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Protocol for a Longitudinal Study into Physical Activity and Cardiovascular Risk in People with Stroke

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Complete List of Authors:	Fini, Natalie; University of Melbourne, School of Health Sciences , Physiotherapy; Alfred Health, Physiotherapy Bernhardt, Julie; Florey Institute of Neuroscience and Mental Health - Austin Campus, Stroke Division Holland, Anne E.; Alfred Health, Physiotherapy; La Trobe University, Physiotherapy
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Title:

Protocol for a Longitudinal Study into Physical Activity and Cardiovascular Risk in People with Stroke

Authors:

Natalie A. Fini [1, 2,3]; Julie Bernhardt [2, 4]; Anne E. Holland [2,5]

Affiliations:

[1] Physiotherapy Department, Caulfield Hospital, Alfred Health

[2] Physiotherapy Department, School of Allied Health, La Trobe University

[3] Physiotherapy Department, Melbourne School of Health Sciences, The University of Melbourne

[4]Stroke Division, Florey Institute of Neurosciences and Mental Health, The University of Melbourne

[5]Physiotherapy Department, Alfred Health

Contact Information:

Corresponding Author:

Natalie A. Fini

Physiotherapy Department, Melbourne School of Health Sciences

Level 7, 161 Barry St

Alan Gilbert Building

The University of Melbourne

Parkville VIC 3010

Australia

Ph: +61 401 303 749; Fax: +61 3 8344 4188

Email: natalie.fini@unimelb.edu.au

Julie Bernhardt

Florey Institute of Neurosciences and Mental Health, The University of Melbourne

Heidelberg

Australia

Anne E. Holland

La Trobe University / Alfred Health

Melbourne

Australia

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ABSTRACT

Introduction:

Physical activity (PA) can modify cardiovascular and other health risks in people with stroke, but we know little about long term PA in this group. This study aims to describe PA levels and investigate relationships between PA, cardiovascular risk, mobility and participant characteristics (eg. age, mood and fatigue) in the two years following rehabilitation discharge after first stroke.

Methods and Analysis

This is a longitudinal observational study with follow up at six, 12, and 24 months after rehabilitation discharge. Inclusion criteria are broad; excluding only those with previous stroke, a palliative diagnosis, living more than two hours from the centre or admitted less than five days.

The primary outcome of interest is duration of moderate-vigorous PA (minutes/day) measured by the Sensewear MF Armband (SWAB). Secondary outcomes include other PA measures measured with the SWAB; cardiovascular risk factors (eg. systolic blood pressure, fasting lipid profile, smoking status), mobility (10 metre walk test), the Hospital Anxiety and Depression Scale and the Fatigue Severity Scale. All outcomes, except blood tests are gathered at each time point.

The target sample size is 77. We will explore associations between PA levels, cardiovascular risk factors, mobility and participant characteristics at baseline compared to 12 and 24 months using random effects regression modelling.

The long term PA of stroke survivors is largely unknown. We hope to identify factors that influence PA and cardiovascular risk in this population, which may help health professionals to target the stroke survivors most at risk and implement appropriate treatment, preventative strategies and education.

Ethics and Dissemination

Approval was granted from Alfred Hospital and La Trobe University Research Ethics Committees. The study results will be disseminated in a number of ways including journal publication and international conference presentations. This study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000196741).

Strengths and Limitations of this Study:

Strengths:

- This study will be the largest longitudinal PA dataset from stroke survivors to date.
- Investigates the important issues of secondary prevention and cardiovascular risk after stroke.
- Measures a number of physical activity outcomes objectively using a device that has been validated in stroke survivors.

Limitations:

- It is a relatively small, single centre study.
- Does not measure PA in the acute phase after stroke.

INTRODUCTION AND RATIONALE

The importance of physical activity (PA) for cardiovascular health is well documented[1-3] and the detrimental effects of sedentary behaviour are substantial.[4-6] Physical activity guidelines for healthy individuals state that 30 minutes of moderate to vigorous intensity PA (MVPA) should be undertaken five days per week.[7] Adherence to these guidelines is associated with a 14% relative risk reduction in all-cause mortality.[8] To achieve cardiovascular benefits, it is recommended that MVPA be accumulated in bouts of at least 10 minutes.[9] Long bouts of uninterrupted sitting are associated with an increased rate of cardiovascular and all-cause mortality in healthy populations.[5, 6] Recommendations about breaking up sitting time have been highlighted in government documents and recommendations internationally.[10-12] Increasing PA and reducing sedentary behaviour are now global targets for better health in a wide range of populations.

Stroke is a major cause of disability worldwide.[13] Mobility limitations are common following a stroke[14] and are associated with poor participation in PA and higher levels of sedentary behaviour than community-dwelling older adults.[15] Depression and fatigue, common in stroke, are also associated with lower PA.[16, 17] Almost one third of stroke patients will suffer another stroke within five years[18, 19] and 50% of people who survive 5-10 years will die of recurrent stroke or another cardiovascular pathology.[20] Increased cardiovascular risk in stroke survivors is largely due to metabolic abnormalities that are further exacerbated by physical inactivity.[18]

While the American Stroke and Heart Associations recommend that stroke survivors engage in regular aerobic exercise and PA to help prevent further stroke and lower cardiovascular disease risk,[19] development of effective interventions is overdue. Many studies have documented low PA[21-28] and high sedentary time following stroke.[15, 21, 29] Surprisingly, only one small study (n=15) has tracked PA for greater than one year.[27] Longitudinal PA data from participants, gathered using the same protocols and the same devices, could help us understand how stroke survivors' PA and cardiovascular risk changes over time.[30] Understanding these associations and their interplay with depression and fatigue would provide a stronger foundation on which to develop treatments that target improved PA in this vulnerable group.

Aims & Hypotheses:

Primary aim: to describe the relationship between PA and cardiovascular risk factors over the 12 months following rehabilitation discharge after first ever stroke (baseline).

Secondary aim: to describe PA levels and their relationship to cardiovascular risk in the two years following rehabilitation discharge.

Tertiary aim: to explore the participant characteristics that are associated with PA (eg. MVPA duration, steps per day) and mobility (eg. walking ability, speed and endurance) at 12

and 24 months. Participant characteristics include demographics (eg. age, stroke severity), mood and fatigue.

Primary hypothesis: at 12 months post discharge from rehabilitation low MVPA duration will be associated with high systolic blood pressure.

Secondary hypothesis: a) there will be an association between PA measures (eg. MVPA duration, sedentary time, energy expenditure, steps per day); and cardiovascular risk factors (eg. systolic blood pressure, total cholesterol, smoking status) at baseline, 12 and 24 months and b) activity levels will not approach levels recommended for cardiovascular risk reduction at any time point.

Tertiary hypothesis: better mobility will be associated with higher levels of PA. Further, older stroke survivors who at baseline have poor mobility and high levels of fatigue and depression are at risk of reduced PA at 12 and 24 months.

METHODS

Design

Single centre, prospective longitudinal observational study, with participants assessed on four occasions: baseline - discharge from outpatient physiotherapy (or inpatient discharge if they don't receive follow-up physiotherapy) and at six, 12 and 24 months after discharge. Recruitment commenced in October 2012 and is anticipated that 24 months follow-ups will be completed by the end of 2017.

This study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000196741). Approval was granted from Alfred Hospital and La Trobe University Research Ethics Committees.

Population

Inclusion criteria are broad: all patients admitted to a large metropolitan rehabilitation hospital (Caulfield Hospital, Melbourne) with first ever stroke, as defined by the World Health Organisation, will be invited to participate. Exclusion criteria: previous stroke (TIA allowed), concomitant diagnosis leading to palliative care, admitted for less than five days, or living greater than two hours from Caulfield Hospital (to improve feasibility and reduce drop outs).

Procedure

Demographic details including age, gender, past medical history, type, location and initial severity of stroke (National Institutes of Health Stroke Scale), stroke and cardiovascular disease family history, living arrangements, social supports and employment will be collected at baseline.

Outcomes and assessment time points are in table 1. Baseline assessment will occur on completion of all physical rehabilitation, to ensure that physiotherapy (specifically encouragement from the physiotherapist and attendance at physiotherapy sessions) would not impact on PA levels.

Primary Outcome

The primary outcome is duration of MVPA (average minutes/day) measured by the Sensewear MF Armband (SWAB). Moderate to vigorous PA is defined as >3 metabolic equivalent tasks (METS). Physical activity is a continuum, beginning with sedentary behaviour at <1.5METS to light PA (LPA) at 1.5 to 3 METS and up to MVPA at >3 METs. The SWAB measures the amount of time spent in these different activity levels. The SWAB is a triaxial accelerometer that uses multiple sensors to measure steps, motion, galvanic skin

response, skin temperature and heat flux. It is valid and reliable for measuring PA and energy expenditure in people with chronic conditions including stroke[31-34] and reliably measures steps in stroke.[35]

The SWAB will be worn for seven days, including at least one full weekend day, at each of the four assessment points, and will be removed only for water-based activities. It will be placed on the unaffected upper arm, which provides more accurate data due to blood flow changes that occur in hemiplegic limbs.[36] Participants will be instructed to partake in their normal activities, not more or less because they are wearing the armband. In line with best practice, we will include PA data for those who have a minimum of 13 hours per day wear time for a minimum of three days.[37, 38]

Secondary Outcomes

Physical Activity

Other measures of PA measured by the SWAB will be collected as secondary outcomes: sedentary time, LPA duration, number of MVPA and sedentary bouts (≥10 minutes) [9] and their duration, energy expenditure (kJ) and number of steps taken per day.

Physical Measurements of Cardiovascular Risk Factors

Systolic blood pressure, an important indicator of cardiovascular risk, is included in the most rigorous cardiovascular disease risk algorithms.[39] Blood pressure will be measured with a portable sphygmomanometer with the participant sitting for approximately 30 minutes prior (after the questionnaires and prior to the mobility assessments) and the average of two seated measurements will be used in accordance with guidelines proposed by the National Vascular Disease Prevention Alliance (NVDPA).[40, 41] Fasting lipid profile (TC, LDL-C, HDL-C, TC: HDL ratio and triglycerides) and plasma glucose samples will be obtained by a phlebotomist. Waist circumference will be measured, along with height and weight to calculate BMI.[40, 41]

Mobility

To assess walking speed, balance, endurance and ability, the 10 metre walk test, timed up and go test, six minute walk test and Functional Ambulation Classification will be undertaken. These measures are considered valid and reliable in stroke survivors.[42] The six minute walk test will be measured on a 40m track. Participants will be instructed to cover as much distance as possible in the six minutes and will be informed as each minute elapses, with standardised phrases of encouragement.

Further Stroke and Cardiovascular Events

At each follow-up assessment participants will be asked if they have had a TIA, stroke or other cardiovascular event, procedure or diagnosis since the previous assessment.

Brief Questions Regarding Cardiovascular Risk Factors

Cigarette smoking, alcohol intake and diet will be established using the NVDPA standard guidelines.

Questions Regarding Physical Activity

At each time point we will acquire information about PA undertaken in a regular week, its duration and frequency. At the baseline assessment we will use standard questions to acquire pre-morbid PA levels.

Mood, Fatigue and Cognition

The Hospital Anxiety and Depression Scale (HADS)[43] and the Fatigue Severity Scale (FSS) will be administered. The FSS has been validated in stroke survivors.[44] The Montreal Cognitive Assessment, a brief valid cognitive screening tool in stroke,[45] will also be administered.

Disability

The Self-Report Barthel Index, a valid and reliable measure of disability in stroke population[46] will be assessed.

Additional Physiotherapy

Any further physiotherapy or activity based intervention since originally completing their therapy will be noted.

Sample Size Estimates

We hypothesise an inverse relationship between MVPA duration and systolic blood pressure at 12 months post baseline assessment. Evidence suggests that an increase in MVPA of 30 minutes/day over 12 months is associated with a 10mm Hg reduction in systolic blood pressure.[47] Assuming that the standard deviation of the independent variable (MVPA) is 29 minutes/day[32] and the standard deviation of the dependent variable is 14.2mmHg,[48] then 70 subjects would be required for a probability of 80 percent that the study will detect a relationship between the independent and the dependent variables at a two-sided 0.05 significance level, if the true change in the dependent variables is 0.167 units per unit change in the independent variable.[49] Allowing for a 10% loss to follow-up over 12 months the target sample size is 77.

Statistical Analyses

Primary Hypothesis: The relationship between MVPA duration and systolic blood pressure at 12 months will be examined using random effects regression modelling adjusted for baseline MVPA duration with individual patients treated as random effects.

Secondary Hypothesis: a) The association between PA measures (eg. MVPA duration, sedentary time, energy expenditure, steps per day); and cardiovascular risk factors (eg. systolic blood pressure, total cholesterol, smoking status) at baseline, 12 and 24 months will be examined using random effects regression modelling, with patients treated as random effects to account for time. The PA and cardiovascular risk profile of participants at baseline,

12 and 24 months and the number of participants who have another stroke or cardiovascular event or diagnosis will be reported descriptively.

b) The percentage of people achieving recommended activity levels to impact CV risk (30 minutes of MVPA per day) will be described.

Tertiary Hypothesis: Once again, random effects modelling will be used to explore the associations between participant characteristics (demographics, mood and fatigue), PA levels and mobility at baseline to 12 and 24 months.

DISCUSSION

Through tracking PA levels and cardiovascular risk factors for two years we will know more about how these factors interact post stroke. By discovering this valuable information we can target the stroke survivors most at risk and implement appropriate treatment, preventative strategies and education.

Ultimately we hope to decrease the risk of further strokes and cardiovascular events in stroke survivors. The cost of another event to this population is enormous: physically, psychologically and emotionally, for the survivors themselves and to their families, carers

and communities. Further cardiovascular events also have a significant financial cost to increasingly overburdened health services.

SUMMARY AND CONCLUSIONS

This study will be the largest longitudinal PA dataset from stroke survivors to date. It will help to identify factors present at discharge from physiotherapy that are associated with PA levels and cardiovascular risk long after formal care ends. The findings of this study will be the first step towards building effective interventions to improve PA in stroke survivors, with the aim of improving long term health and quality of life for this vulnerable group.

Contributorship Statement:

NF, JB and AE contributed to the study design, NF, JB and AE contributed to the statistical analysis plan, NF, JB and AE contributed to the acquisition of funds and NF, JB and AE contributed to the writing of the manuscript.

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Competing Interests:

Ms. Fini reports grants from National Heart Foundation of Australia and grants from Caulfield Hospital, Alfred Health during the conduct of the study. Professor Bernhardt reports grants from National Health and Medical Research Council (Australia) during the conduct of the study and personal fees from Acting as a Scientific Advisor for DART Pharmaceuticals outside the submitted work. Professor Holland reports grants from Caulfield Hospital, Alfred Health during the conduct of the study.

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Protocol for a Longitudinal Study into Physical Activity and Cardiovascular Risk in People with Stroke: Tables

Table 1: Assessment Time-points & Outcomes

Outcomes Measured	Baseline	6 months	12 months	24 months
Demographics	✓			
MVPA Duration	✓	✓	✓	✓
Other PA Outcomes	✓	✓	✓	✓
Fasting Lipid Profile & Plasma Glucose	✓		✓	✓
Blood Pressure, Waist Circumference & BMI	✓	✓	✓	✓
Mobility Measures	✓	✓	✓	✓
Questions Regarding Further Stroke and Cardiovascular Events		✓	✓	✓
Questions Regarding Cardiovascular Risk Factors & PA	✓	✓	✓	✓
HADS, FSS & MOCA	✓	✓	✓	✓
Self-Report Barthel Index	✓	✓	✓	✓

MVPA = moderate to vigorous physical activity; PA = physical activity; BMI = body mass index; HADS = hospital anxiety and depression scale; FSS = fatigue severity scale; MOCA = Montreal cognitive assessment

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	N/A Protocol
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5-6
Methods			**7**
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-12
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	12-13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-14
		(*b*) Describe any methods used to examine subgroups and interactions	13-14
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			N/A Protocol
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			N/A Protocol
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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What is the relationship between Physical Activity and Cardiovascular Risk Factors in Stroke Survivors Post Completion of Rehabilitation? Protocol for a Longitudinal Study.

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Title:

What is the relationship between Physical Activity and Cardiovascular Risk Factors in Stroke Survivors Post Completion of Rehabilitation? Protocol for a Longitudinal Study.

Authors:

Natalie A. Fini [1, 2,3]; Julie Bernhardt [4]; Anne E. Holland [2,5]

Affiliations:

[1] Physiotherapy Department, Caulfield Hospital, Alfred Health

[2] Physiotherapy Department, School of Allied Health, La Trobe University

[3] Physiotherapy Department, Melbourne School of Health Sciences, The University of Melbourne

[4]Stroke Division, Florey Institute of Neurosciences and Mental Health, The University of Melbourne

[5]Physiotherapy Department, Alfred Health

Contact Information:

Corresponding Author:

Natalie A. Fini

Physiotherapy Department, Melbourne School of Health Sciences

Level 7, 161 Barry St

Alan Gilbert Building

The University of Melbourne

Parkville VIC 3010

Australia

Ph: +61 401 303 749; Fax: +61 3 8344 4188

Email: natalie.fini@unimelb.edu.au

Julie Bernhardt

Florey Institute of Neurosciences and Mental Health, The University of Melbourne

Heidelberg

Australia

Anne E. Holland

La Trobe University / Alfred Health

Melbourne

Australia

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ABSTRACT

Introduction:

Physical activity (PA) can modify cardiovascular and other health risks in people with stroke, but we know little about long term PA in this group. This study aims to describe PA levels and investigate relationships between PA, cardiovascular risk factors, mobility and participant characteristics (eg. age, mood and fatigue) in the two years following rehabilitation discharge after first stroke.

Methods and Analysis

This is a longitudinal observational study with follow up at six, 12, and 24 months after rehabilitation discharge. Inclusion criteria are broad; excluding only those with previous stroke, palliative diagnosis, living more than two hours from the centre or admitted less than five days.

The primary outcome of interest is duration of moderate-vigorous PA (minutes/day) measured by the Sensewear MF Armband (SWAB). Secondary outcomes include other PA measures measured with the SWAB; cardiovascular risk factors (eg. systolic blood pressure, fasting lipid profile, smoking status), mobility (10 metre walk test), the Hospital Anxiety and Depression Scale and the Fatigue Severity Scale. All outcomes, except blood tests are gathered at each time point.

The target sample size is 77. We will explore associations between PA levels, cardiovascular risk factors, mobility and participant characteristics at baseline compared to six, 12 and 24 months using random effects regression modelling.

The long term PA of stroke survivors is largely unknown. We hope to identify factors that influence PA and cardiovascular risk in this population, which may help health professionals target the stroke survivors most at risk and implement appropriate treatment, preventative strategies and education.

Ethics and Dissemination

Approval was granted from Alfred Hospital and La Trobe University Research Ethics Committees. The study results will be disseminated in a number of ways including journal publication and international conference presentations. This study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000196741).

Strengths and Limitations of this Study:

Strengths:

- This study will be the largest longitudinal PA dataset from stroke survivors to date.
- Investigates the important issues of secondary prevention and cardiovascular risk after stroke.
- Measures a number of PA outcomes objectively using a device that has been validated in stroke survivors.

Limitations:

- It is a relatively small, single centre study.
- Does not measure PA in the acute phase after stroke.
- The follow-up time points are measured from rehabilitation discharge rather than stroke onset as has recently been recommended by the Stroke Recovery and Rehabilitation Roundtable Taskforce.

INTRODUCTION AND RATIONALE

The importance of physical activity (PA) for cardiovascular health is well documented[1-3] and the detrimental effects of sedentary behaviour are substantial.[4-6] Physical activity guidelines for healthy individuals state that 30 minutes of moderate to vigorous intensity PA (MVPA) should be undertaken five days per week.[7] Adherence to these guidelines is associated with a 14% relative risk reduction in all-cause mortality.[8] To achieve cardiovascular benefits, it is recommended that MVPA be accumulated in bouts of at least 10 minutes.[9] Long bouts of uninterrupted sitting are associated with an increased rate of cardiovascular and all-cause mortality in healthy populations.[5,6] Recommendations about breaking up sitting time have been highlighted in government documents and recommendations internationally.[10-12] Increasing PA and reducing sedentary behaviour are now global targets for better health in a wide range of populations.

Stroke is a major cause of disability worldwide.[13] Mobility limitations are common following a stroke[14] and are associated with poor participation in PA and higher levels of sedentary behaviour than community-dwelling older adults.[15] Depression and fatigue, common in stroke, are also associated with lower PA.[16,17] Almost one third of stroke patients will suffer another stroke within five years[18,19] and 50% of people who survive 5-10 years will die of recurrent stroke or another cardiovascular pathology.[20] Increased cardiovascular risk in stroke survivors is largely due to metabolic abnormalities that are further exacerbated by physical inactivity.[20]

While the American Stroke and Heart Associations recommend that stroke survivors engage in regular aerobic exercise and PA to help prevent further stroke and lower cardiovascular disease risk,[19] development of effective interventions is overdue. Many studies have documented low PA[21-28] and high sedentary time following stroke.[15, 21, 29] Surprisingly, only one small study (n=15) has tracked PA for greater than one year.[27] Longitudinal PA data from participants, gathered using the same protocols and the same devices, could help us understand how stroke survivors' PA and cardiovascular risk changes over time.[30] Understanding these associations and their interplay with depression and fatigue would provide a stronger foundation on which to develop treatments that target improved PA in this vulnerable group.

Aims & Hypotheses:

Overarching Aim

To describe PA levels and their relationship to cardiovascular risk factors over the two years following discharge from rehabilitation after first ever stroke.

Specific Aim 1:

To document PA levels at rehabilitation discharge (baseline), six, 12 and 24 months later.

Specific Aim 2:

To document the relationship between PA levels and cardiovascular risk factors at rehabilitation discharge (baseline), and six, 12 and 24 months later.

Specific Aim 3:

To explore the participant characteristics that are associated with PA (eg. MVPA duration, steps per day) and mobility (eg. walking ability, speed and endurance) at 12 and 24 months. Participant characteristics include demographics (eg. age, stroke severity), mood and fatigue.

Specific Hypothesis 1:

Physical activity levels will not approach levels recommended for cardiovascular risk factor reduction at any time point.

Specific Hypothesis 2:

a) There will be an association between PA measures (eg. MVPA duration, sedentary time, energy expenditure, steps per day); and cardiovascular risk factors (eg. systolic blood pressure, total cholesterol, smoking status) at baseline, six, 12 and 24 months.

b) At 12 months post discharge from rehabilitation low MVPA duration will be associated with higher systolic blood pressure.

Specific Hypothesis 3:

a) Better mobility will be associated with higher levels of PA.

b) Further, older stroke survivors who at baseline have poor mobility and high levels of fatigue and depression are at risk of a reduction in PA at 12 and 24 months post rehabilitation discharge.

METHODS

Design

Single centre, prospective longitudinal observational study, with participants assessed on four occasions: baseline - discharge from outpatient physiotherapy (or inpatient discharge if they don't receive follow-up physiotherapy) and at six, 12 and 24 months after discharge. Recruitment commenced in October 2012 and is anticipated that the 24 month follow-ups will be completed by the end of 2017.

Population

Inclusion criteria are broad: all patients admitted to a large metropolitan rehabilitation hospital (Caulfield Hospital, Melbourne) with first ever stroke, as defined by the World Health Organisation, will be invited to participate. Exclusion criteria: previous stroke (TIA allowed), concomitant diagnosis leading to palliative care, admitted for less than five days, or living greater than two hours from Caulfield Hospital (to improve feasibility and reduce drop outs).

Procedure

Demographic details including age, gender, past medical history, type, location and initial severity of stroke (National Institutes of Health Stroke Scale), stroke and cardiovascular disease family history, living arrangements, social supports and employment will be collected at baseline.

Outcomes and assessment time points are in table 1. Baseline assessment will occur on completion of all physical rehabilitation, to ensure that physiotherapy (specifically

encouragement from the physiotherapist and attendance at physiotherapy sessions) would not impact on PA levels.

Primary Outcome

The primary outcome is duration of MVPA (average minutes/day) measured by the Sensewear MF Armband (SWAB). Moderate to vigorous PA is defined as >3 metabolic equivalent tasks (METS). Physical activity is a continuum, beginning with sedentary behaviour at <1.5METS to light PA (LPA) at 1.5 to 3 METS and up to MVPA at >3 METs. The SWAB measures the amount of time spent in these different activity levels. The SWAB is a triaxial accelerometer that uses multiple sensors to measure steps, motion, galvanic skin response, skin temperature and heat flux. It is valid and reliable for measuring PA and energy expenditure in people with chronic conditions including stroke[31-34] and reliably measures steps in stroke.[35]

The SWAB will be worn for seven days, including at least one full weekend day, at each of the four assessment points, and will be removed only for water-based activities. It will be placed on the unaffected upper arm, which provides more accurate data due to blood flow changes that occur in hemiplegic limbs.[36] Participants will be instructed to partake in their normal activities, not more or less because they are wearing the armband. In line with best

practice, we will include PA data for those who have a minimum of 13 hours per day wear time for a minimum of three days.[37,38]

Secondary Outcomes

Physical Activity

Other measures of PA measured by the SWAB will be collected as secondary outcomes: sedentary time, LPA duration, number of MVPA and sedentary bouts (≥10 minutes) [9] and their duration, energy expenditure (kJ) and number of steps taken per day.

Physical Measurements of Cardiovascular Risk Factors

Systolic blood pressure, an important indicator of cardiovascular risk, is included in the most rigorous cardiovascular disease risk algorithms.[39] Blood pressure will be measured with a portable sphygmomanometer with the participant sitting for approximately 30 minutes prior (after the questionnaires and prior to the mobility assessments) and the average of two seated measurements will be used in accordance with guidelines proposed by the

National Vascular Disease Prevention Alliance (NVDPA).[40, 41] Fasting lipid profile (TC, LDL-C, HDL-C, TC: HDL ratio and triglycerides) and plasma glucose samples will be obtained by a phlebotomist. Waist circumference will be measured, along with height and weight to calculate BMI.[40,41]

Mobility

To assess walking speed, balance, endurance and ability, the 10 metre walk test, timed up and go test, six minute walk test and Functional Ambulation Classification will be undertaken. These measures are considered valid and reliable in stroke survivors.[42] The six minute walk test will be measured on a 40m track. Participants will be instructed to cover as much distance as possible in the six minutes and will be informed as each minute elapses, with standardised phrases of encouragement.

Further Stroke and Cardiovascular Events

At each follow-up assessment participants will be asked if they have had a TIA, stroke or other cardiovascular event, procedure or diagnosis since the previous assessment.

Brief Questions Regarding Cardiovascular Risk Factors

Cigarette smoking, alcohol intake and diet will be established using the NVDPA standard guidelines.[40,41] The following questions will be asked: Have you ever smoked? If so, are you still a smoker? If not, how long ago did you stop? How many packs did you smoke per day and for how many years? Do you have more than 2 standard alcoholic drinks per day? Do you maintain a diet high in fruit and vegetables and low in fat, sugar and salt?

Questions Regarding Physical Activity

At each time point we will acquire information about PA undertaken in a regular week, its duration and frequency. Specific questions include: "Do you participate in regular PA? If so, what activities do you do? How often do you do them in a regular week? How long do you do them for each time? At the baseline assessment we will use the same standard questions to acquire pre-morbid PA levels.

Mood, Fatigue and Cognition

The Hospital Anxiety and Depression Scale (HADS)[43] and the Fatigue Severity Scale (FSS) will be administered. The FSS has been validated in stroke survivors.[44] The Montreal Cognitive Assessment, a brief valid cognitive screening tool in stroke,[45] will also be administered.

Disability

The Self-Report Barthel Index, a valid and reliable measure of disability in stroke population[46] will be assessed.

Additional Physiotherapy

Any further physiotherapy or activity based intervention since originally completing their therapy will be noted.

Sample Size Estimates

We hypothesise an inverse relationship between MVPA duration and systolic blood pressure at 12 months post baseline assessment. Evidence suggests that an increase in MVPA of 30

minutes/day over 12 months is associated with a 10mm Hg reduction in systolic blood pressure.[47] Assuming that the standard deviation of the independent variable (MVPA) is 29 minutes/day[32] and the standard deviation of the dependent variable is 14.2mmHg,[48] then 70 subjects would be required for a probability of 80 percent that the study will detect a relationship between the independent and the dependent variables at a two-sided 0.05 significance level, if the true change in the dependent variables is 0.167 units per unit change in the independent variable.[49] Allowing for a 10% loss to follow-up over 12 months the target sample size is 77.

Statistical Analyses

Specific Aim 1:

The PA and cardiovascular risk profile of participants at baseline, six, 12 and 24 months and the number of participants who have another stroke or cardiovascular event or diagnosis will be reported descriptively. The percentage of people achieving recommended activity levels to influence cardiovascular risk (30 minutes of MVPA per day) will be described.

Specific Aim 2:

a) The association between PA measures (eg. MVPA duration, sedentary time, energy expenditure, steps per day); and cardiovascular risk factors (eg. systolic blood pressure, total cholesterol, smoking status) at baseline, six, 12 and 24 months will be

examined using random effects regression modeling, with patients treated as random effects to account for time.

b) The relationship between MVPA duration and systolic blood pressure at 12 months will be examined using random effects regression modelling adjusted for baseline MVPA duration with individual patients treated as random effects.

Specific Aim 3:

Once again, random effects modelling will be used to explore the associations between participant characteristics (demographics, mood and fatigue), PA levels and mobility at 12 and 24 months relative to baseline.

Ethics and Dissemination:

Approval was granted from Alfred Hospital and La Trobe University Research Ethics Committees. The study results will be disseminated in a number of ways including journal publication and international conference presentations. This study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613000196741).

DISCUSSION

This study will be the largest longitudinal PA dataset from stroke survivors to date. Through tracking PA levels and cardiovascular risk factors for two years we will know more about how these factors interact post stroke. This study will help to identify factors present at discharge from physiotherapy that are associated with low PA levels and increased cardiovascular risk long after formal care ends. By discovering this valuable information we can target the stroke survivors most at risk and implement appropriate treatment, preventative strategies and education prior to discharge from therapy. The ultimate aim is for health professionals to employ behaviour change strategies to facilitate life-long stroke survivor participation in PA. The findings of this study will be the first step towards building effective interventions to improve PA in stroke survivors, with the aim of improving long term health and quality of life for this vulnerable group.

Contributorship Statement:

NF, JB and AE contributed to the study design, NF, JB and AE contributed to the statistical analysis plan, NF, JB and AE contributed to the acquisition of funds and NF, JB and AE contributed to the writing of the manuscript.

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Competing Interests:

Ms. Fini reports grants from National Heart Foundation of Australia and grants from Caulfield Hospital, Alfred Health during the conduct of the study. Professor Bernhardt reports grants from National Health and Medical Research Council (Australia) during the conduct of the study and personal fees from Acting as a Scientific Advisor for DART Pharmaceuticals outside the submitted work. Professor Holland reports grants from Caulfield Hospital, Alfred Health during the conduct of the study.

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Protocol for a Longitudinal Study into Physical Activity and Cardiovascular Risk in People with Stroke: Tables

Table 1: Assessment Time-points & Outcomes

Outcomes Measured	Baseline	6 months	12 months	24 months
Demographics	✓			
MVPA Duration	✓	✓	✓	✓
Other PA Outcomes	✓	✓	✓	✓
Fasting Lipid Profile & Plasma Glucose	✓		✓	✓
Blood Pressure, Waist Circumference & BMI	✓	✓	✓	✓
Mobility Measures	✓	✓	✓	✓
Questions Regarding Further Stroke and Cardiovascular Events		✓	✓	✓
Questions Regarding Cardiovascular Risk Factors & PA	✓	✓	✓	✓
HADS, FSS & MOCA	✓	✓	✓	✓
Self-Report Barthel Index	✓	✓	✓	✓

MVPA = moderate to vigorous physical activity; PA = physical activity; BMI = body mass index; HADS = hospital anxiety and depression scale; FSS = fatigue severity scale; MOCA = Montreal cognitive assessment

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	N/A Protocol
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7-9
Methods			
Study design	4	Present key elements of study design early in the paper	9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-11
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	10-11
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-15
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	15-16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15-16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	16-17
		(*b*) Describe any methods used to examine subgroups and interactions	16-17
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			N/A Protocol
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			N/A Protocol
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.