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# The Impact of Physical Activity Before and After Stroke on Stroke Risk and Recovery: a Narrative Review

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## Abstract

**Purpose of the Review** Summarising the evidence for pre- and post-stroke physical activity (PA) and exercise to reduce stroke risk, and improve recovery and brain health.

**Recent Findings** Pre-stroke PA reduces the risk of stroke, and post-stroke PA and exercise reduce cardiovascular risk factors, which can moderate the risk of recurrent strokes. Pre-clinical evidence indicates that exercise enhances neuroplasticity. The results from clinical studies showed that exercise changes brain activity patterns in stroke survivors, which can be a signal neuroplasticity. The intensity of pre- and post-stroke PA and exercise is a key factor with higher intensities leading to greater benefits, including improvement in fitness. Having low fitness levels is an independent predictor for increased risk of stroke.

**Summary** Higher intensity leads to greater benefits; however, the optimum intensity of PA and exercise is yet unknown and needs to be further investigated. Strategies to decrease sedentary behaviour and improve fitness need to be considered.

**Keywords** Stroke · Physical activity · Exercise · Fitness · Review

## Introduction

The prevalence of stroke in Australia between 2003 and 2015 has been stable at 1.7%, while stroke-related mortality has been declining [1]. Similar trends have been reported in the USA and Europe [2]. Although fewer people are dying from stroke, about two thirds of stroke survivors need some level of assistance in their day-to-day lives [3]. Around 80% of strokes are preventable by addressing modifiable risk factors [4]. Physical activity (PA) is one of these modifiable risk factors, with higher levels of regular PA reducing the risk of stroke. The health benefits of regular PA and exercise are well described [5, 6••]. In more recent years, there has been an increased interest in the effects of PA and exercise on brain health [7–10]. Several studies have shown that PA and exercise not only are beneficial in improving cardiovascular health but also may help to slow down cognitive decline and reduce the risk of dementia [11, 12]. In addition to being a modifiable risk factor for stroke, PA and exercise may also be neuroprotective. Higher levels of pre-stroke PA and exercise are associated with reduced stroke severity [13], while post-stroke PA and aerobic exercise may play an important role in recovery and neuroplasticity [14, 15•].

PA, exercise, and cardiorespiratory fitness (CRF) are closely linked. While these terms are frequently used interchangeably, there are clear distinctions between them. Understanding the interaction between PA, exercise, and brain health is important, given that they play a different role in neuroprotection and neuroplasticity. PA is defined as any bodily movement by skeletal muscles, which results in energy expenditure; it can include any type of movement at any level or intensity [16]. Exercise is more specific in that it also requires bodily movement by skeletal muscle activity and energy, but involves movements that are planned, structured, and repetitive with the aim to improve or maintain physical fitness [16]. The amount of energy required for either PA or exercise depends on the individual and the level of intensity of the activity or exercise. Physical fitness consists of two different

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components: health-related and skills-related fitness [17]. One component is health-related physical fitness and includes cardiorespiratory and muscular endurance, muscular strength, body composition, and flexibility; the other component is skill-related fitness and is more focused on athletic performance and includes agility, balance, coordination, speed, power, and reaction time.

In this review, we discuss the potential of PA and exercise-based interventions, aiming to improve CRF to reduce the impact of stroke. We review the evidence of the effects of pre- and post-stroke PA and exercise on stroke risk and recovery, the mechanisms that underpin the role of PA and exercise in neuroprotection and neuroplasticity, and discuss the important aspects we need to consider to harness these effects to improve outcomes after stroke.

## The Importance of Pre-stroke PA

In a meta-analysis of 18 large epidemiology cohort studies and 5 case-control studies, Lee et al. found that people who are moderately and highly active have a lower risk of stroke incidence or mortality by 20 and 27%, respectively [18]. Although the definitions for PA varied across the studies, the results were consistently in favour of higher levels of PA. Furthermore, the results were geographically consistent, as studies were conducted in different countries and continents, including North America, the UK, Japan, Australia, and the Netherlands. The results from other studies also revealed the potential for pre-stroke PA to positively influence stroke outcomes, particularly reducing stroke severity and improving functional outcomes after stroke.

### Pre-stroke PA Is Associated with Less Severe Strokes and Better Functional Outcomes

Stroke severity is commonly described by using the National Institute of Health Stroke Scale (NIHSS), where higher scores indicate a higher severity of stroke (i.e. larger number of stroke symptoms at greater severity) [19]. The relationships between pre-stroke PA and stroke severity at hospital admission reported in 10 studies we identified are conflicting [13, 20–23, 24•, 25–28]. In the majority of the studies (8 out of 10), the authors observed that greater levels of PA are associated with lower stroke severity [13, 21–23, 24•, 25, 27, 28]. However, the Decourcelle et al. and Stroud et al. found no relationship between pre-stroke PA levels and stroke severity in ischemic stroke patients [20, 26]. The relationship between pre-stroke PA and functional outcomes after stroke are consistent with the results of the majority of the aforementioned studies, showing that higher levels of pre-stroke PA are associated with better functional outcomes after stroke (as measured by the modified Rankin Scale or the Barthel Index) [22, 23, 24•, 26–28].

Stroke features, such as infarct volume, are significantly correlated with stroke severity on admission and are independently associated with functional outcomes after stroke [29]. Stroud et al. investigated the relationship between infarct size and pre-stroke PA and found no association in 673 stroke survivors [26]. However, Ricciardi et al. found that higher levels of pre-stroke PA were independently associated with lower NIHSS scores on admission, presence of distal occlusions, and smaller final infarct volumes (30 days post stroke) in 159 ischemic stroke survivors [25]. Blauenfeldt et al. found that higher levels of pre-stroke PA were associated with a reduction of 39–88% of acute infarct growth (measured within 24 h after stroke admission) and smaller final infarct volumes (measured 1-month post-stroke) in 102 ischemic stroke patients [30]. These findings highlight the importance of pre-stroke PA levels in relation to key clinical prognostic indicators of stroke.

## Study Design and Assessment of Pre-stroke PA

### Prospective and Retrospective Design Considerations

Methodological factors are important to consider when interpreting the study results from pre-stroke PA studies. Firstly, the most common research design used to investigate the effects of pre-stroke PA levels on stroke outcomes is a retrospective case-control study, where stroke patients were identified after a stroke and asked to report their PA levels prior to their stroke. Retrospective studies are relatively less expensive and less time consuming, because stroke admissions can be used as an opportunistic point of contact [31]. Fewer authors used a prospective approach by including a PA assessment prior to the stroke event. The Physician's Health Study is a large cohort study ($n = 21{,}794$), including male physicians who did not have a history of stroke or TIA at the time of enrolment [32]. Another prospective study, which was part of the Women's Health Initiative Study, included a subset of women who suffered a stroke ($n = 3173$) [33]. Prospective studies are more accurate in collecting information on PA levels than retrospective studies. However, prospective studies are expensive and time consuming because waiting for outcomes—in this case a stroke—would involve long periods of follow-up [31]. Although less robust, a retrospective design can be a pragmatic choice and might be the only possibility in case of limited funding.

### Measurement of Pre-stroke PA

Prospective studies have the advantage of potentially using objective measures like activity monitors with accelerometers

or pedometers. However, to-date, objective measures to examine the relationship between pre-stroke PA and stroke outcomes have not been used in prospective studies. For retrospective studies, self-reported PA levels remain to be the most feasible method to assess pre-stroke PA levels. A commonly used approach to assess PA levels was to dichotomize individuals into categories of those who were "active" or "inactive" based on PA recommendations [20–22, 28]. Additionally, a variety of self-reported PA tools have been used to measure pre-stroke PA, including the Saltin-Grimby Physical Activity Scale [34], Physical Activity Scale for the Elderly (PASE) [35], and the International Physical Activity Questionnaire (IPAQ) [36]. Unfortunately, the interpretation of self-reported PA levels can be challenging due to the inherent limitations of recall bias [37]. This may be especially true in stroke patients who may be experiencing changes in cognition and memory, depressive symptoms, and negative self-image and social desirability [38]. Furthermore, self-report PA questionnaires often do not separate the distinct constructs of PA and exercise. Nonetheless, self-report PA questionnaires are valuable measurement tools to study the relationship between PA and health outcomes.

## Translation of Pre-stroke PA Estimation Tools into Exercise Prescriptions

There are several considerations when choosing a tool to measure PA levels. The before mentioned method to categorise participants in groups by dichotomising PA levels allows for ease of measurement within clinical registries or inpatient care settings however; it does not offer much information to help clinicians prescribe the optimal dose of PA or exercise. That is, the adequate frequency, intensity, type, or duration of PA necessary to achieve the benefits observed cannot be elucidated with simple dichotomy of PA participation. A possible option is to use a standardised questionnaire, which can provide some information about the necessary dose of activity. The IPAQ for example is a self-report questionnaire, in which the results are converted to enable authors to express PA levels in metabolic equivalent scores (METs) [36]. López-Cancio et al. used the IPAQ to investigate the effect of pre-stroke PA on stroke outcomes and included 126 participants in their analyses from the Pre-stroke Physical Activity and Functional Recovery in patients with Ischemic Stroke and Arterial Occlusions (AFRICA) study; they found that people with less than 3000 MET-minutes/week of PA were more likely to have severe strokes on admission [24•]. Also, participating in PA with more than 1000 MET-min/week was independently associated with better functional outcomes at 3-month post-stroke [24•]. By expressing PA levels in terms of MET-minutes per week, clinicians could potentially use the PA Compendium to inform recommendations of the appropriate types and amount of PA needed to achieve the observed benefits with their patients [39]. Other ways to conceptualise PA is to focus on time spent walking or step counts. Ursin et al. used the amount of time spent walking—an activity that is common and accessible for most people—to quantify pre-stroke PA levels [27]. They examined the effect on self-reported pre-stroke leisure walking behaviour on stroke outcomes and reported that leisure walking for greater than 30 min per day was associated with favourable functional outcomes post-stroke [27].

A well-considered selection of PA measurement methods can help provide clear clinical recommendations for patients. It can give valuable information for studying the dose-response relationship between pre-stroke PA or exercise levels, stroke severity, and functional outcomes.

## The Importance of Post-stroke PA and Cerebrovascular Risk

Considering that low levels of PA and exercise are risk factors for stroke, it is not surprising that the majority of stroke survivors also have high cardiovascular risk profiles, which includes low levels of PA and CRF. In a systematic review of 103 studies including 5306 participants, Fini et al. showed that PA levels post-stroke (i.e., focusing on step count and time spent on moderate to vigorous intensity activity) are very low regardless of the time point post-stroke (i.e. subacute and chronic phase), and limited data was available on PA levels in the acute phase post-stroke [40]. Similar patterns are seen regarding CRF levels, where stroke survivors tend to have low CRF [41], and it remains unchanged in the first 12 months after stroke onset [42]. Increasing PA and exercise to improve CRF in stroke patients is clinically important to consider as part of secondary stroke prevention. The occurrence of a transient ischaemic attack (TIA) or minor stroke is associated with a 10 to 20% risk of recurrent stroke in the first 90 days after the first event [43–46]. Increasing PA levels and exercise also has beneficial impacts on other known risk factors. Exercise-based interventions after stroke or TIA can improve risk factors, such as reducing systolic blood pressure, fasting glucose, and insulin and increasing high-density lipoprotein cholesterol [47, 48•]. These improvements in risk factors also moderate the risk of recurrent stroke [49].

There is strong evidence for the positive effects of exercise interventions on improving CRF and mobility after stroke [15•]. This evidence is based on a Cochrane Systematic Review conducted by Saunders et al., which included 58 trials involving 2797 participants to investigate the effect of physical fitness training on stroke recovery [15•]. The importance of promoting PA and exercise in post-stroke rehabilitation has been recognised in several clinical guidelines [50, 51]. The recommendation now clearly states that increasing PA and

exercises to improve CRF should be included in stroke rehabilitation programs.

### Measuring Post-stroke PA

The definitions and measurement tools also vary across post-stroke PA studies. A comprehensive review of the different methods used after stroke showed that the majority of researchers (66/91 studies; $n = 3497$ participants) used an accelerometer to quantify PA [52]. The most commonly reported measures of PA were step counts and walking time [52]. The other frequently used method was direct observation; this was mainly applied in inpatient settings, and the outcomes reported were type of activity (e.g. walking, sitting), location, and people present [52]. Even though accelerometers and pedometers provide an objective measure with high temporal resolution, it does not provide information regarding the context, such as where the activity took place and who was present. This contextual information can be collected using observational mapping; however, this method is very time intensive and has poor temporal resolution.

There are no clear recommendations about which PA outcomes are the most relevant in a stroke population. However, in a review that investigated the effect of using activity monitors on PA levels in stroke survivors, step counts and time spent in moderate to vigorous intensity physical activity (MVPA) were the main outcome measures [53]. Furthermore, step count has been identified as an important factor related to recurrent stroke and was identified as an independent predictor of new vascular events in stroke survivors [54].

## Potential Mechanisms of Neuroprotective and Neuroplastic Effects of PA and Exercise

### Neuroprotective Mechanisms

There are many potential neuroprotective mechanisms associated with increased PA and CRF. The beneficial impact of PA on cerebral vascular function in the perspective of stroke prevention has been described as a complex interaction of neuro- and angiogenesis for re-generative and repair mechanisms in the human brain [55]. One mechanism is via the expression of vascular endothelial growth factors (VEGF). López-Cancio et al. found that stroke patients with high pre-stroke PA levels had higher levels of VEGF 7 days after admission, and those with high levels of VEGF measured at 7 days and 3 months post-stroke were more likely to have better functional outcomes 3 months post-stroke [24•]. Furthermore, individuals with higher PA levels prior to stroke had greater increase in VEGF from baseline to 7 days after stroke, and this increase in VEGF within the first 7 days after stroke was associated with better functional outcomes (mRS $\leq 2$) at 3-months follow-up and smaller final infarct size [24•]. Given that VEGF plays important roles in neuroprotection, angiogenesis, and post-ischemic neuronal repair [56], PA may contribute to neuroprotection via upregulation of VEGF expression. However, the exact dose of PA necessary to increase VEGF in elderly people remains unclear [57].

Brain-derived neurotrophic factor (BDNF) plays a key role in neuronal survival, growth, and plasticity in the brain [58] and has been found to be upregulated after exercise in stroke populations to promote neuroprotection and neuroplasticity after stroke. [59–61]. However, López-Cancio et al. did not observe any changes in BDNF levels on admission, 7 and 30 days post-stroke, and this was not related to pre-stroke PA levels [24•]. The exercise-induced upregulation of BDNF seems to be sustained and the least transient compared with other neurotrophins [10]. Furthermore, preclinical studies have shown that the upregulation of BDNF is dose-dependent after stroke. Ploughman et al. investigated the temporal effects of different PA and exercise protocols on the upregulation of different proteins linked to neuroplasticity [62]. While higher intensity forced exercise led to rapid increase of BDNF, the authors showed that less intense and more frequent short bouts of voluntary exercise led to an upregulation of BDNF that was sustained over time compared with higher intensity forced exercise in rats [62]. This concept can potentially be translated to a clinical application for recovery in human stroke survivors. The sustained upregulation of BDNF after short bouts of exercise to increase neuroplasticity may be useful for rehabilitation sessions, such that aerobic exercise could be used as primer for motor training [59].

Plasma fibrinogen plays an important role in platelet aggregation and coagulation. Increased levels of fibrinogen have been strongly correlated with increased risk of ischemic stroke and transient ischemic attacks [63]. Furthermore, Lin et al. found that PA can lead to decrease in fibrinogen levels in their meta-analysis of randomised control trials of exercise training interventions [64]. Ricciardi et al. found that participants with higher levels of pre-stroke PA had lower levels of fibrinogen on admission [25]. Deplanque et al. also found participants who had higher reported levels of PA had lower levels of fibrinogen on admission [22]. Regular PA and exercise have been shown to reduce fibrinogen levels in health older adults [65, 66]. However, the effect of exercise training on fibrinogen levels in stroke patients is unclear.

### Neuroplastic Mechanisms

Neuroplasticity is defined as the ability of the central nervous system to undergo structural and functional changes as a result of new experiences [67]. There is strong evidence from animal models of stroke that a window of opportunity for neuroplasticity opens in the acute phase (3–30 days) [68], and that exercise interventions focussed on improving CRF

performed within this time can enhance neuroplasticity [69••] and facilitate brain repair processes [14]. Furthermore, it seems that higher intensities exercises to improve CRF lead to greater neuroplastic changes in animal models [14].

Several human studies have also demonstrated an association between functional changes and proposed neuroplasticity processes with the brain after participating in exercise interventions. Enzinger et al. investigated the effect of a 4-week intervention involving treadmill training with partial body weight support on functional reorganisation using functional MRI in 18 chronic stroke survivors. The training consisted of four 5-min bouts a week for 4 weeks; participants were encouraged to walk at a speed of 2 mph (0.89 $ms^{-1}$). The fMRI task consisted of unilateral foot movements. The fMRI block design used two 30-s conditions: active ankle dorsiflexion paced by a visual cue (5 times) and passive movement of the ankle by the experimenter (4 times). Active and passive movement blocks alternated with 21-s rest periods. The authors showed that the signal changes after exercise comparing the active movement of the paretic foot versus rest in the cortical and subcortical motor areas were positively correlated with an increase in walking endurance after the intervention [70]. Greater walking endurance was associated with increased brain activity in the primary sensorimotor cortex, the paracentral lobules, the cingulate motor area, and the caudate nuclei bilaterally and in the lateral thalamus of the affected hemisphere [70]. In another study, an exercise intervention of balance, mobility, and aerobic exercise for chronic stroke survivors ($n = 8$) led to improvements in mobility and cognition (i.e. memory and delayed memory) [71]. Using the same fMRI paradigm as described in the Enzinger et al. study, the authors also observed that change in cerebral activation could be a signal of plasticity [71]. Furthermore, a randomised controlled trial conducted by Luft et al. included chronic stroke survivors with mobility impairments ($n = 71$) who received a 6-month program of either aerobic treadmill training or stretching [72]. The authors stated that in a subset of participants (exercises group $n = 15$ and stretching group $n = 17$), the improvements in walking speed in the exercise group vs stretching group correlated with increased activation in posterior cerebellar lobe and midbrain [72]. These results suggest that neuroplastic mechanisms are an important component of the benefit of exercise on stroke recovery.

## Recommendations for Future Research

### Improving PA Levels or Improving CRF?

The results of large epidemiological studies identified CRF as an independent factor related to stroke risk. In a prospective epidemiological study including 2011 men, low CRF, as measured by a graded exercise test on a bicycle ergometer, was an independent predictor for increased risk of stroke, regardless of PA levels [73]. Another large prospective cohort study, including 16,878 men, assessed pre-stroke CRF using a maximal graded exercise testing with gas analysis and examined its relationship to stroke mortality. The authors reported that moderate and high levels of CRF were associated with a lower risk of stroke mortality [74]. Furthermore, CRF is also more related to brain connectivity in elderly compared with PA [75]. This will have implications for the current public health message about PA, as we may need: a stronger focus on improving CRF rather than only increasing PA levels to promote health and healthy ageing [76].

### Strategies to Increase PA Levels: Optimal Dose and Timing?

Well-established principles exist regarding the appropriate exercise parameters required to improve CRF; that is, a minimal intensity threshold is required to induce a cardiorespiratory training effect [77, 78]. Therefore, it is important to consider the difference between interventions aimed to improve CRF and interventions aimed to increase PA levels. Many strategies and interventions to increase PA have been tested, including targeting motivation to be more active [79], emphasis on lifestyle changes [80, 81], or structured exercise programs [82]. While interventions aimed at increasing PA levels in healthy populations can improve CRF, structured exercise programs may be more effective in improving CRF [81]. Physiological regulators for improving CRF are shared between exercise and brain health [83, 84••]. It is important to further investigate the dose-response relationship regarding the effects of PA and exercise on brain health. For example, the results of several studies showed a relationship between moderate to vigorous level pre-stroke PA and neuroprotective markers [13, 23, 24•, 25].

The evidence for strategies to improve PA levels after stroke is limited. The authors of a systematic review, including four small trials, did not find an effect of the use of PA monitors to improve PA levels found [53]. Aguir et al. conducted a systematic review of interventions aimed at improving PA after stroke [85]. In half of the included studies (9 of 18 studies included), the experimental intervention was a structured exercise program, including CRF exercise or resistance training and of the studies that showed an improvement of PA levels in favour of the experimental intervention; the majority included a CRF or resistance training component [85]. These results highlight the close relationship between CRF and PA levels and suggest that by improving CRF, PA levels might increase. The evidence for the effect of physical fitness interventions to improve CRF and mobility after stroke is strong [15•]. While it remains important to promote PA levels in stroke survivors, it may be more effective to implement structured exercise programming to improve CRF. Although there is strong evidence for the effectiveness of CRF training, it remains unclear

what the best timing is to start CRF training post-stroke. If we want to make use of the possible neuroplastic effect, we need to consider an early start after stroke during which the brain is most plastic [68, 69••]. Further research should focus on timing of training, balancing the effect of neuroplasticity and considering potential harmful effects of an early start [86]. In the early stages, post-stroke light intensity PA and exercise may be beneficial [87]. The effects of exercise on brain health after stroke and how it can enhance neuroplasticity need further investigation. The focus should be on determining the optimal intensity and modality of training (i.e. frequent short bouts or continuous training) to prime the brain for motor practice. Furthermore, the relationship between timing, intensity, frequency, and recovery after stroke needs further exploration.

We mainly focused on PA and exercise in this review; however, future studies may consider examining the effects of sedentary activity on stroke outcomes. Sedentary activity is an independent predictor of disease incidence, hospitalisation, and mortality in adults, regardless of PA levels [88]. After stroke, in acute care and inpatient rehabilitation settings, more than 80% of the time was spent sedentary [89]. In one study, sedentary behaviour was measured using an accelerometer in stroke survivors within the first month of inpatient rehabilitation and found that sedentary time was still high (75% of the spent sedentary) [90], but little is known about sedentary time in stroke survivors in the community [91]. Euzeugwu and Manss have shown that an 8-week home-based behavioural change program to reduce sedentary behaviour in stroke survivors is feasible [92]. It is not yet known if this intervention reduces sedentary behaviour; also, it is still unclear if reducing sedentary behaviour is beneficial to improve stroke recovery. Future studies should focus on developing interventions to reduce sedentary behaviour and investigate its effects on stroke outcomes.

## Conclusion

There is strong evidence for the relationship between pre-stroke PA and exercise and stroke risk; this is similar for post-stroke PA and exercise and stroke recovery. There are strong signals that PA and exercise play a role in neuroprotection and neuroplasticity, but these effects and mechanisms need to be further explored. In almost all of the studies discussed in this review, there is an indication that higher intensity leads to greater benefits. However, the optimum intensity of PA and exercise and likewise the optimum timing of post-stroke interventions to enhance recovery are still unclear. Intensity of activity is also important given that low CRF has been identified as an independent factor of increased stroke risk. Therefore, strategies to improve fitness need to be considered. The high levels of sedentary behaviour after stroke will negatively impact on recovery; decreasing sedentary behaviour, increasing PA levels, and improving CRF should all be included in future strategies to prevent stroke and recover from stroke.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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