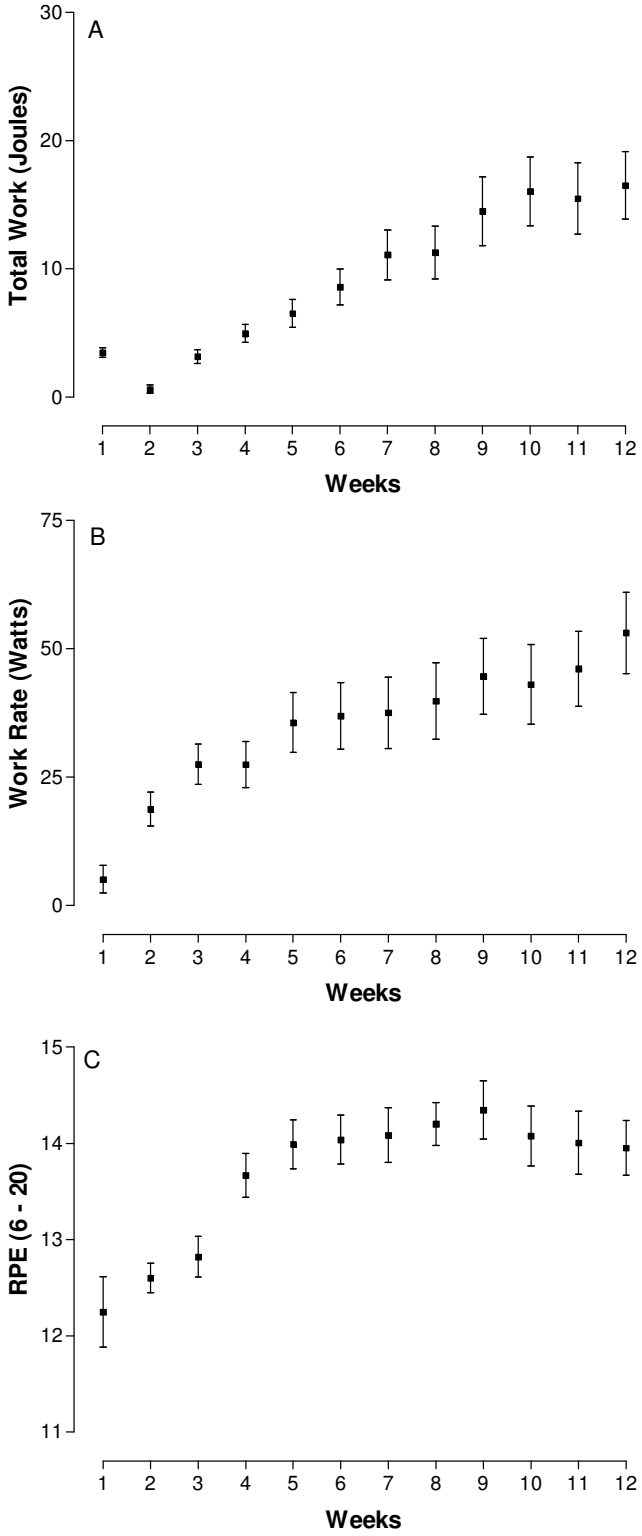


Figure 10.7 Responses to cycling exercise during 12 weeks of training; amount of work completed (Panel A), the intensity of work (Panel B), and rating (6 to 20) of perceived exertion (RPE; Borg 1982; Panel C). Week 1 was a familiarization week with most participants performing unloaded cycling (0 Watts). Weeks 2 to 12 were the core weeks of the training programme. The data are the mean and errors bars 1 standard deviation.

b) Strength training circuit

Compliance with strength training exercises is summarized in Table 10.6. On most occasions the strength exercises were completed per-protocol ranging from 89% (upper back strengthener) to 91% (sit-to-stand) of all attended sessions.

Compliance improved when modified exercises were included, ranging from 97% (upper back strengthener) to 99% (pole raise) of all attended sessions. Modifications included reduced workload, securing Thera-Bands to limbs or physical assistance by the instructor (e.g. to facilitate balance or movement). Non-completion of the protocol (in any form) was rare affecting few people on few occasions. Only 1 to 3% of all instances of strength training were not attempted.

The exercises involving Thera-Band and the weighted poles allow estimation of resistance in Newtons. The product of resistance and number of repetitions represents the strength training 'load' for each of these exercises. Strength training load increased throughout the programme, particularly after week 6, and this exceeded the planned progression of training load (Figure 10.8).

c) Relaxation (attention control)

The data in Table 10.7 summarise the degree to which external and internal factors interfered with relaxation.

Table 10.6 Compliance with strength training shown as the frequency (f; and %) of attended sessions which were completed per protocol, completed with modifications or not completed. Numbers in parentheses are participants affected (n).

Exercise	Total Attended Sessions containing exercise	Per-Protocol		Modified Protocol					Protocol Not Completed			
		f	%	f	%	Modifications	f (n)	Reasons	f (n)	f (n)	%	Reasons	f (n)
Pole Raise	933	850	91%	70	8%	Reduced work	61 (13)	Pain/immobility Emotional Problem Fatigue Recovery from injury Various Rejoining class Unknown / not recorded	22 (2) 1 (1) 12 (2) 2 (1) 3 (1) 3 (1) 18 (6)	13 (5)	1%	Ill from hip arthritis Frail & confused High BP Balance	1 (1) 8 (2) 3 (1) 1 (1)
						Instructor Assistance	32 (3)	Pain/immobility Balance	22 (2) 10 (1)				
Upper back strengthener	933	831	89%	73	8%	Reduced work	10 (3)	Rejoining class Various/frail	2 (1) 8 (2)	29 (8)	3%	Ill from hip arthritis Upper back pain Shoulder pain Recov. From hosp. Frail/confused Balance Recov. From accident Muscle soreness High BP Rejoining class	1 (1) 2 (1) 5 (1) 3 (1) 8 (2) 1 (1) 1 (1) 4 (1) 3 (1) 1 (1)
						Instructor Assistance	63 (2)	Unilateral (Right side) weakness	63 (2)				
						Limb Secured	27 (1)	Unilateral (Right side) weakness	27 (1)				
Sit to Stand	933	868	93%	51	5%	Reduced work	29 (5)	Pain/immobility Balance Rejoining class	22 (2) 23 (1) 2 (2)	14 (4)	2%	Ill from hip arthritis Frail & confused High BP	1 (1) 10 (2) 3 (1)
						Instructor Assistance	52 (4)	Pain/immobility Emotional Problem and forgot stick Balance	22 (2) 1 (1) 23 (1)				
Tricep extension	933	829	89%	74	8%	Reduced work	11 (4)	Rejoining class Various/frail Muscle soreness	2 (1) 8 (2) 1 (1)	30 (9)	3%	Ill from hip arthritis Upper back pain Shoulder pain Recov. From hosp. Frail/confused Balance Recov. From accident Muscle soreness High BP Rejoining class UNKNOWN	1 (1) 2 (1) 5 (1) 3 (1) 8 (2) 1 (1) 1 (1) 3 (1) 3 (1) 1 (1) 2 (1)
						Instructor Assistance	63 (2)	Unilateral (Right side) weakness	63 (2)				
						Limb Secured	27 (1)	Unilateral (Right side) weakness	27 (1)				

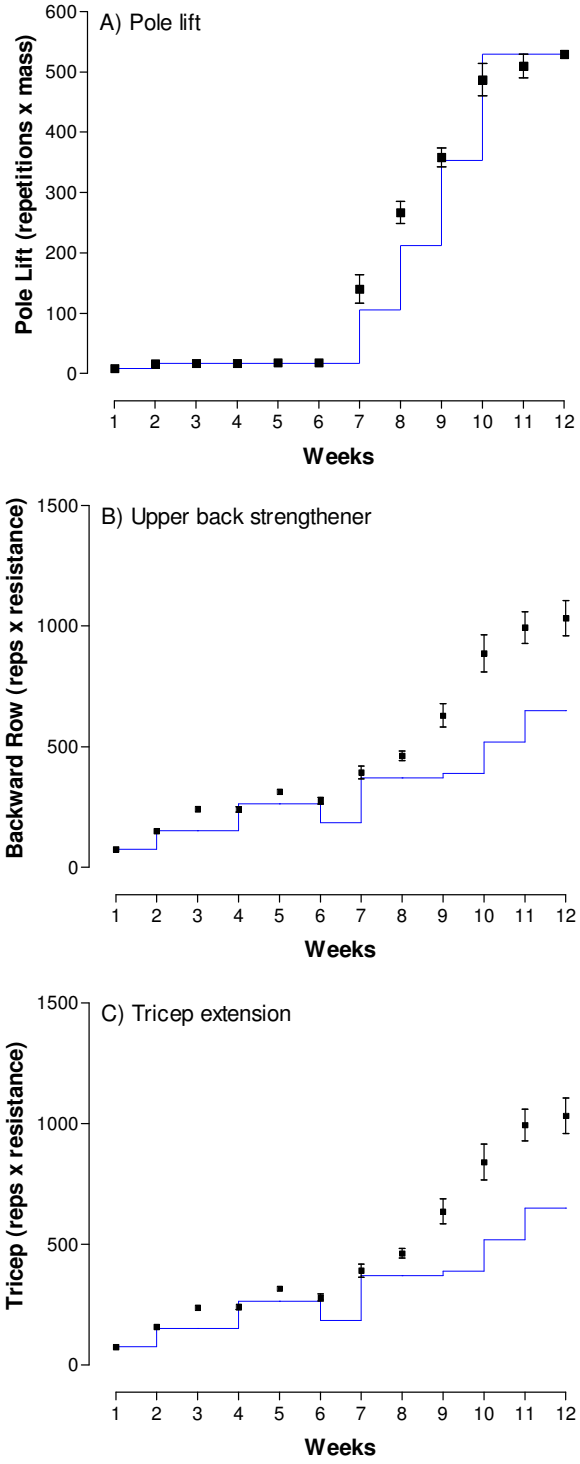


Figure 10.8 Average resistance training load (Newtons x repetitions) achieved by the participants (mean ■; mean ± SD) for the A) pole lift, B) upper back strengthener and C) tricep extension compared with the load intended in the protocol (solid line ——).

Table 10.7 Compliance with each element of the relaxation intervention expressed as the number of attended sessions either completed per-protocol or compromised for a variety of reasons. Numbers in parentheses are participants affected (n).

Exercise	Sessions Attended	Sessions Completed Per-protocol		Sessions Compromised Protocol		Reasons for Compromised protocol* Total sessions lost (d) and participants affected (n)				
	Total	Total	%	Total	%	Noise	Discomfort	Health	Facility	Anxiety
Breathing	998	779	78%	219	22%	9 (n=7)	64 (n=16)	58 (n=14)	27 (n=15)	97 (n=21)
Progressive Muscle Relaxation	998	734	74%	264	26%	11 (n=8)	111 (n=20)	58 (n=14)	28 (n=15)	97 (n=21)
Visualization	998	735	74%	263	26%	11 (n=8)	110 (n=19)	58 (n=14)	29 (n=15)	96 (n=19)
Rest and Review	998	768	77%	230	23%	11 (n=8)	90 (n=16)	51 (n=11)	27 (n=15)	88 (n=14)

* Multiple response variables – concurrent problems can occur

10.5. Results II – Effect of the trial interventions

10.5.1. Characteristics

A total of 66 eligible participants were recruited (Characteristics Table 10.8). The flow of participants entering the trial, remaining in it, and losses to follow-up were shown in Figure 10.6. All those allocated exercise received the intervention and attended all outcome assessments. Two people allocated relaxation did not receive the intervention due to their time commitments, but one was available for all outcome assessments.

10.5.2. Adverse events

At least one fall was reported during the 3-month intervention period in 8/32 participants allocated exercise, and 4/32 allocated relaxation RR = 2.0 (95% CI 0.669 to 5.98) but there was no significant difference between the groups (Fisher's Exact; P =0.337). Since falls were reported to the exercise instructor this did not include the two people who did not commence the relaxation intervention.

Table 14.8 Characteristics of patients at baseline.

Characteristics		Exercise (n=32)	Relaxation (n=34)
Age (mean (SD))		72.0 (10.4)	71.7 (9.6)
No (%) men		18 (56)	18 (53)
Required inpatient treatment for stroke		27 (84)	29 (85)
Length of in-patient stay (median (IQR))		19 (7-39) n=27	16 (6.5-48.5) n=29
Outpatient treatment only		5 (16)	5 (15)
Stroke Type (OCSP)	Lacunar	10 (31)	9 (26)
	Total anterior circulation	1 (3)	1 (3)
	Partial anterior circulation	16 (50)	16 (47)
	Posterior circulation	4 (13)	8 (24)
	uncertain	1 (3)	0
	Ischaemic	28 (88)	32 (94)
	Haemorrhagic	3 (9)	2 (6)
	Unknown	1 (3)	0
Side of brain lesion:	Right	12 (38)	15 (44)
	Left	19 (59)	18 (53)
	Bilateral	0	1 (3)
	unknown	1 (3)	0
Days from:	stroke to baseline (median (IQR))	171 (55-287) n=31	147.5 (78.8-235.5) n=34
	stroke to intervention (median (IQR))	178 (86-307) n=31	161.5 (91.8-242.8) n=32
Smoking habit:	Non-smoker	13 (41)	15 (44)
	Ex-smoker	6 (19)	6 (18)
	Smoker	13 (41)	12 (35)
	Unknown	0	1 (3)
Drugs*†	Antiplatelet drugs	29 (94)	30 (88)
	Antihypertensives	13 (42)	18 (53)
	Statins	18 (58)	26 (77)
	Anticoagulants	1 (3)	4 (12)
	Other	29 (94)	31 (91)
Comorbid disease*‡	Hypertension	12 (46)	19 (56)
	Ischaemic heart disease	9 (35)	14 (41)
	Cancer (prior or current)	4 (15)	2 (6)
	Prior stroke	5 (19)	6 (18)
	Prior TIA	2 (8)	2 (6)
	Diabetes	2 (8)	1 (3)
	Left ventricular failure	1 (4)	1 (3)
	Other	19 (73)	17 (50)
Sitting BP mmHg	**systolic** (mean (SD)	140.6 (18.6) n=31	139.5 (17.9) n=32
	diastolic (mean (SD)	74.7 (10.0) n=31	71.7 (8.9) n=32
Speech:	Normal	21 (66)	24 (71)
	Dysarthria	9 (28)	7 (21)
	Expressive	1 (3)	3 (9)
	Not recorded	1 (3)	0
Any Weakness (<5 on MRC scale)	Arm	9 (28)	13 (38)
	Leg	7 (22)	8 (24)
Any inattention		2 (6)	2 (6)
Functional Ambulation Category	Score = 4	3 (9)	4 (12)
	Score = 5	29 (91)	30 (88)

Data: Values are numbers (percentages) unless otherwise stated.
Abbreviations: OCSP=Oxfordshire Community Stroke Project Classification.
* Multiple response variable - percentages do not add to 100.
† No medications for one patient (exercise group); excluded from calculation of percentages.
‡ No comorbidities for six subjects (all exercise group); excluded from calculation of percentages.

10.5.3. Effect on Outcome measures

10.5.3.1. Effects on physical fitness

There was a small significant difference between the exercise and relaxation groups for the indices of cardiorespiratory fitness at the 3 month assessment, but not at the 7 month assessment. The exercise group had better walking economy (net and gross values) and faster $\dot{V}O_2$ kinetics (Figure 10.9 and Table 10.9). There were no significant between group differences for LLEP (affected or unaffected side).

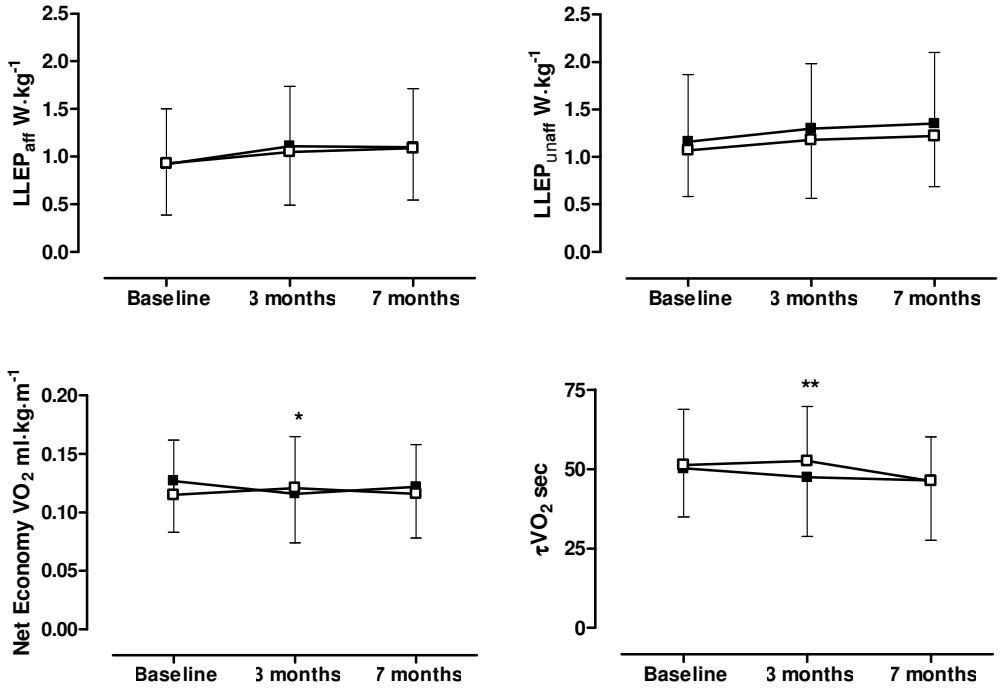


Figure 10.9 Physical fitness parameters in stroke patients allocated exercise (■) or relaxation (□) at baseline, end of intervention (3 months) and after follow up (7 months). Parameters include explosive power of the affected ($LLEP_{aff}$) and unaffected ($LLEP_{unaff}$) lower limbs, and the cardiorespiratory parameters gait economy and time constant for oxygen uptake kinetics ($\tau\dot{V}O_2$). Exercise group gait economy (* P=0.048) and $\tau\dot{V}O_2$ (** P=0.009) data were significantly better (lower) than relaxation group at end of intervention (3 months). Values are mean ± 1SD.

Table 10.9 Physical Fitness: Within group changes from baseline, and between group differences at 3 and 7-months for exercise and relaxation.

Outcome measure		Exercise Group (n=32)		Relaxation Group (n=34)		Between Group Difference	
		Mean (95% CI)*	Within group P†	Mean (95% CI)*	Within group P†	Effect size Partial eta^2	ANCOVA P value
Economy Net ‡ ($\dot{V}O_2$ ml·kg^{-1}·m^{-1})	Baseline	0.127 (0.112 to 0.144)	-	0.115 (0.100 to 0.133)	-	-	-
	3-month	0.116 (0.102 to 0.132)	0.047	0.121 (0.107 to 0.138)	0.27	0.065	0.048
	7-month	0.122 (0.107 to 0.139)	0.34	0.116 (0.102 to 0.132)	0.92	0.002	0.72
Economy Gross ‡ ($\dot{V}O_2$ ml·kg^{-1}·m^{-1})	Baseline	0.224 (0.195 to 0.258)	-	0.203 (0.178 to 0.232)	-	-	-
	3-month	0.193 (0.166 to 0.225)	<0.0001	0.202 (0.174 to 0.234)	0.781	0.104	0.013
	7-month	0.198 (0.172 to 0.228)	0.036	0.185 (0.156 to 0.219)	0.071	0.006	0.552
Oxygen uptake kinetics‡¶ ($\tau\dot{V}O_2$ sec)	Baseline	50.2 (43.0 to 57.3)	-	50.1 (43.6 to 58.5)	-	-	-
	3-month	47.4 (38.9 to 55.9)	0.483	52.3 (44.6 to 59.9)	0.343	0.253	0.009
	7-month	46.5 (37.2 to 55.9)	0.845	46.5 (40.2 to 52.8)	0.230	0.000	0.962
Lower-limb extensor power (affected) § (W·kg^{-1})	Baseline	0.92 (0.72 to 1.14)	-	0.93 (0.75 to 1.13)	-	-	-
	3-month	1.11 (0.89 to 1.35)	<0.0005	1.05 (0.86 to 1.25)	0.054	0.014	0.37
	7-month	1.10 (0.89 to 1.34)	0.003	1.09 (0.91 to 1.29)	0.007	0.001	0.82
Lower-limb extensor power (unaffected) § (W·kg^{-1})	Baseline	1.16 (0.92 to 1.43)	-	1.07 (0.91 to 1.25)	-	-	-
	3-month	1.30 (1.06 to 1.57)	0.014	1.18 (0.98 to 1.41)	0.036	0.001	0.81
	7-month	1.35 (1.08 to 1.64)	0.003	1.22 (1.04 to 1.41)	0.002	0.005	0.61

*Back-transformed, if necessary, following analysis of transformed data:
† Paired t tests, unless otherwise stated comparing baseline data with 3-month and 7-month data
‡ Logarithmic transformation
§ Square root transformation
¶ No LOCF applied since too many missing data

10.5.3.2. Effects on Physical function

Between group comparisons indicated the functional benefits of exercise were limited to the timed up-and-go (Table 10.10). Performance was significantly faster at 3-months (P=0.03) but at 7-months performance had returned to baseline values with no difference between the groups. There was no difference between the groups for the other measures at any follow-up point.

10.5.3.3. Global measures of disability and function

Although our participants were high functioning individuals only the Elderly Mobility Scale showed substantial ceiling effects, these prevented any between group analyses of this outcome. The remaining measures showed no significant between-group differences (Table 10.11).

10.5.3.4. Health-related quality of life

Statistical analysis of 3/8 domains of the SF-36 ('Bodily pain', 'Social functioning', 'Role-emotional') were not possible due to heterogeneity and ceiling effects. 'Role Physical' in the exercise group was significantly greater than the relaxation group at 3-months and 7-months (Table 10.12). The 'General Health' domain showed a smaller difference detectable only in change from baseline scores at 3-months.

10.5.3.5. Mood

However there were no between group effects on the anxiety or depression components of HADS (Table 10.13).

Table 10.10 Physical function: Within group changes from baseline, and between group differences at 3 and 7-months for exercise and relaxation.

Outcome measure		Exercise Group (n=32)		Relaxation Group (n=34)		Between Group Difference	
		Mean (95% CI)*	Within group P†	Mean (95% CI)*	Within group P†	Effect size Partial eta^2	ANCOVA P value
Walking speed ($m \cdot sec^{-1}$)	Baseline	0.66 (0.57 to 0.75)	-	0.67 (0.58 to 0.75)	-	-	-
	3-month	0.73 (0.64 to 0.82)	<0.0005	0.74 (0.64 to 0.83)	0.001	<0.001	0.995
	7-month	0.70 (0.61 to 0.79)	0.059	0.74 (0.64 to 0.83)	<0.0005	0.037	0.14
Timed up & go ‡ (seconds)	Baseline	11.6 (10.0 to 13.8)	-	11.3 (9.9 to 13.1)	-	-	-
	3-month	10.6 (9.2 to 12.5)	0.009	11.4 (9.9 to 13.4)	0.85	0.076	0.03
	7-month	11.3 (9.8 to 13.3)	0.40	11.4 (10.0 to 13.3)	0.66	0.011	0.41
Functional Reach (cm)	Baseline	25.0 (22.0 to 27.8)	-	28.4 (26.3 to 30.2)	-	-	-
	3-month	27.9 (24.6 to 31.0)	0.043	27.2 (24.8 to 29.4)	0.34	0.032	0.16
	7-month	27.4 (23.6 to 30.8)	0.11	26.8 (24.4 to 28.9)	0.21	0.030	0.18
Chair rise time ‡ (seconds)	Baseline	1.18 (1.00 to 1.45)	-	1.14 (0.96 to 1.39)	-	-	-
	3-month	0.96 (0.84 to 1.11)	<0.0005	0.99 (0.84 to 1.21)	0.079	0.01	0.43
	7-month	1.04 (0.89 to 1.25)	0.030	1.08 (0.94 to 1.28)	0.32	0.017	0.31

*Back-transformed, if necessary, following analysis of transformed data:
† Paired t tests, unless otherwise stated comparing baseline data with 3-month and 7-month data
‡ Reciprocal transformation

Table 10.11 Disability: Within group changes from baseline and between group differences at 3 and 7-months for exercise and relaxation.

Outcome measure		Exercise Group (n=32)		Relaxation Groups (n=34)		Between Group Difference	
		Mean (95% CI)*	Within group P†	Mean (95% CI)*	Within group P†	Effect size Partial eta^2	ANCOVA P value
FIM Instrument‡	Baseline	117.9 (115.6 to 119.8)	-	117.8 (115.7 to 119.8)	-	-	-
	3-month	118.2 (115.7 to 120.3)	0.60	118.3 (116.4 to 120.0)	0.47	0.001	0.84
	7-month	118.0 (115.2 to 120.3)	0.91	117.6 (115.3 to 119.6)	0.73	0.001	0.82
Nottingham EADL‡	Baseline	16.2 (14.4 to 17.8)	-	16.5 (15.0 to 17.8)	-	-	-
	3-month	16.3 (14.7 to 17.7)	0.75	16.9 (15.4 to 18.2)	0.31	0.004	0.61
	7-month	16.5 (14.7 to 18.0)	0.62	16.5 (15.0 to 17.9)	0.89	0.002	0.70
Rivermead Motor Assessment‡	Baseline	12.9 (12.0 to 13.6)	-	12.8 (12.2 to 13.4)	-	-	-
	3-month	13.1 (12.3 to 13.8)	0.31	13.0 (12.3 to 13.5)	0.59	0.007	0.50
	7-month	13.2 (12.5 to 13.9)	0.085	13.1 (12.5 to 13.6)	0.34	0.007	0.53
Elderly Mobility Score (0-20)	Baseline	§20 (19.25 to 20)	-	††20 (19.75 to 20)	-	-	-
	3-month	20 (20 to 20)	0.51¶	20 (19.0 to 20)	1.00¶	-	-
	7-month	20 (19.25 to 20)	1.00¶	20 (20 to 20)	1.00¶	-	-

*Back-transformed, if necessary, following analysis of transformed data:
† Paired t tests, unless otherwise stated comparing baseline data with 3-month and 7-month data
‡ Square root of reflected data
§ Median & inter-quartile range
¶ Sign test

Table 10.12 Health Related Quality of Life (SF-36): Within group changes from baseline, and between group differences at 3 and 7-months for exercise and relaxation.

Outcome measure		Exercise Group (n=32)		Relaxation Groups (n=34)		Between Group Difference	
		Mean (95% CI)*	Within group P†	Mean (95% CI)*	Within group P†	Effect size Partial eta^2	ANCOVA P value
Physical functioning	Baseline	62.0 (53.1 to 70.9)	-	57.4 (48.2 to 66.5)	-	-	-
	3-month	63.1 (52.5 to 73.7)	0.65	54.0 (46.1 to 61.9)	0.26	-	-
	7-month	58.0 (47.6 to 68.4)	0.11	55.7 (47.0 to 64.5)	0.62	0.004	0.63
Role – physical	Baseline	77.3 (66.4 to 86.0)	-	77.5 (65.7 to 86.9)	-	-	-
	3-month	90.8 (84.3 to 95.5)	0.001	76.2 (64.6 to 85.4)	0.78	0.16	0.002
	7-month	91.6 (74.3 to 84.5)	0.18	72.5 (61.7 to 81.5)	0.36	0.07	0.038
Bodily pain	Baseline	§92 (43 to 100)	-	§79 (61 to 100)	-	-	-
	3-month	72 (24.5 to 100)	0.36¶	72 (41 to 100)	0.83¶	-	-
	7-month	61.5 (41.25 to 100)	0.29¶	61 (41.75 to 100)	0.003¶	-	-
General health	Baseline	65.7 (55.9 to 74.2)	-	71.5 (62.9 to 78.9)	-	-	-
	3-month	74.7 (66.0 to 82.1)	0.007	69.7 (61.6 to 76.8)	0.65	0.052	0.075
	7-month	62.7 (54.1 to 70.4)	0.32	72.8 (63.6 to 80.8)	0.72	0.032	0.16
Vitality	Baseline	53.0 (46.2 to 59.8)	-	53.3 (45.5 to 61.1)	-	-	-
	3-month	58.9 (52.3 to 65.4)	0.036	57.7 (51.2 to 64.3)	0.20	0.003	0.69
	7-month	55.3 (48.3 to 62.2)	0.50	52.0 (43.9 to 60.1)	0.66	0.01	0.44
Social functioning	Baseline	§100 (53.1 to 100)	-	§100 (62.5 to 100)	-	-	-
	3-month	100 (75 to 100)	0.17¶	93.75 (62.5 to 100)	1.00¶	-	-
	7-month	100 (87.5 to 100)	0.077¶	100 (62.5 to 100)	0.45¶	-	-
Role – emotional	Baseline	§87.5 (75.0 to 100)	-	§95.8 (56.2 to 100)	-	-	-
	3-month	100 (85.4 to 100)	0.041¶	100 (64.6 to 100)	0.65¶	-	-
	7-month	100 (77.1 to 100)	0.12¶	95.8 (50.0 to 100)	0.83¶	-	-
Mental health	Baseline	73.4 (65.1 to 80.7)	-	73.0 (64.7 to 80.3)	-	-	-
	3-month	80.6 (72.7 to 87.1)	0.005	82.1 (73.7 to 88.9)	0.013	0.006	0.56
	7-month	77.4 (69.6 to 84.0)	0.20	79.6 (71.1 to 86.6)	0.022	0.008	0.48

*Back-transformed, if necessary, following analysis of transformed data:
† Paired t tests, unless otherwise stated comparing baseline data with 3-month and 7-month data
§ Median & inter-quartile range;
¶ Sign test

Table 10.13 Mood: Within group changes from baseline, and between group differences at 3 and 7-months for exercise and relaxation.

Outcome measure		Exercise Group (n=32)		Relaxation Groups (n=34)		Between Group Difference	
		Mean (95% CI)*	Within group P†	Mean (95% CI)*	Within group P†	Effect size Partial eta^2	ANCOVA P value
HADS anxiety‡ (0-21)	Baseline	5.93 (4.35 to 7.76)	-	4.15 (2.78 to 5.79)	-	-	-
	3-month	4.26 (2.86 to 5.95)	0.008	3.47 (2.06 to 5.23)	0.26	0.003	0.67
	7-month	4.46 (3.06 to 6.12)	0.049	3.71 (2.31 to 5.44)	0.42	0.002	0.75
HADS depression‡ (0-21)	Baseline	3.65 (2.62 to 4.85)	-	4.17 (3.26 to 5.19)	-	-	-
	3-month	3.78 (2.48 to 5.34)	0.81	3.66 (2.54 to 4.98)	0.39	0.008	0.49
	7-month	3.90 (2.66 to 5.38)	0.66	4.18 (2.95 to 5.62)	0.99	0.001	0.82

*Back-transformed, if necessary, following analysis of transformed data:
† Paired t tests, unless otherwise stated comparing baseline data with 3-month and 7-month data
‡ Square root transformation

10.6. Discussion

10.6.1. Feasibility of the trial design

This exploratory RCT showed that a definitive trial of physical fitness training was feasible.

10.6.1.1. Outcome Measures

Most of the measures used were feasible and are commonly used in stroke trials. Measures of physical fitness in people with stroke are less common and less well characterized. Our procedure to determine the peak LLEP is feasible for people with stroke; it is well tolerated despite involvement of repeated maximal efforts. Measurement of cardiorespiratory fitness during self-paced level walking has advantages over measurement during activities like maximal treadmill walking in patient populations. Measurement of steady state $\dot{V}O_2$ during self-paced walking was feasible this allowed determination of walking economy but not $\dot{V}O_2$ kinetics.

The lack of effect on global measures of disability (FIM Instrument, Nottingham EADL and Rivermead Motor Assessment) may be due to a high-functioning sample and this may be common in any trial of exercise after stroke. In addition the questionnaire items may differ in their responses to participation in exercise and changes in physical fitness. Therefore measures of task-modification may offer a more sensitive option which can identify pre-clinical disability (Section 2.3.2).
A review for the Stroke Association (Bennett and Lincoln 2006) recommended the HADS, GHQ12 or SADQ-H10 to assess mood in community dwelling people with stroke but indicated there is no ideal scale. HADS is intended as a screening tool to

identify low mood in a clinical setting, it may not be sensitive enough to detect small longitudinal changes. Also Bennett and Lincoln (2006) suggest cut-offs in HADS scores >6 for anxiety, and >8 for depression to identify mood problems; our HADS scores were substantially below this throughout the trial.

10.6.1.2. Allocation

The allocation program functioned well and was appropriate for this small RCT; allocation concealment was ensured and exclusion after randomization was prevented. Web-based access to a central source would be a useful for local allocation to a larger multi-centre RCT however the concept of minimisation, to ensure baseline similarity, becomes much less important as trials become larger. Minimisation is currently attracting debate, with a number of arguments both for (Altman and Bland 2005) and against.

10.6.1.3. Intervention

The classes were a feasible way of delivering interventions to groups of stroke patients. The classes were well attended. The content of the training was well tolerated despite the demands of progression. Compliance was facilitated by a protocol which allowed 'tailoring' of exercises for each participant if required. There were no adverse events which could be attributed to the physical fitness training.

10.6.2. Effect of the trial interventions

a) What the results show

There were some fitness and functional benefits associated with the exercise intervention compared with relaxation. In addition the longitudinal increase in cycling performance (amount and rate of work) without an increase in RPE recorded support the idea that cardiorespiratory fitness and exercise tolerance were improved (Section 10.4.4.2).

This RCT and that of Thomas et al. (2007; n=22 women; age 75 to 89 years) both show 12 weeks of training can improve the net economy of comfortable walking without influencing the otherwise confounding factor of walking speed. This suggests economy can be improved in elderly people with stroke, even when levels of impairment are relatively modest. Improved economy could ameliorate the effects of the low $\dot{V}O_2$ peak which is common after stroke, by increasing the fitness reserve.

The small between-group effect sizes for improved economy of walking, faster $\tau\dot{V}O_2$ and faster timed up-and-go performance at the end of intervention were no longer detectable after the 7-month follow-up. This is not surprising since fitness gains deteriorate with inactivity or cessation of exercise (‘*Reversibility’* Section 3.3) and functional benefits deteriorate after completion of rehabilitation interventions (‘*Retention’* Section 9.9.3.3).

Timed up-and-go is a composite measure of function involving chair rising, fast walking, turning and sitting. It is possible that the temporary improvement was due to the extensive 'practice' of the chair rising manoeuvre during the exercise classes. Inclusion of chair rising is of course a good example of specific training ('*Specificity'* Section 3.3). However a 'training' effect on the strength or power output of lower limb muscles could also underpin the benefit. Therefore it remains difficult to attribute the effect to fitness training or simple task-related practice.

SF-36 'Role Physical' was the only variable to remain significantly different between the groups after 7 months. There are known issues with accurate answering of this component of the scale since the questions pertains to 'work/employment/' (Johnson 1999), and the majority of the participants were not involved in waged work.

Ceiling effects were observed in three SF-36 domains ('Bodily pain', 'Role-emotional' and 'Social Functioning'). Similar effects for 'Bodily pain' and 'Role-emotional' domains have also been reported in other stroke studies (Hobart et al. 2002); mild stroke severity may be a cause. 'Social functioning' has been identified as an unreliable summary possibly because only 2 questions contribute to the domain (Hobart et al. 2002); this may underlie the data problem in the current study.

The median values recorded for the anxiety and depression scales of HADS were below those suggested for identification of a clinical disorder in stroke patients (Bennett and Lincoln 2006). Despite room for improvement a '*floor effect'* could have restricted further benefit.

Numerous within-group improvements were observed for both interventions. The changes are unlikely to be associated with neurological recovery since the time between stroke and baseline measures of our participants of 25 weeks (IQR 12-44) was beyond that required for most mild or severe strokes (Section 1.4). Therefore observed benefits could have arisen due to social interaction and/or the increase in physical activity associated with travelling to and from the location of the interventions. Anecdotal observations during this RCT (Mead 2005) and by others (Suri 2002) suggest social benefits associated with attending exercise classes may arise in people with stroke. However a particular strength of this RCT design is that these effects are addressed by the attention control allowing between group comparisons to examine the effects of exercise in isolation.

Relaxation is not an 'inert' intervention; it has a number of effects in different patient groups of relevance to stroke. For example relaxation has hypotensive effects similar in magnitude to exercise, especially in people who are already hypertensive (Santaella et al. 2006). A recent systematic review and meta-analysis (van Dixhoorn and White 2005; 27 studies) showed that supervised relaxation practice benefits both recovery from and secondary prevention of cardiac ischaemic events. Relaxation improved resting heart rate but also exercise tolerance (WMD 0.44 95% CI 0.12-0.75; $P<0.007$) and indices of anxiety and depression. A more recent study involving progressive muscle relaxation led to improvements in HADS anxiety and depression scores, and quality of life in elderly heart failure patients (Yu et al. 2007). The mixed relaxation techniques of Chang et al. (2005) also improved indices of quality of life in elderly heart failure patients. These studies suggest that the lack of between-group

differences in quality of life and mood in this RCT could arise from exercise and relaxation both having an effect; this is plausible since some significant within-group changes were observed for these outcome measure.

Six RCTs have examined mixed fitness training after inpatient stroke care (Dean et al. 2000; Duncan et al. 1998; Duncan et al. 2003; James 2002; Teixeira-Salmela et al. 1999; Yang et al. 2006). Three RCTs (James 2002; Teixeira-Salmela et al. 1999; Yang et al. 2006) do not include a non-exercise attention control and thus the findings are confounded by increased intervention time (see '*intensity of therapy'* Section 1.5.3). One small RCT has an intervention too short to allow physical fitness gains (Dean et al. 2000; 4 weeks). Only the home-based exercise RCTs of Duncan et al. (1998; 2003), are similar to this RCT; they are a pilot study (Duncan et al. 1998; n=20), and full study, all performed by the same research group.

The results of the main RCT (Duncan et al. 2003; Studenski et al. 2005) show that compared with the control group those allocated home-based mixed training showed significantly greater improvement in physical fitness ($\dot{V}O_2$ peak but not muscle strength) and physical function including balance (Berg Balance but not functional reach), cycling endurance, walking (maximum speed and endurance), and in upper limb function (limited to those with greater baseline function). Global scales of disability showed a marginal benefit to the Barthel index, but not FIM Instrument or Lawton ADL. Some components of scales of health related quality of life were assessed using the SF-36 ('Social functioning') and the Stroke Impact Scale (strength, emotion, social participation, physical function) improved after training. Disability

and quality of life measures were followed up six months after the intervention at which time the benefits of the training had disappeared. However a problem remains with this study since 46% of the control group received no physical or occupational therapy. An incomplete attention control means the exercise benefits may be exaggerated as they are confounded by increased intervention exposure time.

However the general pattern of findings in Duncan et al. (2003) are similar to this RCT, namely benefits in fitness and function, little evidence benefit for disability, and a hint of short term advantage in quality of life. Observations that cardiorespiratory and strength training interventions improve fitness and function, but not clinical measures of disability occur in studies of elderly people (Keysor and Jette 2001) and people with stroke (Cochrane Review, Chapter 9). Transient benefits are compatible with both the concept of reversibility of fitness gains (Section 3.3) and rehabilitation benefits (Section 9.9.3.3) after interventions finish.

b) Strengths of trial

In addition to the mechanisms to ensure blinding and allocation concealment a key strength of this RCT was the quality of the attention control. The relaxation intervention involved the same amount of contact, same transport arrangements and took place in the same location with the same instructor. This feature of the experimental design sets STARTER apart from similar RCTs of mixed training for people with stroke, at least for measures of fitness function and disability.

c) Limitations

This RCT was neither designed (Section 10.2.2) nor powered (Section 10.3.2.3) to detect significant effects on its outcome measures. The likelihood of type I errors is increased with significance testing of multiple outcome measures. For the 23 outcome measures assessed there is a 69% chance (66-1 degrees of freedom) of finding one or more significant differences (Sankoh et al. 1997). An appropriate Bonferroni adjustment would lower the alpha value to P=0.002 and consequently there would be no significant differences in variables between the exercise and relaxation groups. However there is currently some debate about whether p values should be adjusted (Feise 2002), the alternative being to focus on effects sizes and consider whether the nature of observations were plausible. Although no large effect sizes were observed, the transient nature of the significant benefits observed in the fitness and function measures is biologically plausible. Data from this RCT were however incorporated into an updated systematic review (see Chapter 11), where pooling of data in meta-analyses increases statistical power.

The eligibility criteria of this trial may seem restrictive, in particular only ambulatory patients were included and this could limit the generalizability. However 64% of stroke survivors do regain independent ambulation after rehabilitation (Jørgensen et al. 1995). Secondly, the eligibility criteria are similar to those which would be applied to elderly people wanting to participate in any therapeutic physical fitness training. Therefore this RCT seems generalizable to community dwelling ambulatory people with stroke who were able to exercise safely.

10.7. Conclusion

This study shows that a substantial proportion of people with stroke for whom it is safe to exercise, can successfully participate in a regular programme of physical fitness training. Overall adherence to the exercise intervention was excellent due to good attendance and compliance. Compliance was facilitated by tailoring the exercises to individual impairments and problems. The participants coped with the progression of the exercise and showed evidence of increased exercise tolerance developing during training.

The benefits observed (in aspects of fitness, function and quality of life) were fairly modest. It is possible that an insufficient training stimulus was applied although good compliance plus substantial progression make this unlikely. Methodological strengths reduce the chance of bias which could otherwise exaggerate benefits.

The benefits observed at the end of the intervention largely disappeared 4 months later. This agrees with current thinking that improvements due to fitness training and rehabilitation disappear once interventions are stopped.

RCT of fitness training or relaxation after stroke - Summary

Feasibility of trial design

- 47% of patients assessed eligible to participate
- 45% of eligible patients recruited (21% of patients assessed)
- Attendance at assessments 94% to 97%
- Measures of fitness and function are feasible – except $\dot{V}O_2$ kinetics
- Scale measures of global disability, quality of life and mood may not be sensitive enough in patients eligible for fitness training
- Internet randomization is feasible
- 3% of those randomized failed to start the intervention (relaxation)
- Attendance at intervention classes >90%
- Compliance with tailored exercises 94% to 99%
- Progression in the demands of fitness training occurred

Effects of mixed fitness training (compared with relaxation)

- Physical fitness
  - cardiorespiratory fitness (economy and $\dot{V}O_2$ kinetics) improved
  - lower-limb explosive power no effect
- Physical function
  - timed up-and-go improved
  - walking speed, chair rising and functional reach no effect
- Disability – no effect
- Quality of life
  – no effect except 1/8 domains of SF-36 (Role Physical)
- Mood – no effect
- Improvements in fitness or function are lost 4-months after training stops

11. Physical Fitness Training after Stroke – updated systematic review

11.1. Abstract

BACKGROUND: Physical fitness is low after stroke and this may cause or exacerbate some common post-stroke problems including disability. It is not known whether improving physical fitness after stroke reduces disability.

OBJECTIVES: The primary aims of the review were to determine whether physical fitness training (cardiorespiratory and/or strength) after stroke reduces death, dependence and disability at the end of intervention or follow-up. The secondary aims of the review were to determine of the effects of fitness training on physical fitness, mobility, physical function, health status and quality of life, mood and the incidence of adverse events.

SEARCH STRATEGY: We searched the Cochrane Stroke Group Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, SPORTDiscus, Science Citation Index Expanded, Web of Science Proceedings, Physiotherapy Evidence Database and Index to UK Theses (March 2007). We screened relevant journals, conference proceedings and reference lists of articles. To identify unpublished and ongoing trials we searched trials directories and contacted experts in the field.

SELECTION CRITERIA: Randomized controlled trials were included where the aim of the intervention was to improve either muscle strength and/or cardiorespiratory fitness, and whose control groups comprised either no-intervention, usual care or a non-exercise intervention.

DATA COLLECTION & ANALYSIS: Trial eligibility and quality were determined by two reviewers. One reviewer extracted outcome data at end of intervention and follow-up, or as change from baseline. Additional data were obtained from authors. Diverse outcome measures limited the intended analysis.

MAIN RESULTS: Twenty four trials with 1147 participants were included. Death was infrequent at end of intervention (1/1147) and follow-up (8/627), dependence could not be determined and effects on disability were unclear. Fitness training may improve physical fitness and cardiorespiratory walking training improves maximum walking speed (WMD (fixed), 6.47 $m \cdot min^{-1}$ 95% CI 2.37, 10.57) and tolerance of walking (6-minute walking test WMD (fixed), 38.9 metres 95% CI 14.3 to 63.5), and reduces dependence on others for walking. Functional benefit appears to be associated with specific 'task-related' training.

CONCLUSIONS: The only finding suitable to guide clinical practice at present is that cardiorespiratory walking training improves walking ability. There are few strength training trials and mixed training trials are frequently confounded by increased therapy time. These interventions remain under-investigated and careful study design will be needed if benefits are to be attributed to physical fitness training.

11.2. Introduction

'Updating' a systematic review is defined as a process which involves a new search for new evidence using a previously used protocol; the protocol may be modified or extended (Moher and Tsertsvadze 2006).

The previous review evaluated twelve trials (n=289 participants) searched for in 2002 (Chapter 9). There were insufficient data to influence practice and diverse outcome measures made analysis difficult; therefore the review recommended substantial further research.

The review was updated with trials identified by searches in 2007. This section will be submitted to the Cochrane Library as an update to Saunders et al. (2004a). The updated review contains new searches, amendments to the objectives and protocol and substantial new RCT data, including that from Chapter 10.

11.3. Objectives - Amendments

Retention of benefits is a key issue for rehabilitation and fitness training interventions. Consequently long term follow-up should be a key component of research in this area. Therefore the objectives were amended to focus on both end of intervention *and the end of follow-up.*

11.4. Methods – protocol amendments

The updated systematic review utilizes the previously reported protocol (Chapter 9). However the approach is based on a more recent Cochrane Handbook (Higgins and Green 2005) and the protocol has the following modifications.

11.4.1. Search strategy for identification of studies

- The updated Cochrane Stroke Group 'stroke' search strategy and the new search strategies for RCTs were adopted from the Cochrane Stroke Group Specialised Register. An example for MEDLINE [OVID] is shown in Appendix 14.15, parts A and B).
- All plain text search strings relating to 'physical fitness' were used, where relevant, to identify controlled vocabulary within each database searched. An example for one database (MEDLINE [OVID]) of plain text and controlled vocabulary (MESH) is shown in Appendix 14.15, part C).
- Science Citation Index and Web of Science Proceedings are now accessed through a single internet gateway (Web of Knowledge).
- Citation tracking of included studies was performed via the Web of Knowledge or the OVID gateway.
- Updated search strategy was applied from the last search date to 31st March 2007.

11.4.2. Methodological quality assessment

Current guidance from the Cochrane Stroke Group is to avoid quality assessment scales therefore the previously used quality assessment scale (Jadad et al. 1996) was omitted and the following information recorded instead; a) method of randomization, b) method of allocation concealment, c) who was blinded and how successful the blinding was, and d) whether an intention-to-treat analysis was possible.

11.4.3. Data extraction

Meta-analysis of continuous variables in the previous review analysed change from baseline, this usually necessitated estimation of variance data (standard deviation of the difference; SD_{diff}). To simplify the updated review and make the analysis more closely reflect the objective the preferred form of data was outcome data reported at end of intervention and/or end of follow-up. If only change scores with SD_{diff} were reported then these were recorded. The data extracted included but were not limited to;

- Participants (number, gender, stage of care, time since stroke, losses to follow-up)
- Intervention (mode, dose, attendance)
- Outcome measures (death, dependence, disability, physical fitness, mobility, physical function, health status and quality of life, mood and the incidence of adverse events).

11.4.4. Analysis of results

The same analyses were use as before calculating weighted mean differences (WMD) and 95% confidence intervals using fixed and random effects models. If studies reported only change from baseline scores (and SD of the difference) the data could be pooled with those reporting end of intervention scores (and SD) by using the weighted mean difference (WMD).

Diverse outcomes meant some data were unsuitable for meta-analysis. Similar outcomes could be combined using SMD however this was avoided where possible instead the WMD was calculated for individual study outcomes and summarised as a table of studies in Appendices 14.19, 14.20 and 14.21.

A more recent release of the statistical analysis software (RevMan Analyses[5]) was used and data from all included studies were re-analyzed as above, not just the new studies added in this update.

11.5. Description of studies

The search strategy identified 14 systematic and other reviews relevant to fitness training after stroke; the bibliographies of these were screened for trials (Ada et al. 2007;Barreca et al. 2003;Eng 2004;Hiraoka 2001;Manning and Pomeroy 2003;Meek et al. 2003;Morris et al. 2004;Moseley et al. 2005;Pang et al. 2006;Ramas et al. 2007;Urton et al. 2007;van de Port et al. 2007;van der Lee et al. 2001;Van Peppen et al. 2004).

The search strategy identified 131 potentially relevant new studies on the basis of information in the title and abstract and full papers obtained. Of these;
74 studies failed to meet inclusion criteria (initial review 31 studies; total 105). The studies and reasons for exclusion are not shown in the thesis. The majority were excluded because they a) included an intervention which did not meet the criteria for

[5] RevMan Analyses [Computer program]. Version 1.0 for Windows. In: Review Manager (RevMan). Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

fitness training, b) did not use a relevant control or c) included physical activity in the control group which could give rise to a training effect.

19 studies are awaiting assessment and require additional information or translation into English in order to apply the inclusion criteria

15 studies are ongoing trials (Summarized in Appendix 14.16).

23 studies with 1147 participants met the inclusion criteria and are included.

Eleven trials were from the previous version of the review (Cuveillo-Palmer 1988 [thesis]; da Cunha et al 2002; Dean et al. 2000; Duncan et al. 1998; Glasser 1986; Inaba et al. 1973; Kim et al. 2001; Pohl et al. 2002b ('A' and 'B'; Potempa et al. 1995; Richards et al. 1993; Teixeira-Salmela et al. 1999).

Twelve new trials were identified (Pohl et al. 2007; Eich et al. 2004a; Bateman et al. 2001; Katz-Leurer et al. 2003a; Salbach et al. 2004; Winstein et al. 2004; Ouellette et al. 2004; Richards et al. 2004; Duncan et al. 2003; James 2002 [thesis]; Yang et al. 2006; Mead et al. 2007b).

The studies took place in and involved participants from Australia (1), Canada (2), Germany (3) Ireland (1) Israel (1) Taiwan (1) USA (12) and the UK (2).
Bateman et al. (2001) randomized patients with brain injury. The data for participants with stroke were provided by the authors. Missing data items at the end of intervention and the end of follow-up were imputed using the LOCF to preserve

the intention to treat (ITT) principle. The effect of doing this was tested using sensitivity analyses and this did not change the outcome of any analyses.

Three studies included multiple intervention groups. Pohl et al. (2002b) included two different treadmill training interventions groups (each n=20) both of which met the inclusion criteria and each shared the same control group (n=20). These data are included in this review as two separate 'trials' referred to as Pohl et al. (2002b 'A') and Pohl et al. (2002b 'B') and analysed with a control group of n=10. The trials of Inaba et al. (1973) and Winstein et al. (2004) each included two intervention arms sharing the same control group, only one from each trial met the inclusion criteria for training. Richards et al. (1993) included two control groups only one was 'usual care'.

In total 24 comparisons from 23 publications are described in the review and the details are summarized as 24 separate entries in the Characteristics of Included Studies table (Appendix 14.17).

Two studies were dissertations (Cuveillo-Palmer 1988; James 2002) and nine studies have secondary publications (da Cunha et al. 2002; Eich et al. 2004a; Katz-Leurer et al. 2003a; Salbach et al. 2004; Winstein et al. 2004; Richards et al. 1993; Duncan et al. 2003; Teixeira-Salmela et al. 1999; Dean et al. 2000) which are included in Appendix 14.17.

11.5.1. Participants

A total of 1147 stroke patients (male to female ratio approximately 3:2) were randomized and attended baseline assessment in the included trials. The mean time

since onset of stroke in participants in the trials ranged from 8.8 days in those examining training before discharge from hospital (Richards et al. 1993) to 7.7 years in trials examining training in patients after discharge (Teixeira-Salmela et al. 1999).

The mean age of the patients was approximately ~63 years**.** Two trials (Richards et al. 1993; Pohl et al. 2007; n=173) recruited patients who were non-ambulatory at baseline, One trial (Bateman et al. 2001; n=84) recruited both ambulatory and non-ambulatory (~1:1 ratio), and the remaining trials (n=868) all recruited ambulatory people with stroke, apart from Winstein et al. (2004; n=42) which is not described.

11.5.2. Interventions

A summary of the cardiorespiratory, strength and mixed training interventions are summarised in Tables 11.1, 11.2 and 11.3.

11.5.2.1. Cardiorespiratory training

Eleven trials (n=629/1147; Glasser 1986; Cuveillo-Palmer 1988; da Cunha et al. 2002; Pohl et al. 2002b 'A' and 'B'; Pohl et al. 2007; Eich et al. 2004a; Bateman et al. 2001; Katz-Leurer et al. 2003a; Potempa et al. 1995; Salbach et al. 2004) examined cardiorespiratory training (Table 11.1). All studies employed different forms of ergometry (cycle, treadmill or Kinetron) apart from one which used circuit training (Salbach et al. 2004). These training programmes comprised regular sessions ($\geq$3 d·wk^{-1}) of sufficient duration (usually >20min) but the exercise intensity was often not described.

The interventions of only 4/11 studies (Eich et al. 2004a; Bateman et al. 2001; Katz-Leurer et al. 2003a; Potempa et al. 1995) met the ACSM (1998b) criteria for cardiorespiratory training. Bateman et al. (2001) stated that participants spent only 56% of the prescribed training time at a sufficient intensity and overall attendance was low (65%) therefore this study is marginal. One of the remaining 7/11 trials (Cuveillo-Palmer 1988) did not meet the ACSM (1998b) criteria since the intervention represented a very small 'dose' of training since it was of short duration (7-12 min) and of very low intensity (heart rate within 20 beats·min^{-1} of resting). The other 6/11 trials did not report intensity so it is unknown whether they meet the ACSM (1998b) criteria. Finally all programmes lasted less than 12 weeks, apart from Bateman et al. (2001).

In 9/11 studies (496/629) the cardiorespiratory training commenced during usual care, of these 3/11 (190/629) in the acute phase <1 month post-stroke (Cuveillo-Palmer 1988; da Cunha et al. 2002; Pohl et al. 2007).

Table 11.1. Cardiorespiratory training studies included in review.

Study	Mode	During or after usual care?	Upper or lower body	Specific training	Intensity of exercise	Duration of sessions minutes	Frequency Days per week	Programme Length Weeks	ACSM (1998b) Criteria		Attendance
									CR	STR	
(Glasser 1986)	Kinetron	During	Lower	No	UN	20 to 60	5	3	UN	-	UN
(Cuveillo-Palmer 1988)	Kinetron	During	Lower	No	HR < resting +20 b/min	7 to 17	5	3	No	-	UN
(da Cunha et al. 2002)	BWS Treadmill	During	Lower	Yes	UN	20	5	2 to 3	UN	-	UN
(Pohl et al. 2002b) 'A'	Treadmill	During	Lower	Yes	UN	30	3	4	UN	-	100%
(Pohl et al. 2002b) 'B'	Treadmill	During	Lower	Yes	UN	30	3	4	UN	-	100%
(Eich et al. 2004b)	Treadmill	During	Lower	Yes	60% HRR	30	5	6	Yes	-	100%
(Pohl et al. 2007)	BWS Treadmill	During	Lower	Yes	UN	20	5	4	UN	-	UN
(Bateman et al. 2001)	Cycle ergometer	Both	Lower	No	60-80% ARHRM	≤ 30	3	12	Yes	-	T=65% C=66%
(Katz-Leurer et al. 2003a)	Cycle ergometer	Both	Lower	No	≤ 60% HRR	20 then 30	5 then 3	2 then 6 (total 8)	Yes	-	UN
(Potempa et al. 1995)	Cycle ergometer	After	Lower	No	30-50% max effort	30	3	10	Yes	-	UN
(Salbach et al. 2004)	Circuit training	After	Lower	Yes	UN	55	3	6	UN	-	T=86% C=72%

Abbreviations: ARHRM age-related heart rate maximum; BWS body weight supported; C control group; CR cardiorespiratory training; HRR heart rate reserve; RPE rating of perceived exertion (Borg Scale); STR strength training; T training group; UN unknown

Table 11.2. Strength training studies included in review.

Study	Mode	During or after usual care?	Upper or lower body	Specific training	Intensity of exercise	Duration of sessions minutes	Frequency Days per week	Programme Length Weeks	ACSM (1998) Criteria		Attendance
									CR	STR	
(Inaba et al. 1973)	Resistance training	During	Lower	No	50% & 100% max weight	UN	'daily'	4 to 8	-	Yes	UN
(Winstein et al. 2004)	Resistance Training; Weights; Thera-Band and grip devices	Both	Upper	No	UN	60	3 high 2 slow	4 to 6*	-	UN	100%
(Kim et al. 2001)	Resistance Training; Isokinetic dynamometer	After	Lower	No	Maximal effort 3 x 10 reps	30	3	6	-	Yes	UN
(Ouellette et al. 2004)	Resistance Training; weights and pneumatic resistance machines	After	Lower	No	70% 1-RM 3 x 8-10 reps	N/A	3	12	-	No †	T=85.4% C=79.9%

Abbreviations: 1-RM one repetition maximum; C control group; STR strength training; T training group; UN unknown
* Target of 20 sessions
† Almost achieves criteria

Table 11.3. Mixed training studies included in review.

Study	Mode	During or after usual care?	Upper or lower body	Specific training	Intensity of exercise	Duration of sessions minutes	Frequency Days per week	Programme Length Weeks	ACSM (1998) Criteria		Attendance
									CR	STR	
(Richards et al. 1993)	Treadmill + Kinetron + tilt table	During	Lower	Yes	UN	104	5	5	UN	UN	84.40%
(Richards et al. 2004)	Treadmill + Kinetron + Limb load monitor	During	Lower	Yes	UN	60	5	8	UN	UN	84%
(Duncan et al. 1998)	Walking or cycle ergometry; elastic resisted contractions	After	Both	Yes	UN	90	3	12	No	Yes	100%
(Teixeira-Salmela et al. 1999)	Walking and stepping or cycle ergometry Resistance training body mass, weights and elastic	After	Lower	Yes	50-70% max work rate (CR) 50-80% 1-RM 3x 10 reps (STR)	60 to 90	3	10	Yes	Yes	UN
(Dean et al. 2000)	Walking and circuit training	After	Lower	Yes	UN	60	3	4	No	No	75%
(Duncan et al. 2003)	Circuit training	After	Lower	Yes	50-60% HRR	90 to 120	3	4	Yes	UC	UN
(James 2002)	Circuit training	After	Both	Yes	UN	90	3	12 to 14*	No	Yes	93%
(Yang et al. 2006)	Functional stepping and chair rising	After	Lower	Yes	UN	30	3	4	No	No	100%
(Mead et al. 2007b)	Circuit including walking, stepping, cycle ergometry Resistance training body mass, weights and elastic	After	Both	Yes	RPE 13-16	40 to 75	3	12 to 14*	UN	UN	T=93% C=92%

Abbreviations: 1-RM one repetition maximum; ARHRM age-related heart rate maximum; BWS body weight supported; C control group; CR cardiorespiratory training; HRR heart rate reserve; RPE rating of perceived exertion (Borg Scale); STR strength training; T training group; UN unknown
* Total of 36 sessions

11.5.2.2. Strength Training

Four trials examined strength training (n=158/1147; Inaba et al. 1973; Winstein et al. 2004; Kim et al. 2001; Ouellette et al. 2004) and are summarised in Table 11.2. All employed muscle contraction resisted by exercise machines, weights or elastic devices. Inaba (1973) and Kim et al. (2001) limited the strength training to the affected lower limb and Winstein et al. (2004) the upper limbs. The training met (Inaba et al. 1973; Kim et al. 2001) or was close to (Ouellette et al. 2004) the ACSM (1998b) criteria for strength training. All programmes were short (<12 weeks) apart from Ouellette et al. (2004). In 2/4 studies (Inaba et al. 1973; n=96/158; Winstein et al. 2004) the strength training commenced during usual care, with Winstein et al. (2004) in the acute phase (<1 month post-stroke).

11.5.2.3. Mixed training

Nine trials (n=360/1147; Richards et al. 1993; Richards et al. 2004; Duncan et al. 1998d; Duncan et al. 2003; Teixeira-Salmela et al. 1999; Dean et al. 2000; James 2002;Yang et al. 2006; Mead et al. 2007b) examined mixed training (Table 11.3). Although Yang et al. (2006) describe their intervention as 'resistance training' the durations of activity involved strongly indicate there would be a cardiorespiratory contribution to this training. Therefore in this review it is classified as mixed training and the affect of this assumption is tested with sensitivity analyses. The modes of exercise used for mixed training were quite diverse with most being presented as circuit training. The lower limbs only were trained in 6/9 trials, and both the upper and lower body were trained in the remaining 3/9 trials. All interventions contained

one or more functionally relevant activities. All interventions were regular and were well attended in the 7/9 trials which reported this. Intensity of exercise was reported sufficiently to classify the cardiorespiratory component of Teixeira-Salmela et al. (1999) and James (2002), and the strength component of three (Duncan et al. 1998; Duncan et al. 2003; Teixeira-Salmela et al. 1999) as meeting the ACSM (1998b) criteria. In 3/9 trials (186/360) the interventions met or exceeded 12 weeks in length. The majority (7/9) commenced after completion of usual care, only one (Richards et al. 1993) commenced in the acute phase (<1 month post stroke).

11.5.3. Adherence to training interventions

Adherence to the interventions was defined in terms of a) *attendance* at planned training intervention sessions, and b) *compliance* with the planned content of intervention sessions which are attended.

Attendance - Rate of attendance could be determined in 13/24 trials (Table 12.1). These ranged from 65% (Bateman et al. 2001) up to 100% (Pohl et al. 2002b; 'A' and 'B'; Eich et al. 2004a; Winstein et al. 2004; Duncan et al. 1998; Yang et al. 2006; Mead et al. 2007b). 4/13 studies reported attendance for the training and control groups separately and showed similar rates (Bateman et al. 2001; Salbach et al. 2004; Ouellette et al. 2004; Mead et al. 2007b).

Mead et al. (2007b) allowed up to 3 additional 'catch-up' sessions to facilitate attainment of the intended dose of training (36 sessions). Teixeira-Salmela et al. (1999) also described attempts to make up missed sessions but did not report

attendance. da Cunha et al. (2002) excluded participants if they attended fewer than 9 training sessions thus removing the possibility of intention to treat analysis (Section 11.6.3).

Compliance - Compliance during attended training sessions was described by several studies. For cardiorespiratory training interventions Pohl et al. (2002b 'A' and 'B') reported 'excellent tolerance' of treadmill training, and Salbach et al. (2005) reported that participants usually completed 9/10 circuit training exercises. For mixed training Duncan et al. (1998) reported good compliance with home-based training and Yang et al. (2006) stated that mixed circuit training was 'performed as planned'. Mead et al. (2007b) reported 94 to 99% compliance with circuit training exercises which were 'tailored, if needed, to individual requirements. Data on compliance were not available for other trials.

11.6. Methodological quality of included studies

11.6.1. Randomization

All included trials were described as randomized. The mechanisms of randomization were reported in 9 trials. These included physical methods such as picking cards (Dean et al. 2000) or envelopes (Pohl et al. 2007; Eich et al. 2004a; Yang et al. 2006) random number tables (da Cunha et al. 2002), or computer-based methods (Bateman et al. 2001; Salbach et al. 2004; James 2002; Mead et al. 2007b).

The methods of randomization were reported in 16 trials. To balance participant numbers matched pairs (Dean et al. 2000) or block randomization (Bateman et al.

2001; Katz-Leurer et al. 2003a; Salbach et al. 2004; Richards et al. 1993; Richards et al. 2004; Duncan et al. 1998; Duncan et al. 2003; Teixeira-Salmela et al. 1999; James 2002) were used.

To balance participant characteristics allocations were stratified by walking performance (Pohl et al. 2002b; 'A' and 'B'; Salbach et al. 2004), by age, gender and time since stroke (Kim et al. 2001), by disability (Richards et al. 1993), stroke severity (Winstein et al. 2004) or by age, gender and disability (Mead et al. 2007b; using minimisation).

11.6.2. Allocation Concealment

Seven trials reported the use of sealed envelopes as a mechanism of allocation concealment (Pohl et al. 2007; Eich et al. 2004a; Bateman et al. 2001; Winstein et al. 2004; Duncan et al. 2003; James 2002; Yang et al. 2006). Duncan et al. (1998) used a third party to administer allocations. For participants in the Mead et al. (2007b) trial randomization and allocation of each participant occurred within the same computerised process, therefore concealment of a sequence is not applicable but unpredictability of allocation is retained.

11.6.3. Intention to Treat

There were 10/24 studies (n=691/1147) which reported using ITT analyses (Pohl et al. 2007; Eich et al. 2004a; Bateman et al. 2001; Potempa et al. 1995; Ouellette et al. 2004; Richards et al. 2004; Duncan et al. 1998d; Duncan et al. 2003; James 2002;

Mead et al. 2007b), although one of these (Bateman et al. 2001) reported not analysing data from some participants who dropped out. ITT analyses designs were permitted by imputation of missing data and recording outcome, where possible, in people who did not complete the interventions.

Eight of the remaining studies which did not report using ITT did not have any dropouts (Glasser 1986; Cuveillo-Palmer 1988; Pohl et al. 2002b; Potempa et al. 1995; Kim et al. 2001; Teixeira-Salmela et al. 1999; Yang et al. 2006) thus retaining some of the benefits of ITT.

11.6.4. Blinding

Participant blinding

Participants could not be blinded to treatment. Two trials attempted to blind participants to the underlying hypothesis. One (Kim et al. 2001) informed participants that they would receive one of two different leg-training interventions, and the other (Mead et al. 2007b) that they would receive one of two different interventions, both of which may have (different) benefits.

Investigator blinding

In 15/24 trials blinding of outcome assessors was described (Pohl et al. 2002b, 'A' and 'B'; Pohl et al. 2007; Eich et al. 2004a; Bateman et al. 2001; Katz-Leurer et al. 2003a; Salbach et al. 2004; Kim et al. 2001; Ouellette et al. 2004; Richards et al. 1993; Richards et al. 2004; Duncan et al. 2003; Dean et al. 2000; James 2002; Yang

et al. 2006; Mead et al. 2007b). In two of these the authors indicate that some blinding might be compromised (Eich et al. 2004a;Salbach et al. 2004), and in another (Dean et al. 2000) the outcome assessor inadvertently observed the training group exercising thus potentially identifying indirectly all participants of this small trial (n=12). Participants were instructed not to reveal group assignments to those assessing outcome in three trials (Bateman et al. 2001; Duncan et al. 2003; Mead et al. 2007). There was no outcome assessment blinding for any measure in the Winstein et al. (2004) trial, and none for the secondary outcome measures (maximum gait speed, gait endurance (6-MWT), Rivermead Mobility Index and Motricity Index) in Pohl et al. (2007). Detail of blinding is not known in the remaining 7/24 trials.

11.6.5. Losses to Follow-up

In all included trials 29/579 (5%) of the training groups and 33/568 (6%) of the control groups were not available for assessment at the end of intervention. In the 8 trials which included follow-up assessments (Pohl et al. 2007; Eich et al. 2004a; Bateman et al. 2001; Katz-Leurer et al. 2003a; Winstein et al. 2004; Duncan et al. 2003; Dean et al. 2000; Mead et al. 2007b) 27/297 (9%) of those allocated training and 37/304 (12%) of the control group were not available for assessment at the end of the follow-up period. The proportion of losses was similar for the intervention and control groups at end of intervention ($Chi^2 = 0.211$; p=0.646 NS) and the end of follow-up ($Chi^2 = 1.50$; p=0.221 NS).

Losses meet or exceed 20% at the end of intervention in Richards et al. (2004; 15/63 [24%]) and Dean et al. (2000; 3/12 [25%]), and at the end of follow-up in Bateman et al. (2001; 18/84 [21%]), Winstein et al. (2004; 11/42 [26%]), Dean et al. (2000; 4/12 [33%]) and Duncan et al. (2003; 20/100 [20%]).

da Cunha et al. (2002) excluded participants (number unknown) with poor attendance, which means ITT analyses were not possible.

A large proportion (101/177) of patients recruited to the three groups of the Inaba et al. (1973) trial were lost both before and after randomization. The distribution of losses across the two included and one excluded arms of the trial remain unknown (total 88 participants). Data for 54/88 patients were analysed per protocol for the two included arms of the trial. One reason given for dropouts was discharge before the end of the study.

11.6.6. Selection Bias

Recruitment in some trials involved media advertisement (Ouellette et al. 2004; Teixeira-Salmela et al. 1999), and involved a database of volunteers (Kim et al. 2001; Dean et al. 2000; Yang et al. 2006). This renders these studies susceptible to self-selection bias and thus affects the generalizability of their findings. Other studies recruited patients during stroke care.

11.6.7. Publication bias

Two outcome measures included in this review contained sufficient studies to employ funnel plots as a means of investigating publication bias and other sources of heterogeneity (Appendix 14.18).

11.6.8. Reliability of Outcome Measures

The disability scales reported in this review are commonly used in stroke trials and are known to be reliable in stroke patients (Section 10.3.3.6). However the Late Life Function and Disability Instrument (LLFDI; reported by Ouellette et al. 2004) has not been validated or reliability tested in people with stroke.

The reliability of the included secondary outcome measures has been established in people with stroke (Appendix 14.13). This includes cardiorespiratory fitness (Section 5.5), muscle strength and power (Section 6), gait speed and gait endurance (Flansbjer et al. 2005), indices of physical function, health and quality of life and mood (Section 10.3.3.6).

11.7. Types of Comparison

The anticipated comparisons published in this review protocol were; a) training plus usual care vs. usual care, and b) training vs. no intervention or non-exercise intervention. However, other relevant comparisons were identified, these are described in Appendix 14.17 and summarised here to give the following;

Comparison during inpatient care *Studies*

i) Training + usual care vs. usual care..... 4/24

ii) Training + % usual care vs. usual care 8/24

iii) Training + usual care vs. non-exercise intervention + usual care 1/24

Comparison after inpatient care

iv) Training vs. no intervention 3/24

v) Training vs. non-exercise intervention 6/24

vi) Training vs. usual care (outpatient) 2/24

Comparisons (ii), (iii) and (v) all ensure that the total time spent exposed to the intervention is the same in both training and controls groups. This is achieved via incorporation of non-exercise 'attention control' or substitution of an appropriate component of usual care with fitness training.

Comparisons (i), (iv) and (vi) (9/24 studies; 407/1147 participants) may be problematic because the training groups have greater time exposed to interventions. This means any treatment effects arising from physical fitness training interventions are confounded by increased 'contact time' i.e. time spent receiving an intervention. In the case of rehabilitation interventions involving exercise this has a known effect on rehabilitation outcomes ('*Augmented Therapy Time'*, Section 1.5.3).

11.8. Results

11.8.1. Effect of training on primary outcome measures

11.8.1.1. Case fatality

For all studies only 1/1147 participant was reported to have died between baseline and end of intervention assessments Pohl et al. (2007; 1/77 control group). For the 9/24 studies (n=627/1147) which included a retention follow-up 8/627 (1.3%) participants were reported to have died between end of intervention and end of follow-up (Duncan et al. (2003; 1/50 training 2/50 control), Katz-Leurer et al. (2003a; 1/42 training, 1/39 control) and Pohl et al. (2007; 1/77 training and 2/78 control). Death is an uncommon event.

11.8.1.2. Death or dependence

The composite outcome of death or dependence was not directly reported by any trial, and it could not be determined by the reviewers since no relevant dichotomised measures of dependence were reported.

11.8.1.3. Disability

Cardiorespiratory training

Few cardiorespiratory training data were suitable for meta analysis (Figure 11.1). Pooled FIM Instrument scores were not influenced by training after usual care (SMD (fixed), 95% CI 0.20, -0.17, 0.58). The Bateman et al. (2001) FIM Instrument data were not assessed in a uniform way and there is a high proportion of missing data

items (38%) at end of intervention; however the meta-analysis of the other studies (SMD (fixed), 95% CI 0.21 -0.10, 0.52) is not influenced by their inclusion. Pooled Rivermead Mobility Index scores were not influenced by training provided during usual care (WMD (random), 95% CI 1.25 -0.74, 3.25). The Barthel Index data reported by Bateman et al. (2001) are not pooled with Pohl et al. (2007) because much of the data were either missing (17%) or reached ceiling values (27%) preventing satisfactory transformation. When available Barthel and FIM outcomes were combined there was a significant benefit (SMD (fixed) 0.45; 95% CI 0.21, 0.70). However most of this effect arises from a single study (Pohl et al. 2007) and there is heterogeneity present and the result becomes non-significant when repeated with a random effect model.

Individual study data at the end of intervention which could not be pooled (Appendix 14.19) Pohl et al. (2007) showed a significant improvement in Barthel Index scores analysed as both a continuous variable (WMD (fixed), 13.6 95% CI 6.89, 20.31) or dichotomised at a value of >75 (OR (fixed), 3.62 95% CI 1.84, 7.10). There were no other significant effects reported for FIM locomotor scale (da Cunha et al. 2002) and the Nottingham EADL (Bateman et al. 2001; 14% missing values).

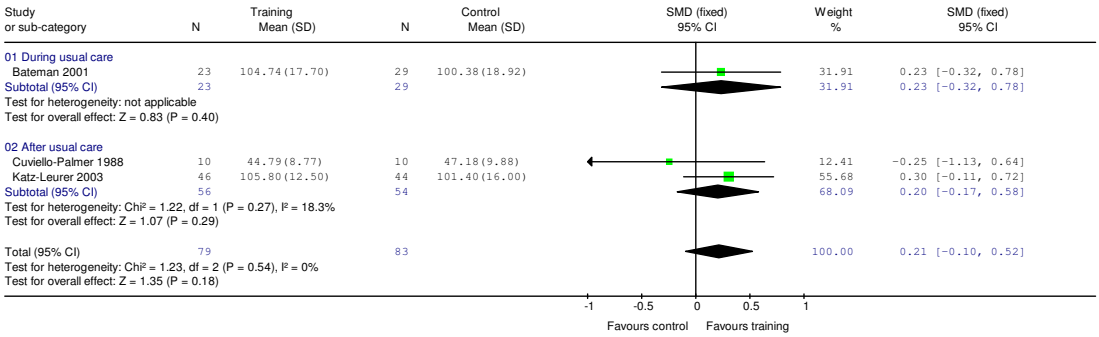
At the end of follow-up there remained no between-group difference in Rivermead Mobility Index (WMD (random), 95% CI 1.01 -1.39, 3.41) but substantial heterogeneity and missing values Bateman et al. (2001; 21%) are evident. The Barthel Index data of Bateman et al. (2001) had substantial missing data (24%) and ceiling values (38%) therefore these data were not included in meta-analyses.

Among the individual study data at the end of follow-up which could not be pooled (Appendix 14.19) Pohl et al. (2007) showed a significant improvement in Barthel Index scores represented as a continuous variable (WMD (fixed), 12.4 95% CI 4.32, 20.48), but not a dichotomised one. There were no effects on the Frenchay Activities Index (Katz-Leurer et al. 2003a) or Nottingham EADL (Bateman et al. 2001; 24% missing values).

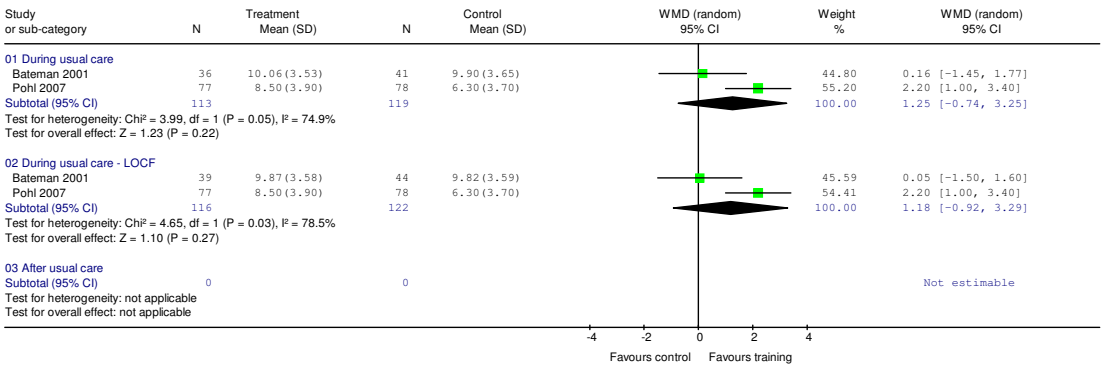
From among the pooled data and individual study data only Pohl et al. (2007) showed significant beneficial effects for the Rivermead Mobility Index and the Barthel Index at both end of intervention and end of follow-up; the Rivermead scores are however not investigator blinded and the study does have a conflict of interest present.

Figure 11.1 Meta analyses of the effects of cardiorespiratory training on indices of disability at the end of intervention.

a) FIM Instrument



b) Rivermead Mobility Index



c) FIM Instrument and Barthel Index Scores

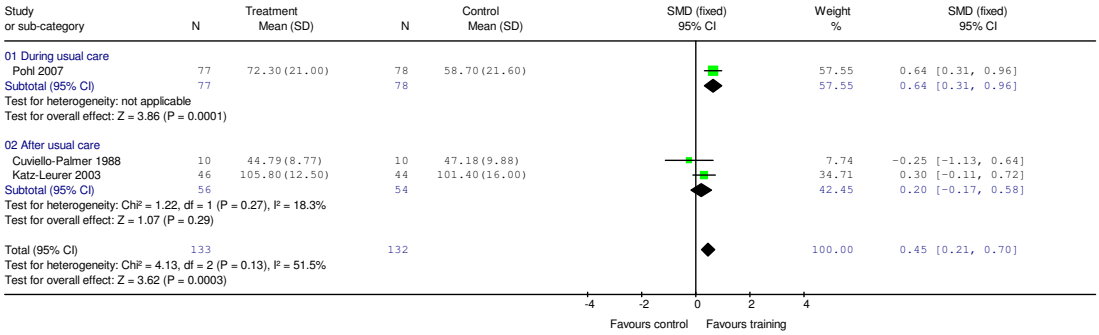
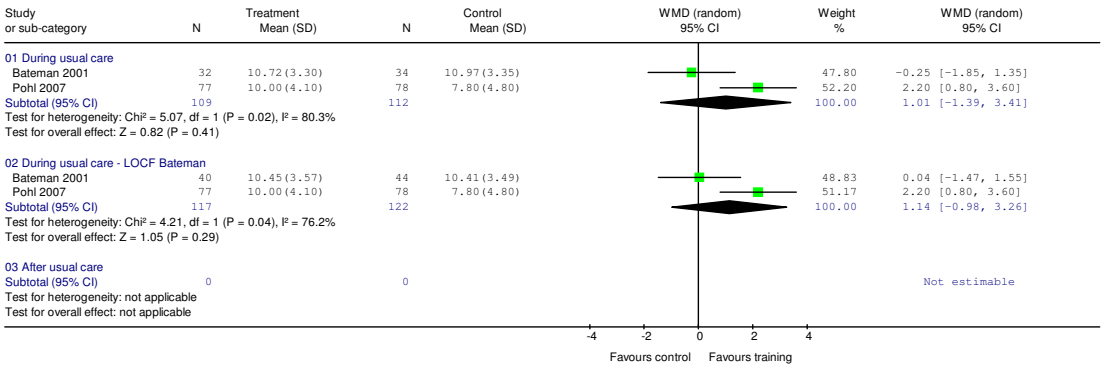


Figure 7.1. Meta analyses of the effects of cardiorespiratory training on indices of disability at the end of follow-up.

Rivermead Mobility Index



Strength training

Two studies reported effects of strength training on scale measures of disability (Winstein et al. 2004;Ouellette et al. 2004) and only one (Winstein et al. 2004) followed this up. No data could be pooled and all individual effect sizes (Appendix 14.20) were non-significant at the end of intervention.

Inaba et al. (1973) reported the proportion of patients that that improved performance of 10 activities of daily living (no scale reported). Although noted as significant in the publication the odds ratio of this effect was borderline (OR (fixed) 2.88; 95% CI (0.95, 8.70); p=0.06). Inaba et al. (1973) state that little additional improvement occurred during a further month of training although these data were not available.

Some data may be weakened due to high patient attrition plus no ITT analyses (Inaba et al. 1973;Winstein et al. 2004) and use of a disability scale unvalidated in people with stroke (LLFDI; Ouellette et al. 2004).

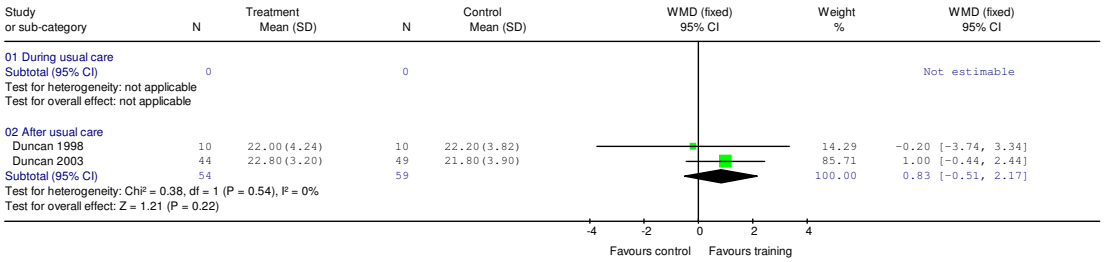
Mixed training

Five studies report the effects of mixed training on scale measures of disability (Richards et al. 1993;Richards et al. 2004;Duncan et al. 1998d;Duncan et al. 2003c;Mead et al. 2007e). Meta-analyses were performed for the Lawton IADL, the Barthel Index and the Barthel Index ambulation subscore (Figure 11.2), none indicate a significant effect. In these meta-analyses two trials (Duncan et al. 1998d;Duncan et al. 2003c) are confounded by increased training time and individual patient data for one of them (Duncan et al. 1998d) shows Barthel Index scores reaching a ceiling of 100 in 5/20 participants at baseline and 10/20 at follow-up.

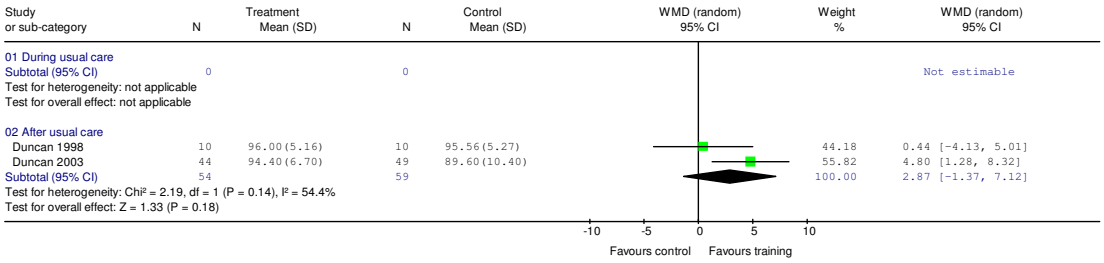
Several other disability outcomes which could not be pooled in meta-analyses were reported (Appendix 14.21). None showed a significant effect of mixed training at either the end of intervention or follow-up.

Figure 11.2 Meta analyses of the effects of mixed training on indices of disability at the end of intervention.

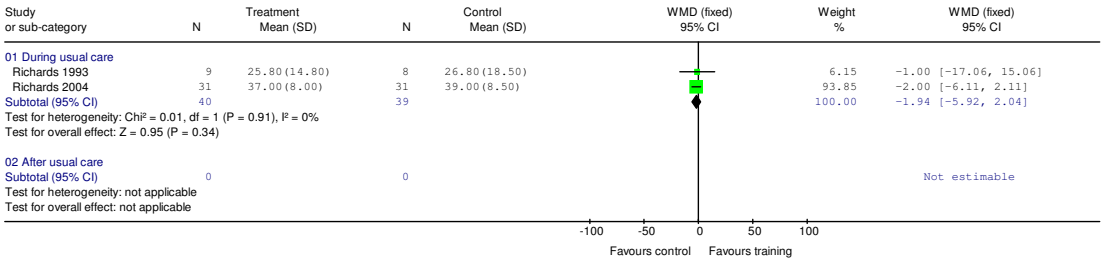
a) Lawton IADL



b) Barthel Index



c) Barthel Index - Ambulation Subscale



d) FIM Instrument and Barthel Index scores

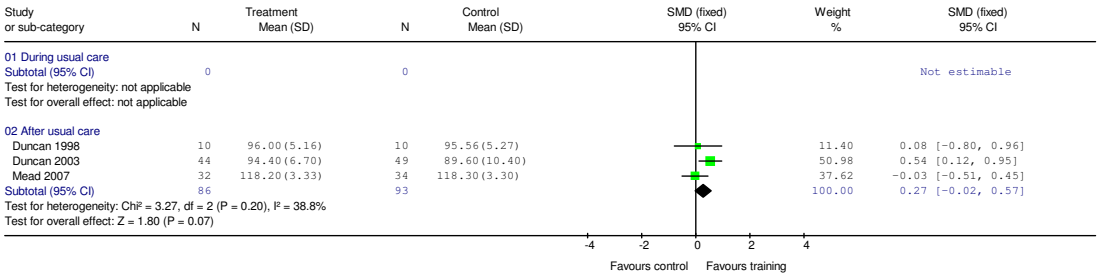
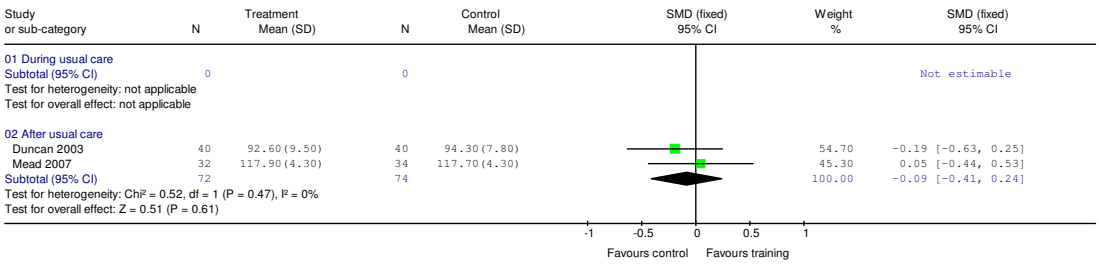


Figure 11.3 Meta analyses of the effects of mixed training on indices of disability at the end of intervention.

a) FIM Instrument and Barthel Index scores



11.8.2. Effect of training on secondary outcomes

11.8.2.1. Adverse effects

Adverse events were not reported systematically for all trials. However in 10/24 trials (n=461/1147 (40%) participants) the authors did comment on the tolerance to the training and there were no adverse reactions or events such as falls, fractures or injuries arising during the intervention. Mead et al. (2007b) reported 11 falls in 8/32 patients in the exercise group and 5 falls in 4/34 patients in the control group (ns); none occurred during the interventions.

For all studies 3/1147 (0.3%) participants were reported to have had a cerebrovascular event between baseline and end of intervention assessments. In the 9/24 studies (n=627/1147) which included a follow-up 6/627 (1.0%) participants were reported to have had a stroke between end of intervention and end of follow-up.

For all studies 6/1147 (0.5%) participants were reported to have had a cardiovascular event between baseline and end of intervention assessments; none (0/627) were reported between end of intervention and end of follow-up.

Few data regarding modification of risk factors for cardiovascular and cerebrovascular events were available. Three studies (n=144) reported blood pressure at the end of cardiorespiratory training (Potempa et al. 1995; da Cunha et al. 2002; Katz-Leurer et al. 2003). There was no significant effect on systolic (WMD (random)

-3.46 mmHg 95%CI -9.57, 2.64) or diastolic measures (WMD (fixed) -0.23 mmHg 95%CI -3.33, 2.87).

11.8.2.2. Physical fitness

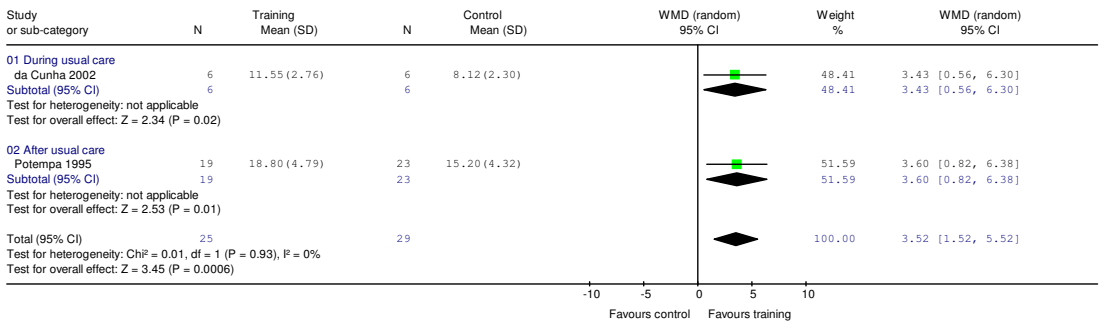
Cardiorespiratory Fitness

Pooled data from cardiorespiratory training trials shows a significant difference in the $\dot{V}O_2$ peak (WMD 3.5 ml·kg^{-1}·min^{-1}, 95% CI 1.52, 5.52; p<0.0001), and the maximal cycling work rate (SMD (Random) 0.60, 95% CI 0.18, 1.02) at the end of intervention (Figure 11.4). The Bateman et al. (2001) work rate data were transformed to a normal distribution (Log_e) data with 8% missing values. da Cunha et al. (2002) assessed the gross economy of gait and reported a moderate (0.7 SD units) but non-significant effect size; however profound baseline variability in this very small study limit its contribution.

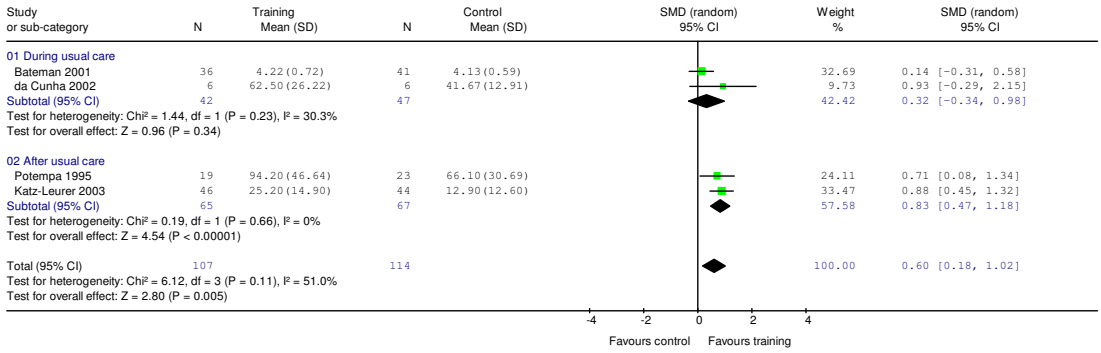
Individual mixed training trials (Appendix 14.21) show small significant differences in $\dot{V}O_2$ peak (Duncan et al. 2003) and net economy of gait (Mead et al. 2007b) at the end of intervention, although the benefit in economy disappeared after a 3-month follow-up. Bateman et al. (2001) reported significant retention of maximum cycling workload at a 3-month follow-up; however there are many missing values (21%).

Figure 11.4 Meta analyses of the effects of cardiorespiratory training on indices of cardiorespiratory fitness.

a) $\dot{V}O_2$ peak



b) Maximum cycling work rate (Watts)*



* Bateman et al. (2001) data included as Log_e transform therefore SMD is calculated

Muscle Strength

Two studies examine the effects of strength training on muscle strength (Kim et al. 2001; Winstein et al. 2004) that can be pooled in a meta-analysis (Figure 11.5). Kim et al. (2001) examined the effect of strength training of the involved lower limb on a composite measure of strength of the involved lower limb (sum of the percentage change in 6 muscle groups). Winstein et al. (2004) examined strength training of the upper-limbs on a composite measure of upper limb strength (sum of the torque of the extensors and flexors of the wrist, elbow and shoulder). The pooled effect size was marginally significant (SMD (fixed) 0.58, 95% CI 0.06, 1.10). However the larger

individual effect (Winstein et al. 2004) is biased by two interacting factors, unblinded assessment and use of a dynamometer which is hand-hand by the investigator; these data are also confounded by augmented training time.

Ouellette et al. (2004) examined strength bilaterally in the lower limb extensors, and unilaterally in the knee extensors and the ankle flexors (plantar and dorsi). All strength measures were reported to improve after resistance training significantly compared with the control group, except for ankle dorsiflexion on the unaffected side. This study also suggested peak power is improved during unilateral knee extensions, but not during bilateral extension of the whole lower limb. However strength and power data are limited to graphs and cannot be satisfactorily interpolated for further analysis.

Inaba et al. (1973) reported that patients allocated strength training of the involved lower limb made significantly greater gains in the 10 repetition maximum compared with controls (12.18 versus 8.58 kg, $p<0.02$) after 1 month of intervention. There were no differences between groups after 2 months of training. No measures of variance were included with these data.

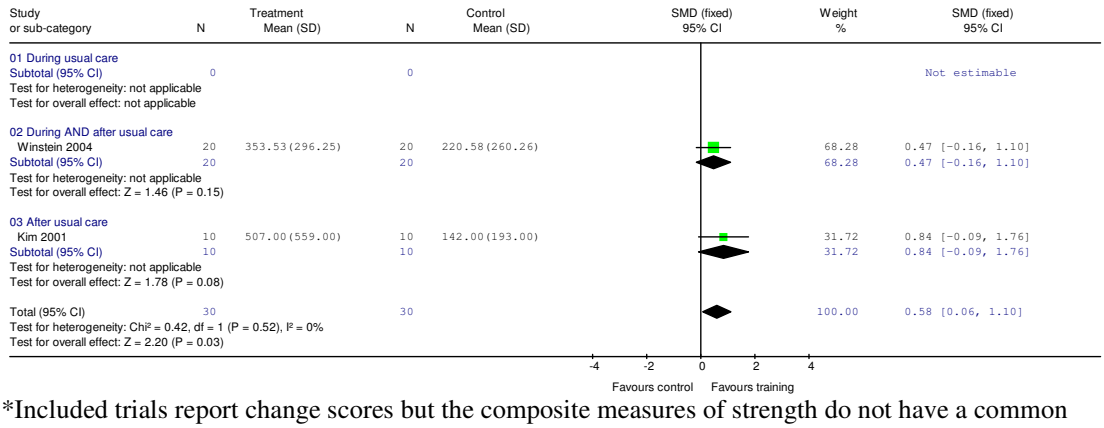
Meta analysis of the Duncan et al. (2003) and Yang et al. (2006) show no effects of mixed training (

Figure 11.6) on knee extension or ankle dorsiflexion strength. This meta-analysis is problematic due to substantial heterogeneity and both studies being confounded for augmented training time. The Yang et al. (2006) paper reports a range of other lower-limb strength improvements but all measures were made using a hand-held dynamometer which is vulnerable to bias. Assuming Yang et al. (2006) to instead be classified as strength training (sensitivity analysis) only the data of Duncan et al. (2003) would remain along with no significant effects.

Individual mixed training trials (Appendix 14.21) show no evidence of immediate or retained effect on explosive power of the lower limb (Mead et al. 2007b) or an immediate effect on handgrip strength (Duncan et al. 2003).

Figure 11.5 Meta analyses of the effects of strength training on indices of muscle strength.

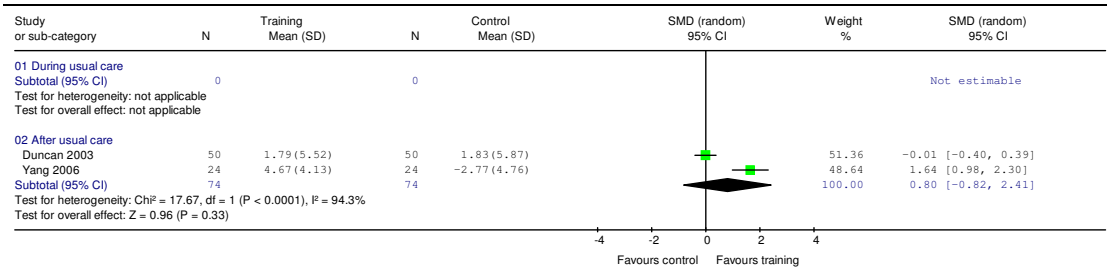
a) Composite measure of strength*



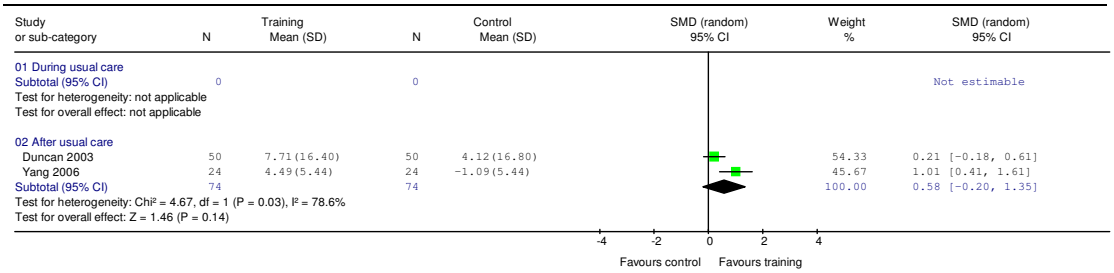
*Included trials report change scores but the composite measures of strength do not have a common unit of measurement therefore SMD is used.

Figure 11.6 Meta analyses of the effects of mixed training on indices of muscle strength.

a) Ankle dorsiflexion*



b) Knee extension*



* Duncan et al. (2003) data as change scores in torque (Nm; leg unknown) and Yang et al. (2006) report change scores in force (kg) therefore SMD used.

11.8.2.3. Mobility

Cardiorespiratory training

Meta-analyses of the effects of cardiorespiratory training were possible at the end of intervention (Figure 11.7) and the end of follow-up (Figure 11.8). These data show that treadmill training interventions during usual care lead to significantly lower Functional Ambulation Category (FAC) scores at the end of intervention (WMD (fixed), 0.72 95% CI 0.46, 0.98); only one study (Pohl et al. 2007) followed-up FAC (Appendix 14.19) and showed significant retention (WMD (fixed), 1.20 95% CI 0.65, 1.75).

A range of cardiorespiratory training interventions lead to improvements in gait performance assessed by maximal gait speed (WMD (fixed), 6.47 $m \cdot min^{-1}$ 95% CI 2.37, 10.57), preferred gait speed (WMD (fixed), 5.15 $m \cdot min^{-1}$ 95% CI 2.05, 8.25) and gait endurance (WMD (fixed), 38.9 metres 95% CI 14.3, 63.5) at the end of intervention (Figure 11.7). Most data are available for interventions during usual care however the direction and magnitudes of the effects appear similar after usual care.

Less data are available regarding the retention of mobility benefits (Figure 11.8). There is no effect on maximal gait speed after follow-up (WMD (random), 6.95 $m \cdot min^{-1}$ 95% CI -0.79, 14.70). However if the Bateman et al. (2001) data based on cycle ergometry are excluded, then the remaining gait-specific treadmill trial data (Pohl et al. 2007; Eich et al. 2004a) are homogenous and show significant retention of maximum gait speed (WMD (fixed) 10.6 $m \cdot min^{-1}$ 95% CI 4.91, 16.29) and gait endurance at follow-up (WMD (fixed) 57.51 metres 95% CI 25.82, 89.19). Eich et al. (2004a) reported continued improvement in these outcomes during the follow-up period.

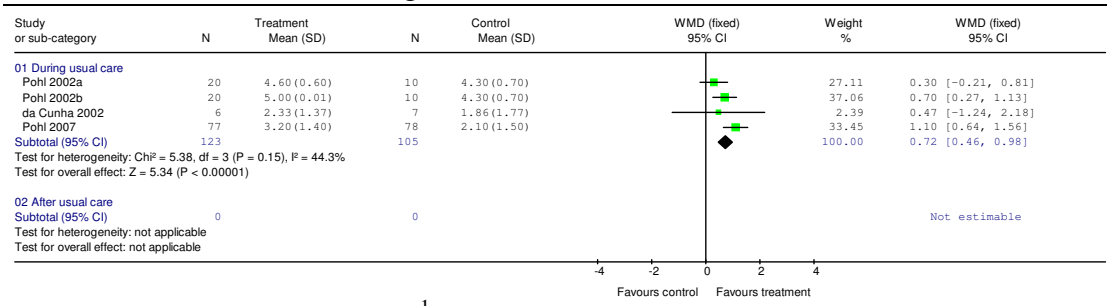
Apart from one trial (Katz-Leurer et al. 2003a) none of these studies examining gait outcomes are confounded by additional training time, in fact the time spent receiving the training interventions in Pohl et al. (2002c; 'A' and 'B') was less than the control group. Interventions were wholly or partly walking specific apart from one which used a Kinetron device (Glasser 1986), and two which used cycle ergometry (Bateman et al. 2001; Katz-Leurer et al. 2003a).

Subgroup analysis (not shown) indicated studies which met the ACSM (1998c) criteria for cardiorespiratory training had no effect on maximum gait speed (n=2), whilst those which do not (or are unknown) had a significant effect. One plausible reason may be due to the Bateman et al. (2001a) intervention not being specific to gait outcomes.

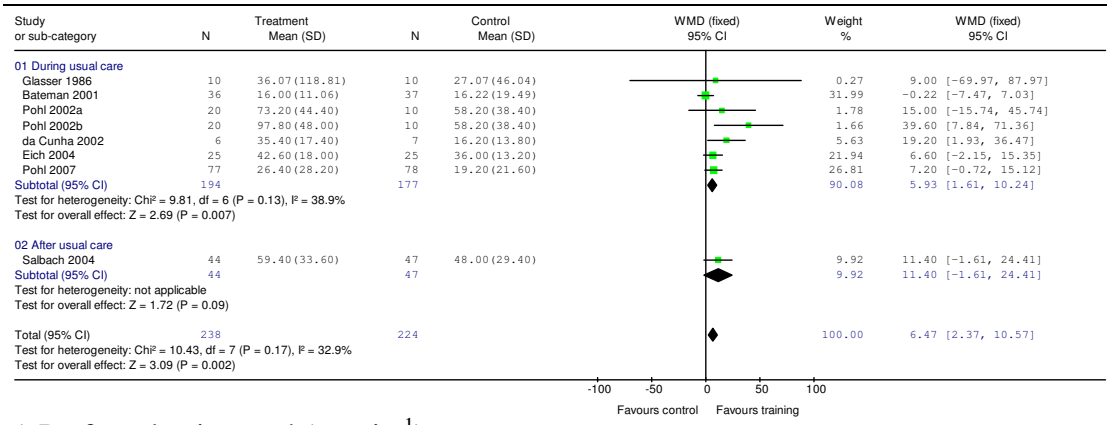
A funnel plot of the eight studies in Figure 11.7(b) had a tendency toward asymmetry suggesting there may be some heterogeneity such as that which might arise from publication bias (Appendix 14.18a); however there are too few data points to explore this further.

Figure 11.7 Meta analyses of the effects of cardiorespiratory training on gait performance at the end of intervention.

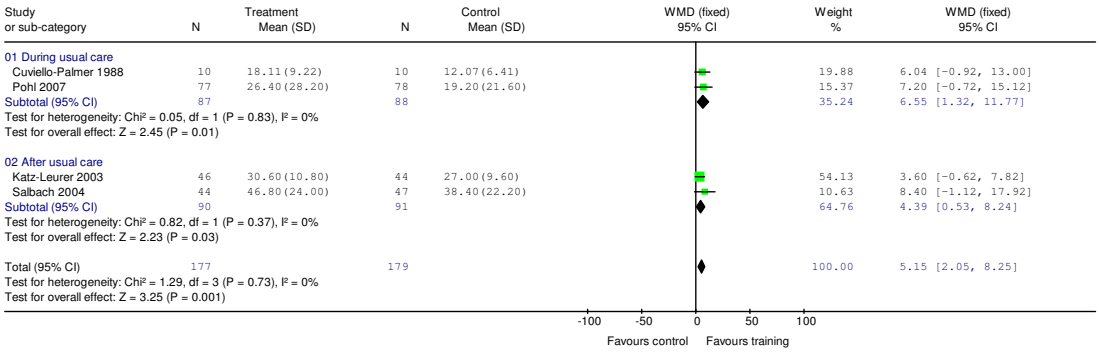
a) Functional Ambulation Categories (0-5)* †



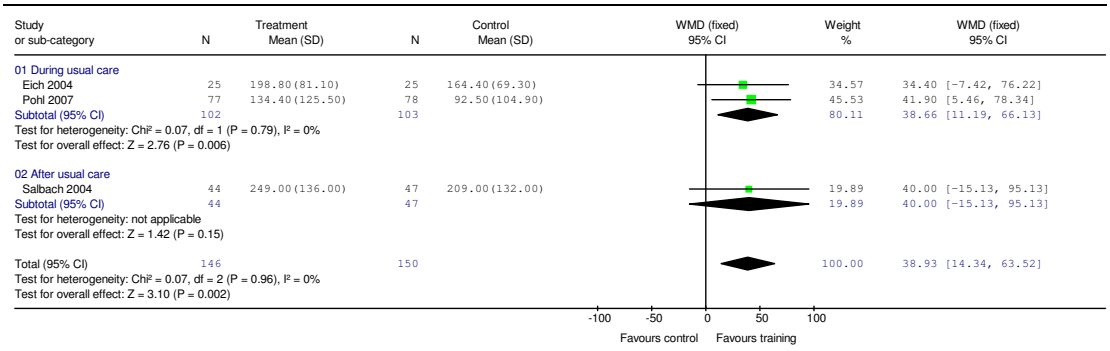
b) Maximum gait speed (m·min^{-1})



c) Preferred gait speed (m·min^{-1})



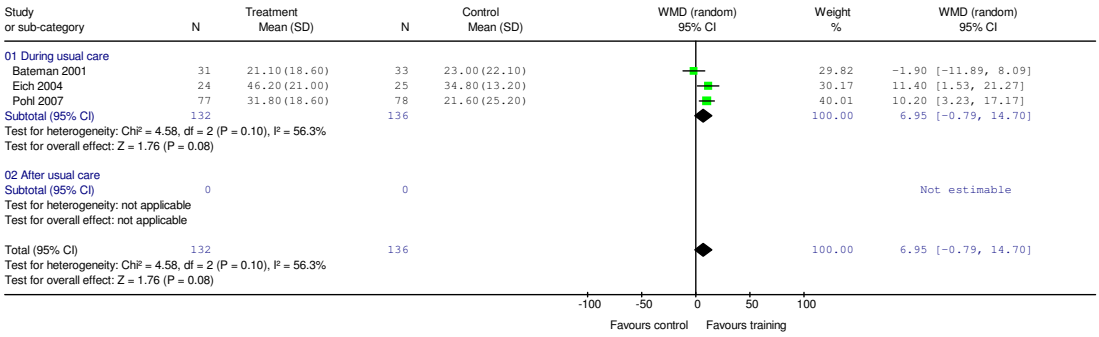
d) Gait endurance (6-MWT metres)



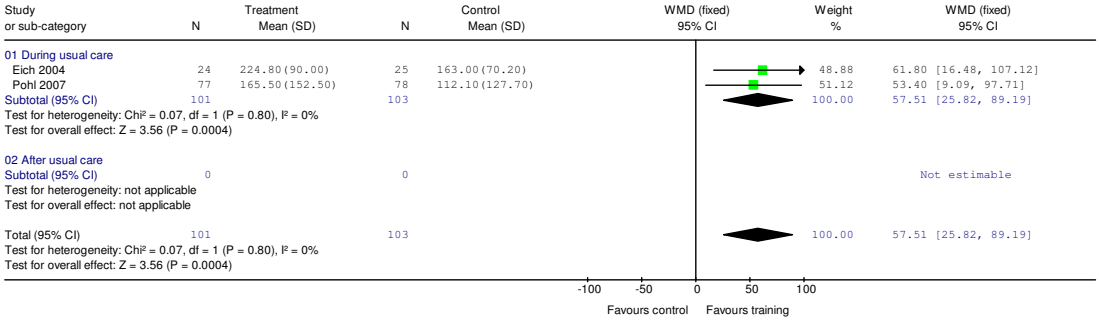
* SD of 0.01 inserted for (Pohl et al. 2002b 'B') training group to avoid a value of zero.
† Control group (n=20) are divided between the two comparisons of Pohl et al. (2002b; 'A' and 'B')

Figure 11.8 Meta analyses of the effects of cardiorespiratory training on gait performance at the end of follow-up.

a) Maximum gait speed ($m \cdot min^{-1}$)



b) Gait endurance (6-MWT metres)



Strength Training

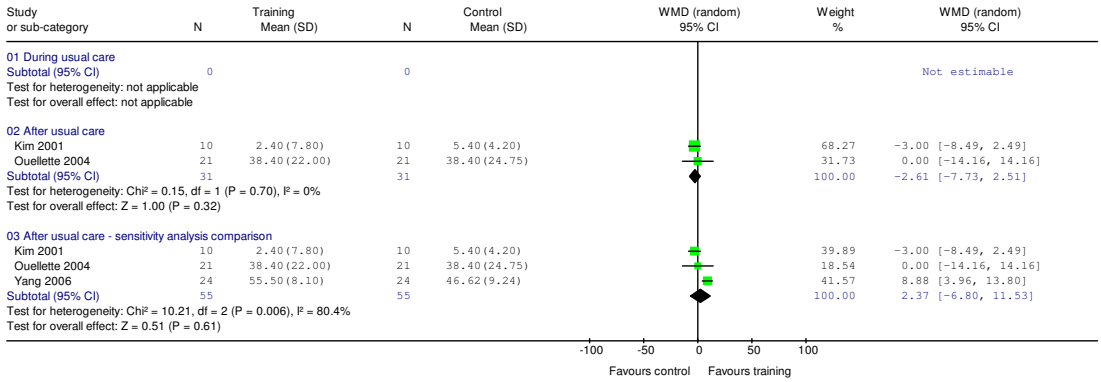
Strength training (Figure 11.9) showed no significant benefits for preferred gait speed (SMD (fixed) -0.14; 95% CI -0.65, 0.36) or maximal gait speed (SMD (fixed) -0.08 95% CI -0.58, 0.41). There was no training content in the strength training studies which is specific to the performance of walking.

A sensitivity analysis was performed by including the Yang et al. (2006) data categorised as strength training instead of mixed training. This introduced heterogeneity and the pooled effect of strength training on preferred gait speed

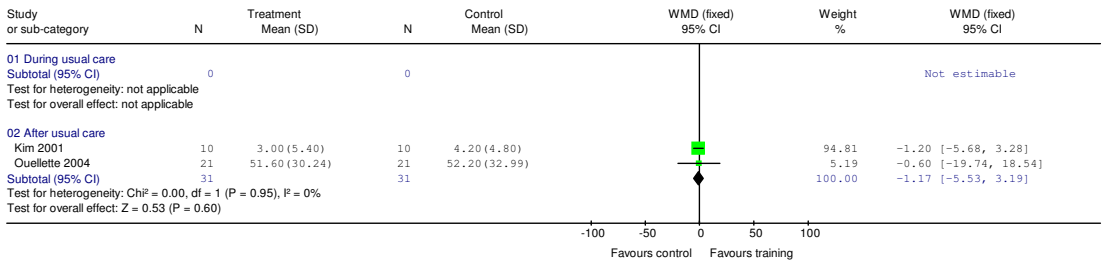
remained not significant (SMD (random) 0.22 95% CI -0.62, 1.06). Inclusion of Yang et al. (2006) as a strength training trial allows pooling with the Ouellette et al. (2004) data (Figure 11.9c), but there was no effect on gait endurance (WMD (fixed) 39.3 m 95% CI -8.20, 86.85).

Figure 11.9 Meta analyses of the effects of strength training on gait performance at the end of intervention.

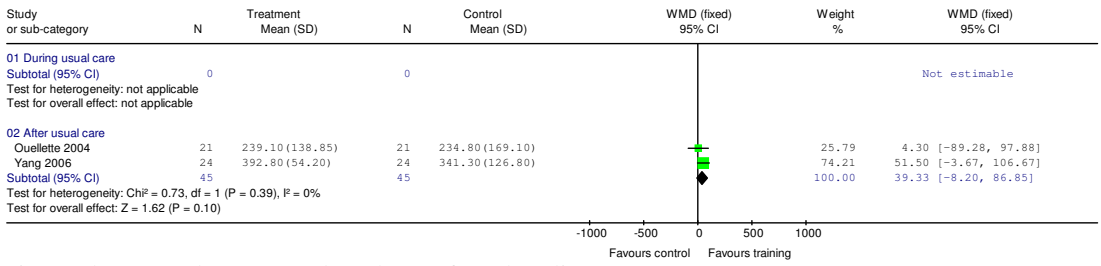
a) Preferred gait speed (m·min^{-1}); sensitivity analysis including Yang et al. (2006)



b) Maximum gait speed (m·min^{-1})



c) Gait endurance (6-MWT metres)



Kim et al. (2001) data reported as change from baseline scores

Mixed training

Meta analysis of eight studies (n=332) reporting the effects of mixed training on preferred gait speed (Figure 11.10a) showed no improvement at the end of intervention (WMD (random) 2.58 $m \cdot min^{-1}$ 95% CI -0.33, 5.5). There was a borderline effect in the 5/8 studies confounded for additional training time (WMD (random) 4.43 $m \cdot min^{-1}$ 95% CI -0.13, 8.99; Figure 11.10b). One study (Richards et al. 1993) showed an indication of dose-response where the improvement in preferred gait speed was positively associated with the amount of time spent on the gait training component ($R^2 = 0.63$).

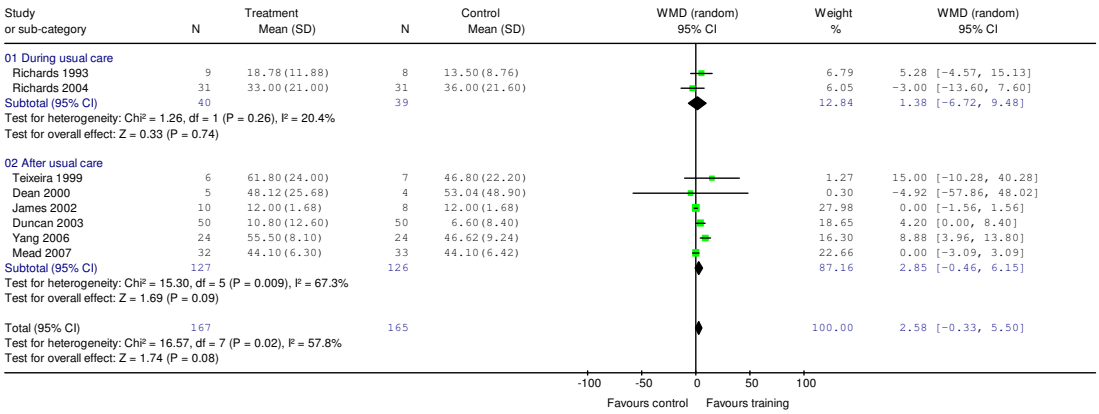
There was small significant of effect of mixed training on gait endurance (WMD (fixed) 30.04 metres 95% CI 8.49, 51.6). However 3/4 included studies, the majority of the data (n=168/177), are confounded for contact time. This leaves only one small study (Dean et al. 2000) for which assessment of this outcome was not blinded, and which showed no effect of mixed training at the end of intervention or the end of follow-up.

Three studies examined retention of benefits in preferred gait speed but no benefits were observed at follow-up (Figure 11.11).

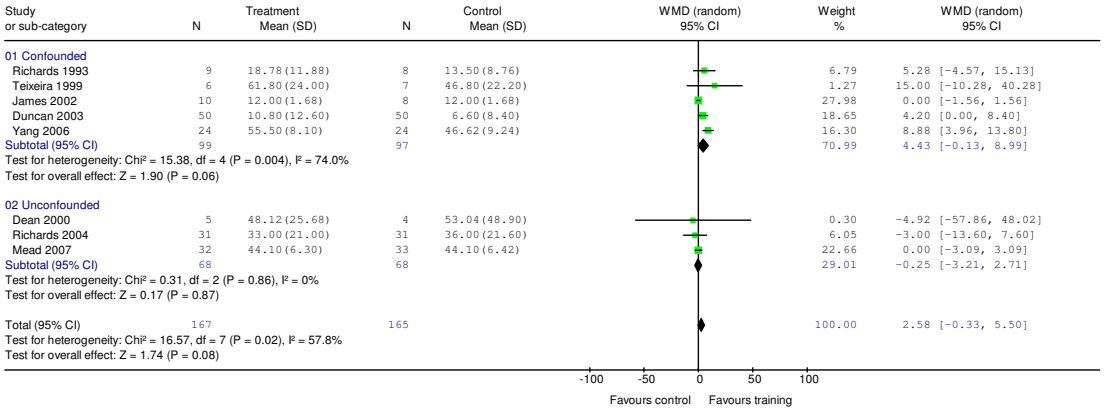
A funnel plot of the n=8 studies in Figure 11.10(a) was symmetrical and did not show any indication of heterogeneity which might arise from publication bias (Appendix 14.18a).

Figure 11.10 Meta analyses of the effects of mixed training on gait performance at the end of intervention.

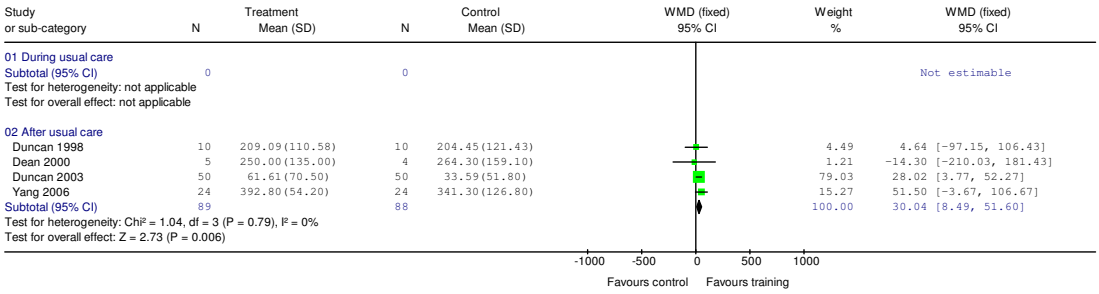
a) Preferred gait speed ($m \cdot min^{-1}$)*



b) Preferred gait speed ($m \cdot min^{-1}$); Subgroup analysis for additional training time*



c) Gait endurance (6-MWT metres)*

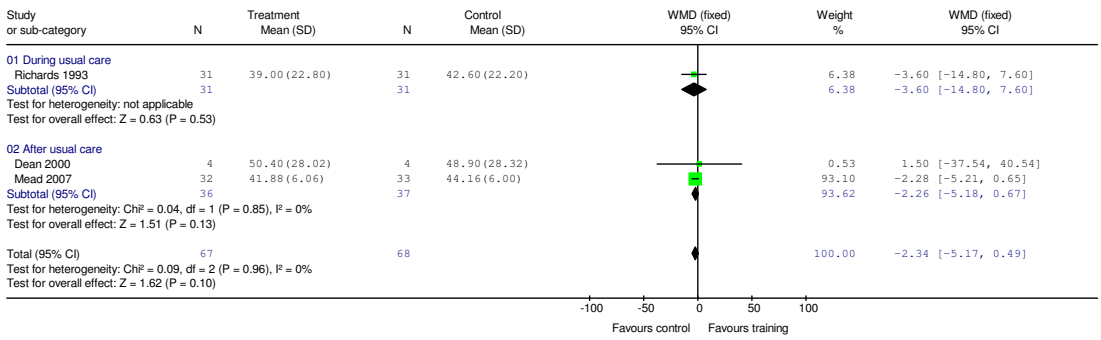


*Mixed change and end of intervention scores

Subgroup analysis in panel (b) compares the pooled effect sizes of the studies confounded for additional training time and the studies whose groups were balanced for training time.

Figure 11.11 Meta analyses of the effects of mixed training on gait performance at the end of follow-up.

a) Preferred gait speed (m·min^{-1})

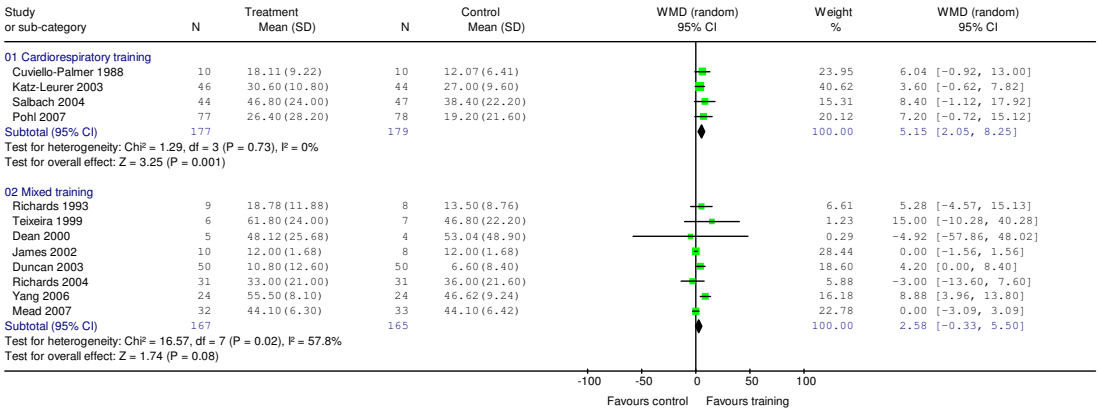


Comparison of cardiorespiratory and mixed training

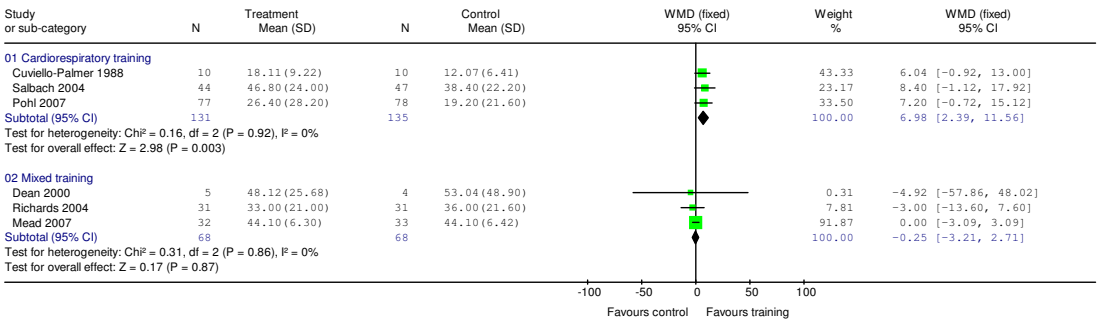
There were sufficient cardiorespiratory and mixed training trials assessing preferred gait speed to perform a meaningful sub-group analysis to compare the effects of the two training types. Meta analyses suggest the effect of cardiorespiratory training is greater than mixed training (5.15 vs. 2.58 m·min^{-1}; Figure 11.12a). If this is repeated without studies confounded for additional training time the difference is increased further (6.98 vs. -0.25 m·min^{-1}; Figure 11.12b).

Figure 11.12 Meta analyses comparing the effects of cardiorespiratory training and mixed training on preferred gait speed at the end of follow-up.

a) Preferred gait speed ($m \cdot min^{-1}$)*



b) Preferred gait speed ($m \cdot min^{-1}$); sensitivity analysis, studies confounded for additional training time are removed*



*Mixed change and end of intervention scores

11.8.2.4. Physical function

Meta analysis was possible for scored indices of physical and motor function (Fugl-Meyer scores, Berg Balance scale), and measures of performance of specific physical functions (functional reach, timed up-and-go, stair climbing). Apart from Berg Balance after cardiorespiratory training (Figure 11.13; not significant) and stair climbing speed after strength training (Figure 11.14; not significant) most data related to mixed training (Figure 11.15).

Meta analyses showed no significant overall effect of mixed training on Fugl-Meyer scores (upper and lower extremity), Berg Balance scores or functional reach (Figure 11.15). Timed 3-m up-and-go performance was significantly faster by a small margin (WMD (fixed), -1.14 sec 95% CI -2.06, -0.22) at the end of mixed training. However the data of Yang et al. (2006) are confounded for augmented training time, if excluded the effect is no longer significant (WMD (fixed) -1.16 sec 95% CI -2.93, 0.62). At follow-up there was no significant retention of benefit (Figure 11.16).

Of individual study data which could not be pooled there was little evidence of benefit (Appendices 14.19, 14.20, 14.21). Pohl et al. (2007) showed improvement in the Motricity Index (physical function of upper and lower extremities) at end of cardiorespiratory training intervention and the end of follow-up; however there was no blinded assessment of this outcome measure plus there is a competing interest present. The Adjusted Activity Score data reported by Teixeira-Salmela et al. (1999) improved but this is a very small study.

Figure 11.13 Meta analysis of the effects of cardiorespiratory training on indices of physical function at the end of intervention.

Berg Balance Scale scores

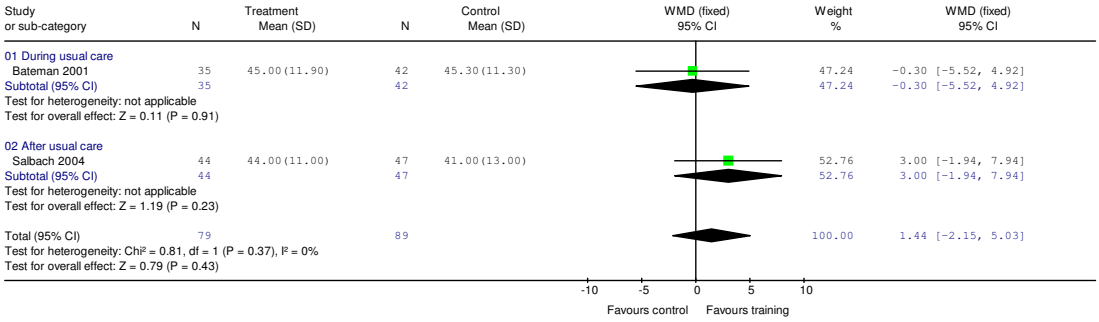
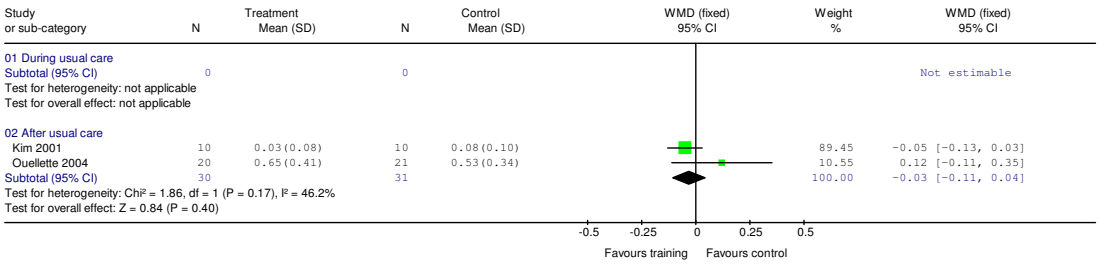


Figure 11.14 Meta analysis of the effects of strength training on indices of physical function at the end of intervention.

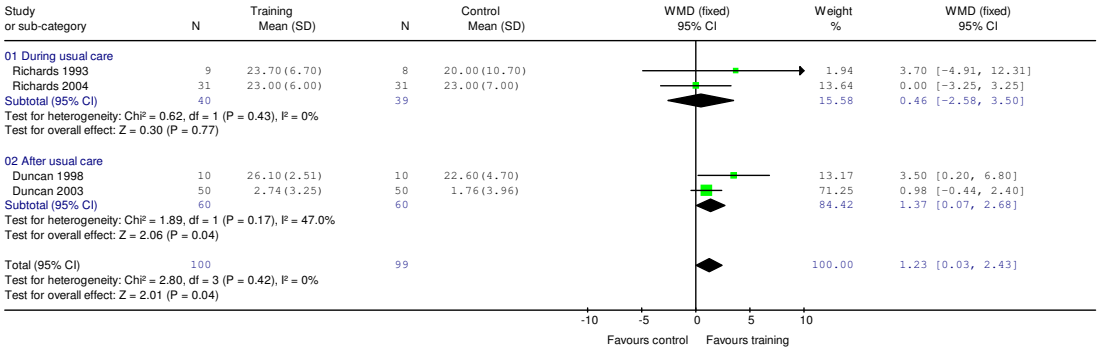
Maximum stair climbing speed (sec·step^{-1})*



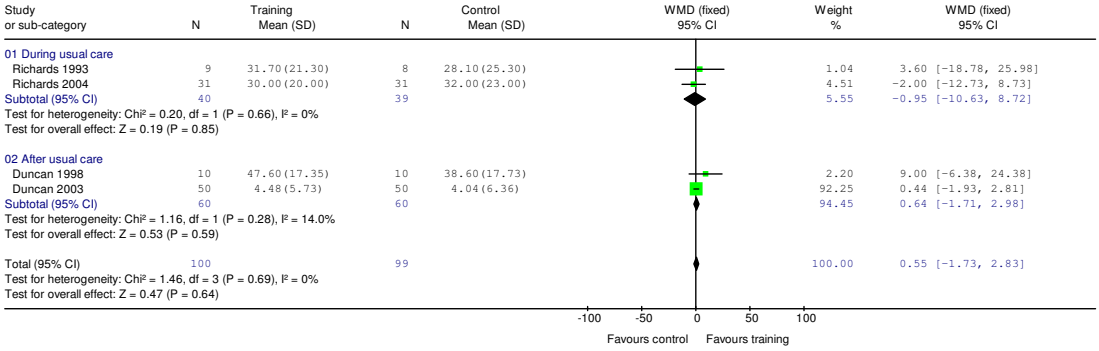
*Mixed change and end of intervention scores

Figure 11.15 Meta analyses of the effects of mixed training on indices of physical function at the end of intervention.

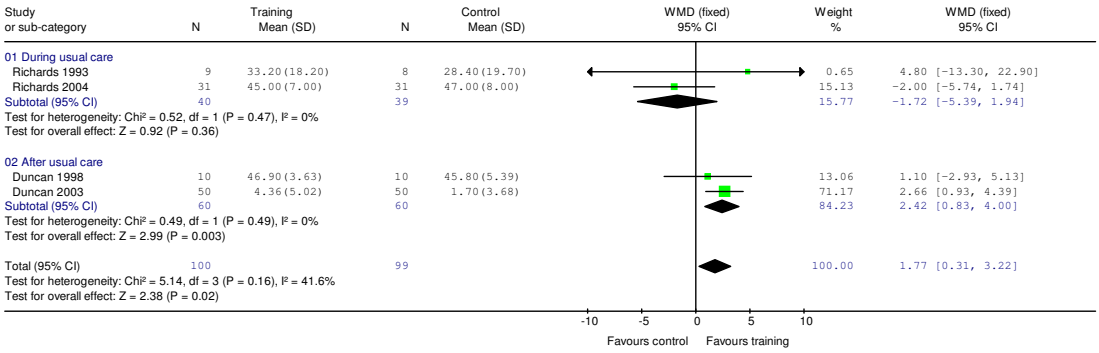
a) Fugl-Meyer Score (lower extremity)*



b) Fugl-Meyer Score (upper extremity)*



c) Berg Balance Scale score*



d) Functional Reach*

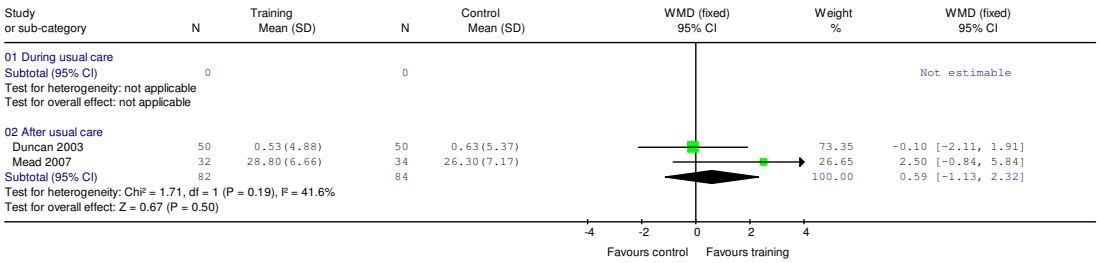
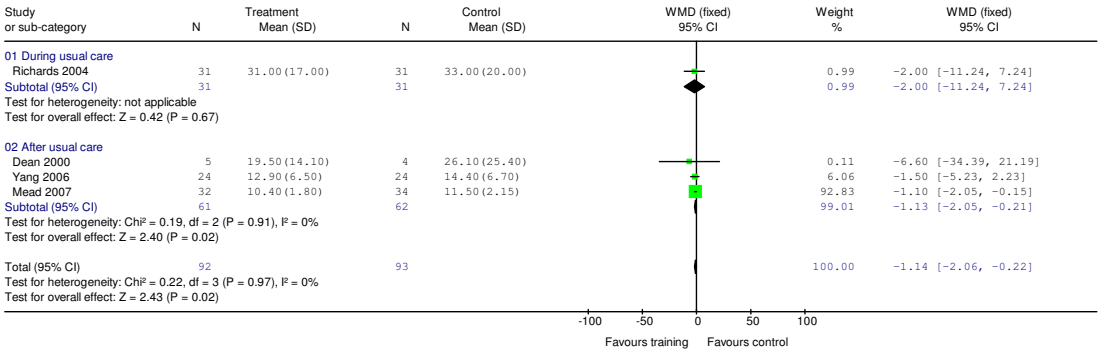


Figure 11.15 Cont./

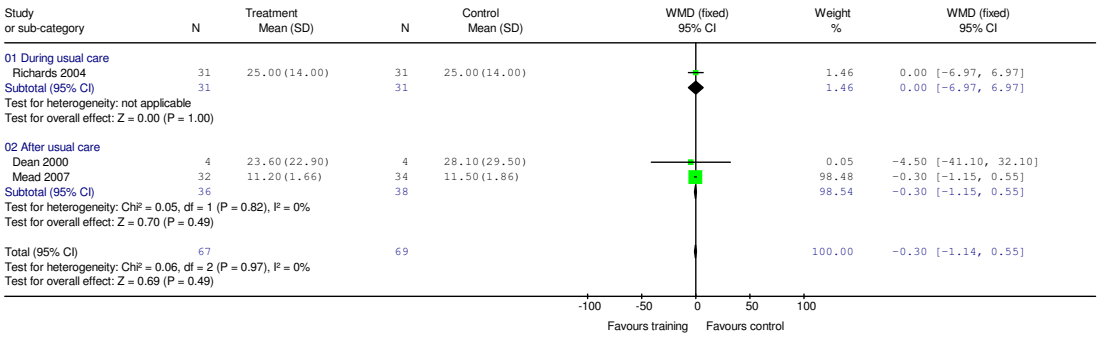
e) 3-metre Timed up-and-go (sec)



* Duncan et al. (2003) reports change from baseline scores

Figure 11.16 Meta analyses of the effects of mixed training on indices of physical function at the end of follow-up.

3-metre Timed up-and-go (sec)



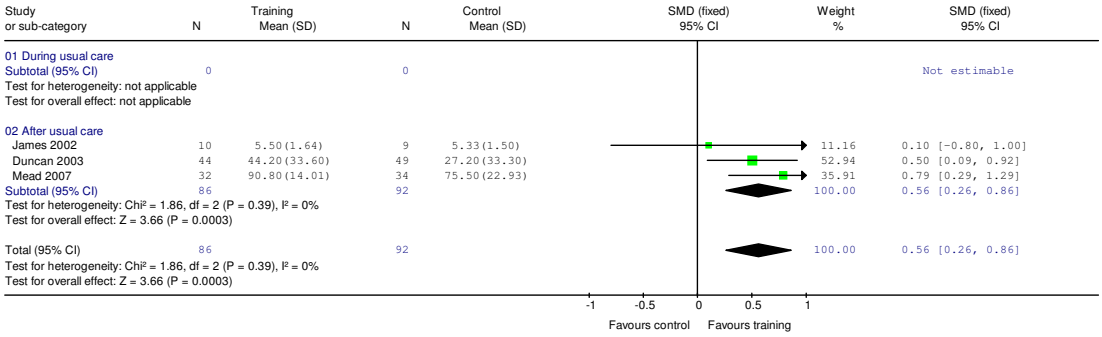
11.8.2.5. Health status and quality of life

No data exist examining the role of cardiorespiratory training on health status and quality of life. For strength training only one small study (Kim et al. 2001; n=20) reported mean change in SF-36 domains of 'Physical Health' and 'Mental Health'; there were no effects of training (Appendix 14.20)

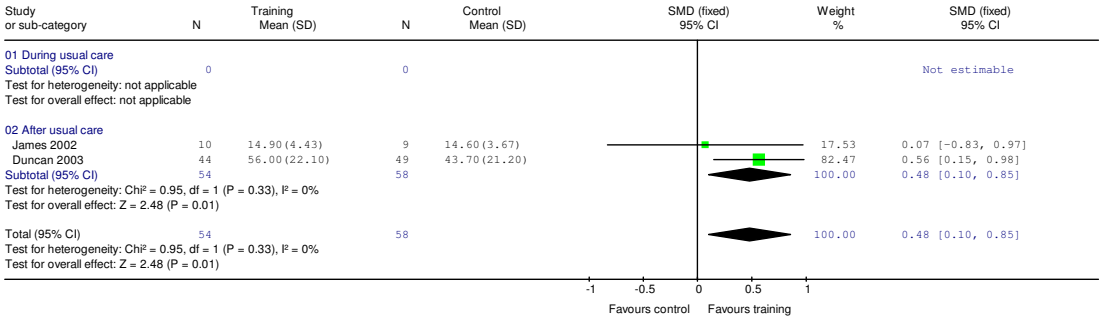
Three mixed training studies reported SF-36 domains (Duncan et al. 2003; James 2002; Mead et al. 2007b) which could be pooled at the end of intervention (Figure 11.17) and end of follow-up (Figure 11.18). However James (2003) and Duncan et al. (2003) are confounded for additional training time. The remaining unconfounded study (Mead et al. 2007b) showed a significant improvement in SF-36 'Role Physical' after intervention which was retained after a 4-month follow-up.

Figure 11.17 Meta analyses of the effects of mixed training on indices of health and quality of life at the end of intervention.

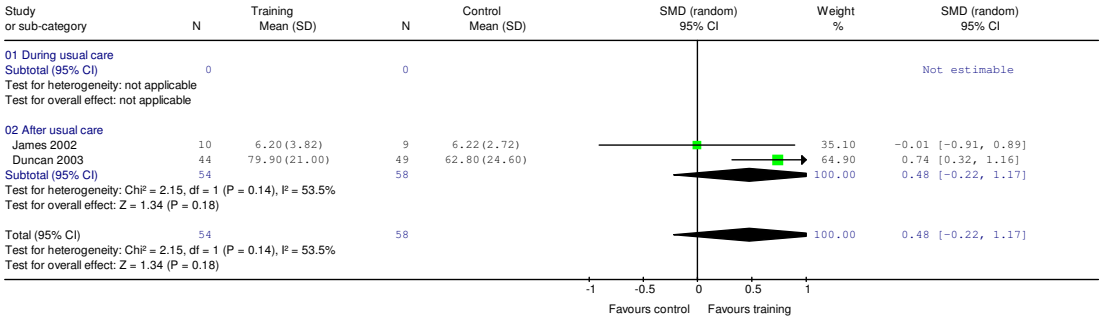
a) SF-36 'Role Physical'*



b) SF-36 'Physical Function'*



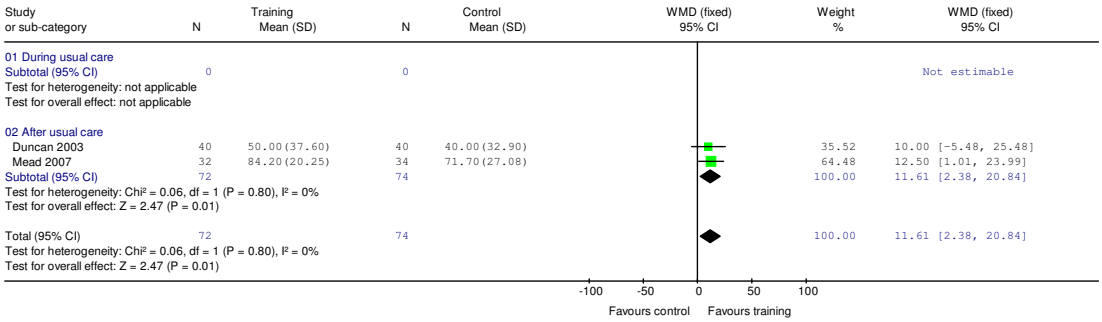
c) SF-36 'Social Function'*



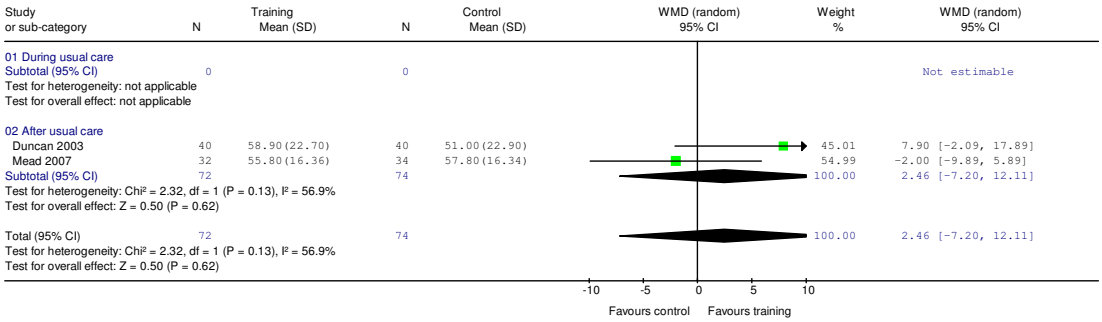
*James (2001) reports an older version of the SF-36 analyses are SMD

Figure 11.18 Meta analyses of the effects of mixed training on indices of health and quality of life at the end of follow-up.

a) SF-36 'Role Physical'



b) SF-36 'Physical Function'



11.8.2.6. Mood

Two studies examined the effect of cardiorespiratory training (Bateman et al. 2001) and mixed training (Mead et al. 2007b) on mood. Neither showed any immediate or retained effects on the anxiety and depression components of HADS (Appendices 14.19, 14.21). The Bateman et al. (2001) data had substantial missing values at end of intervention (29%) and end of follow-up (37%).

11.9. Discussion

The outcome measures from included trials were very diverse. This has been typical of stroke rehabilitation trials for some time (Greener and Langhorne 2002) and continues to present a problem when combining data in systematic reviews.

11.9.1. Effect of training on primary outcome measures

11.9.1.1. Case fatality

It is not known whether physical fitness training reduces case fatality. The observed numbers of deaths in this review may be low because participants included were at lower risk of death compared the wider stroke population. This may occur firstly because the inclusion criteria of the trials of exercise may select participants with milder strokes (most were ambulatory) and reduced risk factors (e.g. blood pressure ceiling criteria). Secondly there may be self-selection by participants who are physically active and who have a higher $\dot{V}O_2$ peak, both of which are associated with reduced risk of stroke and mortality (*Physical activity*, Section 1.1; $\dot{V}O_2$ *peak* Section 5.5.5.1). In addition the majority of the training programmes in this review are all very short duration (≤12 weeks). A systematic (Cochrane) review of the effect of exercise-only interventions showed that exercise reduced deaths in people with coronary heart disease (Jolliffe et al. 2000) but the training programmes often lasted several years. Since many stroke patients have co-existing heart disease training might influence post-stroke mortality provided it comprised cardiorespiratory training delivered over long periods of time. This requires investigation.

11.9.1.2. Death or Dependence

There are no data available to draw conclusions about the influence of training on the composite outcome of death or dependence after stroke. Death is infrequent, and measures of dependency such as those based on simple questions, Barthel Index score of <20 or modified Rankin Scale score of 3, 4 or 5 are lacking (Lindley et al. 1994). Both elements of this composite outcome are likely to be rare in the types of cohort eligible for physical fitness training.

11.9.1.3. Disability

A number of different global indices of disability, including subscales, were assessed. Limited data were suitable for meta-analysis and there was no good evidence of either an immediate or retained effect of fitness training on disability. There may be several reasons for this. Firstly, a number of methodological issues were identified which weaken and bias these limited data. Secondly, some measurement tools lacked sensitivity due to the recruitment of patients typically presenting with milder strokes. There was evidence of ceiling effects in the Barthel Index data of two trials (Bateman et al. 2001; Duncan et al. 1998), and the FIM Instrument is also known to show ceiling effects, particularly in community living patients (Hall et al. 1996). Thirdly, a lack of effect on disability measures despite functional benefits has been reported in trials of exercise for healthy elderly people (Keysor and Jette 2001).

The lack of an immediate effect however does not preclude longer term benefits. An increased fitness reserve may ameliorate the deterioration of function which will occur with increasing age and thus postpone crossing thresholds of independence

(Section 2.3). Therefore pre-clinical measures of disability (Section 2.3.2) coupled with long-term follow-up may be a more useful approach for assessing outcome in trials of fitness training after stroke.

There were insufficient data to investigate any secondary objectives or to perform any subgroup analyses on the primary outcome measures. Few conclusions can be drawn about the impact of physical fitness training on death, dependence or disability after stroke.

11.9.2. Effect of training on secondary outcome measures

11.9.2.1. Adverse events

There was no evidence of adverse events arising from training in patients who meet the criteria for participation in physical fitness training. However this may not be generalizable to the wider stroke population and few trials specifically intended recording adverse events.

11.9.2.2. Physical Fitness

Cardiorespiratory fitness

$\dot{V}O_2$ peak measured at baseline in three trials (da Cunha et al. 2002; Potempa et al. 1995; Duncan et al. 1998) was 25%, 55% and 50% of values expected in untrained age- and sex-matched healthy people (Section 5.5). Mixed training, and in particular cardiorespiratory training, significantly improved $\dot{V}O_2$ peak, and improved exercise tolerance during continuous exercise. This may be beneficial because low $\dot{V}O_2$ peak is

associated with functional limitation in elderly people. In people with stroke the functional benefits are less clear (Section 5.6) however low $\dot{V}O_2$ peak is linked to increased risk of having a stroke risk and mortality from stroke (Section 5.5.5.1).

Economy of walking may improve in response to training which contains walking activity. However one of the two studies had a small sample size and variable baseline data making interpretation difficult. A limited 'fitness reserve' caused by low $\dot{V}O_2$ peak coupled with poor walking economy is a common post-stroke problem (Sections 5.5 and 5.5.2). Therefore training to improve walking economy and increase $\dot{V}O_2$ peak may be beneficial for walking performance and exercise tolerance after stroke. There are too few data to examine the post-training retention of cardiorespiratory fitness.

Muscle strength

There are limited data to quantify whether mixed training or strength training improves muscle strength after stroke. Analyses showing improvements are all associated with studies which are either confounded for training time or biased. There are no data to examine the post-training retention of strength.

Mead et al. (2007b) assessed explosive lower limb extensor power but showed no immediate or retained effect of mixed training. Non-response could be due to a lack of explosive, fast movements during resistance training. Explosive power output may have greater functional importance than muscle strength (Section 2.2.2.3) and it is

associated with physical function and disability after stroke (Chapter 8). Interventions to improve explosive power after stroke remain under-researched.

11.9.2.3. Mobility

There is consistent evidence that cardiorespiratory training which involves walking can benefit walking ability when provided during inpatient stroke care. This intervention reduces dependence on other people for ambulation, increases walking speed and improves tolerance of continuous walking. Improvement may occur due to an increased fitness reserve (arising from increased $\dot{V}O_2$ peak and/or improved economy of walking) and the effect of repetitive task-related practice of walking.

There is no evidence that strength training benefits walking. None of the interventions incorporated walking as a mode of exercise, they are therefore not specific. In addition improvements in strength may not necessarily produce functional benefits (e.g. Kim et al. 2001) and this may be due to complex relationships between fitness and function (*Complex Relationships*; Section 2.3.1) which may arise from factors such as non-linear associations and the action of co-impairments such as balance.

Evidence examining the effect of mixed training on walking performance is problematic since the majority of studies are confounded by increased training time. There is no effect of mixed training on gait outcomes in the un-confounded studies. All studies except one (Yang et al. 2006) include an element of walking therefore benefits may be due to the additional volume of time spent of walking along with any

other potential 'attention' effects. Two studies (n=205) hint that some gait benefits persist after training finishes but one (Pohl et al. 2007) has some methodological issues and a high drop-out rate at follow-up.

11.9.2.4. Physical function

There is no good evidence that training in any form improves a whole spectrum of functional limitations. The limited pooled data which suggests a small effect of mixed training after usual care on balance and lower extremity function are confounded by increased training time. Any promising effects reported by individual studies are similarly compromised though bias and confounding. Studies clear of these problems are associated with no effect.

11.9.2.5. Health status and quality of life

Little is known about whether training can improve self-perceived health status and quality of life after stroke. Health status and quality of life is reported by one small study of strength training and not at all by those investigating cardiorespiratory training. Two of the three mixed training studies reporting SF-36 are confounded for increased training time. The SF-36 'role physical' domain showed both immediate and persistent benefits but the scoring of this domain is problematic in those who are not engaged in employment (Section 10.6.2), in addition various elements of the SF-36 are prone to ceiling effects in these studies (Section 10.6.2).

11.9.2.6. Mood

There were too few data to examine the effects of training on mood.

11.9.3. Factors influencing primary and secondary outcome measures

11.9.3.1. Dose of training

All the training interventions occurred regularly and were progressive in nature. The interventions differed in the dose of training quantified in terms of a) overall volume of training time, and b) the intensity of the exercise used.

The ACSM (1998b) criteria were used to define an effective overall 'dose' of fitness training as defined by the parameters of intensity, duration and frequency. One of the few intended subgroup analyses which explored this showed benefit was not clearly linked to those studies which met the criteria. This illustrates the problem of performing meaningful analyses from the subgrouping of small numbers of trials, the consequences are reduced power and the influence of characteristics unrelated to the grouping factors in this case the potentially powerful effect of specificity of training.

Some study interventions may have a sufficient dose of training but failure to record or report intensity meant they could not assigned to a category. Conversely, interventions meeting the criteria may have a low dose of training because they were short in duration (e.g. Kwakkel et al. 2004).

Underestimation of benefits may arise if interventions are poorly attended or complied with. Full attendance was reported in 6 trials. This may have been facilitated because the interventions occurred partly or completely during inpatient care, were home-based or very short (4 weeks).

Overestimation of benefits may arise in interventions confounded by increased training time. Theoretically this exaggeration would have the greatest opportunity to emerge in those studies with the biggest training volumes. In 7/9 confounded studies ≥20hrs training was used whilst only 2/15 un-confounded studies exceeded 20hrs training. Meta-analysis has shown that when stroke rehabilitation is augmented with an additional 16 hours exercise therapy there are benefits in ADL (Kwakkel et al. 2004). This offers an explanation for the repeated observation that significant training effects were associated with the studies confounded by increased training time. However this in itself is confounded since the benefits are also by definition associated with the greater training volumes involved. The data of Richards et al. (1993) add further support to these observations showing that time spent gait training was associated with mobility outcomes - this also may be indicative of a dose-response relationship.

Exercise intensity is probably one of the most important fitness training variables. Only the interventions of Pohl et al. (2002b; 'A' and 'B') examined this directly and showed that the higher intensity walking intervention (comparison 'B') was more beneficial for maximal walking speed than lower intensity walking (comparison 'A'). However this intervention was also the most rapidly progressing so this effect is difficult to separate the effect from that of intensity.

This review indicates stroke patients can participate in and complete a variety of different short-term training interventions, but the optimal dose of training for people with stroke is difficult to establish from these data.

11.9.3.2. Type of training

No included studies directly compare cardiorespiratory, strength and mixed training. In this review it was only feasible to compare the effect of cardiorespiratory training and mixed training on one shared outcome, preferred gait speed. The greater benefits associated with cardiorespiratory training is difficult to draw conclusions from since the cardiorespiratory training interventions comprised a greater amount of gait-related training and the effect could therefore be one of specificity rather than training type.

There were too few data to determine the relative effects training the upper vs. lower limbs, or the affected vs. unaffected limbs.

Numerous positive findings in this review demonstrate the specificity of the training response (*Specificity*, Section 3.3), for example;

i) $\dot{V}O_2$ peak improvements were associated with training interventions containing cardiorespiratory training component

ii) Improvements in physical fitness were seen during exercise that mirrored that used during the intervention.

iii) walking improvements were associated with training interventions employing walking as a mode of exercise

Conversely no effects were associated with non-specific training, for example;

i) lack of gait and other physical function benefits from strength training containing no functionally relevant movements.

ii) lack of increase in muscle explosive power output in a programme containing no explosive movements.

In summary, it is not known which type of training, if any, is most beneficial, however the findings support the concept of training specificity.

11.9.3.3. Retention of benefits

8/24 studies incorporate follow-up data. Some benefits observed at the end of intervention remained at the end of follow-up. These included maximum cycling workload (Bateman et al. 2001), Functional Ambulation Categories and Motricity Index (Pohl et al. 2007), maximum gait speed and gait endurance (Pohl et al. 2007; Eich et al. 2004a) and SF-36 'Role Physical' (Duncan et al. 2003; Mead et al. 2007b). These observations should be viewed with caution because of unblinded assessments (Pohl et al. 2007), high participant attrition (>20% in Pohl et al. 2007; Bateman et al. 2001; Duncan et al. 2003) and measurement validity issues (SF-36 'Role Physical').

The only significant benefit to emerge after follow-up which was not previously present at the end of intervention was SF-36 'Social Function' but this is only based on one study (Duncan et al. 2003).

Functional advantages observed at the end of rehabilitation interventions are known to be transient disappearing at a later stage (Kwakkel et al. 1999; Kwakkel et al. 2002), probably due to continued improvements in the control group rather than deterioration in function (Langhorne 2002). However, fitness improvements

observed at the end of training interventions are known deteriorate (*Reversibility*, Section 3.3). An immediate improvement in economy of walking disappeared at the end of follow-up (Mead et al. 2007), but other cardiorespiratory and strength follow-up data are lacking. There were limited data examining retention of benefits as a whole, and no clear pattern of retention emerges from it.

In summary functional benefits mediated by increased physical fitness may not be sustained unless some form of training stimulus is maintained. At present there are no data examining long-term fitness training, or facilitation of continued exercise after the end of fitness training. Long-term follow-up should be incorporated into future trials of physical fitness training.

11.9.3.4. Effect of initial patient status on outcome measures

Two studies dichotomised their participants on measures of stroke severity and showed those with lower severity benefited from training the most in terms of Fugl-Meyer scores at the end of training (Winstein et al. 2004) and the Frenchay Activities Index scores at the end of follow-up (Katz-Leurer et al. 2003a). However this type of sub-grouping reduces statistical power and there are methodological issues associated with both these studies. Other than this there were too few suitable data to determine the effects of disability, ambulatory status or degree of hemiparesis using meta-analyses. Nothing can be concluded about initial patient status.

11.9.3.5. Effect of physical activity performed by control groups

Training effects arising from physical activity in the control group interventions could explain the frequent lack of effect in some of the higher quality studies. However a strength of this review are the inclusion criteria which ensure that control group interventions other than usual care were restricted to being passive or being unlikely to provide a benefit which could influence outcome measures.

11.9.3.6. Effect of trial quality

There were insufficient data to examine the effects of trial quality on outcome measures. However 5/24 studies reported outcome assessments unblinded from the outset or were subject to subsequent inadvertent unblinding. This inadvertent unblinding may have happened in other studies but was not reported. Unblinded outcome assessment risks biasing the data of 350/1147 (31%) participants.

11.10. Summary of findings

- Most available data relate to ambulatory people in the chronic phase (>1 month) post-stroke.
- It is feasible for stroke patients to participate in a variety of short-term fitness training regimens presented in a range of settings either during usual stroke care or after discharge.
- There is no evidence of adverse events arising from participation in fitness training.

- Little is known about the effect of any form of training on the primary outcomes of death and dependence.
- Few studies reported global indices of disability, no meta-analyses showed effects on measures of disability.
- There is some evidence that cardiorespiratory fitness can be improved via training containing some cardiorespiratory training content.
- There is good evidence that that cardiorespiratory training during usual care, which involves walking as a mode of exercise can reduce dependence on others during ambulation and improve walking performance in terms of speed (maximum speed + 9.85 $m \cdot min^{-1}$; preferred speed + 5.85 $m \cdot min^{-1}$) and the distance walked in 6 minutes (+38.9 m).
- Few strength training data exist. Some studies hint at an improvement in muscle strength but there is no other evidence of benefit from the studies, either individually or collectively.
- The majority (6/9) of mixed training interventions are confounded for training time; without these there is no clear evidence of any benefits. Currently little can be safely concluded about mixed training interventions.
- There are very few outcome data relating to physical function, health status and quality of life, and mood.
- It was not possible to determine the effect of fitness training variables, such as 'dose' or type of training, on outcome measures.
- A consistent pattern of findings supports the idea that benefits may be greater when fitness training is specific or 'task-related'.

- No conclusions can be drawn about retention or loss of benefits after training is completed.
- There were methodological problems and study design issues which bias and confound much of the available data, and affect its generalizability.

11.10.1.1. Issues for research

Control groups

In terms of trial designs there should be a concerted effort to balance total contact time across all arms of trials to avoid confounded results. Whatever control exposure is chosen to balance time spent training should contain minimal or preferably no physical activity since even performing activities of daily living may be sufficient to cause training effects in elderly people (Young 2001). One robust way of clarifying whether the content of the training itself is beneficial would be comparison of two doses of training (e.g. Pohl et al. 2002b), this has not been repeated.

Intervention

In people with stroke muscle strength and power are more clearly associated with functional advantages (Section 6.5) than cardiorespiratory fitness (Section 5.6) yet well controlled studies containing interventions to improve muscle force production are lacking. In addition resistance training often involves exercise modes in which the movements performed in training bear little resemblance to those relevant to everyday life, although strength may improve no functional benefit arises. The nature of the associations between physical fitness and functional benefit are complex

(Section 2.3) and this suggests that training interventions should be more complex and address other co-impairments such as balance.

Outcome measures

Currently used measures of disability and dependence are problematic since stroke patients who are eligible for fitness training have typically mild disability. This is difficult to detect (as many disability measures have ceiling effects) yet it may be a precursor to the later onset of disability arising from functional decline. Therefore an appropriate way of assessing long-term outcome in this group of stroke patients may be measures of pre-clinical disability (*Pre-clinical disability*, Section 2.3.2).

Long term studies

Improvements in physical fitness after training, and improvements in physical function after rehabilitation are transient. Since physical fitness may be linked to functional status the long-term retention of any benefits should be examined routinely in training studies. Fitness and function deteriorate with increasing age in everybody, and this is exacerbated with physical inactivity; therefore it is plausible that short-term effects of training only emerge as being beneficial after a period of functional decline.

Related to this is the need to examine strategies aimed promoting physical activity and maintaining physical fitness in the long term after stroke. This has not been investigated.

In general terms there remains a general need for more, larger trials of functionally relevant physical fitness training which should include participants with a greater range of stroke severity, including non-ambulatory patients

Updated Review of Physical Fitness Training after Stroke - Summary

11.10.2. Implications for Practice (2008)

- Cardiorespiratory walking training during usual stroke care can increase walking speed and walking distance, and reduce dependence on other people during walking.

- No other evidence is sufficient to influence practice at the present time. Other than the observation that most benefits in fitness, mobility and physical function appear to be associated with 'task-related' training.

11.10.3. Implications for Research (2008)

- Little is known about the benefits of physical fitness training after stroke, or the optimal regimen for improving fitness. More trials are needed.

- Resistance training interventions to improve muscle strength and power need investigation but the training must be functionally relevant.

- Trials need to be longer: Long-term follow-up should be incorporated in all training RCTs. Long-term training interventions (>12 weeks) and strategies to facilitate long-term maintenance of physical fitness are under investigated.

- Time of exposure to training intervention and control interventions must be matched to prevent overestimation of treatment effects.

- The content of an attention control intervention should be chosen carefully to minimize impact on key outcome measures; this will prevent underestimation of treatment effects caused by control group training effects.

- Systematic review of the effects of physical fitness training after stroke is complicated with the availability of new data and would now benefit from being split in relation to specific outcomes of interest.

12. Thesis Discussion

Physical fitness training can result in range of physiological and other effects, many of which seem to offer a plausible means of reducing or compensating for a number of common problems which are experienced after a stroke. Participation in exercise may have social and other benefits, but adaptations in physical fitness are of particular relevance to common physical problems experienced after stroke. This thesis has shown many aspects of physical fitness are impaired and that many of these impairments are associated with poor function.

Importantly, there is good evidence from the systematic review that improvements in some aspects of walking function can be achieved from cardiorespiratory training, involving walking, presented during usual care. Evidence for other benefits in particular from physical fitness training presented after discharge from usual stroke rehabilitation is more limited and under-researched.

This process followed in this thesis is allied to phases 0 (Theory), I (Modelling) and II (Exploratory trial) of the MRC model for development and evaluation of complex interventions (Medical Research Council 2000a). This process has identified that the frequent lack of significant effects that were observed could arise due to the combination of too few data, architecture of existing study designs and diversity of interventions. More trials are required to address deficits in current research. The

findings of the exploratory RCT and systematic reviews of RCTs can help guide the content of a definitive trial (MRC Phase III).

12.1. A definitive trial of physical fitness training?

It is not possible to define a single definitive trial to examine physical fitness training, for example there is a need for trials both during and after stroke usual care. The design of definitive trials includes an optimal intervention, control and outcome measures and other design features such as sample size. Few recommendations can be made based on systematic review evidence therefore findings of the exploratory RCT and the observational studies are used in addition.

12.1.1. Optimal intervention

Systematic review findings suggest that training mode(s) should include activities which are specific to the patterns of movement in desired functional outcomes. For example walking would be the training mode most likely to benefit ambulation, and this would be relevant to many stroke patients.

Exploratory RCT findings: The model of frequency, intensity, duration and programme length previously formulated on current best practice was feasible and is recommended again. The exploratory RCT (STARTER) also suggested that training mode(s) should allow individual 'tailoring' of exercise to improve compliance.

Observational studies suggest a greater range of benefits should arise from a combination of components addressing cardiorespiratory fitness and muscle force production (strength and power).

For community dwelling people with stroke, home-based interventions reduce cost of participant travel but greatly increase contact time per participant for those delivering the intervention (1:1 ratio). Conversely, for class-based interventions, demands on staff decrease (e.g. 1:5 to 1:10), but at the expense of participant travel costs – these may be associated with attrition if not funded by the trial. Individually tailored exercise was feasible in the exploratory RCT even though the staff to participant ratio was low. In terms of cost, there may be little to choose between these, but in terms of aquiring larger numbers group exercise may be the most useful vehicle.

12.1.2. Optimal control intervention

Systematic review evidence indicates that if fitness training interventions are being evaluated then without exception a control group should have an equivalent exposure time to the experimental group to avoid overestimation of effects.

Exploratory RCT evidence showed that relaxation was a feasible attention control, it was well attended and compliance was good. However relaxation may not be an 'inert' intervention and although well-suited as a control for physical and functional outcomes it may dilute the benefits of fitness training on other outcomes such as mood and quality of life.

It is logical to minimize physical activities within control interventions. If activities are included these should be of trivial intensity and/or skill-based, functionally unrelated to the outcome measures and certainly not progressive; this will minimize underestimation of effects.

12.1.3. Optimal evaluation

Mortality, incidence of recurrent stroke or cardiovascular events, disability and dependence (degree of disability) should remain important outcome measures. However the influence of fitness training on these outcomes may emerge only after long-term training and/or long term follow-up periods.

Systematic review data and observations in elderly people suggest current measures of disability are not sufficiently sensitive for high-functioning people with stroke. Pre-clinical disability (e.g. self-reported tiredness and task modification) may be present in participants who have recovered from the immediate effects of stroke. Although manifest disability is not detectable in this group it may develop with time due to the effects of increasing age.

Mänty et al. (2007) recently validated a measure of 'preclinical disability' in elderly people (N=632; mean age 77 years), this involved a identifying those who did not report difficulty walking or stair climbing but did report tiredness or modification of of the task (e.g. use of walking aid or handrail). Compared with those with no limitations they showed that those with preclinical mobility limitation had a 3- to 6-fold increase in risk of developing major manifest disability within 2 years, and those with minor limitation a 14 to 18 fold risk of progressing to major limitation.

Interestingly LLEP was determined in this study using a Nottingham Power Rig. Compared to those with no limitation LLEP was lower in those with preclinical disability (1.3 $W \cdot kg^{-1}$) and manifest disability (1.1 $W \cdot kg^{-1}$). These values are similar to the unaffected leg of our younger group of high functioning people with stroke (1.05 $W \cdot kg^{-1}$; mean age 72 years; Chapter 8) suggesting they could be susceptible to the same age-related functional decline. Preclinical disability in stroke survivors needs further investigation as it may be the only class of measure suitable for assessing disability in relatively high-functioning people with stroke.

Long term follow-up after fitness training interventions is important. Unless there is a continuation of activity any benefits from training may disappear due to the lack of training stimulus. In addition there is the functional decline which occurs due to increasing age; the data of Mänty et al. (2007) suggest a 2-year follow-up period may be sufficient to detect this.

12.1.4. Other trial design issues

Sample size calculations ($p<0.05$; power 0.9) based on the SD's and pooled effect sizes (WMD) in meta-analyses can be made for some physical fitness and mobility outcomes ($\dot{V}O_2$ peak N=40, Functional Ambulation Categories N=103, maximum walking speed N=196, comfortable walking speed N=496 and 6-minute walking test N=235). However it seems inappropriate to calculate sample sizes based on the disability outcome measures since these may not be the most appropriate measures in the high functioning individuals typical of most training studies (e.g. ceiling effects).

12.2. Implementation of physical fitness training?

The final phase (IV) in the MRC (2000a) Framework would examine the implementation of the training intervention in practice, outside a research environment. There are several ways in which implementation could occur.

Implementation could occur through exercise referral schemes. Referral occurs either via the GP (or other health professional) or self-referral in which case the GP must approve suitability. These procedures should adhere to the standards described in the NHS National Quality Assurance Framework for Exercise Referral Systems (Department of Health 2001). However two recent systematic reviews of exercise referral schemes (NICE Guideline 2006; 4 studies; Sörensen et al. 2006; 22 studies) both state there is a lack of evidence for benefit. However both were limited to physical activity and physical fitness outcomes focussing largely on risk factor modification in sedentary non-patient groups and may therefore not be generalizable to people with stroke.

Unlike many other healthcare therapies, lifestyle interventions such as physical activity and physical fitness training may be independently implemented by community dwelling stroke patients. Therefore a need has been identified for specialist instructors in exercise after stroke in order that people with stroke who are commencing programmes of exercise can do so as safely and effectively as possible (Mead et al. 2007a).

Since the evidence for a full exercise prescription for stroke is incomplete the best approach is an extension of the best-practice approach which formed the basis of the exploratory trial intervention and an evaluation of whether this is feasible to implement in real-life, in the community.

One important issue for evaluating the effectiveness of this is the provision of a consistent intervention outside a research environment. One step which would facilitate this is provision of training of specialist instructors in exercise after stroke. One such course has been designed and implemented in Edinburgh (*Exercise for Stroke Specialist Instructor Training Course*; Mead et al. 2007a).

12.3. Long Term Issues

The National Stroke Strategy (Department of Health/Vascular Programme/Stroke 2007) highlights the importance addressing the long term effects of stroke. However little is known about the best ways of achieving this (Rodgers and Thomson 2008).

Functional status after stroke is associated with long-term mortality. A recent prospective cohort study (Bruins Slot et al. 2008; n=7710) showed that dependence on other people for activities of daily living six months after stroke is associated with reduced long-term survival (6.0 years) compared with those who are independent (9.4 years). One could hypothesize that maximizing functional status soon after stroke might be associated with improved long-term mortality. It is plausible that fitness training could make a contribution to this.

Functional status will decline after stroke as a consequence of increasing age. In frail elderly people functional decline can eventually precipitate the same dependency issues which are often a more immediate concern after stroke. The data of Mänty et al. (2007) indicate a period of just 2 years is sufficient for this effect to be apparent (Section 12.1.3). However physical fitness training or physical activity is an important countermeasure against frailty. Therefore one can hypthesize that post-stroke physical fitness training strategies may help maintain function, or at least slow its (inevitable) long-term decline.

Even small reductions in mortality and dependence can have considerable value. Although systematic review data relating to mortality and dependence were inconclusive, there remain some strong theoretical reasons why physical fitness training might be beneficial if performed soon after stroke and in particular if continued in the long term.

Long-term facilitation of physical fitness training could include a) provision of specific programmes of physical fitness training and b) promotion of increased habitual and leisure-time physical activity; both remain under-researched in people with stroke.

Promotion of physical activity is not easy. Among a sample of community dwelling elderly people aged 65 to 84 years (Crombie et al. 2004; N=409) the majority (95%) believed that physical activity was beneficial, yet 53% reported little or no physical

activity; this indicates the presence of barriers to physical activity. Some of the reasons detering people from leisure-time physical activity were;

- Lack of interest in physical activity
- Perceived lack of physical fitness
- Accessibility issues

  (lack of car, lack of facilities, dislikes going out in the evening or alone)
- Physical symptoms

  (shortness of breath, lack of energy, painful joints)

Effective promotion of physical activity for inactive elderly people would depend on overcoming some of these barriers. All the barriers listed above may be exacerbated by post stroke problems and little is known about attitudes and barriers to physical activity after stroke.

12.4. Conclusions

Physical fitness is low in people with stroke and the impairments are associated with some common post-stroke functional limitations. Therefore fitness training may improve functional limitations and/or counteract the effects of functional decline.

However the current RCT evidence-base gives little support to this theoretical framework, suggesting that relatively short-term periods of physical fitness training offer few detectable benefits. Further carefully designed trials are desirable and these should evaluate long-term delivery of interventions and determine long-term outcome.

There is increasing provision of fitness training opportunities for people with stroke who live in the community, even though the evidence for this is incomplete. However physical fitness training can be an enjoyable social activity which can be performed safely by many people with stroke; it is cheap, flexible and may provide a wide spectrum of benefits which are plausible but not revealed by current research designs.

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14. Appendices

14.1. Candidate Contribution to Systematic Reviews

The systematic reviews in Chapters 10 and 12 involved three other researchers (CG, GM and AY).

DS lead the reviews, the contributions were;

- designed and constructed all literature search strategies,
- performed the literature searches,
- screened the titles and abstracts,
- applied inclusion criteria and methodological quality assessments;
- liaised with authors,
- extracted and analysed data and entered this into Review Manager;
- analysed and interpreted data;
- wrote text of document and assembled the reviews text into Review Manager.

GM & GG applied inclusion criteria and methodological quality assessments; extracted and interpreted data; wrote text of the review and provided critical comment on interim drafts of the review.

AY reviewed and provided critical comment on interim drafts of the review.

14.2. Candidate Contribution to STARTER Trial

Pilot Work

Involvement in design, data collection, analysis and reporting during pilot work which preceded the trial

- Validity of Metamax $\dot{V}O_2$ measures (Saunders et al. 2002)
- Self-paced walking studies (Fitzsimons et al. 2005)
- Muscle strength & power measurement (Greig et al. 2003)
- Construction of data tool for smoothing, time aligning and ensemble averaging of $\dot{V}O_2$ and modelling of the $\tau\dot{V}O_2$

Trial Administration

- Co-applicant on the trial grant (Chief Scientist Office).
- Assisted prior to recruitment of trial coordinator.
- Participation in trial meetings throughout the trial.

Intervention

- Assisted with the design of the cardiorespiratory training circuit, and a model of progression for the cycling intensity.
- Involved in delivery of 1/6 12 week exercise programmes. This involved getting participants to and from transport and managing participants during the cardiorespiratory training (whilst using the cycle ergometers).

Outcome Assessments

- Responsible for 107/192 (56%) of all outcome assessments, assisted with many others.

Trial Data

- Data collection form design.
- Trial database construction and maintenance; included all patient demographic data, outcome data and intervention logging data.
- Data checking and preparation of data for analysis (random & other checks).

Trial Reporting

Contributions to all sections of drafts of;

- Report of findings for the funding body (Chief Scientist Office)
- Primary publication (Mead et al. 2007b)

Lead the analysis and reporting of secondary publications

- Lower limb extensor power (Saunders et al. 2006;Saunders et al. 2008)

14.3. Reliability of Strength and Power Measures

Indices of reliability for measures of muscle force production (strength and power) are reported in people with stroke, these include;

a) Isometric strength measures

Handgrip, both hands

Boissy et al. (1999)	ICC = 0.91/0.86

Dorsi- and plantarflexion, both ankles

Ng and Hui-Chan (2005)	ICC = 0.85-0.98

Extensor strength, affected knee

Clark et al. (2006)	ICC = 0.91

b) Isokinetic strength measures

Flexion and extension of the knee, hip and ankle

Eng et al. (2002)	ICC = 0.95 to 0.99

c) Peak power measures

Both lower limbs

LeBrasseur et al. (2006)	ICC = 0.79-0.87
Bohannon (1992b)	ICC $\geq$ 0.975
Dawes et al. (2005)	ICC = 0.664-0.763

14.4. Saunders et al. (2002) abstract

28 EFFECT OF MASSAGE ON RECOVERY FROM HIGH INTENSITY EXERCISE

A. Robertson,[1] J.M. Watt,[2] S.D.R. Galloway. *[1]Department of Sports Studies; [2]University Physiotherapy Clinic, University of Stirling, Stirling, FK9 4LA*

The potential effect of massage on recovery from high intensity exercise is an area of considerable debate. This study aimed to control for many confounding factors that may limit the conclusions of previous work. Nine male games players participated in this study. Subjects attended the lab on two occasions one week apart and at the same time of day. Dietary intake and activity was replicated for two days prior to attending. On attending, following baseline measurements subjects undertook a standardised warm up on the cycle ergometer, followed by six 30 second high intensity exercise bouts, interspersed with 30 seconds of active recovery. Following five minutes of active recovery and either 20 minutes of massage or supine passive rest, subjects performed a second warm up and a 30 second Wingate test. Capillary blood samples, heart rate, peak power, mean power, and fatigue index were measured. There were no significant differences in mean power during the initial high intensity exercise bouts (p=0.92). No main effect of massage intervention was observed on blood lactate concentration between trials (p=0.82; Table 1) or heart rate (p=0.81). There was no difference in the maximum power (p=0.75) or mean power (p=0.66) but a significantly lower fatigue index was observed in the massage trial (p=0.04; 30.2% vs. 34.2%).

No measurable physiological changes were observed in the present study but the significant effect upon fatigue index warrants further investigation.

29 CONCURRENT VALIDITY AND RELIABILITY OF VO_2 MEASURED USING THE METAMAX 3B SYSTEM DURING MODERATE INTENSITY CYCLING

D.H. Saunders,[1] C. Greig, [2] A. Young.[2] *[1]Department Physical Education Sport and Leisure Studies; [2]Department Clinical and Surgical Sciences, University of Edinburgh, Scotland, UK*

The study aimed to assess the accuracy and reliability of the Metamax-3B ambulatory gas analysis system (MM) during measurement of low rates of oxygen utilisation (VO_2).

Five familiarised volunteers (3 male, 2 female, aged 22–40) performed constant load cycling on an electrically braked ergometer at workloads 50W and 100W (cadence 60 rev/min), each repeated within 1–7d. During each visit VO_2 was monitored continuously using the MM, for 12-minutes rest followed by eight minutes of cycling. Additional VO_2 measures were made at rest (minutes 4–8) and during exercise (minutes 6–8) using Douglas bags (DB) fitted in series to the MM, and compared to concurrent MM data averaged over these time frames.

The systematic differences between repeated MM and DB measures, and between concurrent DB/MM measures were negligible (ANOVA not significant), and associated with narrow 95% limits of agreement (Atkinson G, Nevill AM. *Sports Medicine* 1998;**26**:217–38) (Table 1; Bias ± LA).

Measures of VO_2 up to ~1.5 l/min, made using the MM, demonstrate high concurrent validity (Portney LG, Watkins MP. *Foundations of Clinical Research*. Norwalk, Connecticut: Appleton & Lange, 1993:509–16) with the criterion DB method, and show acceptable repeatability (similar to DB) during exercise and even at rest (Table 1. cv%).

In conclusion, the Metamax-3B system provides an accurate, reliable measure of energy expenditure within the low range of VO_2 typical of patients and elderly subjects.

30 HOMOEOPATHIC *ARNICA* REDUCES MUSCLE SORENESS INDUCED BY DOWNHILL RUNNING

R.A. Synge, J.R. Burbidge, I.A. Nimmo. *Division of Biomedical and Clinical Laboratory Sciences, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh EH8 9XD*

We wanted to find out if ingesting homoeopathic *Arnica* reduces the muscle soreness experienced by individuals after they have run downhill. We were prompted to do so by anecdotal evidence, subsequently confirmed, that some hill-runners routinely ingest homoeopathic *Arnica* when competing.

We carried out a double blind, cross over trial, over a two week period on 16 healthy adult volunteers of varying degrees of physical fitness. On days one to five of the trial they ingested four tablets/day of either *Arnica* (30C strength) or a placebo. On day two they ran as many laps as they could safely manage (range 1–10, mode 3 laps) of a fast downhill course (0.9 km long, 90 m descent). On days two to five they filled in a questionnaire to locate and quantify muscle soreness. On days three to five they completed two timed 190 m sprints to assess muscle performance. On days eight to12 they repeated the process, ingesting placebo instead of *Arnica* or vice versa.

Abstract 29 Repeated measures of VO_2 l/min (SD) recorded concurrently using Douglas bags and the Metamax-3B at rest and during exercise. Bias and 95% limits of agreement (bias ± LA) describe the repeatability of each system (V1 *v* V2) and their concurrent validity (DB *v* MM)

	50W		100W	
System	Resting	Cycling	Resting	Cycling
Douglas bags				
Visit 1	0.27 (0.05)	0.98 (0.08)	0.28 (0.05)	1.52 (0.04)
Visit 2	0.29 (0.05)	1.00 (0.07)	0.30 (0.03)	1.52 (0.05)
V1 *v* V2 (bias ± LA) cv%	–0.02 ± 0.083 10.6%	–0.02 ± 0.10 3.6%	–0.02 ± 0.017 18.7%	0.008 ± 0.135 2.9%
Metamax 3B				
Visit 1	0.30 (0.07)	0.97 (0.09)	0.31 (0.05)	1.48 (0.03)
Visit 2	0.33 (0.07)	1.03 (0.12)	0.33 (0.06)	1.50 (0.09)
V1 *v* V2 (bias ± LA)	–0.025 ± 0.060	–0.060 ± 0.076	–0.007 ± 0.052	–0.017 ± 0.142
cv%	8.4%	4.9%	5.8%	3.2%
DB *v* MM (bias ± LA)	–0.032 ± 0.059	–0.008 ± 0.135	–0.006 ± 0.079	0.033 ± 0.133

cv%, coefficient of variation; DB, Douglas Bags; MM, Metamax 3B

14.5. Greig et al. (2003) abstract

LOWER LIMB MUSCLE STRENGTH AND POWER FOLLOWING 'RECOVERY' FROM STROKE

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Introduction
Acute stroke often causes motor weakness of the limbs contralateral to the brain lesion. In addition, voluntary muscle strength of the apparently unaffected lower limb falls shortly after stroke (Harris and Polkey 2001, Clin Rehab 15, 274-281). Our aim was to compare lower limb muscle strength and power in volunteers who had recovered from a stroke, with data from the general population.

Methods
Nine men and 2 women (median age 73 years, range 57-85) participated. Median time since stroke was 14 months (range 9-20). Inclusion criteria were completion of rehabilitation and independent ambulation. Exclusion criteria were significant receptive dysphasia or confusion and lower limb arthritis resulting in inability to perform strength measurements without pain. Maximum voluntary isometric knee extensor strength (STR) and maximum lower limb extensor power (POW) were measured on each leg on 2 or 3 occasions.

Results
Comparison of each subject's highest values with sex-matched UK population values (sample values for >70 years) showed that for the unaffected limb, 8 volunteers were below the mean value for STR and 3 were below the mean -2SD. For the affected limb 9 were below the mean and 4 below mean –2SD. All volunteers were below the mean value for POW with 6 and 7 below the mean -2SD for the unaffected and affected limbs respectively.

Conclusion
Despite making an apparently full motor recovery from their stroke and after allowing for familiarisation, the majority of the group were placed within the lower range of normal for muscle strength and power of both lower limbs, suggesting that strength training after stroke may be beneficial.

14.6. Saunders et al. (2006) LLEP Abstract

Proceedings of The Physiological Society

University College London 2006 (2006) **Proc Physiol Soc 3, PC120**

Poster Communications

Disability in ambulatory stroke survivors is associated with impaired explosive power in both lower limbs

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Reduced lower limb extensor power (LLEP) is associated with poor performance of functional tasks in healthy people (1). Little is known about LLEP after stroke, other than it is lower than in healthy people when matched for age and gender (2) and that the impairment is bilateral, suggesting the involvement of factors not directly caused by the stroke. We hypothesised that low values of LLEP would be associated with reduced physical function and increased disability after stroke. LLEP (W kg^{-1}) was determined for each leg in 66 ambulatory stroke survivors (mean (SD): age 72 (10) years, wt 72.6 (15.3) kg, ht 1.67 (8.59) m), using a Nottingham Power Rig (3). We measured physical function (comfortable walking velocity, functional reach, chair rise time and 3-metre timed up-and-go), and disability (Functional Independence Measure, Rivermead Mobility Index and Nottingham Extended ADL). The associations between LLEP and both function and disability were analysed using stepwise multiple linear regression models which included the likely confounding factors age, gender, time since stroke, smoking and use of walking aids. The median value of LLEP of the affected limb ($LLEP_{aff}$ 0.92 W kg^{-1}) was significantly lower than that of the unaffected limb ($LLEP_{unaff}$ 1.05 W kg^{-1}; p=0.002) but the difference was small (~10%). Low LLEP of either limb was associated with poor performance in each measure of physical function (p<0.0001) and was the exclusive predictor of those which were dynamic (walking, chair rise and timed up-and-go). LLEP showed pronounced curvilinear associations with chair rise time and timed up-and-go, with reductions in performance when LLEP was below 1.0 W kg^{-1} but with no increase in performance above this value (Fig. 1). Low LLEP was also associated with poor scores in each measure of disability; these associations were strongest for the affected side (p<0.0001) with $LLEP_{aff}$ being the only predictor from among the variables included in the regression models. The ratio of $LLEP_{aff}/LLEP_{unaff}$ had no predictive importance for any measure of function or disability. In ambulatory stroke survivors reduced performance of physical function and increased disability are associated with deficits in LLEP of both lower limbs, and not the severity of any residual asymmetry. Interventions to increase LLEP in both legs might improve function and reduce disability after stroke.

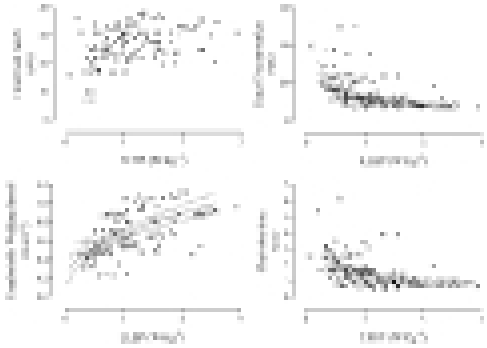

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Figure 1. LLEP of the affected (filled symbol) and unaffected (unfilled) lower limbs and specific disabilities. x (affected) and + (unaffected) denote use of arms for chair rise. Where LLEP was the only significant independent variable its regression coefficient (from transformed data) was used to generate a best fit line (and 95% CI) on the untransformed non-linear data (for clarity shown only on the unaffected side).

Funded by the Chief Scientist Office of the Scottish Executive (STARTER trial). C.G. is a Research into Ageing Research Fellow.

Skelton DA et al. (1994). Age & Ageing 23, 371-377.
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14.7. Saunders et al. (2008) LLEP full publication

ORIGINAL ARTICLE

Association of Activity Limitations and Lower-Limb Explosive Extensor Power in Ambulatory People With Stroke

David H. Saunders, MPhil, Carolyn A. Greig, PhD, Archie Young, MD, Gillian E. Mead, MD

ABSTRACT. Saunders DH, Greig CA, Young A, Mead GE. Association of activity limitations and lower-limb explosive extensor power in ambulatory people with stroke. Arch Phys Med Rehabil 2008;89:677-83.

Objective: To determine whether the explosive lower-limb extensor power of the affected and unaffected sides, and any asymmetry, are associated with activity limitations after stroke.

Design: Cross-sectional observational study of baseline data from a randomized controlled trial.

Setting: Measurements made in a hospital clinical research facility.

Participants: Community-dwelling (N=66) subjects with stroke who were independently ambulatory. Subjects' mean age was 72±10 years.

Interventions: Not applicable.

Main Outcome Measures: The lower-limb extensor power of each lower limb (in W/kg), performance of specific functional activities (comfortable walking velocity, Functional Reach Test, chair-rise time, Timed Up & Go test), and global indices of activity limitation (FIM instrument, Rivermead Mobility Index, Nottingham Extended Activities of Daily Living).

Results: Low lower-limb extensor power in either lower limb was the principal factor from among the confounders we recorded that significantly (R^2 range, .21–.46) predicted the limitation of specific functional activities, and low lower-limb extensor power in either lower limb was the principal predictive factor for global indices of activity limitation (R^2 range, .13–.38). The degree of asymmetry of lower-limb extensor power between legs was low and had little or no predictive value.

Conclusions: In ambulatory persons with stroke, activity limitations are associated with deficits in lower-limb extensor power of both lower limbs, and not the severity of any residual asymmetry. These findings suggest that interventions to increase lower-limb extensor power in both lower limbs might reduce activity limitations after stroke.

Key Words: Activities of daily living; Cerebrovascular accident; Physical fitness; Rehabilitation.

THE ABILITY OF MUSCLE to generate force can be described in terms of muscle strength and explosive power. Strength is the magnitude of maximal force generation whereas explosive power output is a velocity-dependent characteristic defined as the greatest rate of work achieved during a single, ballistic, resisted contraction.[1] Explosive power deteriorates faster than strength (3%–4% vs 1%–2% a year) during healthy aging.[2]

Although strength and power are both important for execution of functional activities, lower-limb extensor power is more important than knee extensor strength for stair climbing, chair rising, and walking,[3-5] and when impairment is asymmetrical, lower-limb extensor power is a better predictor of the frequency of falling than strength alone.[6]

Although people who have survived a stroke are often elderly, may be less active than prior to their stroke, and may have unilateral limb weakness, surprisingly little is known about the extent to which explosive power might be impaired and whether this might have adverse functional consequences. A pilot study of 11 ambulatory subjects 1 year after stroke with virtually no residual neurologic deficit[7] found that both lower-limb extensor power and knee extensor muscle strength of both lower limbs were substantially lower than that of age- and sex-matched healthy subjects.[8,9] Further unpublished data indicated that impairment in lower-limb extensor power was approximately double that of muscle strength.

Bilateral impairment in explosive power,[7] or muscle strength,[7,10,11] observed after stroke could arise for several reasons both directly and indirectly associated with stroke. First, bilateral motor deficits can arise directly from a unilateral lesion.[12] Second, reduced habitual physical activity, either before and/or after stroke may cause muscle atrophy.[13] Third, the presence of comorbid disease (including poor nutrition) before and/or after stroke could impair motor function.

Low muscle strength after stroke is associated with poor performance of walking and stair climbing,[14] chair rising,[15] and impaired motor function.[16] Only 1 small study (N=14) has explored the functional associations of explosive power after stroke.[17] It showed that asymmetry in lower-limb extensor power was associated with reduced walking performance. The participants were unusually young (mean, 46.4±8.4y), and this relationship should be examined in people with stroke of more typical age (ie, >70y).[18] Moreover, the relationship of power with other aspects of activity limitation should be examined to explore the potential benefits that might result from attempts to improve explosive power after stroke. This is important because fitness training can be presented in such a way as to specifically improve explosive power[19] and this might reduce activity limitations, and so reduce participation restriction after stroke.

The aim of this study was to determine in older, ambulatory people with stroke, whether the lower-limb extensor power of the affected and unaffected sides, and any asymmetry, were associated with (1) performance of specific functional activities (reaching, walking, and rising from a chair), and (2) global indices of activity limitation (FIM instrument, Nottingham

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Table 1: Participant Characteristics

Characteristics	n	Mean ± SD	Median (IQR)
Age (y)	NA	71.85±9.91	NA
Sex (male/female)	36/30	NA	NA
Stature (m)	NA	1.67±0.09	NA
Time from stroke (d)	NA	NA	152 (83–278)
Smoking history			
Smoker/Ex-/Non-/UC	25/12/28/1	NA	NA
Walking aids			
Stick/orthosis/zimmer/none	28/4/2/32	NA	NA
Body mass (kg)	NA	72.64±15.29	NA
Stroke type (TAC/LAC/PAC/POC/UC)	2/19/32/12/1	NA	NA
Lesion type (ischemic/hemorrhagic/UC)	60/5/1	NA	NA
Lesion side (left/right/both/UC)	37/27/1/1	NA	NA
Hospital care (inpatient/outpatient)	56/10	NA	NA
Inpatient length of stay (d)	NA	NA	19 (9–44)
Blood pressure			
Systolic (mmHg)	NA	140.03±18.10	NA
Diastolic (mmHg)	NA	73.16±9.50	NA
Comorbidities			
Prior stroke	11	NA	NA
Prior transient ischemic attack	4	NA	NA
Ischemic heart disease	22	NA	NA
Left ventricular failure	2	NA	NA
Hypertension	31	NA	NA
Prior malignancy	7	NA	NA
Diabetes	3	NA	NA
Miscellaneous	50	NA	NA
None	5	NA	NA
Total no. per participant	NA	1.97±1.35	NA

Abbreviations: IQR, interquartile range; LAC, lacunar; NA, not applicable; PAC, partial anterior circulation; POC, posterior circulation; SD, standard deviation; TAC, total anterior circulation; UC, unclear.

Extended Activities of Daily Living [NEADL], Rivermead Mobility Index [RMI]).

METHODS

Participants

All participants in this study (N=66) were recruited to a randomized trial of exercise or relaxation after stroke (table 1).[20] We selected these 66 patients after screening 301 patients for trial eligibility (all 301 had required either inpatient or outpatient care after an acute stroke in 1 of 4 Edinburgh hospitals). Trial inclusion criteria were (1) independently ambulatory (with or without walking aids), (2) living within the recruitment catchment area, (3) completion of inpatient and outpatient stroke rehabilitation, and (4) absence of dysphasia or confusion judged severe enough to prevent safe participation in exercise

Table 2: Untransformed Data for Lower-Limb Extensor Power, Measures of Performance of Specific Functional Activities, and Global Indices of Activity Limitation

Variable	n	Mean ± SD	Median (IQR)
Lower-limb extensor power			
Affected side LLEP (W/kg)	64	NA	0.92 (0.53–1.49)*†
Unaffected side LLEP (W/kg)	61	NA	1.05 (0.73–1.56)†
Asymmetry ratio (aff LLEP/unaff LLEP)	60	0.89±0.24	NA
Specific functional activities			
FRT (cm)	63	26.53±6.65	NA
Comfortable walking velocity (m/s)	64	0.67±0.24	NA
TUG test (s)	61	NA	11.68 (8.17–16.09)‡
Chair-rise time (s)	60	NA	1.28 (0.83–1.70)‡
Global indices of activity limitation			
FIM instrument	66	NA	117.5 (114–122)§
RMI	66	NA	13 (11–14)§
NEADL	65	NA	17 (12–19)§

Abbreviations: aff, affected; LLEP, lower-limb extensor power; unaff, unaffected.
*Affected LLEP lower than unaffected LLEP (t=3.77, P<.001).
†The non-normal data included in this table could be transformed to a normal distribution using square root.
‡The non-normal data included in this table could be transformed to a normal distribution using reciprocal.
§The non-normal data included in this table could be transformed to a normal distribution using square root of reflected data.

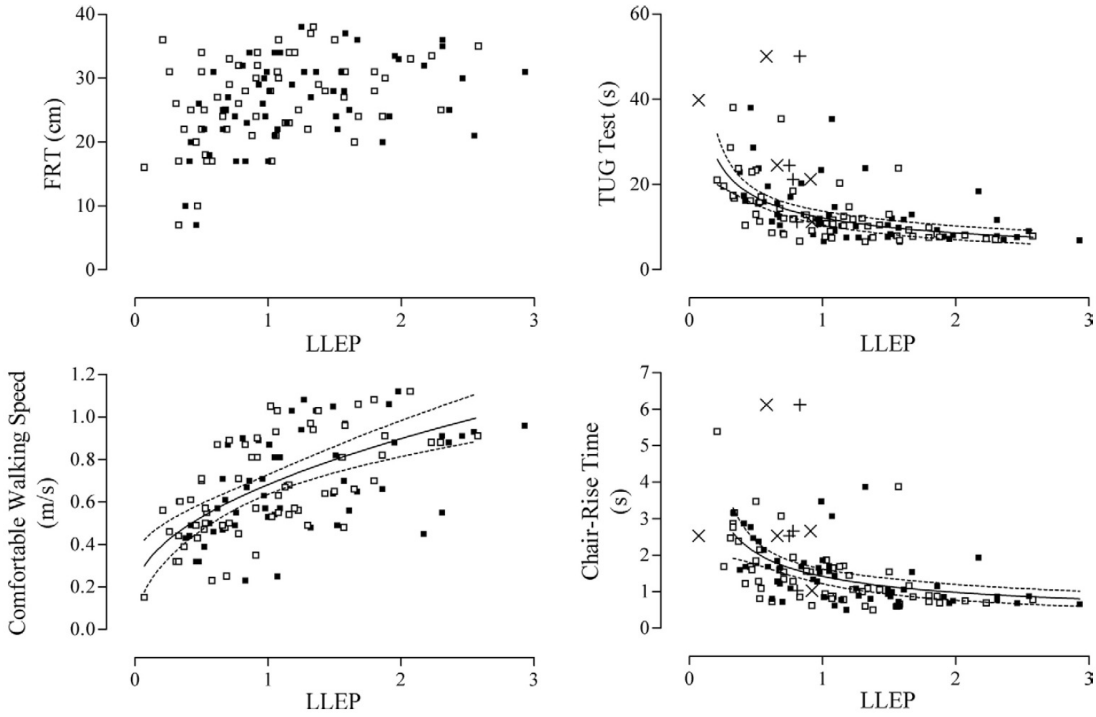

Fig 1. The relationships between the explosive lower-limb extensor power (LLEP), measured in W/kg, of the affected (■) and unaffected (□) lower limbs and performance of specific functional activities assessed using the FRT, TUG test, chair-rising time, and comfortable walking velocity. When arms were used for assistance during chair rising and TUG test the data are marked differently (× affected, + unaffected). For clarity the lines of best fit with 95% CIs are included only for the unaffected lower-limb extensor power data.

or relaxation classes or to preclude informed consent. Absolute contraindications to exercise in elderly people[21] and walking limited by pain were applied as exclusion criteria. Approval was obtained from the local research ethics committee.

For participants who presented with no lateralizing signs but had relevant stroke lesions evident on brain imaging, we considered the affected side to be ipsilateral to the side of posterior circulation lesions, and contralateral for all others.

Measurements

Prior to randomization, we measured lower-limb extensor power during hip and knee extension while the subject was seated on a Nottingham Power Rig.[22,a] Ten maximal pushes were encouraged using each lower limb with a rest (minimum 30s) between each push. Mitchell et al[23] reported that 10 repetitions were sufficient to obtain peak lower-limb extensor power values in elderly people rehabilitating after proximal femoral fracture. Power to body mass ratio (W/kg of body mass) was recorded for each push and the highest value achieved was recorded for the affected and unaffected lower limbs. Asymmetry in lower-limb extensor power was expressed as a ratio (affected lower-limb extensor power/unaffected lower-limb extensor power) and used to indicate hemiparesis. The lower-limb extensor power technique is valid and reliable in healthy elderly people[22] and reliable in persons with stroke.[17]

Functional Reach Test (FRT),[24] Timed Up & Go (TUG) test,[25] and chair-rising time[9] were recorded in triplicate. Participants were asked not to use walking aids or arms during chair rising. The average velocity of comfortable walking was determined during three 3-minute bouts of self-paced walking around a 17-m circuit with a 5-minute break between each walk. Participants were instructed to walk at their "comfortable pace."[26] The following global indices of activity limitation were recorded during face-to-face interview: FIM instrument,[27] RMI,[28] and NEADL.[29] The above measures have been found to be reliable in persons with stroke[30-33] or elderly people.[34]

We recorded age, sex, time since stroke, stature, smoking, use of walking aids, the incidence of key comorbid diseases, and the total number of comorbid diseases (see table 1) as potential confounding factors.[8,10,35]

Data Analysis

Normally distributed data were reported as mean and standard deviation (SD). Non-normal data were expressed as median and interquartile range (IQR) and transformed to a normative distribution prior to any statistical analysis. Affected and unaffected legs were compared using a paired *t* test. Stepwise multiple linear regression was used to identify (1) whether any of the confounders predicted lower-limb extensor power, and (2) whether lower-limb extensor power and confounders predicted activity limitation measures. When lower-

Table 3: The Results of Stepwise Multiple Linear Regression Analysis of the Lower-Limb Extensor Power (affected side, unaffected side, ratio) and Potential Confounding Predictor Variables (age, sex, stature, time since stroke, use of walking aids, comorbid disease, smoking history) on Performance of Specific Functional Activities and Global Indices of Activity Limitation

Dependent Variable	Measure of LLEP Included in Regression Model								
	Affected Side for LLEP			Unaffected Side for LLEP			Asymmetry Ratio (affected LLEP/unaffected LLEP)		
Specific functional activities									
FRT*	LLEP	.32	$P<.01$	LLEP	.48	$P<.001$	Stature	.38	
	Stature	.28	$P<.023$	Stature	.54	$P<.001$			
				Sex	.39	$P<.019$			
	R^2	.21	$P<.001$	R^2	.33	$P<.001$	R^2	.13	$P<.003$
Comfortable walking speed	LLEP	.54		LLEP	.65		Age	−.31	
	R^2	.28	$P<.001$	R^2	.41	$P<.001$	R^2	.08	$P<.020$
TUG test	LLEP	.68		LLEP	.60				
	R^2	.46	$P<.001$	R^2	.35	$P<.001$	R^2	NA	NS
Chair-rise time*	LLEP	.63		LLEP	.56		Age	−.30	
	R^2	.38	$P<.001$	R^2	.30	$P<.001$	R^2	.07	$P<.026$
Global indices of activity limitation									
FIM instrument	LLEP	−.64	$P<.001$	LLEP	−.38				
	Stature	.23	$P<.039$						
	R^2	.35	$P<.001$	R^2	.13	$P<.003$	R^2	NA	NS
RMI	LLEP	−.58		LLEP	−.53				
	R^2	.33	$P<.001$	R^2	.27	$P<.001$	R^2	NA	NS
NEADL	LLEP	−.64	$P<.001$	LLEP	−.41		LLEP	−.29	
	Smoking	.21	$P<.045$						
	R^2	.38	$P<.001$	R^2	.16	$P<.001$	R^2	.07	$P<.027$

NOTE. Standardized β coefficients are reported for each individual independent variable having significant predictive value, and adjusted R^2 values for each overall model where this could be fitted.
Abbreviation: NS, no significant regression model solution.
*Use of walking aids omitted from models.

limb extensor power was the only significant predictor of activity limitation, the regression coefficients were used to generate nonlinear models (and 95% confidence interval [CI]) of the untransformed graphed data. Analyses were performed with SPSS[b] and Graphpad Prizm.[c] A P value of less than .05 was considered statistically significant.

RESULTS

A successful measure of lower-limb extensor power was achieved in both legs of 60 (91%) of 66 participants and at least 1 leg of 65 (98%) of 66 participants. The reasons preventing data collection were leg pain (n=4) and equipment failure (n=2). The average lower-limb extensor power increased by 76% (affected) and 55% (unaffected) throughout the 10 repetitions, but approached asymptotic values between repetitions 8 and 10 during which further increase was trivial (2.3% affected leg, 0.3% unaffected leg). The proportion of participants with ceiling values in the global indices was low (FIM instrument, 2/66; RMI, 11/66; NEADL, 3/66). The data for lower-limb extensor power, specific functional activities, and global indices of activity limitation are summarized in table 2.

Median affected lower-limb extensor power was 42% (IQR, 27–66) and unaffected lower-limb extensor power was 54% (IQR, 37–71) of that expected in age- and sex-matched subjects.[8,9] Affected lower-limb extensor power was significantly lower than unaffected lower-limb extensor power ($t=3.77$, $P<.001$), but the difference was small (≈10%; median, .14W/kg) and the extensor power of each lower limb were highly correlated ($R^2=.68$, $P<.001$). When the influence of age, sex, time since stroke, smoking, and incidence of comorbid disease(s) on lower-limb extensor power was examined, unaffected lower-limb extensor power was predicted (weakly) only by sex and age ($R^2=.18$, $P=.001$), and affected lower-limb extensor power by sex only ($R^2=.14$, $P=.002$). None of the factors predicted the asymmetry ratio.

Low values of affected or unaffected lower-limb extensor power appear associated with limitation in each specific functional activity (fig 1). Lower-limb extensor power showed pronounced curvilinear associations with chair-rising time, and TUG test. When walking speed (in m/s) was expressed as a function of time (in s/m), the same curvilinear association was observed. All 3 dynamic physical functions showed reduced performance when lower-limb extensor power was below approximately 1W/kg with no increase in performance above this value.

Both affected and unaffected lower-limb extensor power were significant predictors of performance in each functional activity (table 3). Comfortable walking velocity, chair-rise time, and TUG test performance were predicted exclusively by affected and unaffected lower-limb extensor power, with each leg having similar influence. Five participants with low values of lower-limb extensor power (<1W/kg) found chair rising impossible without using their arms; their data were excluded from the regression analysis of the TUG test and chair rising. Functional reach was predicted by lower-limb extensor power, but not exclusively or as strongly as were other activities. The ratio of affected/unaffected lower-limb extensor power had no predictive importance for performance of specific functional activities.

Lower-limb extensor power was nearly exclusive as a predictor of global indices of activity limitation from among the variables included in the regression models (fig 2, see table 3), the only exceptions being marginal contributions of stature to FIM instrument, and smoking to NEADL scores. Associations

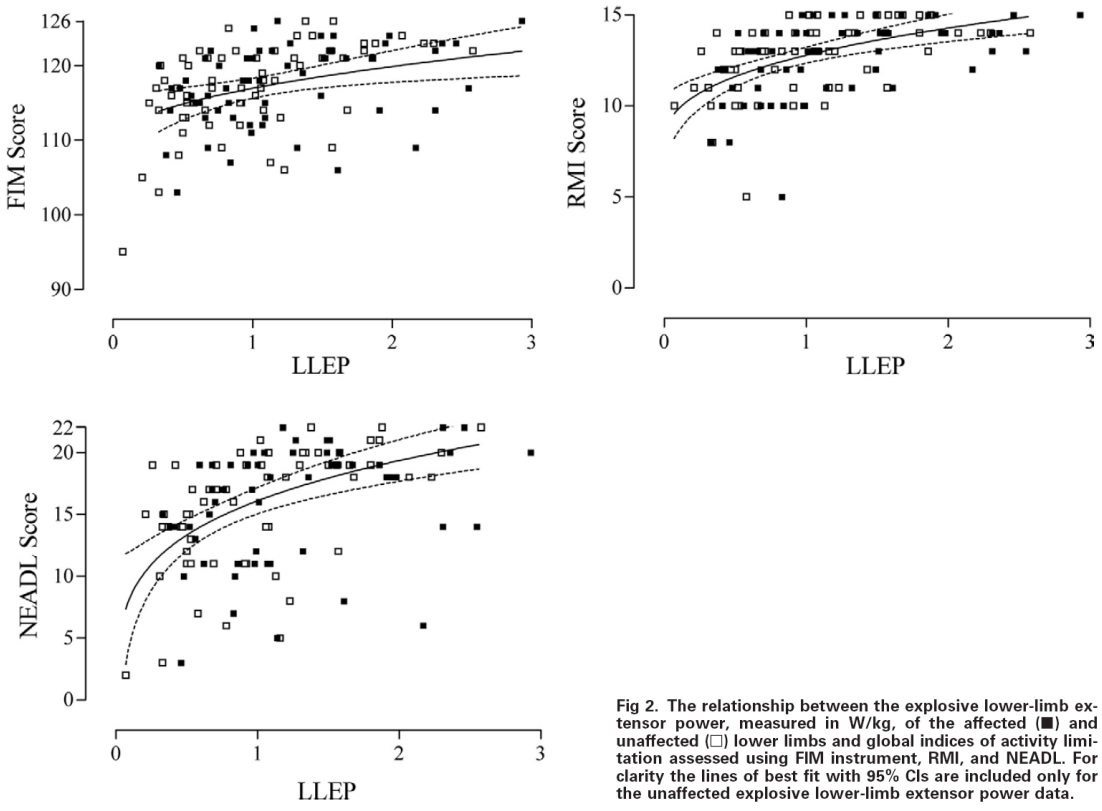

Fig 2. The relationship between the explosive lower-limb extensor power, measured in W/kg, of the affected (■) and unaffected (□) lower limbs and global indices of activity limitation assessed using FIM instrument, RMI, and NEADL. For clarity the lines of best fit with 95% CIs are included only for the unaffected explosive lower-limb extensor power data.

tended to be stronger for affected lower-limb extensor power than unaffected lower-limb extensor power, but asymmetry in lower-limb extensor power did not predict FIM instrument or RMI scores and had only marginal predictive value for NEADL scores.

When statistical analyses were repeated after excluding subjects with prior stroke (11/66) the multivariate R^2 values increased slightly and marginal variables were dropped from the models, leaving affected and unaffected lower-limb extensor power as the exclusive predictors of performance or limitation of activities.

DISCUSSION

This study shows that among a sample of ambulatory subjects with stroke (mean age, 72y), the unaffected lower-limb extensor power was lower than expected and that low lower-limb extensor power in either leg was associated with (1) reduced performance in some everyday dynamic functional activities that involve the legs, and (2) activity limitation as assessed using more global scale indices. Asymmetry in lower-limb extensor power was small and not predictive of limitations.

Our data suggest lower-limb extensor power is important for the performance of dynamic day-to-day lower-limb activities that require rapid rates of muscle contraction. Associations were strongest with comfortable walking velocity, TUG test, and chair-rising time. When lower-limb extensor power is very low, performance of chair rising may be impossible for some unless modified (eg, use of arms). This is compatible with similar observations in healthy elderly people.[2] As expected, the weakest association between lower-limb extensor power (of either leg) and physical function was with functional reach, probably because this is not limited by speed of movement.

Our data show a convincing association between low lower-limb extensor power and increased global indices of activity limitation even though not all questions within each scale directly addressed performance of activities involving the lower-limb extensors.

In elderly persons with functional impairments, power output during leg-press exercise, a procedure similar to lower-limb extensor power determination, was found to be associated with stair climbing ability, chair-rise time and habitual gait velocity,[36] and with self-reported functional status.[5] These observations resemble the types of association found in our study.

In a small study of unusually young (46y) ambulatory subjects with stroke[17] substantial asymmetry in lower-limb extensor power was observed (mean, 43%) and this was inversely associated with walking speed (Spearman $\rho=-.76$, $P<.01$). These younger participants had RMI values with a mean of 13 and walking speeds with a mean of .70m/s, which were similar to our data (see table 2). It is plausible that the greater lower-limb extensor power of their stronger side, with a mean of 1.99W/kg, allowed functional compensation. Asymmetry in our typically older participants (mean age, 72y) was not pre-

dictive of activity limitation to any important extent, probably because little asymmetry (10%) existed. This lack of asymmetry may have occurred because our participants had made a good neurologic recovery. Second, substantial asymmetry may be unusual in the older ambulatory person with stroke simply because lower-limb extensor power is already low prior to stroke, and a threshold effect limits the reduction in lower-limb extensor power that can occur without rendering the participant nonambulatory. The lack of asymmetry in our data suggests that the low values of lower-limb extensor power could have arisen due to the influence of factors that act bilaterally (ie, bilateral motor effects, comorbid disease, habitual physical inactivity).

Longitudinal poststroke deterioration could cause bilateral loss of lower-limb extensor power. Although no longitudinal data of lower-limb extensor power are available, 1 small study has reported an approximate 30% loss of strength of the ipsilateral leg during the week after stroke.[10] Another, however, found no poststroke deterioration.[37] In our study, neither time after stroke nor comorbid disease(s) were predictive of lower-limb extensor power or activity limitations, perhaps because our sample was homogeneous due to restrictive eligibility criteria. Although it is not possible to identify the underlying cause for low lower-limb extensor power and activity limitations, habitual physical inactivity before and/or after stroke remains a possible cause.

High-velocity resistance training in 25 healthy elderly persons (age, 60–80y) increased explosive power of the knee extensors and this is associated with significant improvements in chair rising, walking, and reaching ability.[38] Extrapolating findings from studies of elderly people suggest that increasing affected and unaffected lower-limb extensor power might improve activity and independence after stroke. We are unaware of any studies to date that have examined this type of training after stroke.

We successfully measured peak lower-limb extensor power in more than 90% of our participants; this compares favorably with our experience of this measurement in healthy elderly people (78%) using the same equipment.[8] This suggests that ambulatory persons who have had stroke can perform the repeated, high-velocity, resisted muscle contractions needed to improve explosive power. In addition, if lower-limb extensor power is impaired due to reduced habitual physical activity, there is no reason why reversal through suitable training should not occur. Therefore training lower-limb extensor power after stroke may be feasible.

Study Limitations

The main limitation of this study was that we recruited a homogeneous sample of high functioning independently ambulatory subjects with stroke. Homogeneity may have limited the strength of the observed associations. The potential self-selection of fitter participants would also tend give rise to a higher functioning cohort. Participants had minimal hemiparesis so it is difficult to speculate on the functional importance of lower-limb extensor power for those with more severe impairment. Future work should therefore include more impaired participants and examine the role of other confounding factors, such as stage of motor recovery and pre- and poststroke habitual physical activity levels. Outcome measures could be extended to include indices of participation restriction.

CONCLUSIONS

In a sample of ambulatory subjects with stroke of mean age 72 years activity limitations were associated with bilateral deficits in lower-limb extensor power and not with the severity of any residual asymmetry. These data suggest that the feasibility and effectiveness of training interventions to improve muscle explosive power after stroke should be explored.

Acknowledgments: Gillian E. Mead, MD, was the principal investigator for a trial of exercise or relaxation after stroke from which these data are derived.

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Suppliers

a. Medical Engineering Unit, University of Nottingham, Queens Medical Centre, Nottingham, NG7 2UH, UK.
b. Version 12; SPSS, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.
c. Version 4.0; Graphpad Prizm, 11452 El Camino Real, #215, San Diego, CA 92130.

14.8. LLEP repetition data

The average LLEP increased by 76% (affected) and 55% (unaffected) throughout the 10 repetitions with around 50% of participants achieving peak values of LLEP after 8 to 10 repetitions, and many doing so on the final effort (Figure 14.1). LLEP approached asymptotic values between repetitions 8 and 10 during which the increases were trivial (2.3% affected leg, 0.3% unaffected leg).

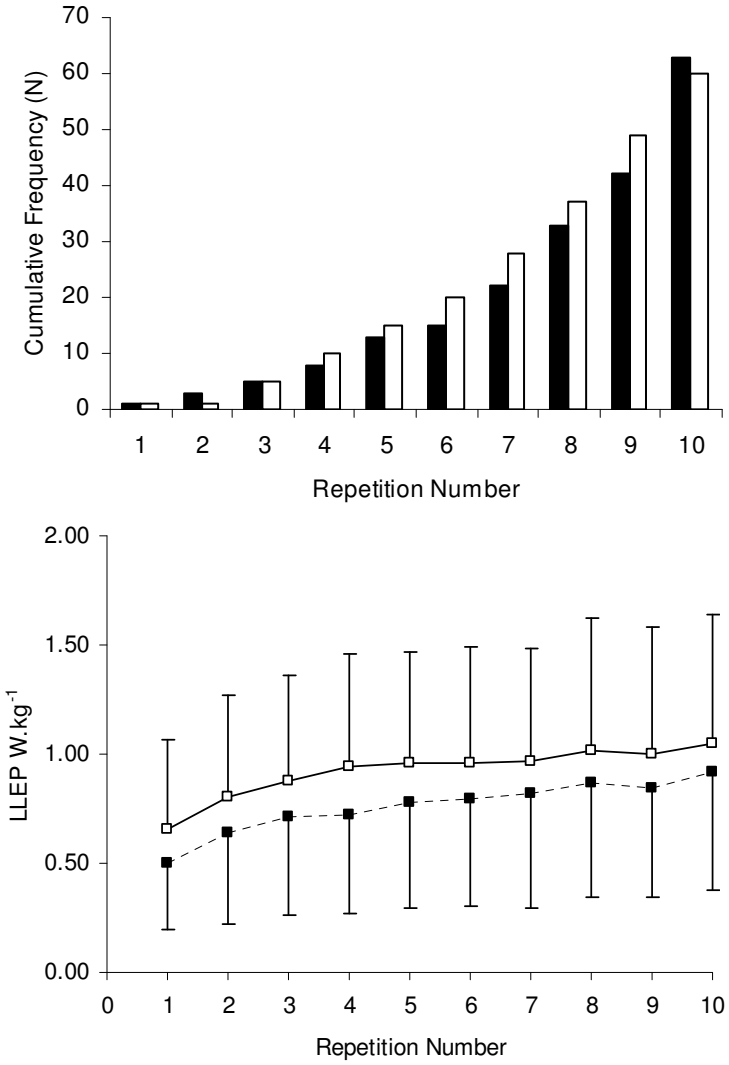

Figure 14.1 Panel A shows the frequency distribution of participants having achieved peak lower limb extensor power (LLEP) after each of 10 maximal leg extensions. Panel B shows the mean LLEP (± SD) for each repetition. LLEP data are shown for the affected (■) and unaffected (□) lower limbs.

14.9. Saunders et al. (2004b) abstract

Cochrane Corner

Section Editor: Graeme J. Hankey, MD, FRACP

Physical Fitness Training for Stroke Patients

David H. Saunders, BSc, MPhil; Carolyn A. Greig, BSc, MSc, PhD;
Archie Young, BSc, MBChB, MD, FRCP; Gillian E. Mead, MB, BChir, FRCP, MD, MA

Physical fitness is important for the performance of everyday activities. Although muscle strength and cardiorespiratory fitness are impaired in stroke patients, it is not known whether improving fitness by physical fitness training reduces disability after stroke.

Objectives

The objective of this study was to perform a systematic review to establish whether strength and/or cardiorespiratory fitness training reduces death, dependence, and disability after stroke. Secondary aims were to evaluate the effects of fitness training on physical fitness, mobility, physical function, health and quality of life, mood, and the incidence of adverse events.

Methods

Search Strategy

We searched the Cochrane Stroke Group Trials Register (last searched June 2003). In addition, the following electronic databases were searched: Cochrane Central Register of Controlled Trials (*Cochrane Library*, Issue 4, 2002), MEDLINE (1966 to December 2002), EMBASE (1980 to December 2002), CINAHL (1982 to December 2002), SPORTDiscus (1949 to December 2002), Science Citation Index Expanded (1981 to December 2002), Web of Science Proceedings (1982 to December 2002), PEDro (December 2002), REHABDATA (1956 to December 2002), and Index to UK Theses (1970 to December 2002). We hand-searched relevant journals and conference proceedings and screened reference lists. To identify unpublished and ongoing trials, we searched trial directories and contacted experts in the field.

Selection Criteria

Randomized controlled trials were included when an intervention represented a clear attempt to improve muscle strength and/or cardiorespiratory fitness, and whose control groups comprised either usual care or a non-exercise intervention.

Data Collection and Analysis

Data from eligible studies were independently extracted by 2 reviewers. The primary outcome measures were death, disability, and dependence. Standardized mean differences (SMD) and weighted mean differences (WMD) of variables were calculated using fixed and random effects models, but lack of common outcome measures limited the analysis.

Results

Twelve trials comprising 289 participants met the inclusion criteria. Only 3 trials commenced soon (<1 month) after stroke, and only 2 examined the effect of strength training. No trials reported death and dependence data. Two small trials reporting disability showed no evidence of benefit (SMD, −0.06; 95% CI, −0.76 to 0.65). There were few secondary outcome measures common to the included trials. Significant improvements were observed only in Functional Ambulation Category scores (WMD, 0.60; 95% CI, 0.14 to 1.06) and maximal walking speed (SMD, 0.42 m/s; 95% CI, 0.04 to 0.79) after cardiorespiratory walking training. Like ambulation outcomes, the incidence of other physical benefits was associated with interventions using modes of physical activity closely related to the outcome task.

Reviewer Conclusions

There are inadequate data to either encourage or discourage physical fitness training after stroke. Beyond improvements in some measures of ambulation, little is known about the benefits of fitness training in stroke patients or the optimal regimen for improving fitness. Any training-induced functional benefits appear to be associated with specific or "task-related" training.

Fitness training after stroke is an under-researched area. Further trials are needed to determine the efficacy and feasibility of fitness training, particularly soon after stroke. The optimal training regimen for improving fitness remains unknown; therefore, smaller more specific studies are also required. These should explore the effect of "dose" and type of training, particularly strength training.

Note: The full text of this review is available in The Cochrane Library (for subscribers: www.update-software.com/Cochrane). The full article should be cited as: Saunders DH, Greig CA, Young A, Mead GE. Physical fitness training for stroke patients (Cochrane Review). In: *The Cochrane Library*. Issue 1, 2004. Oxford, UK: Update Software, © Cochrane Library, John Wiley & Sons, Ltd.

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(*Stroke*. 2004;35:2235.)

***Stroke* is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000137413.94706.ba**

14.10. MEDLINE (OVID) Search Strategy (2004 review)

1. exp cerebrovascular disorders/
2. (stroke$ or cva$ or cerebrovascular or cerebral vascular).tw.
3. ((cerebral or cerebellar or brain$ or vertebrobasilar) adj5 (infarct$ or isch?emi$ or thrombo$ or emboli$ or apoplexy)).tw.
4. ((cerebral or brain$ or subarachnoid) adj5 (haemorrhage or hemorrhage or haematoma or hematoma or bleed$)).tw.
5. hemiplegia/ or brain injuries/
6. (hemipleg$ or hemipar$ or poststroke or post-stroke or brain injur$).tw.
7. or/1-6
8. exercise/
9. exercise therapy/
10. exercise tolerance/
11. exercise test/
12. exertion/
13. physical fitness/
14. physical endurance/
15. physical therapy/
16. locomotion/
17. early ambulation/
18. sports/ or weight lifting/ or bicycling/ or running/ or swimming/ or walking/ or sports equipment/
19. leisure activities/ or recreation/
20. isometric contraction/ or isotonic contraction/
21. (physical adj3 (exercise$ or therap$ or conditioning or activit$ or fitness)).tw.
22. (exercise adj3 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
23. (fitness adj3 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
24. ((training or conditioning) adj3 (intervention$ or protocol$ or program$ or activit$ or regim$)).tw.
25. (sport$ or recreation$ or leisure or cycl$ or bicycl$ or treadmill$ or run$ or swim$ or walk$).tw.
26. ((endurance or aerobic or cardio$) adj3 (fitness or train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
27. (muscle strengthening or progressive resist$).tw.
28. ((weight or strength$ or resistance) adj (train$ or lift$ or exercise$)).tw.
29. ((isometric or isotonic or eccentric or concentric) adj (contraction$ or exercise$)).tw.
30. or/8-29
31. randomized controlled trial.pt.
32. randomized controlled trials/
33. controlled clinical trial.pt.
34. controlled clinical trials/
35. random allocation/
36. single-blind method/
37. clinical trial.pt.
38. exp clinical trials/
39. (clin$ adj5 trial$).tw.
40. (single adj5 (blind$ or mask$)).tw
41. placebos/
42. placebo$.tw.
43. random$.tw.
44. research design/
45. multicenter study.pt.
46. intervention studies/
47. cross-over studies/
48. control$.tw.
49. alternate treatment.tw.
50. latin square.tw.
51. comparative study/
52. exp evaluation studies/
53. follow-up studies/
54. prospective studies/
55. prospective.tw.
56. counterbalance$.tw.
57. versus.tw.
58. or/31-57
59. 7 and 30 and 58
60. animal/ not (human/ and animal/)
61. heat stroke/ or heat stroke.tw.
62. 59 not (60 or 61)

14.11. Ongoing studies (2004 systematic review)

Study Name/Title *Investigator & Trial Code*	**Participants**	**Interventions**	**Outcomes**
The effect of aerobic training after recent severe brain injury *Bateman A*	N=157 brain injured patients including 70 with stroke	Intervention: up to 30min/d, 3 d/wk, 12wks, cardiorespiratory cycling training. Control; 30min/d, 3 d/wk, 12wks, relaxation therapy	Peak work rate, peak heart rate, BMI, Modified Ashworth Scale, Berg balance scale, Rivermead Mobility Index, 10-m walk velocity, Barthel Index FIM, Nottingham EADL, fatigue questionaire, HADS
Water-based exercises for cardiovascular fitness in people with stroke *Chu KS,*	N=12 individuals with chronic stroke (> 1 year), moderate impairments	Intervention: 60 min/d, 3 d/w, 8 wks, water-based group cardiorespiratory exercise program in chest deep water Control: 60 min/d, 3 d/w, 8 wks, arm function group exercise program	VO_2max, gait speed, Nottingham Health Profile, maximal workload, Berg
EXERT (exercise evaluation randomised trial) *Isaacs N0484008696*	N=1500 stroke patients randomized to 3 groups	Intervention 1: exercise scheme in local leisure centre. Intervention 2: home based walking programme or Control: Simple advice. All for 10 wks.	1. Biological status, cardiovascular risk factors, health outcomes and quality of life 2. Continuation of exercise after prescribed programme; 3. Economic evaluation of different interventions.
Does aerobic or resistance training improve walking ability in chronic stroke patients? *Kilbreath*	N = UN Chronic stroke patients	Intervention 1: cardiorespiratory cycle training Intervention 2: Strength training. Intervention 3: Mixed training Control: No other rehabilitation	6-min walk
Effects of strength training on upper-limb function in post-stroke hemiparesis *Lum NCT00037908*	N=60 expected. Community dwelling stroke survivors (< 6 mths).	Intervention: Standard functional rehabilitation + high-intensity upper-body strength training. Control: Standard functional rehabilitation	Strength, Modified Ashworth Scale, Barthel Index, FIM, Fugl-Meyer (upper body).

Cont./

Ongoing studies. Cont.

Trial name or title	Participants	Interventions	Outcomes
STARTER (Stroke: A Randomised Trial of Exercise or Relaxation) *Mead*	N=90 Community dwelling stroke patients	Intervention: Mixed cardiorespiratory and strength training Control: Relaxation therapy	Disability (FIM), Nottingham Extended ADL, Rivermead Motor Assessment, Timed up and go, Cardiorespiratory fitness, Muscle strength and power output, Mood (HAD)
Stroke rehabilitation outcomes with supported treadmill ambulation training *Protas NCT00037895*	N=48 recent unilateral stroke	Intervention: Supported treadmill ambulation training + usual care. Control: Usual care	FIM, oxygen consumption, Brain motor control assessment (BMCA)

BRIEF REPORTS

Stroke: A Randomized Trial of Exercise or Relaxation

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OBJECTIVES: To determine the feasibility and effect of exercise training after stroke.

DESIGN: Randomized exploratory trial comparing exercise training (including progressive endurance and resistance training) with relaxation (attention control).

SETTING: Interventions were performed in a rehabilitation hospital.

PARTICIPANTS: Sixty-six independently ambulatory patients (mean age 72, 36 men) without significant dysphasia, confusion, or medical contraindications to exercise training who had completed their usual rehabilitation and had been discharged from hospital.

INTERVENTION: Both interventions were held three times a week for 12 weeks. Up to seven patients attended each session.

MEASUREMENTS: The Functional Independence Measure; Nottingham Extended Activities of Daily Living; Rivermead Mobility Index; functional reach; sit-to-stand; elderly mobility score; timed up-and-go; Medical Outcomes Study 36-Item Short Form Questionnaire, version 2 (SF-36); Hospital Anxiety and Depression Score; aspects of physical fitness (comfortable walking speed, walking economy, and explosive leg extensor power) were measured at baseline, immediately after interventions (3 months), and 7 months after baseline.

RESULTS: The median number of intervention sessions attended was 36 (interquartile range (IQR) 30.00–36.75) for exercise and 36 (IQR 30.50–37.00) for relaxation. Adherence to the individual exercises ranged from 94% to 99%. At 3 months, role-physical (an item in SF-36), timed up-and-go, and walking economy were significantly better in the exercise group (analysis of covariance). At 7 months, role-physical was the only significant difference between groups.

CONCLUSION: Exercise training for ambulatory stroke patients was feasible and led to significantly greater benefits in aspects of physical function and perceived effect of physical health on daily life. J Am Geriatr Soc 2007.

Key words: stroke; exercise training; relaxation; randomized trial

Stroke patients have impaired aerobic fitness (endurance) and muscle strength, which almost certainly contributes to impaired physical function and disability. Physical fitness (exercise) training is "planned, structured and regular physical activity performed to improve one or more components of physical fitness."[1] Mixed (a combination of endurance and resistance) training might, via improvements in physical fitness, improve physical function and reduce disability. A recent Cochrane review[2] found only four trials of mixed training, of which only two (33 patients) were of sufficient duration to improve physical fitness.[3,4] There was little information about feasibility (e.g., whether patients could tolerate training) or about long-term retention of benefits.[2]

A recent home-based trial of mixed training reported significantly greater improvements in balance, endurance, peak aerobic capacity, and aspects of quality of life than with fortnightly visits from a therapist,[5] but the training was resource intensive, with each patient receiving more than 50 hours of one-to-one therapy. Another study suggested benefits of a community-based fitness intervention, but the control group received upper limb strength training, not a nonexercise control intervention.[6] Other small, recent trials did not provide mixed training and did not investigate long-term retention of benefits.

Because of the paucity of data about the feasibility and effect of exercise training,[2] an exploratory randomized, controlled trial of exercise training after stroke was designed, using a well-recognized framework for evaluating complex interventions.[7] Group exercise sessions that were less resource intensive than one-to-one instruction were provided. The control group attended relaxation sessions (attention control) to control for the effects of social interaction and activity associated with travel. Long-term retention of benefits was investigated.

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The aims were to determine the feasibility of key parts of the trial (including acceptability of the interventions and outcome measurements) and to assess the effect of exercise training on important outcomes.[7] Because this was an exploratory trial, power calculations were not performed; rather, the goal was to obtain reliable data to inform power calculations for a definitive trial.[7] It was estimated that 90 patients could be recruited.

METHODS

Design

This was a randomized exploratory trial comparing "mixed" (endurance and resistance) training with relaxation (attention control) in stroke patients who had completed their usual rehabilitation (including physiotherapy, occupational therapy, and speech and language therapy) and who had been discharged from the hospital. Between October 2002 and July 2004, the exercise instructor (IC), one of the trial coordinators, or the principal investigator, (GM) screened inpatients at three hospitals in Edinburgh, Scotland, for eligibility. From August 2003, eligible patients who had been inpatients or who had attended the stroke clinic at a fourth hospital (Western General Hospital) were referred. All hospitals were part of the same clinical network, so stroke management was similar in all four hospitals.

Eligibility criteria were independently ambulatory, living within central or south Edinburgh, absence of dysphasia or confusion severe enough to prevent informed consent or impair safety in exercise classes, and absence of medical contraindications to exercise training (uncontrolled angina pectoris, resting systolic blood pressure >180 mmHg or resting diastolic blood pressure >100 mmHg, resting heart rate >100 beats per minute, unstable or acute heart failure, uncontrolled systemic illness, uncontrolled visual or vestibular disturbance, recent injurious fall without medical examination, and proven inability to adhere to the exercise program).[8]

Baseline Assessment

Eligible consenting patients attended the Human Performance Laboratory at the Royal Infirmary, Edinburgh, after hospital discharge and shortly before randomization. One of four physicians (including GM and AY) checked fulfillment of eligibility criteria and performed a limited neurological examination. One of four exercise physiologists (including CG, DH and CF) assessed Functional Independence Measure (FIM);[9] Nottingham Extended Activities of Daily Living (NEADLs);[10] Rivermead Mobility Index (RMI);[11] functional reach;[12] timed up-and-go;[13] sit-to-stand time; Elderly Mobility Scale (EMS);[14] functional ambulation category;[15] Medical Outcomes Study 36-item Short Form Questionnaire, version 2 (SF-36), which measures domains of quality of life,[16] and Hospital Anxiety and Depression Score (HADS).[17] Comfortable walking velocity (m/s) was measured during three sessions (separated by 5 minutes) of self-paced comfortable walking around a marked 17-m circuit, completing sufficient laps to achieve at least 3 minutes of walking per session.[18] During each walk, walking economy (oxygen consumption (VO_2) mL/kg per m), derived from walking speed and VO_2 toward the end of the walk minus VO_2 while standing, was calculated using data from a portable breath-by-breath metabolic measurement system (Metamax 3B, Cortex Biophysik, Leipzig, Germany). Leg extensor explosive power (W/kg) was measured using a Nottingham Power Rig (Medical Engineering Unit, University of Nottingham, Nottingham, UK).[19] Power was measured rather than muscle strength, because it is functionally more relevant.

Randomization was by the trial coordinator or principal investigator (not by the outcome assessors) via a secure Internet randomization service that stratified by sex, age, and FIM score (dichotomized at age 70 and FIM score of 120).

Interventions

An advanced exercise instructor delivered both interventions in a rehabilitation hospital three times a week (Monday, Wednesday, Friday) for 12 weeks to groups of up to seven patients. During Week 1, the instructor familiarized patients with techniques and equipment. At the start of the sessions, the instructor measured blood pressure (as an additional safety check) and inquired whether the patients had fallen since the last session. Each session lasted 1 hour 15 minutes (including "tea and chat" after the interventions). Transport (minibus or taxi) was provided. Patients unable to attend every session of the 12-week program were offered up to three additional make-up sessions.

There was insufficient information from the Cochrane review about the optimum training regime for stroke patients.[2] Therefore, the mode of exercise, initial exercise level, and rate of progression were based on the Falls and Exercise Management Study to reduce falls in older frailer participants (many of whom had had a previous stroke)[20] and community exercise sessions designed for the UK charity "Different Strokes" (further details available on request). Further adaptations (e.g., inclusion of the stair climbing and descending exercise) were by the study physiotherapist (see Acknowledgments). Patients unable to perform or complete a particular exercise were given a shortened, modified, or alternative task. Although progression every 2 to 4 weeks was aimed for, individuals not ready to progress (e.g., insufficient strength, endurance, or technique) remained at their current prescription and only progressed when assessed by the instructor to be ready. The length of the exercise program (12 weeks) was similar to those of previous studies in stroke patients.[3,4]

Each session started with a warm-up to enhance circulation and mobility (15–20 minutes). The total duration of the exercise training increased from 15 minutes at Week 1 to 40 minutes by Week 12. The endurance component began in Week 1 as a circuit of cycle ergometry, raising and lowering a 1.4-kg, 55-cm exercise ball, shuttle walking, and standing chest press performed consecutively. Between each circuit station, patients walked or marched in place to ensure continuous movement. A stair climbing and descending exercise was added in Week 4. The circuit duration increased from 9 minutes to 21 minutes by Week 12. Cycling intensity was increased weekly by small increments in pedaling resistance, cadence or both while maintaining perceived rate of exertion in the range of 13 to 16.[21] Brisker efforts were encouraged during all endurance exercises as

patients became more familiar with the session. The endurance training ended with a graded cool-down and standing stretches.

The resistance training included upper back strengthening and triceps extension exercise, both performed seated using elastic resistance training bands and progressing from four repetitions using the lowest-resistance band to 10 repetitions using the highest-resistance band by Week 12; a pole-lifting exercise performed standing, progressing from four repetitions with a 0.22-kg pole to 15 repetitions with a 3.6-kg pole by Week 12; and a sit-to-stand exercise, resisted by body mass, progressing from four to 10 repetitions by Week 12 and becoming more difficult by introducing pauses during lowering into the chair and then increasing the frequency and duration of the pauses and increasing the angle of the knee bend and the upper body levers (i.e., the arms). The resistance training ended with a gentle cool-down and flexibility exercises lasting 10 to 15 minutes.

The relaxation intervention was seated and included deep breathing and progressive muscular relaxation. Techniques involving muscular contraction were omitted to avoid unintentional fitness training. Duration increased from 20 minutes (Week 1) to 49 minutes (Week 12).

Patients were blinded to the underlying hypothesis by reiterating the possible benefits of both interventions. Outcome assessors were blinded by asking patients not to discuss their allocated intervention.

The exercise instructor recorded patient attendance at sessions and whether each exercise station was performed according to the protocol (i.e., adherence).

Follow-Up Assessments

Patients were reassessed as soon as possible after completion of the interventions (3-month assessment) and then 4 months after completion of the interventions (7-month assessment).

Analysis of Outcome Data

Raw data with skewed distributions were appropriately transformed to a normal or near-normal distribution when possible (Table 1). Outcome measures with large ceiling or floor effects (i.e., a large proportion of measures reached the maximum or minimum possible score) could not be transformed and so were omitted from the main analyses. Comparison of the exercise and relaxation groups was by intention to treat (ITT), missing outcome data at the 3- and 7-month assessments being replaced using the last observation carried forward method. Baseline measurements of the outcome variables were occasionally missing for different reasons (e.g., pain or dizziness in the patient, equipment failure). This affected 2.7% of these data points. Where possible, these missing data were replaced using the next measurement to preserve the ITT design as closely as possible.[22] Sensitivity analyses applied to the original data and to data with missing values replaced produced similar results.

Analysis of covariance (ANCOVA) was used to test whether, and by how much, the outcome measures at 3 and at 7 months differed between the groups, controlling for their baseline levels. Adjustment was also made for age, sex, and time from stroke to baseline. Other patient characteristics were also considered for inclusion as independent variables, including hospital of origin, but none was sufficiently influential. Possible reasons for outliers were investigated, but none was excluded. All models used the Type III sum-of-squares method. All two-way interactions were tested for significance.

Results are expressed as means of the outcome measures, adjusted for the influence of independent variables, and the significance of the difference between the exercise and relaxation groups (Table 1). Effect size is also given as a standardized measure of the size of the treatment effect, independent of sample size. For this unbalanced ANCOVA design, partial eta-squared is the appropriate effect size index (intervention effect sum of squares (SS) divided by error SS plus intervention SS). This measure of effect size is small at 0.01, medium at 0.09, and large at 0.25.[23]

For each intervention, baseline assessments were also compared with the 3- and 7-month assessments using univariate analysis to determine the effect of each intervention on the outcome measures (paired *t* tests for normally distributed and transformed data and sign tests for nonnormal data).

RESULTS

Patients

Baseline characteristics are shown in Table 2. Progress of patients through the trial is shown in Figure 1.

Feasibility

Interventions

Nineteen of 32 (59%) patients allocated to exercise and 17 of 34 (50%) allocated to relaxation achieved full attendance ($\geq$36 sessions). The timing of absences was variable but infrequent; hence, the median number of sessions attended was 36 (interquartile range (IQR) 30.00–36.75) for exercise, and 36 (IQR 30.50–37.00) for relaxation. Adherence to the exercise stations ranged from 94% (cycle ergometry) to 99% (pole raise) of the total of all patients' attendances.

Assessments

Sixty-four (97%) patients attended the 3-month assessment and 62 (94%) the 7-month assessment (Figure 1). In total, 192 assessments were performed, and data were obtained for the majority of outcome measures. Less than 3% of data were missing for outcome measures using questionnaires (i.e., FIM, NEADL, RMI, SF-36, HADS), whereas the amount of missing data was higher for physical measurements (timed up-and-go (8/192, 4%), sit-to-stand (9/192, 5%), functional reach (10/192, 5%), EMS (12/192, 6%), extensor power of unaffected leg (15/192, 8%), extensor power of affected leg (10/192, 5%), walking speed (14/192, 7%), and walking economy (21/192, 11%)). The most common reasons for noncompletion of the physical tests were limb pain or illness.

Analysis

Although it was possible to satisfactorily transform most of the outcome variables to a normal or near-normal distribution, this was not possible for EMS or SF-36 social functioning, bodily pain, or role-emotional, because many of the

Table 1. Outcome Measurements* 3 and 7 Months After Baseline Assessment, Adjusted for Patient Characteristics

Outcome Measure	Months	Exercise Group (n = 32)		Relaxation Group (n = 34)		Effect Size (Partial Eta^2)	*P*-value for Difference Between Intervention Groups†
		Adjusted Mean (95% Confidence Interval)					
Functional Independence Measure (range 18–126)	3	118.2	(116.9–119.3)	118.3	(117.1–119.4)	0.001	.84
	7	117.9	(116.3–119.4)	117.7	(116.1–119.1)	0.001	.82
Nottingham Extended ADLs (range 0–22)	3	16.5	(15.8–17.1)	16.7	(16.1–17.4)	0.004	.61
	7	16.7	(15.7–17.5)	16.4	(15.5–17.3)	0.002	.70
Rivermead Motor Index (range 1–15)	3	13.2	(12.7–13.6)	13.0	(12.5–13.4)	0.007	.50
	7	13.3	(12.8–13.7)	13.1	(12.6–13.5)	0.007	.53
Functional Reach, cm‡	3	28.8	(26.3–31.1)	26.3	(23.7–28.7)	0.032	.16
	7	28.3	(25.7–30.7)	25.8	(23.1–28.3)	0.030	.18
SF-36 (range 0–100)							
Physical functioning§	3						
	7	55.8	(49.9–61.7)	57.8	(52.1–63.5)	0.004	.63
Role physical	3	90.8	(85.1–95.2)	75.5	(66.8–82.8)	0.16	.002
	7	84.2	(76.1–90.7)	71.7	(61.4–80.3)	0.07	.04
General health	3	76.2	(69.9–81.8)	68.1	(60.0–74.4)	0.052	.08
	7	65.0	(57.8–71.5)	71.5	(65.1–77.2)	0.032	.16
Vitality	3	59.0	(53.6–64.3)	57.5	(52.3–62.7)	0.003	.69
	7	55.2	(49.2–61.2)	51.9	(46.1–57.7)	0.01	.44
Mental health	3	80.4	(74.4–85.5)	82.5	(77.1–87.2)	0.006	.56
	7	77.3	(71.4–82.5)	79.9	(74.6–84.7)	0.008	.48
HADS score (range 0–21)							
Anxiety	3	3.65	(2.63–4.82)	3.99	(2.96–5.17)	0.003	.67
	7	3.95	(2.89–5.16)	4.20	(3.15–5.41)	0.002	.75
Depression	3	4.05	(2.99–5.27)	3.51	(2.56–4.61)	0.008	.49
	7	4.21	(3.18–5.37)	4.03	(3.07–5.13)	0.001	.82
Leg extensor power (affected leg) W/kg‖	3	1.11	(1.01–1.23)	1.04	(0.95–1.15)	0.014	.37
	7	1.11	(0.99–1.22)	1.09	(0.98–1.20)	0.001	.82
Leg extensor power (unaffected leg) W/kg‖	3	1.25	(1.13–1.36)	1.23	(1.12–1.33)	0.001	.81
	7	1.29	(1.19–1.40)	1.25	(1.16–1.36)	0.005	.61
Walking speed, m/sec¶	3	0.735	(0.697–0.773)	0.735	(0.697–0.773)	<0.001	1.0
	7	0.698	(0.662–0.735)	0.736	(0.701–0.772)	0.037	.14
Walking economy (oxygen uptake) mL/kg per meter¶	3	0.112	(0.103–0.121)	0.126	(0.116–0.136)	0.065	.05
	7	0.118	(0.108–0.129)	0.120	(0.110–0.136)	0.002	.72
Timed Up-and-Go, seconds	3	10.4	(9.8–11.1)	11.5	(10.8–12.3)	0.076	.03
	7	11.2	(10.6–11.8)	11.5	(10.9–12.2)	0.011	.41
Sit-to-stand, seconds	3	0.94	(0.85–1.06)	1.01	(0.90–1.14)	0.01	.43
	7	1.02	(0.93–1.13)	1.09	(1.00–1.21)	0.017	.31

* Back-transformed, if necessary, after analysis of transformed data (square root of reflected data: Functional Independence Measure, Nottingham Extended Activities of Daily Living (ADLs), Rivermead Motor Index; functional reach, Medical Outcomes Study 36-item Short Form Questionnaire (SF-36) (role physical, general health, and mental health); square root: Hospital Anxiety and Depression Scores, leg extensor power; reciprocal: Timed Up-and-Go and sit-to-stand; logarithmic: walking economy).

† From analysis of covariance effects table.

‡ Time from stroke to baseline omitted from both models because of strong interaction with other covariates.

§ Analysis of the 3-month assessment not done because of heterogeneity of regression slopes.

‖ One subject in exercise group omitted because no extensor power data were available for either leg at any stage. One subject in exercise group omitted because no extensor power data were available for unaffected leg at any stage.

¶ One subject in relaxation group omitted because no walking data were available at any stage.

Table 2. Characteristics of Patients at Baseline

Characteristic	Exercise Group (n = 32)	Relaxation Group (n = 34)
Age, mean ± SD	72.0 ± 10.4	71.7 ± 9.6
Men, n (%)	18 (56)	18 (53)
Required inpatient treatment for stroke, n (%)	27 (84)	29 (85)
Length of inpatient stay, median (IQR)	19 (7–39) n = 27	16 (6.5–48.5) n = 29
Outpatient treatment only, n (%)	5 (16)	5 (15)
Subtype of stroke (Oxfordshire Community Stroke Project Classification), n (%)		
Total anterior circulation	1 (3)	1 (3)
Partial anterior circulation	16 (50)	16 (47)
Lacunar	10 (31)	9 (26)
Posterior circulation or uncertain	5 (16)	8 (24)
Pathological type, n (%)		
Ischemic	28 (88)	32 (94)
Hemorrhagic or unknown	4 (12)	2 (6)
Side of brain lesion, n (%)		
Right	12 (38)	15 (44)
Left	19 (59)	18 (53)
Bilateral or unknown	1 (3)	1 (3)
Days between stroke and baseline, median (IQR)	171 (55–287) n = 31	147.5 (78.8–235.5) n = 34
Days between discharge and baseline, median (IQR)	106 (50–230) n = 27	80 (49–154) n = 29
Days between stroke and start of intervention, median (IQR)	178 (86–307) n = 31	161.5 (91.8–242.8) n = 32
Smoking, n (%)		
Nonsmoker	13 (41)	15 (44)
Ex-smoker	6 (19)	6 (18)
Smoker	13 (41)	12 (35)
Drugs, n (%)*†		
Antiplatelets or anticoagulants	30 (97)	34 (100)
Antihypertensives	13 (42)	18 (53)
Statins	18 (58)	26 (77)
Other	29 (94)	31 (91)
Comorbid disease, n (%)*‡		
Hypertension	12 (46)	19 (56)
Ischemic heart disease or left ventricular failure	10 (39)	15 (44)
Cancer (prior or current)	4 (15)	2 (6)
Prior stroke or transient ischemic attack	7 (27)	8 (24)
Other	21 (81)	18 (53)
Sitting blood pressure, mmHg, mean ± SD		
Systolic	140.6 ± 18.6 n = 31	139.5 ± 17.9 n = 32
Diastolic	74.7 (10.0) n = 31	71.7 (8.9) n = 32
Speech, n (%)		
Normal	22 (69)	24 (71)
Dysarthria	9 (28)	7 (21)
Expressive dysphasia	1 (3)	3 (9)
Weakness (score <5 on Medical Research Council motor scale), n (%)		
Arm	9 (28)	13 (38)
Leg	7 (22)	8 (24)
Inattention, n (%)	2 (6)	2 (6)
Functional Ambulation Category score, n (%)		
4	3 (9)	4 (12)
5	29 (91)	30 (88)

*Multiple response variable; percentages do not add to 100.
†There were no medications for one patient (exercise group); excluded from calculation of percentages.
‡There were no comorbidities for six subjects (all exercise group); excluded from calculation of percentages.
IQR = interquartile range; SD = standard deviation.

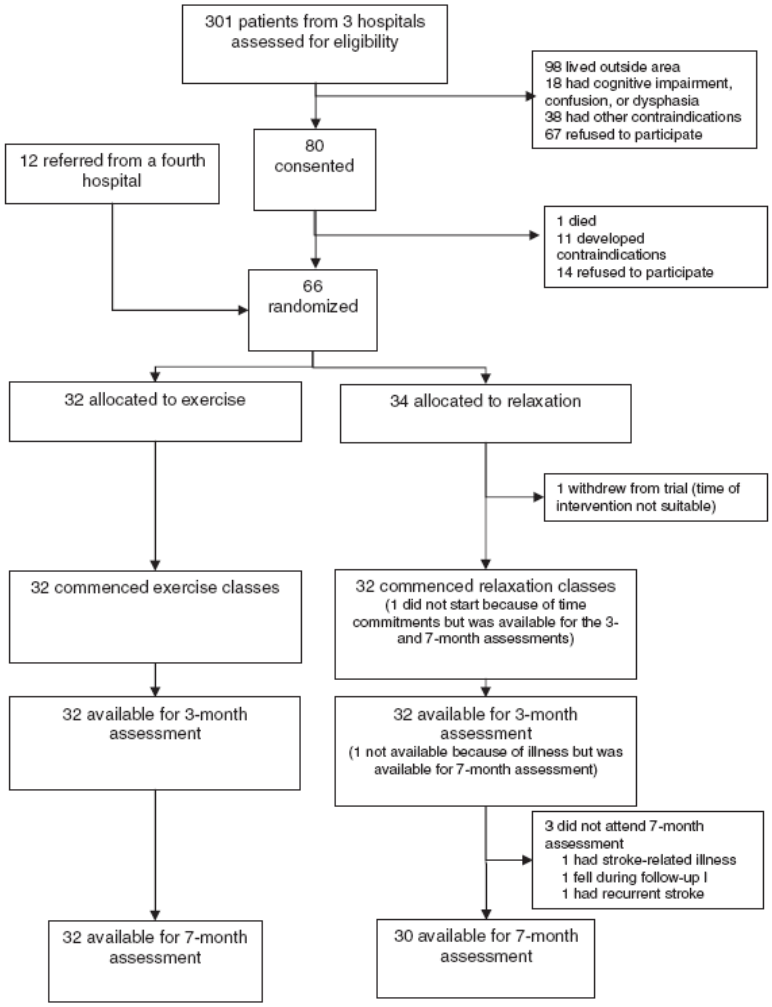

Figure 1. Patient flow through the trial.

data (77%, 54%, 46%, and 43%, respectively, at baseline) reached the maximum possible score for that particular variable (i.e., ceiling effect). Therefore, these measurements had to be excluded from ANCOVA.

Outcomes

Comparison of Exercise and Relaxation

At 3 months, SF-36 role-physical, timed up-and-go and walking economy were significantly better for exercise than relaxation (Table 1), although by 7 months, only role-physical remained significantly better in the exercise group.

Changes Between Baseline and 3- and 7-Month Assessments for Each Group

In the exercise group, there were statistically significant improvements between baseline and 3 months for SF-36 role-physical, sit-to-stand time, extensor power of the affected lower limb, and comfortable walking speed (all $P<.001$); SF-36 general health, SF-36 mental health, timed up-and-go, and HADS anxiety (all $P<.01$); SF-36 vitality, SF-36 role-emotional, functional reach, extensor power of the unaffected lower limb, and walking economy (all $P<.05$). At 7 months, significant improvements were maintained only in the extensor power of both lower limbs ($P<.01$), HADS anxiety, and sit-to-stand (both $P<.05$).

In the relaxation group, there were statistically significant improvements between baseline and 3 months in walking speed ($P<.001$), SF-36 mental health and extensor power of the lower unaffected limb (both $P<.05$). Significant improvement was maintained in all of these outcomes at 7 months ($P<.05$, $P<.01$, and $P<.001$, respectively),

but SF-36 bodily pain was significantly worse ($P<.01$) (all data available on request).

Adverse Events

During the 3-month period of the interventions, eight of 32 patients in the exercise group reported 11 falls, and four of 34 patients in the relaxation group reported five falls (P = ns); all falls occurred outside the sessions. One patient allocated to relaxation fell at the 3-month assessment.

DISCUSSION

This is the largest randomized trial to compare in detail the feasibility and effect of mixed exercise training performed in a group setting with that of a nonexercise "attention control" intervention for ambulatory stroke patients.

The interventions were feasible, with high rates of attendance at both classes and, for patients attending the exercise classes, excellent adherence to individual exercises. The battery of outcome measures was feasible, particularly the questionnaires. The rate of missing data from even the least-well-tolerated measurement (walking economy) was only 11%. The analysis was feasible, although the EMS and some items of the SF-36 could not be used in the multivariate analysis because of ceiling effects (i.e., a large proportion of scores reached the maximum possible). Generally, floor or ceiling effects greater than 20% are likely to cause problems with data analysis.

The between-group comparison demonstrated that, at the 3-month assessment, patients allocated to exercise performed significantly better than those allocated to relaxation on the timed up-and-go test, one item on the SF-36, and walking economy. The effect sizes were small for timed up-and-go and walking economy and medium for role-physical.[23] At the 7-month assessment, the only significant difference between groups was in role-physical (small effect), suggesting that benefits of exercise training are lost after the exercise sessions cease.

There were many statistically significant improvements between baseline and 3 months in the exercise group and a few also in the relaxation group. Social interaction may have mediated some of these.[24]

There were several methodological strengths to the study. First, particular attention was paid to problems such as bias (e.g., the Internet randomization service ensured that the investigator randomizing patients had no prior knowledge of likely treatment allocation, and the outcome assessors could not obtain information about treatment allocation). Second, an attention-control intervention rather than usual care was used, which means that between-group differences were due to the exercise training per se, rather than social interaction. Third, a 7-month assessment was performed to investigate whether any benefits were maintained in the long term.

There are some limitations. First, like with previous studies,[2–4] patients unable to mobilize independently had to be excluded, because a single instructor taught the classes. Groups of more severely impaired patients would require a higher instructor–patient ratio and safe transport. Second, prestroke function or severity of stroke was not measured. This information was not available in standardized format from the hospital records, and the study personnel who recruited patients could not obtain these data retrospectively. However, stroke subtype, which provides an indication of stroke severity, was similarly distributed between the groups.

This exploratory study will inform the design of a definitive study. The same methods of recruitment and randomization and the same exercise program will be used. The assessments will be simplified by excluding scales with a large proportion of ceiling values. It had been expected that a definitive trial would determine the effect of exercise training on disability, but preliminary power calculations using data from this study have demonstrated that several hundred patients would be required in each group for a primary endpoint of the NEADL scale. Therefore, a definitive trial may need to focus on functionally relevant physical measures and indices of fitness. Disability data from a definitive trial could be incorporated into a meta-analysis of data from other trials. The data from the 7-month assessment suggest that the benefits of exercise training are not retained long term, so a definitive trial should also evaluate strategies to facilitate long-term participation in physical activity.

In summary, a randomized, controlled trial of physical fitness training in ambulatory poststroke patients is feasible. This exploratory study suggests significant benefits that justify a larger clinical trial to evaluate the effectiveness of an endurance and resistance exercise intervention on measures of physical functioning.

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Approval was obtained from Lothian Research Ethics Committee.

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Author Contributions: All authors except Ms. Cunningham and Ms. Fitzsimons devised the protocol and obtained funding. Dr. Mead was the principal investigator, led the study, and recruited patients. Ms. Dinan designed and quality assured the exercise intervention. Mr. Saunders advised on the incremental progression and recording of the exercises. Dr. Greig, Mr. Saunders, and Ms. Fitzsimons performed the baseline assessments and postintervention assessments. Ms. Cunningham assisted with recruitment and delivered the interventions. Dr. Lewis advised on the trial design and performed the statistical analysis. Professor Young assisted with recruitment of patients. All authors were involved in preparation of the manuscript. Dr. Mead is the guarantor.

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14.13. Intra-Rater Reliability of fitness and function measures

Table of studies reporting reliability of physical fitness and physical function measures, where possible in people with stroke

Outcome measures	Reliability Study	Group	Number	Age	Time since stroke	Result	Intra-rater test retest reliability
a) Physical fitness							
Economy	(da Cunha-Filho et al. 2003)	Stroke	n=9	60 (15.2)	45.46 (51.35)	0.25 (0.11) $m \cdot kg^{-1} \cdot m^{-1}$	$ICC_{3,1}$ = 0.95 $\bar{d}$ = 0.0189 95%CI (-0.04 to 0.078)*
$\dot{V}O_2$ Tau	(Fitzsimons et al. 2007)	Elderly	n=5	Median 78	-	36 (12) sec	SEM 4.4 sec
LLEP	(Dawes et al. 2005)	Stroke	n=14 (n=9)†	46 (8)	>6 months	Weaker leg † 1.07 (0.50) $W \cdot kg^{-1}$ Stronger leg† 1.99 (0.85) $W \cdot kg^{-1}$	$ICC_{3,10}$ = 0.763 95%CI (0.252 to 0.941) † $\bar{d}$ = 4.6 ± 46.7† $ICC_{3,10}$ = 0.664 95%CI (0.055 to 0.913) † $\bar{d}$ = 10.9 ± 94.3†
b) Specific Measures of physical function							
Comfortable walking speed	(Flansbjer et al. 2005)	Stroke	n=50	58 (6.4)	6-46 mths	0.89 (0.3) $m.sec^{-1}$	$ICC_{2,1}$ = 0.94 95%CI (0.90 to 0.97) $\bar{d}$ = 0.05 95%CI (-0.02 to -0.04)
Timed up-and-go	(Flansbjer et al. 2005)	Stroke	n=50	58 (6.4)	6-46 mths	14.3 (5.2) sec	$ICC_{2,1}$ = 0.96 95%CI (-1.01 to -0.15) $\bar{d}$ = -0.58 95%CI (-0.02 to -0.04)
Functional Reach	(Tyson and DeSouza 2004)	Stroke	n=83 (n=25)†	66.7 (12.5)	11 wks (IQR 5 to 23)	16.68 (7.48) cm†	ICC = 0.95 95%CI (0.88 to 0.98) †
Chair rise	(Skelton 1995)	Elderly	n=28		-	UN	CV% = 9% (n=26 without knee pain)

Data are mean (SD) or range.

Abbreviations: ICC intra-class correlation coefficient; CV% coefficient of variation; $\bar{d}$ mean difference ± reliability coefficient; SEM standard error of the mean

* reanalyzed from raw data in paper

† Repeatability data are derived from a subset of the participants recruited and for whom characteristics are reported

14.14. Example of minimisation procedure

An example of the process of minimization showing how the distribution of existing group characteristics influences the outcome of a subsequent participant (who was male, ≥75 years and with a FIM Instrument score of ≥ 115.

Patient Characteristics		Existing Allocations		Category of Current patient	Calculations	
		Exercise (freq.) *a*	Relaxation (freq.) *b*	*c*	Exercise *a x c*	Relaxation *b x c*
Age	≥75 yrs	6	4	1	6	4
	<75 yrs	5	5	0	0	0
Gender	Male	4	2	1	4	2
	Female	7	7	0	0	0
FIM	≥ 115	4	3	1	4	3
	< 115	7	6	0	0	0
		n=33	n=27		∑=14	∑=9

The data describing the category of current patient denotes the presence (1) or absence (0) of the characteristic. Since 9 < 14 the patient allocation favours *Relaxation;* where the ∑ values are equal a simple randomization is used (probability 0.50). Based on an unpublished example (Lewis, S.C.).

14.15. MEDLINE (OVID) updated search strategy

Part A: Stroke search strings (Cochrane Stroke Group)

1. cerebrovascular disorders/
2. exp basal ganglia cerebrovascular disease/
3. exp brain ischemia/
4. exp carotid artery diseases/
5. cerebrovascular accident/
6. exp brain infarction/
7. exp cerebrovascular trauma/
8. exp hypoxia-ischemia, brain/
9. exp intracranial arterial diseases/
10. intracranial arteriovenous malformations/
11. exp "Intracranial Embolism and Thrombosis"/
12. exp intracranial hemorrhages/
13. vasospasm, intracranial/
14. vertebral artery dissection/
15. aneurysm, ruptured/
16. brain injuries/
17. brain injury, chronic/
18. exp carotid arteries/
19. endarterectomy, carotid/ or endarterectomy/
20. *heart septal defects, atrial/
21. *atrial fibrillation/
22. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$1 or neurologic$ deficit$ or SAH or AVM).tw.
23. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj10 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm or obstruction or vasculopathy)).tw.
24. ((lacunar or cortical) adj5 infarct$).tw.
25. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa) adj10 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
26. ((brain or cerebral or intracranial or communicating or giant or basilar or vertebral artery or berry or saccular or ruptured) adj10 aneurysm$).tw.
27. (vertebral artery dissection or cerebral art$ disease$).tw.
28. ((brain or intracranial or basal ganglia or lenticulostriate) adj10 (vascular adj5 (disease$ or disorder or accident or injur$ or trauma$ or insult or event))).tw.
29. ((isch?emic or apoplectic) adj5 (event or events or insult or attack$)).tw.
30. ((cerebral vein or cerebral venous or sinus or sagittal) adj5 thrombo$).tw.
31. (CVDST or CVT).tw.
32. ((intracranial or cerebral art$ or basilar art$ or vertebral art$ or vertebrobasilar or vertebral basilar) adj5 (stenosis or isch?emia or insufficiency or arteriosclero$ or atherosclero$ or occlus$)).tw.
33. ((venous or arteriovenous or brain vasc$) adj5 malformation$).tw.
34. ((brain or cerebral) adj5 (angioma$ or hemangioma$ or haemangioma$)).tw.
35. carotid$.tw.
36. (patent foramen ovale or PFO).tw.
37. ((atrial or atrium or auricular) adj fibrillation).tw.
38. asymptomatic cervical bruit.tw.
39. exp aphasia/ or anomia/ or hemiplegia/ or hemianopsia/ or exp paresis/ or deglutition disorders/ or dysarthria/ or pseudobulbar palsy/ or muscle spasticity/
40. (aphasi$ or apraxi$ or dysphasi$ or dysphagi$ or deglutition disorder$ or swallow$ disorder$ or dysarthri$ or hemipleg$ or hemipar$ or paresis or paretic or hemianop$ or hemineglect or spasticity or anomi$ or dysnomi$ or acquired brain injur$ or hemiball$).tw.
41. ((unilateral or visual or hemispatial or attentional or spatial) adj10 neglect).tw.
42. or/1-41

Part B: Randomized controlled trial search strings (Cochrane Stroke Group)

43. Randomized Controlled Trials/
44. random allocation/
45. Controlled Clinical Trials/
46. control groups/
47. clinical trials/ or clinical trials, phase i/ or clinical trials, phase ii/ or clinical trials, phase iii/ or clinical trials, phase iv/
48. Clinical Trials Data Monitoring Committees/
49. double-blind method/
50. single-blind method/
51. Placebos/
52. placebo effect/
53. cross-over studies/
54. Multicenter Studies/
55. Therapies, Investigational/
56. Drug Evaluation/
57. Research Design/
58. Program Evaluation/
59. evaluation studies/
60. randomized controlled trial.pt.
61. controlled clinical trial.pt.
62. clinical trial.pt.
63. multicenter study.pt.
64. evaluation studies.pt.
65. meta analysis.pt.
66. meta-analysis/
67. random$.tw.
68. (controlled adj5 (trial$ or stud$)).tw.
69. (clinical$ adj5 trial$).tw.
70. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
71. (surgical adj5 group$).tw.
72. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
73. ((multicenter or multicentre or therapeutic) adj5 (trial$ or stud$)).tw.
74. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
75. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
76. (coin adj5 (flip or flipped or toss$)).tw.
77. latin square.tw.
78. versus.tw.
79. (cross-over or cross over or crossover).tw.
80. placebo$.tw.
81. sham.tw.
82. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
83. controls.tw.
84. (treatment$ adj6 order).tw.
85. (meta-analy$ or metaanaly$ or meta analy$ or systematic review or systematic overview).tw.
86. or/43-85
87. 42 and 86
88. 87 not exp animals/
89. 87 and humans/
90. 88 or 89

Part C Physical fitness training search strings

91. exp exercise/
92. exercise test/
93. exp exertion/
94. exercise therapy/
95. physical fitness/
96. exp sports/
97. isometric contraction/
98. isotonic contraction/
99. walking/
100. exp physical endurance/
101. exp locomotion/
102. early ambulation/
103. "sports equipment"/
104. tai ji/
105. yoga/
106. fitness centers/
107. leisure activities/
108. recreation/
109. (physical adj3 (exercise$ or therap$ or conditioning or activit$ or fitness)).tw.
110. (exercise adj3 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
111. (fitness adj3 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
112. ((training or conditioning) adj3 (intervention$ or protocol$ or program$ or activit$ or regim$)).tw.
113. (sport$ or recreation$ or leisure or cycl$ or bicycl$ or treadmill$ or run$ or swim$ or walk$).tw.
114. ((endurance or aerobic or cardio$) adj3 (fitness or train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
115. (muscle strengthening or progressive resist$).tw.
116. ((weight or strength$ or resistance) adj (train$ or lift$ or exercise$)).tw.
117. ((isometric or isotonic or eccentric or concentric) adj (action$ or contraction$ or exercise$)).tw.
118. or/91-117

14.16. Ongoing studies (updated systematic review)

Study Name/Title *Investigator & Trial Code*	Participants	Interventions	Primary Outcomes	Start & End Dates
Efficacy of a Mechanical Gait Repetitive Training Technique in Hemiparetic Stroke Patients *Brissot NCT00284115*	N=122 <2 month post stroke -Non ambulatory patient	**Intervention**: Body weight support treadmill gait training + physiotherapy for 4 weeks **Control**: Physiotherapy alone	Walking speed	Start: Mar 2006 End: UN
The Effect of a Supplementary Exercise Program for Upper Extremity Function in Stroke Rehabilitation *Eng NCT00359255*	N=250 Arm recovery as a rehabilitation goal	**Intervention**: usual care + arm and hand exercise 60 min/d for 4 weeks during inpatient care **Control**: Usual care only	Ability to use the paretic arm in activities of daily living.	Start: Jul 2006 End: Jun 2008
EXERT: Exercise evaluation randomised trial *Issacs N0484008696*	N=1500	**Intervention 1:** exercise scheme in leisure centre. **Intervention 2**: home based walking programme **Control**: Simple advice. All for 10 wks.	Biological status, cardiovascular risk factors, health outcomes and quality of life	UN
FAME: A Randomised Controlled Trial of Family Mediated Exercises Following Stroke *NCT00666744*	N=40 Patients receiving physiotherapy Family willing to participate	**Intervention**: routine therapy + 'family mediated exercise therapy' 1200 minutes over 8 weeks **Control**: routine therapy only	Fugl Meyer Assessment, Berg Balance Scale Motor Assessment Scale Six Minute Walk Test Barthel Index Re-integration into Normal Living Index Nottingham EADL	Start: Apr 2008 End: Mar 2009
A RCT of Power Training and Treadmill Training to Improve Walking Ability in Sub-Acute Stroke Patients *Kilbreath NCT00108030*	N=102 Age 45-80 Years Distance walked in 6-min walk test is less than the lower limit of 'normal'	**Intervention 1**: Treadmill training + Power training + usual care **Intervention 2**: Treadmill training + usual care **Control**: Usual Care Interventions 3d/wk for 10 weeks followed by home-based training for 6 months	Distance walked in 6-min	Start: Mar 2004 End: Dec 2006

Structural Neuroplasticity Associated With Aerobic Treadmill Training in Geriatric Chronic Stroke Survivors *Luft NCT00614224*	N=40 Age>60 years ≥months post stroke Completed rehabilitation	Intervention: Progressive aerobic treadmill training 10-45 min/d; 3 d/wk for 3 months **Control**: attention control.	VO_2 peak Gait velocity	Start: Jan 2008 End: Jul 2009
Evaluation of an Intervention Program Targeted at Improving Balance and Functional Skills After Stroke *Olsson NCT00377689*	N=50 Age =>55 years; 3-6 months post stroke Ambulatory	**Intervention**: High intensity functional exercise + theory session. **Control**: Theory session	Balance Incidence of falls Self-efficacy ADL Walking ability	Start: Sep 2006 End: Feb 2008
Effects of strength training on upper-limb function in post-stroke hemiparesis *Patten NCT00037908*	N=60 Community dwelling < 6 months post stroke	**Intervention**: Standard functional rehabilitation + high-intensity upper-body strength training. **Control**: Standard functional rehabilitation	Strength, Modified Ashworth Scale, Barthel Index, FIM, Fugl-Meyer	Start: Oct 2000 End: Sep 2003
Evaluation of Whether Functional Strength The Effects of Functional Strength Training on Weakness and Function of the Lower Limb After Stroke *Pomeroy NCT00322192*	N=300 Age > 50 years 1 week-3 months post stroke some voluntary movement in the paretic lower limb	**Intervention 1**: conventional therapy + additional conventional therapy **Intervention 2**: conventional therapy + functional strength training **Control**: Conventional therapy alone 1 hr/d, 4d/wk for 6 weeks	Knee strength Gait velocity	Start: Jan 2004 End: Dec 2006
Stroke rehabilitation outcomes with supported treadmill ambulation training *Protas NCT00037895*	N=48 Age ≥18 yrs	**Intervention**: Supported treatmill ambulation training + usual care **Control**: Usual care	FIM, oxygen consumption, Brain motor control assessment	Start: Jan 2001 End: Dec 2003
Effect of Cardiovascular Fitness on Motor Learning and Executive Function in Individuals After Stroke *Quaney NCT00228306*	N=40 Age 18- 85 Years 6-72 months post stroke	**Intervention**: Aerobic training 3d/wk for 8 weeks **Control**: usual daily activities.	Primary outcome Motor learning behavioral measures; Executive function behavioral measures.	Start: Sep 2005 End: Dec 2009
REHAB: Reshaping Exercise Habits and Beliefs *NCT00431821*	N=90 Age 40-85 years <90 days post stroke Ambulatory with hemiparetic gait disorder	**Intervention**: Home-based exercise prescriptions with weekly motivational telephone calls. **Control**: Stroke education program with matched attention phone calls	Ambulatory Activity Profile	Start: Oct 2006 End: Jun 2010
SIRROWS: Stroke Inpatient	N=500	**Intervention**: Daily reinforcement of walking	Gait speed	Start: May 2007

Rehabilitation Reinforcement of Walking Speed *NCT00428480*	Age ≥ 35 years Ambulatory; able to take 5 steps with not more than the assistance of one person	speed during a daily 10-meter walk as part of usual care. **Control**: No reinforcement of walking speed during a daily 10-meter walk as part of usual care		End: Apr 2009
Early Aerobic Training Program After Ischemic Stroke *Tanne NCT00248222*	N=unknown Age 18-80 Years	**Intervention**: Immediate aerobic training program **Control**: Low intensity stretching and coordination exercises (followed by a supervised aerobic training program) 6 weeks	6 Minute Walk Test Modified Bruce Exercise Test Activity by Ankle accelerometer	Start: Oct 2005 End: UN

14.17. Included studies - 2004 review and update

The systematic reviews of physical fitness training after stroke contained 12 included studies in the initial review performed in 2003 (Chapter 9) and an additional 12 (total 24 studies) when updated in 2007 (Chapter 11). All studies below are collated alphabetically in the following pages (the content is equivalent to the '*Table of Included Studies*' used in Cochrane Reviews.

Included Studies in Initial Review (2003) – Chapter 9

1	(Cuveillo-Palmer 1988)
2	(da Cunha et al. 2002)
3	(Dean et al. 2000)
4	(Duncan et al. 1998)
5	(Glasser 1986)
6	(Inaba et al. 1973)
7	(Kim et al. 2001)
8	(Pohl et al. 2002b; comparison 'A')
9	(Pohl et al. 2002b; comparison 'B')
10	(Potempa et al. 1995)
11	(Richards et al. 1993)
12	(Teixeira-Salmela et al. 1999)

Additional Studies in Updated Review (2007) – Chapter 11

13	(Bateman et al. 2001)
14	(Duncan et al. 2003)
15	(Eich et al. 2004a)
16	(James 2002)
17	(Katz-Leurer et al. 2003a)
18	(Mead et al. 2007b)
19	(Ouellette et al. 2004)
20	(Pohl et al. 2007)
21	(Richards et al. 2004)
22	(Salbach et al. 2004)
23	(Winstein et al. 2004)
24	(Yang et al. 2006)

Bateman et al. 2001

METHODS

Design;	Training + usual care vs. non-exercise intervention + usual care 12-wk follow-up
Randomization;	Mechanism, computer; Method, blocks size n=10
Allocation concealment;	sealed envelopes
Blinding;	Investigator blinded, participants encouraged to maintain blinding. Efficacy unknown
Intention to treat;	Yes; however participants were excluded after recruitment and baseline assessments due to discharge
Losses to follow-up;	Intervention (n=12); n=4 before and n=8 after the 12 week follow-up. Control (n=12); n=2 before and n=10 after the 12 week follow-up. Reasons unclear but included early discharge.

PARTICIPANTS

Randomised;	n=84
Intervention;	n=40; m/f 20/20; Age 47.0 ± 13.1 yrs; 144 ± 84 d post-stroke
Control;	n=44; m/f 29/14; Age 50.3 ± 10.1 yrs; 184 ± 127 d post-stroke
Inclusion Criteria;	i) single stroke ii) could comply with planned interventions, iii) could sit on a cycle ergometer
Exclusion Criteria;	i) likely to be inpatient for < 3 mths ii) impairments severe enough to limit training compliance and participation, iii) cardiac disease, iv) co-morbidities contraindicated for exercise.

INTERVENTIONS

Intervention;	Cardiorespiratory training; cycle ergometry at 60-80% of age-related heart rate maximum for up to 30 min/d, 3 d/wk for 12 wk
Control;	Relaxation; programme individualised. Included i) breathing exercises, ii) progressive muscle relaxation, iii) autogenic exercises and iv) visualisation techniques.
Setting:	Multi-centre, four rehabilitation units

OUTCOME MEASURES

Included Outcomes	FIM Instrument, Barthel Index (0-20 scale), Nottingham EADL, Rivermead Mobility Index, Hospital Anxiety and Depression Scale, Berg Balance scale, gait maximum speed, maximum cycling workload (Log_e transformed)
Other Outcomes	Fatigue questionnaire, BMI,

NOTES

Mixed brain injury data provided by author, stroke only data retained and re-analysed.
A lot of missing data items makes analysis of this data difficult.

Cuveillo-Palmer 1988

METHODS

Design;	Training + %usual care vs. usual care; No follow-up
Randomization;	Unknown
Allocation concealment;	Unknown
Blinding;	Unknown
Intention to treat;	No
Losses to follow-up;	n=0

PARTICIPANTS

Randomized;	n=20
Intervention;	n=10; m/f 6/4; Age 69.5 ± 14.1 yrs; 20.7 ± 13.2 d post-stroke
Control;	n=10; m/f 7/3; Age 71.8 ± 12.0 yrs; 12.0 ± 16.8 d post-stroke
Inclusion Criteria;	Unknown
Exclusion Criteria;	Unknown

INTERVENTIONS

Intervention;	Cardiorespiratory training. Isokinetic ergometer allowing resisted reciprocal leg movements (Kinetron II); commencing at 2 x 7min/d for 5 d/wk, and 1 x 7min/d for 1 d/wk (total 6 d/wk) for 3 wks. Progressing to 10min per session in wk 2 and 12min in wk 3. Exercise intensity maintained at a heart rate of <20 beats/min above resting,
Control;	Usual care: 2 x 45min/d for 5 d/wk, and 1 x 45min/d for 1 d/wk (total 6 d/wk) for 3 wks. Gait training, mat exercises and transfer training achieved via strengthening exercises, post-neuromuscular facilitation (PNF), FES, Brunnstum, Rood and neurodevelopment techniques.
Setting:	Rehabilitation centre

OUTCOME MEASURES

Included Outcomes	FIM Instrument (old version); Gait speed preferred (7 sec)
Other Outcomes	Stance symmetry; Contact time (sec); Stride cadence steps/min and other biomechanical gait parameters

NOTES

da Cunha et al. 2002

METHODS

Design;	Training + %usual care vs. usual care; No follow-up
Randomization;	Mechanism; random number table
Allocation concealment;	Unknown
Blinding;	Unknown
Intention to treat;	No
Losses to follow-up;	n=0

PARTICIPANTS

SETTING; Rehabilitation centre	
Randomized;	n=15
Intervention;	n=7; m/f 6/1; Age 57.8 ± 5.5 yrs; 15.7 ± 7.7 d post-stroke
Control;	n=8; m/f 7/1; Age 58.9 ± 12.9 yrs; 19.0 ± 12.7 d post-stroke
Inclusion Criteria;	i) recent stroke (onset <6wk), ii) significant gait deficit (<36m/min; FAC score of 0,1 or 2), iii) sufficient cognition to participate in training (MMSE>=21), iv) able to stand and take 1 or more steps without assistance
Exclusion Criteria;	i) co-morbidity or disability other than hemiparesis, ii) recent MI, iii) any uncontrolled health condition, iv) joint disease or rheumatoid arthritis, v) obesity (>110kg), vi) cognitive impairment (mini-mental state exam <21).

INTERVENTIONS

Intervention;	Cardiorespiratory training. Treadmill walking with body weight support; 20min/d, 6 d/wk for 2-3 wks (until discharge). Intensity unknown, but rapid progression imposed by increasing speed and reducing body weight support. The 20min training replaced the 20min gait training component of the control.
Control;	Usual care. 3hr/d for 6d/wk for 2-3 wks until discharge. Included kinesiotherapy (1hr/d), occupational therapy (1hr/d) and physical therapy (1hr/d). The physical therapist included 20min of gait training comprising stepping, standing, turning etc. but not continuous walking.
Setting:	Rehabilitation centre

OUTCOME MEASURES

Included Outcomes	Cycle performance work rate (Watts); VO_2 max ; Blood pressure; Functional ambulation categories; functional independence measure (lower limb; FIM-L); gait speed maximal (5m); gait endurance (5 minutes); gait economy
Other Outcomes	Stance symmetry; Contact time (sec); Stride cadence steps/min and other biomechanical gait parameters

NOTES

Secondary publications; (da Cunha Filho et al. 2001)

Dean et al. 2000

METHODS

Design;	Training vs. non-exercise intervention; 2 mth follow-up
Randomization;	Mechanism, drawing cards; Method, pairs matched on walking speed
Allocation concealment;	N/A
Blinding;	Investigator; for all except one outcome measure. Outcome assessor unblinded on observing a group training session.
Intention to treat;	No
Losses to follow-up;	n=4; 2 losses in the intervention group; 1 withdrew before training, 1 unavailable for follow-up. 2 losses in the control group; 1 withdrew before training, 1 withdrew due to illness.

PARTICIPANTS

Randomized;	n=12
Intervention	n=6; 3 Male; Age 68.8 ± 4.7 yrs; 1.3 ± 0.9 yrs post-stroke.
Control	n=6; 4 Male; Age 64.8 ± 3.3 yrs; 2.1 ± 0.5 yrs post-stroke.
Inclusion Criteria;	i) First stroke resulting in hemiplegia, ii) at least 3 mths post-stroke, iii) discharged from all usual rehabilitation, iv) available to attend all training sessions, v) able to walk 10m with or without walking aids
Exclusion Criteria;	i) no medical condition which would prevent fitness training.

INTERVENTIONS

Intervention;	Mixed training. Performed in a group for 60min/d, 3d/wk for 4wks. Task-related lower-limb circuit training comprising i) cardiorespiratory training (treadmill and graded walking), ii) strength training (stepping, raising & reaching). Training intensity not quantified, but subjects observed as being 'tired and sweaty' post-exercise.
Control;	Upper limb functional exercises, considered 'sham' lower limb training. Performed in a group for 60min/d, 3d/wk for 4wks.
Setting:	Rehabilitation centre

OUTCOME MEASURES

Included Outcomes	Gait endurance (6-MWT; outcome assessor not blinded), gait preferred speed, 3m timed up-and-go, step test
Other Outcomes	Peak vertical ground reaction force on sit to stand, Grip strength (upper extremity), Biomechanical analysis of gait, bi- and uni-manual Purdue Pegboard

NOTES

Secondary publications; (Richards et al. 2000)

Duncan et al. 1998

METHODS

Design;	Training vs. usual care (outpatient); No follow-up
Randomization;	Mechanism, unknown; Method, blocks of 10
Allocation concealment;	Third party involvement
Blinding;	Unclear
Intention to treat;	Yes
Losses to follow-up;	n=0

PARTICIPANTS

Randomized;	n=20
Intervention;	n=10; m/f unknown; Age 67.3 ± 9.6 yrs; 66 d post-stroke
Control;	n=10; m/f unknown; Age 67.8 ± 7.2 yrs; 56 d post-stroke
Inclusion Criteria;	i) 30-90d post-stroke, ii) minimal/moderately impaired sensorimotor function, iii) available to attend all training sessions, iv) ambulatory with or without supervision or walking aids, v) living at home, within 50 miles
Exclusion Criteria;	i) medical condition which compromised outcome assessment or prevented fitness training, ii) mini-mental state score <18 or receptive aphasia

INTERVENTIONS

Intervention;	Mixed training. Performed ~90 min/d, 3 d/wk for 12 wks (8 wks supervised 1:1 with therapist, 4wks alone). Functional exercises comprising i) assistive/resistive exercise, ii) balance exercises, iii) upper limb functional activities and iv) walking or cycling. Apart from some resisted exercise the training intensity was not quantified.
Control;	Usual outpatient care. Physical and occupational therapy as advised by the patient's physician. Averaging 44 min/d, 3.25 d/wk for 12 wks. Therapeutic interventions were during home or outpatient visits and comprised balance training (60%), strength training (40%), bimanual activities (50%) and facilitative exercise (30%). Cardiorespiratory training was not provided (0%).
Setting:	Home-based; therapist-supervised for first 8 wks

OUTCOME MEASURES

Included Outcomes	Barthel Index; Lawton Instrumental ADL; Gait endurance (6-MWT); Berg Balance Scale; Fugl Meyer (upper and lower extremity)
Other Outcomes	Gait preferred speed (data lacks variance measures), SF-36 (non-standard pooling of data), Jebsen Hand Test

NOTES

Duncan et al. 2003

METHODS	
Design;	Training vs. usual care (outpatient); 6 mth follow-up
Randomization;	Mechanism, unknown; Method, blocks of 6
Allocation concealment;	Sealed envelopes
Blinding;	Investigator; participants asked to maintain blinding
Intention to treat;	Yes
Losses to follow-up;	Intervention (n=10); n=6 before (n=1 renal insufficiency, n=1 subclavian steal syndrome, n=1 chose withdrawal, n=3 recurrent stroke) n=4 after the 3-mths follow-up (n=1 died, n=1 hospital, n=2 recurrent stroke) Control (n=11); n=2 before (n=1 withdrew, n=1 non-return) n=9 after 3-mths follow-up (n=2 died, n=2 hospital, n=5 withdrew)

PARTICIPANTS	
Randomized;	n=100
Intervention;	n=50; m/f 23/27; age 68.5 ± 9.0 yrs; 77.5 ± 28.7 d post-stroke
Control;	n=50; m/f 27/23; age 70.2 ± 11.4 yrs; 73.5 ± 27.1 d post-stroke
Inclusion Criteria;	i) 30-150d post-stroke, ii) independent ambulation for 25ft, iii) Fugl-Meyer scores 27-90, iv) Orpington Prognostic Scale 2.0-5.2, v) Folstein Mini-Mental State score ≥16
Exclusion Criteria;	i) serious cardiac condition, ii) oxygen dependence, iii) severe weight bearing pain, iv) serious organ system disease, v) life expectancy <1 year

INTERVENTIONS	
Intervention;	Mixed training. Performed ~90 min/d, 3 d/wk for 12-14 wks (36 sessions). Training included i) range of motion and flexibility, ii) strength training, iii) balance, iv) functional upper extremity practice, v) endurance training via interval training on cycle ergometer. All elements progressive but intensity not quantified.
Control;	Those who required it received usual outpatient care including PT and OT. All controls received 30-min visit/2weeks including provision of health promotion information.
Setting:	Home-based; therapist-supervised for first 8 wks

OUTCOME MEASURES	
Included Outcomes	FIM cognitive and motor subscales, SF-36 subscales, ankle dorsiflexion and knee extension isometric strength (Nm), isometric grip strength (N), Fugl Meyer scores, Berg Balance Scale, Functional reach, $\dot{V}O_2$ peak, gait speed preferred (10-m), 6-MWT, Community ambulation (>0.8 m/sec)
Other Outcomes	Stroke impact scale, cycle duration

NOTES

Some outcomes reported as change from baseline scores (Duncan et al. 2003c).
Others reported as means at end of 6-mth follow-up (Studenski et al. 2005)

Eich et al. 2004a

METHODS	
Design;	Training + usual care vs. usual care; 3 mth follow-up
Randomization;	Mechanism, picking envelopes; Method, restricted
Allocation concealment;	Sealed envelopes
Blinding;	Investigator; efficacy was compromised
Intention to treat;	Yes
Losses to follow-up;	Intervention n=1 (refusal) after the 6-wks follow-up

PARTICIPANTS	
Randomized;	n=50
Intervention;	n=25; male n=17; age 62.4 ± 4.8 yrs; 43 ± 15 d post-stroke
Control;	n=25; male n=16; age 64 ± 9 yrs; 44 ± 18 d post-stroke
Inclusion Criteria;	i) aged 50-75 yrs, ii) first stroke, iii) time since stroke <6wks, iv) walk ≥12-m with/without assistance, v) Barthel score 50-80, vi) participating in 12-wk comprehensive rehabilitation programme, vii) stable cardiovascular responses, viii) no non-stroke walking impairments, ix) able to understand purpose and content of study
Exclusion Criteria;	-

INTERVENTIONS	
Intervention;	Cardiorespiratory training. Performed 30 min/d, 5 d/wk for 6 wks. Progressive treadmill training with either no or minimal support of bodyweight. Intensity was 60% of heart rate reserve.
Control;	Both groups received usual care comprising individual physiotherapy based on Bobath concept plus occupational and speech therapy, and neuropsychology as required.
Setting:	Rehabilitation unit - inpatient care

OUTCOME MEASURES	
Included Outcomes	gait speed maximal (10-m), gait endurance (6-MWT)
Other Outcomes	Rivermead motor assessment (non-normal data) Walking quality scale (non-normal data)

NOTES

Secondary publications; (Eich et al. 2004b;Hesse et al. 2005)

Glasser 1986

METHODS

Design;	Training + % usual care vs. usual care; No follow-up
Randomization;	Unknown
Allocation concealment;	Unknown
Blinding;	Unknown
Intention to treat;	No
Losses to follow-up;	n=0

PARTICIPANTS

Randomized;	n=20
Intervention;	n=10; m/f 4/6
Control;	n=10; m/f 6/4
	All participants age 40 to 75 yrs and were 3-6 mths post-stroke. All participants exhibited hemiparesis with upper and lower extremity motor dysfunction; some showed sensory deficits and mild expressive or receptive aphasia.
Inclusion Criteria;	Unknown
Exclusion Criteria;	Unknown

INTERVENTIONS

Intervention;	Cardiorespiratory training. Isokinetic ergometer (Kinetron) training twice a day 5 d/wk for 10 wks. The intensity was maintained at 50 - 100psi and duration of each session progressed from 10 to 30 min over the first 5 weeks.
Control;	Therapeutic exercise and gait training 1 hr/session; 2 sessions/d, 5 d/wk for 5wks.
Setting:	Physical therapy department

OUTCOME MEASURES

Included Outcomes	Gait speed maximal (6-m)
Other Outcomes	Functional Ambulation Profile Score,

NOTES

Inaba et al. 1973

METHODS	
Design;	Training + usual care vs. usual care; 2 mth follow-up
Randomization;	Unknown
Allocation concealment;	Unknown
Blinding;	Outcome assessor - unclear
Intention to treat;	No
Losses to follow-up;	Unclear; 101/177 patients lost to follow up across the control and both intervention groups. The 54 patients completed the control vs. strength training comparison; estimated dropouts ~n=60. One reason given for dropouts was discharge before end of the study.

PARTICIPANTS	
Randomized;	n=54
Intervention;	n=28; m/f 11/17; Age 55.6 yrs; <3mths post-stroke
Control;	n=26; m/f 15/11; Age 56.9 yrs; <3mths post-stroke All participants had hemiparesis.
Inclusion Criteria;	i) Hemiparesis arising from cerebrovasular accident secondary to thrombosis, embolus or hemorrhage; ii) Able to follow verbal or demonstrated directions; iii) Extend the involved lower limb against a load of 1.1kg; iii) independent ambulation.
Exclusion Criteria;	i) etiology of aneurysm or trauma

INTERVENTIONS	
Intervention;	Strength Training. Progressive resistive exercise; once per day for 4-8 wks; extension of the affected lower limb from 90º to full knee extension whilst in the supine position on an Elgin table (machine weights). 5 repetitions at 50% maximum weight, and 10 at maximum.
Control;	Usual care; Conventional functional training, including stretching. 4-8 weeks until discharge.
Setting:	Rehabilitation centre

OUTCOME MEASURES	
Included Outcomes	-
Other Outcomes	Leg strength (10 repetition maximum) lacked variance measures Number able to perform 8 ADL

NOTES

James 2002

METHODS

Design;	Training vs. no intervention; No follow-up
Randomization;	Mechanism, computer; Method blocks of 4
Allocation concealment;	Sealed envelopes
Blinding;	Investigator
Intention to treat;	Yes
Losses to follow-up;	Control group 2 dropped out (neurological problems)

PARTICIPANTS

Randomized;	n=20
Intervention;	n=10; m/f 4/6; Age 76.1 ± 12.33 yrs; 1826 ± ? d post-stroke
Control;	n=10; m/f 2/8; Age 80.8 ± 9.0 yrs; 1845 ± ? d post-stroke
Inclusion Criteria;	*i*) stroke with hemiplegia, ii) ability to give informed consent
Exclusion Criteria;	i) no complicating medical history (cardiac, pulmonary or neurological), ii) no severe deficits in communication, memory or understanding, iii) no painful orthopaedic conditions which could limit participation

INTERVENTIONS

Intervention;	Mixed training. Performed 90-120 min/d, 3 d/wk for 4 wks. Warm-up followed by i) half squats, ii) Chair squats, iii) small knee bends, iv) Standing on affected leg, v) single-leg half squat on affected leg, vi) standing on unaffected leg and bending affected hip and knee, vii) stair stepping, viii) stepping on spot, ix) walking indoors and outdoors, x) stepping forwards, backwards and sideways, xi) opening and closing doors, xii) walking and placing/lifting objects, xiii) placing objects on shelves. Finished with a cool down. Progression achieved increasing pulse rate from 50% (first 2 weeks) to 60% (last 2 weeks) of HRR, increasing total distance walked, and increasing step height and repetition number.
Control;	No intervention
Setting:	Patients homes

OUTCOME MEASURES

Included Outcomes	Gait speed preferred (5-m with mixed surfaces and a dead turn at 2.5m)
Other Outcomes	Functional walking ability questionnaire, Upright motor control test, SF-36 - older version

NOTES

Unpublished thesis

Katz-Leurer et al. 2003a

METHODS

Design;	Training + usual care vs. usual care; Follow-up 6-mth post stroke
Randomization;	Mechanism, unknown; Method blocks based on side of lesion
Allocation concealment;	Sealed envelopes
Blinding;	Investigator; efficacy unknown
Intention to treat;	Unknown
Losses to follow-up;	Intervention no losses at end of intervention, n=5 losses at 6-month follow-up (n=4 not located, n=1 died). Control n=2 discontinued intervention (n=1 acute MI, n=1 DVT), n=6 losses to follow-up (n=3 not located, n=1 died, n=2 recurrent stroke)

PARTICIPANTS

Randomized;	n=90
Intervention;	n=46; m/f 26/20; Age 62 ± 11 yrs; time since stroke unknown
Control;	n=46; m/f 23/23; Age 65 ± 11 yrs; time since stroke unknown
Inclusion Criteria;	i) age >50yrs, ii) >6mths after first ever stroke, iii) walk 40m with +/- rest, +/- assistive device, iv) => stage 3 of Chedoke-McMaster Stroke Assessment, v) tolerate 45min of exercise with rest intervals, vi) non-participation in other therapy programmes.
Exclusion Criteria;	i) Comprehensive aphasia, ii) not medically stable, ii) musculoskeletal problems not associated with stroke.

INTERVENTIONS

Intervention;	Cardiorespiratory training. Cycle ergometer; 8 week programme. a) 20 min/d 5 d/wk for 2wks of intermittent (10x1-min) exercise progressing to 20 min continuous exercise by end of week 2. b) 30 min/d 3 d/wk for 6wks not exceeding 60% HRR. ACSM cardiorespiratory training guidelines met.
Control;	Usual PT, OT, ST and group activity/exercise
Setting:	Rehabilitation centre

OUTCOME MEASURES

Included Outcomes	Functional independence measure, blood pressure, maximum cycle workload (Watts), comfortable walking speed (10-m) gait endurance, distance until fatigue, Frenchay activity index Stairs climbed
Other Outcomes	Scandinavian Stroke Scale

NOTES

Secondary publications; (Katz-Leurer et al. 2003d)

Kim et al. 2001

METHODS	
Design;	Training vs. non-exercise intervention; No follow-up
Randomization;	Mechanism, unknown; Method, stratified based on gender (M/F), age (50-59 or 60+ yrs) and time since onset of stroke (6 months - 2 yrs/ 2+ yrs)
Allocation concealment;	Unknown
Blinding;	Investigator; Participants blinded to purpose of interventions
Intention to treat;	Unknown
Losses to follow-up;	n=0

PARTICIPANTS	
Randomized;	n=20
Intervention;	n=10; m/f 7/3; Age 60.4 ± 9.5 yrs; 4.9 ± 3.3 yr post-stroke
Control;	n=10; m/f 7/3; Age 61.9 ± 7.5 yrs; 3.2 ± 1.2 yr post-stroke All participants had hemiparesis.
Inclusion Criteria;	i) age >50yrs, ii) >6mths after first ever stroke, iii) walk 40m with +/- rest, +/- assistive device, iv) ≥ stage 3 of Chedoke-McMaster Stroke Assessment, v) tolerate 45min of exercise with rest intervals, vi) non-participation in other therapy programmes.
Exclusion Criteria;	i) Comprehensive aphasia, ii) not medically stable, ii) musculoskeletal problems not associated with stroke.

INTERVENTIONS	
Intervention;	Strength training. Isokinetic Dynamometer (Kin-Com); 45 min/d, 3 d/wk for 6wks. After a warm up this comprised 30min of 3 x 10 resisted repetitions of maximal effort concentric hip flexion/extension, knee flexion/extension and ankle dorsiflexion/plantarflexion of the affected lower limb. Progression in the resistance was achieved by increasing the preload on the Kin-Com device (Eng et al. 2002). ACSM guidelines met.
Control;	Exactly the same as intervention except the resisted contractions replaced with passive range of motion movements.
Setting:	Rehabilitation centre

OUTCOME MEASURES	
Included Outcomes	gait preferred speed (m/min over 8m), gait maximum speed (m/min), stair climbing speed (stairs/sec), composite strength score for the affected (trained) lower limb
Other Outcomes	stair walking performance (4 x 18cm steps) self selected and maximal, SF-36 Physical and Mental Health Component Summary Scores, Composite strength score for the affected (trained) lower limb

NOTES

Mead et al. 2007b

METHODS	
Design;	Training vs. non-exercise intervention; 4 mth follow-up
Randomization;	Mechanism, internet application; Minimization dichotomised on i) gender, ii) FIM score (120), iii) age (70 yrs)
Allocation concealment;	N/A sequence generation and allocation occurred simultaneously
Blinding;	Investigator; participants encouraged to maintain blinding
Intention to treat;	Yes
Losses to follow-up;	Intervention n=0; Control n=4; n=1 withdrew before intervention; n=3 after end of intervention follow-up (n=1 stroke related illness, n=1 fall, n=1 recurrent stroke)

PARTICIPANTS	
Randomized;	n=66
Intervention;	n=32; m/f 18/14; Age 72.0 ± 10.4 yrs; median 171 (IQR 55 to 287) d post-stroke
Control;	n=34; m/f 18/16; Age 71.7 ± 9.6 yrs; median 147.5 (IQR 78.8 to 235.5) d post-stroke
Inclusion Criteria;	i) independently ambulatory ii) living within central or south Edinburgh
Exclusion Criteria;	i) dysphasia or confusion severe enough to prevent informed consent or impair safety in exercise classes, ii) medical contraindications to exercise training.

INTERVENTIONS	
Intervention;	Mixed training. Group circuit training performed 40-75 min/d, 3 d/wk for 12-14 wks (36 sessions). After a warm up the training comprised two components: i) a cardiorespiratory circuit (cycle ergometry, raising and lowering an exercise ball, shuttle walking, standing chest press, and stair climbing and descending). ii) Resistance training circuit (upper back exercise and tricep extension using Thera-Band, lifting a weighted pole, a sit-to-stand exercise). Progression in duration, repetition number, speed, mass of objects and resistance of Thera-Band whilst maintaining an RPE (6-20 scale) of 13 to 60.
Control;	Non-exercise intervention; Seated relaxation involving deep breathing and progressive muscular relaxation; no muscle contractions were involved.
Setting:	Rehabilitation hospital

OUTCOME MEASURES	
Included Outcomes	FIM Instrument , Nottingham Extended ADL, Rivermead Mobility Index, functional reach, timed up-and-go, sit-to-stand time, SF-36 ver 2, Hospital Anxiety and Depression Score, Gait preferred speed, Gait economy ($\dot{V}O_2$ ml·kg^{-1}·m^{-1}), lower limb extensor explosive power (W·kg^{-1})
Other Outcomes	Elderly Mobility Scale (ceiling effect), Functional ambulation category (ceiling effect)

NOTES

Ouellette et al. 2004

METHODS	
Design;	Training vs. non-exercise intervention; No follow-up
Randomization;	Unknown
Allocation concealment;	Unknown
Blinding;	Investigator
Intention to treat;	Yes
Losses to follow-up;	Intervention; n=1 withdrawn (cardiac problem), n=1 no follow-up (hernia). Control n=2 withdrew during intervention, n=1 no follow-up (abnormal ECG).

PARTICIPANTS	
Randomized;	n=42
Intervention;	n=21; m/f unknown; Age 65.8 ± 11.5 yrs; 968 ± 460 d post-stroke
Control;	n=21; m/f unknown; Age 66.1 ± 9.62 yrs; 779 ± 558 d post-stroke
Inclusion Criteria;	i) age => 50 yrs, ii) 6mth to 6 yrs after single unilateral mild/moderate stroke with residual lower extremity hemiparesis, iii) community dwelling, iv) independently ambulatory +/- walking aids, v) report of ≥2 limitations on the physical function subscale of the SF36, vi) ability to travel to the exercise laboratory, and vii) willing to be randomized.
Exclusion Criteria;	-

INTERVENTIONS	
Intervention;	Strength training. Progressive resistive training of both lower limbs performed 3 d/wk for 12 wks comprising 3 sets of 8-10 repetitions at 70% of 1-RM. Exercises were i) seated bilateral leg press and ii) unilateral knee extension, both using pneumatic resistance, and unilateral ankle, iii) dorsiflexion and iv) plantarflexion, both using weights. Progression achieved via weekly assessment of 1-RM. Warm-up for each exercise was 4 repetitions of 25% 1-RM.
Control;	Non-exercise: Bilateral range of motion and upper body flexibility exercises 3 d/wk for 12 wks
Setting:	Exercise laboratory

OUTCOME MEASURES	
Included Outcomes	Muscle strength (bilateral lower limb extension Force), Muscle strength (unilateral knee extension, ankle dorsiflexion and ankle plantarflexion); Gait endurance (6-MWT), preferred speed (10m) and maximal speed (10m); Chair rise time (5 repetitions); Stair climb time (10 steps); Late life function and disability instrument scale, SF36 Physical function subscale
Other Outcomes	Muscle power - bilateral lower limb extension and unilateral knee extension, Geriatric depression scale (data not reported), Sickness impact profile Ewarts self efficacy scale

NOTES

Pohl et al. 2002b 'A'

METHODS

Design;	Training Training + % usual care vs. usual care; No follow-up
Randomization;	Mechanism, unknown; Method, equal block based on gait speed
Allocation concealment;	Unknown
Blinding;	Investigator; efficacy unknown
Intention to treat;	No
Losses to follow-up;	None

PARTICIPANTS

Randomized;	n=40
Intervention;	n=20; m/f 14/16; Age 57.1 ± 13.9 yrs; 118 ± 144 d post-stroke
Control;	n=20; m/f 13/17; Age 61.6 ± 10.6 yrs; 113 ± 130 d post-stroke
Inclusion Criteria;	i) L or R hemiparesis for >4 wks, ii) impaired gait, iii) no or slight abnormal muscle tone (Ashworth Score 0 and 1), iv) walk without assistance (FAC=3), v) 10-metre walk time >5sec and < 60sec, vi) class B exercise risk (ACSM 1998b), vii) absence of known heart disease, viii) no evidence of heart failure, ischaemia or angina at rest or exercise, ix) appropriate rise in systolic blood pressure and absence of ventricular tachycardia during exercise.
Exclusion Criteria;	i) Previous treadmill training, ii) class C or D exercise risk (ACSM 1998b), ii) cognitive deficits (MMSE<26 of 30), iii) movement disorders, orthopaedic or gait influencing-diseases.

INTERVENTIONS

Intervention;	i) Cardiorespiratory training. Treadmill walking (limited progression treadmill training); 30 min/d, 3 d/wk for 4wks. Minimal (≤10%) body weight support for first 3 sessions. Speed progressed ≤5% of maximum per week (20% over 4wks). Gradient maintained at 0%. ii) Conventional Physiotherapy 45 min/d, 2 d/wk for 4 wks (included some gait training). Total 12 hrs of treatment.
Control;	i) Conventional gait training 30 min/d, 3 d/wk for 4wks. Comprised PNF and Bobath techniques ii) Conventional Physiotherapy 45 min/d, 2 d/wk for 4 wks (included some gait training). Total 15 hrs of treatment.
Setting:	Rehabilitation centre

OUTCOME MEASURES

Included Outcomes	Gait maximum speed; Functional ambulation categories
Other Outcomes	Stride cadence (steps/min); Stride length (m)

NOTES

Pohl et al. 2002b 'B'

METHODS	
Design;	Training Training + % usual care vs. usual care; No follow-up
Randomization;	Mechanism, unknown; Method, equal block based on gait speed
Allocation concealment;	Unknown
Blinding;	Investigator; efficacy unknown
Intention to treat;	No
Losses to follow-up;	None

PARTICIPANTS	
Randomized;	n=40
Intervention;	n=20; m/f 16/4; Age 58.2 ± 10.5 yrs; 113 ± 115 d post-stroke
Control;	n=20; m/f 13/17; Age 61.6 ± 10.6 yrs; 113 ± 130 d post-stroke
Inclusion Criteria;	i) L or R hemiparesis for >4 wks, ii) impaired gait, iii) no or slight abnormal muscle tone (Ashworth Score 0 and 1), iv) walk without assistance (FAC=3), v) 10-metre walk time >5sec and < 60sec, vi) class B exercise risk (ACSM 1998b), vii) absence of known heart disease, viii) no evidence of heart failure, ischaemia or angina at rest or exercise, ix) appropriate rise in systolic blood pressure and absence of ventricular tachycardia during exercise.
Exclusion Criteria;	i) Previous treadmill training, ii) class C or D exercise risk (ACSM 1998b), ii) cognitive deficits (MMSE<26 of 30), iii) movement disorders, orthopaedic or gait influencing-diseases.

INTERVENTIONS	
Intervention;	i) Cardiorespiratory training. Treadmill walking (structured speed dependent treadmill training); 30 min/d, 3 d/wk for 4wks. Minimal (≤10%) body weight support for first 3 sessions. Training sessions comprised repeated bouts increasing from 50% maximum up to maximum speed with rests between. Speed progressed maximally at each training visit. Gradient maintained at 0%. ii) Conventional Physiotherapy 45 min/d, 2 d/wk for 4 wks (usual care, included some gait training).Total 12 hrs of treatment.
Control;	i) Conventional gait training 30 min/d, 3 d/wk for 4wks. Comprised PNF and Bobath techniques ii) Conventional Physiotherapy 45 min/d, 2 d/wk for 4 wks (included some gait training). Total 15 hrs of treatment.
Setting:	Rehabilitation centre

OUTCOME MEASURES	
Included Outcomes	Gait maximum speed; Functional ambulation categories
Other Outcomes	Stride cadence (steps/min); Stride length (m)

NOTES

Pohl et al. 2007

METHODS	
Design;	Training + % usual care vs. usual care; Follow-up at 6 mths
Randomization;	Mechanism, picking envelopes; Method, restricted randomization
Allocation concealment;	Sealed envelopes
Blinding;	Investigator; (only for Barthel Index and Functional Ambulation Categories); efficacy unknown
Intention to treat;	Yes
Losses to follow-up;	Intervention n=13 losses to follow-up; n=5 at end of intervention (1 cardiovascular unstable, 1 tumour, 1 intra-cranial pressure, 2 refusals) rising to n=13 at end of follow-up (1 died, 6 moved, 6 refusals). Control n=13 losses to follow-up; n=6 at end of intervention (1 died (MI), 1 MI, 4 refusals) rising to n=13 at end of follow-up (1 died (stroke), 1 moved, 11 refusals)

PARTICIPANTS	
Randomized;	n=155
Intervention;	n=77; m/f 50/27; Age 62.3 ± 12.0 yrs; 29.4 ± 12.6 d post-stroke
Control;	n=78; m/f 54/24; Age 64.0 ± 11.6 yrs; 31.5 ± 13.3 d post-stroke
Inclusion Criteria;	i) first stroke ii) age 18-79 yrs, iii) <60 d since stroke, iv) sit unsupported, v) non-ambulatory dependent on assistance for ambulation, vi) understand the meaning of the study and follow instructions
Exclusion Criteria;	-

INTERVENTIONS	
Intervention;	Cardiorespiratory training; body weight supported electromechanical gait trainer (Reha-Stim). Performed 20 min/d, 5 d/wk for 4 wks; 10-20% bodyweight support progressive unloading over programme, and increase in number of steps taken. Plus individual physiotherapy based on Bobath concept; performed 25 min/d, 5 d/wk for 4 wks
Control;	Individual physiotherapy based on Bobath concept; performed 45 min/d, 5 d/wk for 4 wks
Setting:	Rehabilitation hospital

OUTCOME MEASURES	
Included Outcomes	Functional ambulation categories, Barthel index, Gait maximal speed (10-m), Gait endurance (6-MWT), Rivermead Mobility Index, Motricity Index
Other Outcomes	-

NOTES

DEGAS Study. Competing interest; the patent for the gait trainer device (Reha-Stim) is owned by the spouse of one of the authors (Hesse, S).

Potempa et al. 1995

METHODS	
Design;	Training vs. non-exercise intervention; No follow-up
Randomization;	Unknown
Allocation concealment;	Unknown
Blinding;	Unknown
Intention to treat;	No
Losses to follow-up;	n=0

PARTICIPANTS	
Randomized;	n=42
Intervention;	n=19; m/f 8/11
Control;	n=23; m/f 15/8; All participants aged 43 to 70 yrs and were 216 ± 43 d post-stroke. All participants had upper and lower limb hemiparesis
Inclusion Criteria;	i) medically stable, ii) at least 6 mths post-stroke, iii) completed formal rehabilitation
Exclusion Criteria;	i) patients with brain stem lesions, ii) any clinical evidence that would preclude maximal exercise testing

INTERVENTIONS	
Intervention;	Cardiorespiratory training. Cycle ergometer training for 30 min/d, 3 d/wk for 10 wks. Intensity; 30-50% of maximal effort, increasing to maximum sustainable over first 4 wks
Control;	Non-exercise intervention. Passive range of motion exercises for 30 min/d, 3 d/w for 10 wks.
Setting:	Unknown

OUTCOME MEASURES	
Included Outcomes	Fugl Meyer score, blood pressure, $\dot{V}O_2$ max, cycling work rate (Watts)
Other Outcomes	Body mass, heart rate at rest and during maximal exercise, RER and other respiratory variables, exercise duration,

NOTES

Variance reported as SEM and converted to SD

Richards et al. 1993

METHODS

Design;	Training + usual care vs. usual care; No follow-up
Randomization;	Mechanism, unknown; Method, stratified on Barthel Index scores
Allocation concealment;	Unknown
Blinding;	Investigator; efficacy unknown
Intention to treat;	No
Losses to follow-up;	Control group n=3 (1 refusal, 2 unknown)

PARTICIPANTS

Randomized;	n=18
Intervention;	n=10; m/f 5/5; Age 69.6 ± 7.4 yrs; 8.3 ± 1.4 d post-stroke
Control;	n=8; m/f 2/6; Age 67.3 ± 11.2 yrs; 8.8 ± 1.5 d post-stroke
Inclusion Criteria;	i) within 50km of treatment center, ii) men or women aged 40 - 80 yrs, iii) 0 - 7 d after first stroke, iv) middle cerebral artery syndrome identified by CT, v) under care of neurologist involved in study, vi) willing to sign informed consent.
Exclusion Criteria;	i) other major medical conditions that would interfere with functional capacity or interfere with rehabilitation, ii) patients who were independently ambulatory 1 wk after stroke, iii) patients who were unconscious at onset.

INTERVENTIONS

Intervention;	Mixed training. Task-oriented gait training programme (Malouin et al. 1992) which used a tilt table, resisted exercises using a Kinetron, and treadmill walking. Intervention 104 min/d, 5 d/wk for 5 wks. Progression achieved via velocity and resistance (Kinetron) increments.
Control;	Traditional neurophysical techniques. 109 min/d, 5 d/wk for 5 wks.
Setting:	Hospital

OUTCOME MEASURES

Included Outcomes	Fugl-Meyer balance (FM-B), upper (FM-U) and lower (FM-L) extremity scores. Barthel Ambulation scores, Berg Balance, gait velocity.
Other Outcomes	-

NOTES

A second control group of early conventional therapy was not used for comparison since it differed from the institutions usual care; it commenced earlier than usual during hospital care and had substantially longer contact time.
Secondary publications; (Malouin et al. 1993)

Richards et al. 2004

METHODS	
Design;	Training + % usual care vs. usual care; 3 mth follow-up
Randomization;	Mechanism, unknown; Method, variable blocks stratified on time since stroke, disability and age
Allocation concealment;	Unknown
Blinding;	Investigator; efficacy unknown
Intention to treat;	Yes
Losses to follow-up;	Intervention n=8; n=2 discontinued Intervention (n=1 hip fracture, n=1 cardiac problem); n=5 unavailable for follow-up. Control n=8; n=1 withdrew from intervention; n=7 unavailable for follow-up

PARTICIPANTS	
Randomized;	n=63
Intervention;	n=32; m/f 22/10; Age 62.9 ± 12 yrs; 52 ± 22 d post-stroke
Control;	n=31; m/f 21/10; Age 60.7 ± 12 yrs; 52.8 ± 18 d post-stroke
Inclusion Criteria;	i) first or second stroke, ii) men or women aged 30 - 89 yrs, iii) impaired walking, iv) follow verbal instructions, v) Barthel ambulation score ≥ 10, vi) gait speed of 10 - 60 cm/sec
Exclusion Criteria;	i) cerebral and subarachnoid haemorrhage, ii) major medical problems (cancer, heart conditions, diabetes), iii) receptive or expressive aphasia, iv) lower extremity musculoskeletal disorders affecting gait

INTERVENTIONS	
Intervention;	Mixed training. Task-oriented gait training programme (Malouin et al. 1992) which used a limb-load monitor, resisted exercises using a Kinetron, and treadmill walking. Intervention occurred during PT sessions of 60 min/d, 5 d/wk for 8 wks. Progression achieved via velocity and resistance (Kinetron) increments.
Control;	PT sessions of 60 min/d, 5 d/wk for 8 wks not including the task-oriented gait training content above.
Setting:	Two rehabilitation units

OUTCOME MEASURES	
Included Outcomes	Preferred walking speed, Fugl-Meyer leg and arm scores, Timed up-and-go, Barthel Index (ambulation sub-score), Berg Balance Scale
Other Outcomes	Kinematic gait analysis weakened by missing data in 50% participants

NOTES

A second control group of conventional therapy was not used for comparison since i) it was much shorter in duration and ii) commenced later then the training intervention.

Outcome data imputed from graphs in publication.

Salbach et al. 2005

METHODS	
Design;	Training vs. non-exercise intervention; No follow-up
Randomization;	Mechanism, computer; Method, stratified on gait speed
Allocation concealment;	Unknown
Blinding;	Investigator blinded; unblinding during assessment of intervention group 18/42 and control group 16/43
Intention to treat;	Yes
Losses to follow-up;	Intervention n=3 discontinued Intervention (refused to travel, wanted both interventions, groin pain) with n=2 of these lost to follow-up. Control n=4 discontinued control (MI, prostate cancer, fall+fracture, wanted other intervention) with n=3 of these lost to follow-up

PARTICIPANTS	
Randomized;	n=91
Intervention;	n=44; m/f 26/18; Age 71 ± 12 yrs; 239 ± 83 d post-stroke
Control;	n=47; m/f 30/17; Age 73 ± 8 yrs; 217 ± 73 d post-stroke
Inclusion Criteria;	i) first or recurrent stroke, ii) gait deficit from recent stroke, iii) mental competency, iv) independently ambulatory for 10-m +/- aids or supervision, v) ability to comprehend instructions, vi) resident in community, vii) discharged from rehabilitation, viii) recent stroke 1 yr or less
Exclusion Criteria;	i) neurological deficit caused by metastatic disease, ii) gait function (6-MWT) equivalent to healthy norms, iii) discharged to permanent care, iv) comorbidity preventing participation in either intervention.

INTERVENTIONS	
Intervention;	Cardiorespiratory training; task-oriented circuit training. Performed 55 min/d, 3 d/wk for 6 wk. Comprising a warm-up followed by 10 walking-related tasks (step ups, balance beam, kicking ball, stand up and walk, obstacle course, treadmill, walk and carry, speed walk, backward walking, stairs). Progression of speed, load and degree of assistance.
Control;	Functional practice, whilst seated of writing, keyboard use and manipulating cards; some practice encouraged at home.
Setting:	Two centre location; rehabilitation centre or hospital

OUTCOME MEASURES	
Included Outcomes	Gait endurance 6-MWT, gait comfortable speed, gait maximal speed, timed up-and-go, Berg Balance Scale
Other Outcomes	Activity specific balance confidence scale

NOTES

Secondary publications; (Salbach et al. 2004)

Teixeira-Salmela et al. 1999

METHODS	
Design;	Training vs. no intervention; No follow-up. First iteration only of a lag control design. Subjects randomly allocated to immediate or delayed. Subjects allocated delayed intervention initially received no intervention.
Randomization;	Mechanism, unknown; Method, unclear ('balanced blocks')
Allocation concealment;	Unknown
Blinding;	Unknown
Intention to treat;	No
Losses to follow-up;	n=0

PARTICIPANTS	
Randomized;	n=13
Intervention;	n=6; m/f 6/1; Age 65.9 ± 10.2 yrs; 9.15 ± 12.7 yrs post-stroke
Control;	n=7; m/f 1/5; Age 69.4 ± 8.85 yrs; 6.4 ± 6.23 yrs post-stroke. All participants had unilateral stroke resulting in residual weakness and/or abnormal muscle tone.
Inclusion Criteria;	i) at least 9 mths post-stroke, ii), independently ambulatory +/- walking aids and iii) no comprehensive aphasia
Exclusion Criteria;	i) non-stroke related disability

INTERVENTIONS	
Intervention;	Mixed training; Cardiorespiratory and lower extremity strength training. 60-90 min/d, 3 d/wk for 10wks. Cardiorespiratory training; graded walking, plus stepping or cycling progressing from 10 to 20 min/d, and from 50-70% of maximal cycling work rate over first 5 wk. Strength training; seven exercises involving use of body weight and progressive resistive exercise using different masses and elastic bands (Thera-Band). Each performed as 3 x 10 repetitions and progressing from 50-80% of 1 repetition maximum. Warm-up and warm-down 10 - 20min/d.
Control;	No intervention
Setting:	Unclear

OUTCOME MEASURES	
Included Outcomes	Gait preferred speed (22-m), Adjusted Activity Score, Nottingham Health Profile
Other Outcomes	Insufficient data to compare Lower limb muscle strength (peak torque Nm), Muscle tone assessment and Stair climbing.

NOTES

Secondary publications; (Teixeira-Salmela et al. 2001;Teixeira et al. 1998)

Winstein et al. 2004

METHODS	
Design;	Training + usual care vs. usual care; Follow-up 9 mths post-stroke. During AND after usual care.
Randomization;	Mechanism, unknown; Method, stratified on Orpington Prognostic Scale (1.6 to 1.4 and 4.2 to 6.8)
Allocation concealment;	Sealed envelopes
Blinding;	Principal Investigator bit NOT outcome assessor
Intention to treat;	No
Losses to follow-up;	Before end of intervention n=1 (exp; medical complications) n=1 (cont: lost interest); before end of follow-up n=9 (n=4 exp, n=5 cont; moved away or lost contact)

PARTICIPANTS	
Randomized;	n=42
Intervention;	n=21; m/f 12/8; time since stroke 17.3 ± 10.6 days
Control;	n=20; m/f 12/8; time since stroke 15.4 ± 5.5 days age 29-76yrs, most 35-75 yrs
Inclusion Criteria;	i) first stroke, ii) 2-35 d post stroke, iii) FIM score; UC
Exclusion Criteria;	i) peripheral nerve or orthopaedic condition limiting arm movement, ii) function limited by cardiac disease, iii) SAH without infarction, iv) progressive hydrocephalus, v) history of brain injury, vi) severe aphasia, neglect, agitation or depression which could limit participation.

INTERVENTIONS	
Intervention;	Strength training. Upper limb movements resisted by gravity, free weights, Thera-Band and grip devices for fingers. 60 min/d, 5 d/wk for 4 to 6 wks. High intensity for 3 d/wk and low intensity higher velocity for 2 d/wk. Training target 20hr total.
Control;	Standard care delivered by OT. Included muscle facilitation exercises using neuro-developmental approach, electrical stimulation, stretching, ADL and caregiver training. Activities included use of upper limbs.
Setting:	Inpatient rehabilitation hospital and outpatient clinic

OUTCOME MEASURES	
Included Outcomes	FIM mobility and self care, Fugl-Meyer scores, Functional test of the hemiparetic upper extremity (FTHUE), Composite measure of strength (sum of torque from extension and flexion of the wrist elbow and shoulder), Grip and pinch force.
Other Outcomes	-

NOTES

Secondary publications; (Rose et al. 1999; Rose et al. 2001; Winstein et al. 2001)
Change from baseline scores reported and analysed

Yang et al. 2006

METHODS	
Design;	Training vs. no intervention. No follow-up
Randomization;	Mechanism, picking envelopes
Allocation concealment;	Sealed envelopes
Blinding;	Investigator
Intention to treat;	Unknown
Losses to follow-up;	n=0

PARTICIPANTS	
Randomized;	n=48
Intervention;	n=24; m/f 16/8; Age 56.8 ± 10.2 yrs; time since stroke >1year
Control;	n=24; m/f 18/8; Age 60 ± 10.4 yrs; time since stroke >1year
Inclusion Criteria;	i) first stroke <1yr ago, ii) not receiving rehabilitation, iii) ambulatory, independent with no aids, iv) medically stable to participate, v) able to understand instructions and follow commands.
Exclusion Criteria;	i) medical condition preventing participation, ii) uncontrolled health condition for which exercise was contraindicated

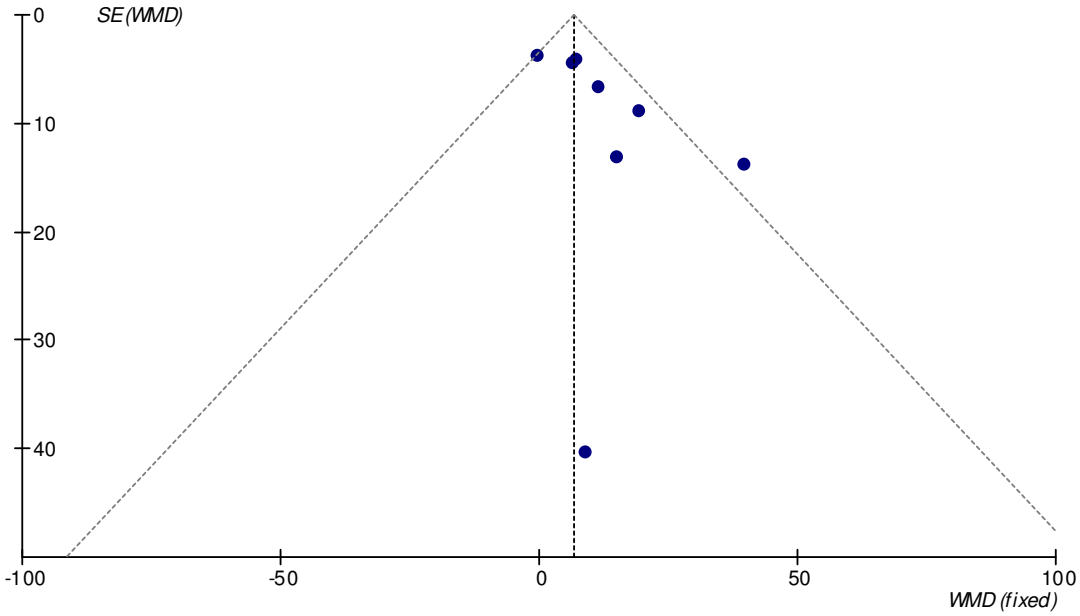
INTERVENTIONS	
Intervention;	Mixed Training. Performed as a circuit 30 min/d, 3 d/wk for 4 wks. Circuit comprised 6 x 5-min lower extremity workstations (standing & reaching, sit to stand from chair, stepping forwards and backwards onto blocks, stepping sideways onto blocks, forward step-up onto blocks). Participants encouraged to work hard, progression achieved by increasing number of repetitions in each 5-min block, and increasing step and chair height, and the complexity of task. Extended periods (5-min) warrant acknowledgement of a cardiorespiratory component despite the author's title (progressive resistance strength training).
Control;	No intervention
Setting:	Medical centre and district hospital

OUTCOME MEASURES	
Included Outcomes	Gait endurance (6-MWT; outcome assessor not blinded), Gait speed preferred (10-metres), 3-m timed up and go, Step test, Isometric strength of knee and hip ankle extension and flexion, and ankle dorsi-flexion and plantar-flexion (using handheld dynamometer).
Other Outcomes	Gait cadence and stride length

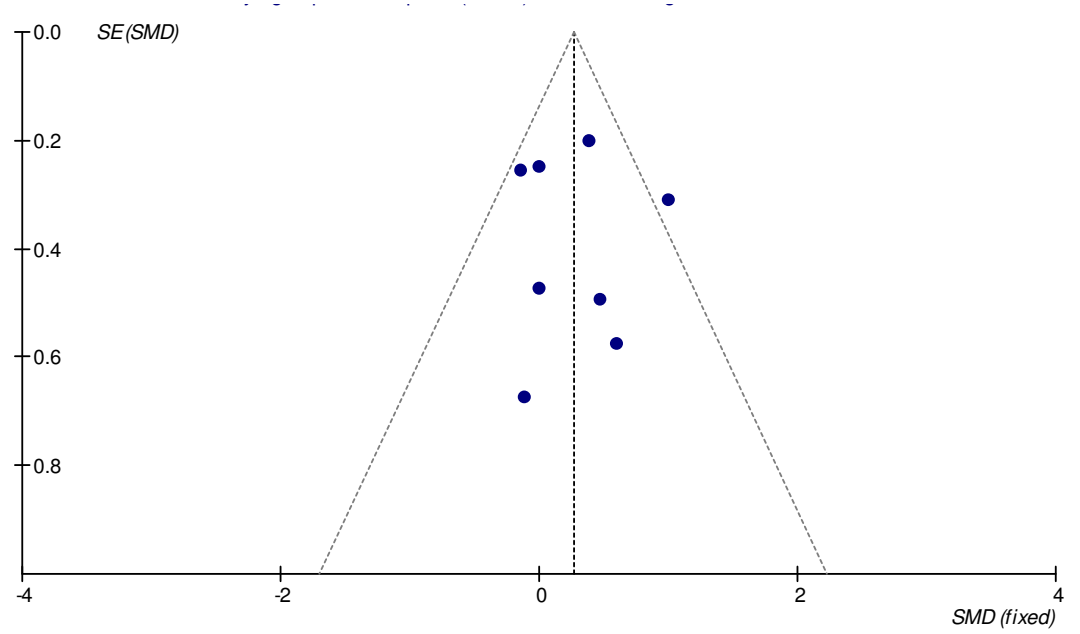
NOTES

14.18. Funnel Plots - publication bias

a) Funnel plot of n=8 studies reporting the effect of cardiorespiratory training on maximum gait speed at the end of intervention



b) Funnel plot of n=8 studies reporting the effect of mixed training on preferred gait speed at the end of intervention



14.19. Individual study data – cardiorespiratory training

Individual study data unsuitable for meta-analyses comparing cardiorespiratory training versus control at (a) end of intervention and (b) end of follow-up.

Type of Outcome Measure		Study	Participants	Statistical Method	Effect size	Significance
a) End of intervention						
Disability	FIM locomotor subscale	(da Cunha et al. (2002)	12	WMD (fixed), 95% CI	-0.17 [-2.46, 2.12]	NS
	Barthel index	(Pohl et al. 2007)	155	WMD (fixed), 95% CI	13.6 [6.89, 20.31]	P<0.0001
	Barthel Index > 75	(Pohl et al. 2007)	155	OR (fixed), 95% CI	3.62 [1.84, 7.10]	P=0.0002
	Motricity index	(Pohl et al. 2007)	155	WMD (fixed), 95% CI	11.60 [3.54, 19.66]	P=0.005
Physical function	Timed up and go (sec)	(Salbach et al. 2004)	91	WMD (fixed), 95% CI	-3.90 [-13.75, 5.95]	NS
	Fugl-Meyer score	(Potempa et al. 1995)	42	WMD (fixed), 95% CI	-10.00 [-15.68, -4.32]	NS
Mood	Anxiety - HADS	(Bateman et al. 2001)	60	WMD (fixed), 95% CI	-1.94 [-3.80, -0.08]	NS
	Depression - HADS	(Bateman et al. 2001)	60	WMD (fixed), 95% CI	-1.40 [-3.21, 0.41]	NS
	Body mass - kg	(Bateman et al. 2001)	72	WMD (fixed), 95% CI	5.38 [-1.69, 12.45]	NS
b) End of follow-up						
Disability	Nottingham EADL	(Bateman et al. 2001)	64	WMD (fixed), 95% CI	2.64 [-5.57, 10.85]	NS
	Barthel index	(Pohl et al. 2007)	155	WMD (fixed), 95% CI	12.40 [4.32, 20.48]	P=0.003
	Frenchay Activities Index	(Katz-Leurer et al. 2003)	79	WMD (fixed), 95% CI	1.00 [-1.55, 3.55]	NS
	Barthel Index >75	(Pohl et al. 2007)	155	OR (fixed), 95% CI	1.64 [0.87, 3.10]	NS
Physical fitness	Maximum cycling work (Watts)	(Bateman et al. 2001)	66	WMD (fixed), 95% CI	2.59 [1.69, 3.49]	P<0.00001
Mobility	Functional Ambulation Categories	(Pohl et al. 2007)	155	WMD (fixed), 95% CI	1.20 [0.65, 1.75]	P<0.0001
Physical function	Berg Balance scale	(Bateman et al. 2001)	66	WMD (fixed), 95% CI	-2.90 [-7.88, 2.08]	NS
	Motricity index	(Pohl et al. 2007)	155	WMD (fixed), 95% CI	11.90 [3.63, 20.17]	P=0.005
Mood	Anxiety - HADS	(Bateman et al. 2001)	53	WMD (fixed), 95% CI	-1.60 [-3.58, 0.38]	NS
	Depression - HADS	(Bateman et al. 2001)	53	WMD (fixed), 95% CI	-2.70 [-4.40, -1.00]	P=0.002
Risk	Body mass - kg	(Bateman et al. 2001)	64	WMD (fixed), 95% CI	2.81 [-4.63, 10.25]	NS

14.20. Individual study data – strength training

Individual study data unsuitable for meta-analyses comparing strength training versus control at (a) end of intervention and (b) end of follow-up.

Type of Outcome Measure		Study	Participants	Statistical Method	Effect size	Significance
a) End of intervention						
Disability	LLFDI (Frequency Dimension)	(Ouellette et al. 2004)	41	WMD (fixed), 95% CI	0.10 [-4.65, 4.85]	NS
	LLFDI (Limitation Dimension)	(Ouellette et al. 2004)	41	WMD (fixed), 95% CI	1.30 [-5.02, 7.62]	NS
	FIM Mobility	(Winstein et al. 2004)	40	WMD (fixed), 95% CI	0.90 [-3.66, 5.46]	NS
	FIM Self-care	(Winstein et al. 2004)	40	WMD (fixed), 95% CI	-0.85 [-4.26, 2.56]	NS
	Improvement in n=10 ADL	(Inaba et al. 1973)	54	OR (fixed), 95% CI	2.88 [0.95,8.70]	NS
Physical function	Timed up and go (sec)	(Yang et al. 2006)	48	WMD (fixed), 95% CI	-1.50 [-5.23, 2.23]	NS
Health & QoL	SF36 Physical Health	(Kim et al. 2001)	20	WMD (fixed), 95% CI	1.47 [-4.24, 7.18]	NS
	SF36 Mental Health	(Kim et al. 2001)	20	WMD (fixed), 95% CI	2.80 [-4.95, 10.55]	NS
a) End of follow-up						
Disability	FIM Mobility	(Winstein et al. 2004)	31	WMD (fixed), 95% CI	-3.23 [-6.14, -3.32]	P=0.03
	FIM Self-care	(Winstein et al. 2004)	31	WMD (fixed), 95% CI	-3.32 [-6.48, -0.16]	P=0.04

Abbreviations: LLFDI Late Life Function & Disability Instrument

14.21. Individual study data – mixed training

Individual study data unsuitable for meta-analyses comparing mixed training versus control at (a) end of intervention and (b) end of follow-up.

Type of Outcome Measure		Study	Participants	Statistical Method	Effect size	Significance
a) End of intervention						
Disability	FIM Instrument	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	-0.10 [-1.70, 1.50]	NS
	Nottingham EADL	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	-0.20 [-1.08, 0.68]	NS
	Rivermead Motor Index	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	-0.41 [-6.14, 0.81]	NS
	FIM motor subscale	(Duncan et al. 2003)	93	WMD (fixed), 95% CI	2.60 [-0.29, 5.49]	NS
	FIM cognitive subscale	(Duncan et al. 2003)	93	WMD (fixed), 95% CI	0.10 [-0.37, 0.57]	NS
Physical fitness	VO_2peak	(Duncan et al. 2003)	100	WMD (fixed), 95% CI	0.99 [0.35, 1.63]	P=0.002
	Net gait economy ml/kg/10m	(Mead et al. 2007b)	65	WMD (fixed), 95% CI	-0.14 [-0.27, -0.01]	P=0.03
	Strength, handgrip (N)	(Duncan et al. 2003)	100	WMD (fixed), 95% CI	0.32 [-1.85, 2.49]	NS
	Power, LLEP, affected (W/kg)	(Mead et al. 2007b)	65	WMD (fixed), 95% CI	0.07 [-0.07, 0.21]	NS
Physical function	Adjusted Activity Score	(Teixeira-Salmela et al. 1999)	13	WMD (fixed), 95% CI	13.79 [2.11, 25.47]	P=0.02
Health & QoL	Nottingham Health Profile	(Teixeira-Salmela et al. 1999)	13	WMD (fixed), 95% CI	-8.97 [-12.84, -5.10]	P=0.00001
Mood	Anxiety (HADS)	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	-0.34 [-1.84, 1.16]	NS
	Depression (HADS)	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	0.54 [-0.93, 2.01]	NS
b) End of follow-up						
Disability	FIM Instrument	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	0.20 [-1.88, 2.28]	NS
	Nottingham EADL	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	0.30 [-0.93, 1.53]	NS
	Rivermead Motor Index	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	0.20 [-0.41, 0.81]	NS
	Lawton IADL	(Duncan et al. 2003)	80	WMD (fixed), 95% CI	0.80 [-0.96, 2.56]	NS
	Barthel ADL	(Duncan et al. 2003)	80	WMD (fixed), 95% CI	-1.70 [-5.51, 2.11]	NS
	Barthel ambulation subscale	Richards et al. 2004	62	WMD (fixed), 95% CI	-2.00 [-5.13, 1.13]	NS
	FIM cognitive subscale	(Duncan et al. 2003)	80	WMD (fixed), 95% CI	0.40 [-0.25, 1.05]	NS
	FIM motor subscale	(Duncan et al. 2003)	80	WMD (fixed), 95% CI	1.90 [-1.88, 5.68]	NS

/cont.

continued/

Physical fitness	Net gait economy ml/kg/10m	(Mead et al. 2007b)	65	WMD (fixed), 95% CI	0.00 [-0.02, 0.02]	NS
	Power, LLEP, affected (W/kg)	(Mead et al. 2007b)	65	WMD (fixed), 95% CI	0.02 [-0.13, 0.17]	NS
Mobility	Gait endurance (6 MWT metres)	(Dean et al. 2000)	9	WMD (fixed), 95% CI	16.20 [-175.76, 208.16]	NS
Physical function	Berg Balance	(Richards et al. 2004)	62	WMD (fixed), 95% CI	-2.00 [-5.48, 1.48]	NS
	Functional reach	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	2.50 [-0.97, 5.97]	NS
Health & QoL	SF36 social function	(Duncan et al. 2003)	80	WMD (fixed), 95% CI	10.60 [0.53, 20.67]	P=0.04
Mood	Anxiety (HADS)	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	-0.25 [-1.79, 1.29]	NS
	Depression (HADS)	(Mead et al. 2007b)	66	WMD (fixed), 95% CI	0.18 [-1.27, 1.63]	NS