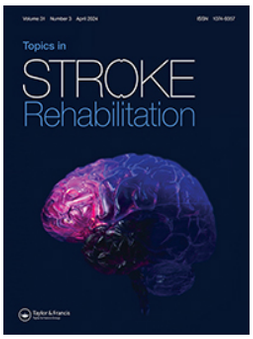

Topics in Stroke Rehabilitation

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ytsr20

Cardiorespiratory fitness, physical activity, and fatigue three months after first-ever ischemic stroke

Petra Larsson, Elisabeth Edvardsen, Caryl L Gay, Marie Ursin, Ulrich Mack & Anners Lerdal

To cite this article: Petra Larsson, Elisabeth Edvardsen, Caryl L Gay, Marie Ursin, Ulrich Mack & Anners Lerdal (27 Mar 2024): Cardiorespiratory fitness, physical activity, and fatigue three months after first-ever ischemic stroke, Topics in Stroke Rehabilitation, DOI: 10.1080/10749357.2024.2333191

To link to this article: https://doi.org/10.1080/10749357.2024.2333191

TOPICS IN STROKE REHABILITATION
https://doi.org/10.1080/10749357.2024.2333191

Cardiorespiratory fitness, physical activity, and fatigue three months after first-ever ischemic stroke

Petra Larsson[a,b], Elisabeth Edvardsen[c,d], Caryl L Gay[e,f], Marie Ursin[g], Ulrich Mack[h], and Anners Lerdal[a,f]

[a]Department of Interdisciplinary Health Sciences, Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway; [b]Surgical Department, Lovisenberg Diaconal Hospital, Oslo, Norway; [c]Department of Physical Performance, Norwegian School of Sport Sciences, Oslo, Norway; [d]Department of Pulmonary Medicine, Oslo University Hospital, Oslo, Norway; [e]Department of Family Health Care Nursing, University of California, San Francisco, CA, USA; [f]Research Department, Lovisenberg Diaconal Hospital, Oslo, Norway; [g]Department of Medical Research, Bærum Hospital, Gjettum, Norway; [h]Medical Department, Lovisenberg Diaconal Hospital, Oslo, Norway

ABSTRACT

Background: Research on cardiorespiratory fitness (CRF) in relation to physical activity (PA) and fatigue after stroke is limited. Increased knowledge of interrelationships between these factors can help optimize rehabilitation strategies and improve health-outcomes.

Objectives: We aimed to: 1) evaluate CRF, PA, and fatigue, 2) characterize patients with impaired versus non-impaired CRF, and 3) examine associations of CRF with PA and fatigue, three months after first-ever ischemic stroke.

Methods: In this cross-sectional study CRF was measured as peak oxygen uptake (VO_{2peak}) by cardiopulmonary exercise testing. PA was measured using accelerometers. Fatigue was assessed with the 7-item Fatigue Severity Scale (FSS).

Results: The sample (n=74, mean age 64±13 years, 36% women) had a mean VO_{2peak} of 27.0±8.7 (86% of predicted). Fifty-one percent met the World Health Organization's recommendation of ≥150 min of moderate PA/week. Mean steps-per-day was 9316±4424 (113% of predicted). Thirty-five percent of the sample had moderate-to-high fatigue (FSS≥4), mean FSS score was 3.2±1.8. Patients with impaired CRF (VO_{2peak}<80% of predicted) had higher body-fat-percent (p<0.01), less moderate-to-vigorous PA (MVPA) (p<0.01) and a trend toward higher fatigue (p=0.053) compared to the non-impaired. Backward regression analysis showed that higher CRF was associated with more MVPA (unstandardized beta [95% CI]: 0.38 [0.15, 0.63], p=0.002) and less fatigue (unstandardized beta [95% CI]: -3.9 [-6.4, -1.6], p=0.004).

Conclusions: Stroke patients had lower CRF compared to reference values. Impaired CRF was mainly related to overweight. Higher CRF was associated with more MVPA and less fatigue. Exercise after stroke may be especially beneficial for patients with impaired CRF.

ARTICLE HISTORY
Received 24 January 2024
Accepted 17 March 2024

KEYWORDS
Accelerometer; cardiorespiratory fitness; ischemic stroke; limitation to exercise; peak oxygen uptake; physical activity; post-stroke fatigue

Introduction

Post-stroke fatigue (PSF) affects nearly half of stroke survivors (pooled prevalence of 47%)[1] and has a significant impact on physical, emotional, cognitive, and perceptual domains.[2] It often remains unaffected by rest[2] and is a major burden for stroke survivors due to negative effects on rehabilitation,[3] quality of life,[4] and even survival.[5]

There is a "deconditioning hypothesis" suggesting that reduced physical fitness contributes to PSF, creating a cycle of fatigue, decreased physical activity (PA), and further physical decline.[6] Although PSF is a barrier to exercise rehabilitation, evidence indicates exercise therapy could reduce fatigue.[7] Thus, examining physical fitness, PA, and fatigue levels is essential for developing effective exercise interventions, targeting PSF.

In this study, physical fitness was evaluated as cardiorespiratory fitness (CRF). CRF is measured as peak oxygen uptake (VO_{2peak}) obtained from a cardiopulmonary exercise test (CPET).[8] CRF is one of the most important determinants of cardiovascular disease and is a key outcome of exercise rehabilitation.[8] CRF is substantially reduced after stroke,[8] with mean values of less than 80% of healthy reference values.[9] One review reported VO_{2peak} to be 14.34 $mL \cdot kg^{-1} \cdot min^{-1}$ on average in the sub-acute phase (14 days to six months after

CONTACT Petra Larsson petra.hs.larsson@outlook.com Department of Interdisciplinary Health Sciences, Institute of Health and Society, Faculty of Medicine, University of Oslo, Forskningsveien 3A, Oslo 0373, Norway

Supplemental data for this article can be accessed online at https://doi.org/10.1080/10749357.2024.2333191

stroke). However, they found the lowest mean VO_{2peak} values early in the sub-acute phase and reported that spontaneous recovery may occur up until 6 months.[8] After six months to a year, CRF remained low, but stable (mean VO_{2peak} 16.54 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$).[8] Although mean CRF is lower in stroke patients than in healthy individuals, there is considerable variability in individual CRF-levels after stroke.[9] We believe it is particularly important to identify patients with impaired CRF below 80% of predicted values and examine if there are any characteristics that distinguish patients with impaired CRF from the non-impaired, as these are the patients that could benefit the most from interventions to improve CRF.

Furthermore, research on the relationship between CRF and PSF is limited and often involves small sample sizes.[10,11] A link between CRF and PSF has not conclusively been established, especially when considering the confounding effects of anxiety and depression.[10] While the associations between CRF, PA and stroke health outcomes have been well-documented,[8,12,13] the specific interaction between CRF and PA in the context of PSF requires further exploration. More knowledge about interrelationships between CRF with PA and fatigue may help enhance rehabilitation strategies and improve outcomes for stroke survivors.

Our study objectives are to:

1) describe CRF, including the cardiopulmonary response to exercise, PA, and fatigue; 2) characterize patients with impaired versus non-impaired CRF; and 3) investigate the associations of CRF with PA and fatigue in a cohort of patients three months after a first-ever ischemic stroke.

Materials and methods

Study design, setting, and patients

This cross-sectional analysis is part of NORFAST, the Norwegian Study of Fatigue After Stroke, aiming to explore fatigue phenotypes following first-ever ischemic stroke. NORFAST consecutively recruited patients from Lovisenberg Diaconal Hospital and Oslo University Hospital (OUS) between October 2018 and November 2021. Eligible patients were adults (≥18 years) diagnosed with first-ever ischemic stroke, who were able to complete study questionnaires independently or with assistance within 14 days after stroke onset. Patients were excluded if they had a life expectancy <6 months, pre-stroke dementia, unstable psychiatric disorder, severe substance abuse, or were unable to give informed consent. NORFAST patients able to complete a cardiopulmonary exercise test (CPET) at Lovisenberg three months post-stroke were eligible for the present analysis. All patients provided written informed consent. The study has been approved by the Regional Committee for Medical Ethics, South-Eastern Norway (Ref # 2016/1111D). This manuscript conforms to the reporting guidelines outlined in Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE).[14]

Data collection

Baseline data on stroke characteristics, demographics, other relevant background information, and patient-reported outcome measures was collected from medical records and by electronic self-report questionnaires, administered in the acute phase while admitted to the hospital.

Three-month follow-up data for the Norwegian Study of Fatigue After Stroke (NORFAST), including CRF and body composition, were collected at Lovisenberg Diaconal Hospital over one or two days. Patients were equipped with the accelerometer at the follow-up visit and physical activity data was recorded in the following week. Patient-reported outcomes were collected by electronic self-report either at the hospital or via an e-mail link at home. All testing was administered by trained NORFAST Study research assistants (nurses, physiotherapists, and/or exercise physiologists).

Outcomes

Cardiopulmonary exercise test

CRF was measured as VO_{2peak} from a maximal CPET on a Woodway PPS Med treadmill (Waukesha, WI, USA) using an uphill walking, modified Balke protocol, consistent with reference population methodology.[15] Speed ranged from 1.2 to 4.8 km/h, based on self-reported fitness, with a 4% incline increasing by 2% every minute. If 20% incline was reached, speed increased by 0.5 km/h

every minute until exhaustion. Gas exchange was measured breath-by-breath and reported as 30s averages using Jaeger Vyntus™ CPX Metabolic Cart (CareFusion Corporation, Höchberg, Germany) and SentrySuite™ software (Vyaire Medical Inc., USA). Oxygen saturation, blood pressure and ECG were continuously monitored. Except for safety concerns, the CPET ended when patients were unable to continue. Rating of perceived exertion (RPE) used the $BORG_{6–20}$ scale post-termination,[16] and capillary blood lactate was measured 60s post-termination (Lactate Scout 4 analyzer, EKF Diagnostics Holding plc, Cardiff, UK).[15]

Impaired CRF was defined as VO_{2peak} <80% of predicted value based on age, sex, and body mass. Borg ratings ≥ 17, lactate concentrations ≥ 3.5–9.0 mmol/L (depending on age and sex), and respiratory exchange ratio ≥ 1.0–1.1 were indicators of maximal effort.[17] See Supplemental Table S1 for data handling.

Physical activity

PA level was measured during waking hours for seven consecutive days using a hip-worn accelerometer (ActiGraph wGT3X-BT, LLC, FL, USA). Data were extracted from the vertical axis using ActiLife software (ActiGraph LLC, Pensacola, FL, USA) and averaged over 10-second epochs using the KineSoft analytical software (version 3.3.80, Loughborough, UK). Data were included if patients had ≥10 hours of recordings/day for a minimum of three days.

Fatigue

Fatigue over the last 7 days was measured using the 7-item Fatigue Severity Scale (FSS-7),[18,19] scored on a 1–7 Likert scale. Low fatigue was defined as a mean score of 1–3.9, moderate fatigue as 4–4.9 and severe fatigue as 5–7.[20] PSF cases were defined using a cutoff of ≥ 4.[1]

Other measures (alphabetic order)

Anthropometric measures: Body mass index (BMI) was obtained from height and weight. Body composition (total lean body mass, total fat mass, body fat percentage) was assessed by Dual-energy X-ray Absorptiometry (DXA) (Lunar Pro iDXA, GE HealthCare Technologies Inc. and enCORE Software 14.10, GE Healthcare, IL, USA). Overweight was defined as BMI > 25 and obesity was defined as fat percentage > 37.1% (women) and > 25.8% (men).[21]

Anxiety and depression symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS),[22] using the anxiety (HADS-A) and depression (HADS-D) subscales, which have seven items each.

Disability was assessed with the Modified Rankin Scale (mRS).[23] Scores range from 0 (no symptoms) to 6 (deceased).

Pulmonary function: Spirometry was performed prior to CPET in accordance with American Thoracic Society/European Respiratory Society recommendations.[24] Predicted values for spirometry were taken from GLI.[25]

Statistical analyses

NORFAST recruited 115 patients to allow for multiple regression analysis including ≥ 5 independent variables after accounting for attrition. Between-group differences in continuous data were tested using Student's T-test and confirmed with Mann Whitney U-test; for categorical data, we used Chi-square test or Fischer's Exact test, as appropriate. Stepwise backward linear regression analysis was used to explore associations of CRF with PA and fatigue, controlling for anxiety and depression as potential confounders. Age, sex and body mass was controlled for indirectly by using VO2peak/kg(%) as dependent variable. Variables were retained in the models if $p < 0.10$. The final model was re-run with bootstrapping for improved precision estimates. Sample sizes varied from $n = 62$ to $n = 74$ in different analyses due to missing data on specific variables. Statistical analyses were conducted using the Statistical Package for Social Science (SPSS) version 28, (IBM Corporation, Armonk, NY) and Stata version 15 (StataCorp, College Station, TX). Statistical significance was set at p-value ≤0.05.

Results

Of the 115 NORFAST patients recruited at baseline, the 74 (67%) with valid VO_{2peak} measures three months post-stroke were included in this analysis (Figure 1).

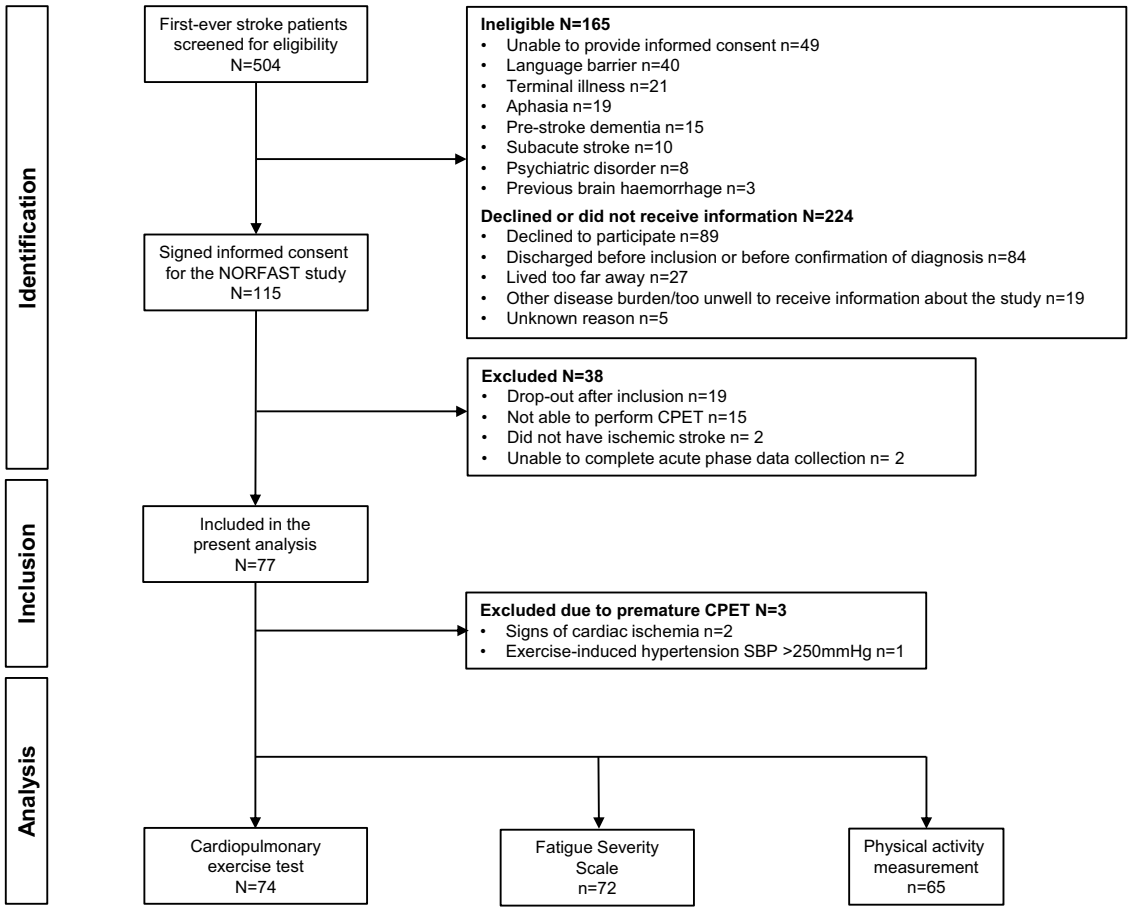

Figure 1. Flow chart of patient inclusion.

Representativeness

Compared to first-ever ischemic stroke patients in the Norwegian Stroke Registry 2022 (mean age = 73 years, 55% male, mean mRS = 1.4), our sample had a similar sex distribution, but was younger and had less disability (both $p < 0.001$).

Except for reported hypertension, included patients did not differ from those who dropped out or were excluded regarding age, sex, BMI, body fat%, heart disease, respiratory disease, diabetes, stroke disability, PSF, or PA. Patient characteristics are reported in Table 1.

Cardiorespiratory fitness

No adverse events occurred during CPET. The indicators for maximal effort were high indicating excellent effort during CPET and valid results (Table 2). Dyspnea was the most frequent reason for stopping ($n = 34$, 51%), followed by leg muscle fatigue ($n = 17$, 25%), other (e.g. pain, discomfort, impaired balance) ($n = 9$, 13%) and general exhaustion ($n = 7$, 10%). VO_{2peak} and VO_{2peak}/kg was 24% and 14% lower than reference values, respectively (both $p < 0.001$). Thirty-three (45%) patients had impaired CRF (Figure 2).

Characteristics of patients with impaired cardiorespiratory fitness

Table 3 compares the patient characteristics of those with impaired and non-impaired CRF. Among the impaired, two displayed poor chronotropic response, five experienced exercise-induced hypoxemia, seven had ventilatory limitation, and eight showed an elevated VE/VCO_2 slope indicating ventilation/perfusion mismatch. Six patients had more than one limiting factor

Table 1. Patient characteristics.

	All ($N = 74$)	Women ($n = 27$)	Men ($n = 47$)
Sociodemographic characteristics			
Age (years)	64 ± 13 [33–87]	65 ± 11 [42–87]	63 ± 14 [33–84]
Married/Partnered	45(64)	13(52)	32(71)
College/University (>12 years)	53(74)	18(69)	35(76)
Working 3 months after stroke	24(34)	8(32)	16(36)
Anthropometric characteristics			
Height (cm)	174.4 ± 8.7 [152–191]	167.6 ± 8.6 [152–190]	178 ± 6.0 [165–191]
Body mass (kg)	81.8 ± 13.8 [53.0–112.0]	74.9 ± 14.3 [53.0–100.9]	85.8 ± 11.9 [64.0–112.0]
BMI (kg/m^2	26.9 ± 4.5 [17.9–42]	26.8 ± 5.7 [17.9–42]	27.0 ± 3.7 [21.1–36.2]
Body composition			
Total fat mass (kg)	26.7 ± 8.8 [8.8–51.7]	29.3 ± 9.7 [10.9–51.7]	25.1 ± 7.9 [8.8–45.3]
Total fat mass (%)	32.5 ± 8.2 [12.4–51.6]	38.1 ± 7.8 [19.1–51.6]	29.4 ± 6.7 [12.4–42.6]
Lean body mass (kg)	51.1 ± 9.4 [16.6–71.8]	43.9 ± 6.6 [34.2–62.8]	55.2 ± 6.2 [16.6–71.8]
Self-reported comorbidities			
Hypertension	39(56)	15(60)	24(53)
Heart disease	23(33)	6(24)	17(38)
Respiratory disease	4(6)	3(12)	1(2)
Diabetes	9(13)	1(4)	8(18)
Stroke characteristics			
Stroke location			
Right	28(44)	9(43)	19(45)
Left	23(37)	8(38)	15(36)
Other (bilateral, posterior, right/posterior)	12(19)	4(19)	8(19)
Modified Rankin Scale	1.1 ± 0.8 [0–3]	1.1 ± 0.6 [0–2]	1.1 ± 0.9 [0–3]
Psychological symptoms			
Anxiety (HADS-A sum score)	3.5 ± 3.9 [0–19]	4.3 ± 3.7 [0–12]	3.1 ± 4.0 [0–19]
Score <8	61(85)	20(77)	41(89)
Score ≥8	11(15)	6(23)	5(11)
Depression (HADS-D sum score)	2.9 ± 2.3 [0–13]	3.2 ± 2.6 [0–11]	2.7 ± 2.2 [0–13]
Score <8	67(93)	23(89)	44(96)
Score ≥8	5(7)	3(11)	2(4)
Fatigue			
FSS-7 mean score	3.2 ± 1.8 [1–7]	3.6 ± 1.7 [1–7]	3.0 ± 1.9 [1–7]
Low fatigue (scores 1–3.9)	47(65)	15(58)	32(69)
Moderate fatigue (scores 4–4.9)	10(14)	5(19)	5(11)
Severe fatigue (scores 5–7)	15(21)	6(23)	9(19)
Physical activity			
Steps/day	9316 ± 4424 [1024–19036]	9507 ± 4634 [1024–18874]	9188 ± 4335 [2400–19036]
MVPA (min/day)	27.6 ± 22.5 [0–90]	25.7 ± 19.6 [0–64]	28.9 ± 24.3 [22–90]
≥150 min/week of moderate PA	33(51)	12(46)	21(54)
Pulmonary function			
FVC (% of predicted)	102 ± 2 [62–137]	104 ± 3 [78–127]	101 ± 3 [62–137]
FEV_1 (% of predicted)	97 ± 2 [53–141]	97 ± 3 [67–125]	97 ± 3 [53–141]

Data are presented as mean±standard deviation [range] or n (%).

Abbreviations: BMI: body mass index, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, FSS-7: 7-item Fatigue Severity Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety Subscale, HADS-D: Hospital Anxiety and Depression Scale-Depression Subscale, MVPA: moderate-to-vigorous physical activity.

Sample sizes for analyses ranged from $n = 65$–74 due to missing data.

and were counted twice. Seventeen (52%) of the impaired patients had no cardiopulmonary limitations and were classified as deconditioned. Those with impaired CRF were less likely to have a partner or be working, were more likely to have hypertension, had higher body fat%, lower MVPA and a trend toward a higher proportion of fatigue cases (45% vs. 25%, $p = 0.053$).

Physical activity level

PA levels (steps-per-day and MVPA) are presented in Table 1. Mean steps-per-day was higher (113% of predicted) than reported for the general population.[26] Fifty-one percent of our sample met WHO's recommendations of 150 min of moderate PA/week compared to about 75% of the general population.[26]

Table 2. Cardiorespiratory fitness and physiological response from the cardiopulmonary exercise test.

	All ($N = 74$)	Women ($n = 27$)	Men ($n = 47$)
Cardiorespiratory fitness			
VO_{2peak} ($L \cdot min^{-1}$)	2.19 ± 0.72	1.75 ± 0.42	2.44 ± 0.74
Predicted VO_{2peak} in $L \cdot min^{-1}$ (%)	76 ± 21	62 ± 13	84 ± 20
VO_{2peak}/kg ($mL \cdot kg^{-1} \cdot min^{-1}$)	27.0 ± 8.7	23.8 ± 6.4	28.9 ± 9.4
Predicted VO_{2peak}/kg (%)	86 ± 22	87 ± 22	85 ± 22
VO_2 at VT ($L \cdot min^{-1}$)	1.75 ± 0.55	1.43 ± 0.31	1.93 ± 0.58
Cardiovascular response			
HR_{peak} ($beats \cdot min^{-1}$)	156 ± 20	152 ± 18	158 ± 21
Heart rate reserve (%)	5.3 ± 0.8	8.0 ± 9.4	3.8 ± 11.3
O_2-$pulse_{peak}$ ($mL \cdot beat^{-1}$)	14.0 ± 4.0	11.5 ± 2.6	15.4 ± 4.1
SBP_{peak} (mmHg)	198 ± 25	203 ± 23	196 ± 26
DBP_{peak} (mmHg)	84 ± 14	84 ± 12	85 ± 15
Respiratory response			
VE_{peak} ($L \cdot min^{-1}$)	88.65 ± 23.35	70.56 ± 18.82	99.04 ± 29.92
Breathing reserve (%)	23.3 ± 15.4	20.7 ± 13.0	24.9 ± 16.6
SpO_{2peak} (%)	95 ± 1.1	93.5 ± 6.8	95.4 ± 4.3
VE/VCO_2 slope	30.8 ± 4.8	31.2 ± 4.0	30.6 ± 5.2
Indicators for maximal effort			
RER (VCO_2/VO_2)	1.13 ± 0.09	1.13 ± 0.09	1.14 ± 0.09
Blood lactate ($mmol \cdot L^{-1}$)	8.6 ± 3.0	7.6 ± 3.0	9.3 ± 2.8
Borg RPE $scale_{(6–20)}$	17.7 ± 1.1	17.8 ± 1.0	17.6 ± 1.2

Data are presented as mean±standard deviation.
Abbreviations: BMI: body mass index, DBP: diastolic blood pressure, HR: heart rate, O_2-pulse: oxygen pulse. RER: respiratory exchange ratio, RPE: ratings of perceived exertion, SpO_2: peripheral oxygen saturation, SBP-. systolic blood pressure, VCO_2: carbon dioxide elimination, VE: ventilation, VO_2: oxygen uptake, VT: ventilatory. threshold

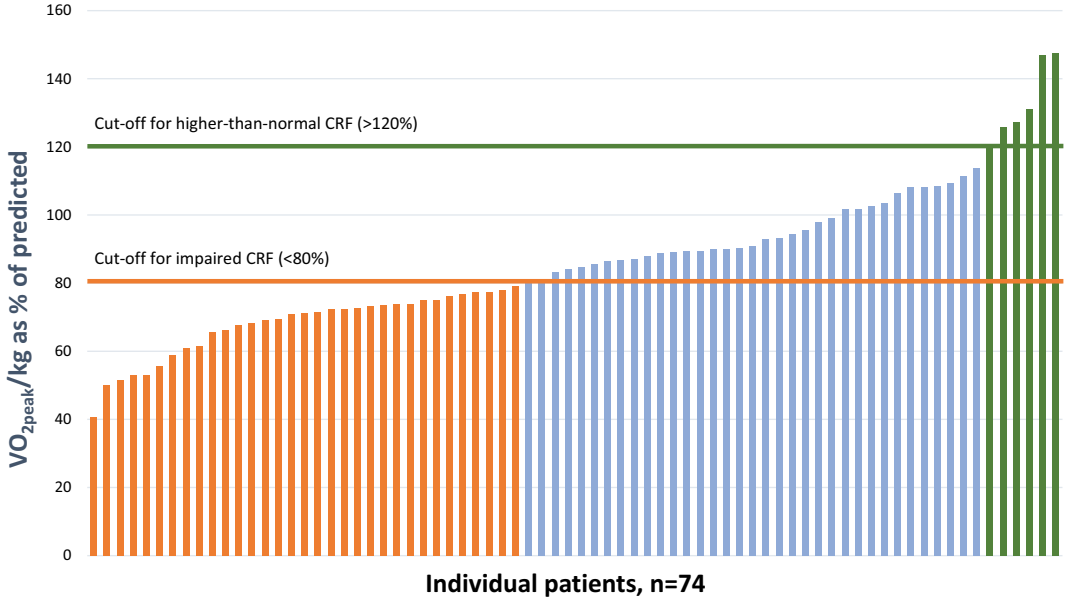

Figure 2. Waterfall plot for impaired (red), normal (blue) and high (green) cardiorespiratory fitness (CRF) for each patient. Each vertical bar represents one patient. CRF was calculated as percent of predicted VO_{2peak}/kg based on normative reference values according to Edvardsen et al.[15]

Associations of cardiorespiratory fitness with physical activity and post-stroke fatigue

Table 4 and Supplemental Table S2 show the final and full backward multiple linear regression model. VO_{2peak}/kg(% predicted) was significantly associated with MVPA and fatigue. For every one-point increase in FSS score and MVPA/day, there was a 4% decrease and a 0.4% increase in VO_{2peak}/kg, respectively.

Table 3. Characteristics of patients with impaired versus non-impaired cardiorespiratory fitness.

	Impaired CRF ($n = 33$)	Non-impaired CRF ($n = 41$)	P-value for difference
Sociodemographic characteristics			
Age (years), mean [95% CI]	64 [60,67]	63 [59,68]	0.823
Sex (women/men)	11/22(33/67)	16/25(39/61)	0.613
Married/Partnered	16(50)	29(76)	0.022
Working 3 months after stroke	7(21)	17(45)	0.045
College/University (>12 years)	23(72)	30(75)	0.765
Anthropometric characteristics			
Overweight (BMI ≥25)	28(85)	20(49)	0.001*
Obese (fat percentage ≥ 37.1(women) or 25.8(men))	26(87)	18(50)	0.002
Self-reported comorbidities			
Hypertension	23(72)	16(42)	0.012
Heart disease	14(44)	9(24)	0.075
Respiratory disease	2(7)	2(5)	1.000
Diabetes	7(23)	2(5)	0.680
Stroke disability			
Modified Rankin Scale > 2	2(6)	0(0)	0.195
Post-stroke fatigue			
FSS-7 score ≥ 4	15(47)	10(25)	0.053
Physical activity			
Steps/day, mean [95% CI]	8454 [6721,10187]	10010 [8572,11449]	0.160
MVPA ≥150 min/week	8(28)	25(69)	0.001
Pulmonary function			
FEV_1/FVC <70%	11(33)	7(17)	0.105
Cardiorespiratory fitness			
VO_{2peak} ($L \cdot min^{-1}$)	1.83 [1.65, 2.01]	2.47 [2.24, 2.71]	<0.001
VO_{2peak} in $L \cdot min^{-1}$ (% predicted)	64 [59, 69]	85 [79, 92]	<0.001
Cardiovascular response during CPET			
Poor chronotropic response (HRR <20%)	2(6)	2(5)	1.000
Low oxygen-pulse (<80% of predicted)	15(46)	5(12)	0.001
Exercise induced hypertension	10(31)	15(42)	0.374
Respiratory response during CPET			
Ventilatory limitation (BR < 15% or <11 L)	7 (21)	7 (17)	0.651
Hypoxemia (SpO_2 <88%)	5 (15)	5 (14)	1.000
VA/VQ-mismatch (VE/VCO_2 slope > 34)	8 (24)	4 (10)	0.093
End-criteria for maximal effort[17]			
RER above end-criteria[a]	29(88)	39(95)	0.397
Blood lactate above end-criteria[a]	27(90)	36(95)	0.648
BORG above end-criteria[a] (≥17)	28(85)	38(93)	0.454

Data are presented as n(%) or mean[CI].

Abbreviations: CI: confidence interval, DBP: diastolic blood pressure, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, FSS-7: 7-item Fatigue Severity Scale, HR: heart rate, HRR: heart rate reserve, MVPA: moderate-to-vigorous physical activity level, PA: physical activity, RER: respiratory exchange ratio, RPE: ratings of perceived exertion, SpO_2: peripheral oxygen saturation, SBP: systolic blood pressure, VCO_2: carbon dioxide elimination, VO_2: oxygen uptake.

Sample sizes for analyses ranged from $n = 65$–74 due to missing data.

Stroke location and psychological symptoms did not differ between groups.

Table 4. Final four-step backward regression model of associations of cardiorespiratory fitness with post-stroke fatigue and physical activity.

Variable	Unstandardized Beta [95% CI]	Standardized Beta	p-value
FSS (score)	−3.88 [−6.36, −1.60]	−0.31	0.004
MVPA (min/day)	0.38 [0.15, 0.63]	0.40	0.002

Dependent variable: CRF (VO_{2peak}/kg [%]).

Bootstrapping was used in the final model for improved precision estimates.

Abbreviations: FSS: Fatigue Severity Scale; MVPA: moderate-to-vigorous physical activity.

Due to 11 patients with missing data on one or both of the included variables, the regression analysis had a sample size of $n = 63$.

Discussion

Our study showed that patients with first-ever ischemic stroke exhibited a 14% lower CRF than predicted. Patients with impaired CRF demonstrated higher BMI and body fat percentage and spent less time in MVPA, compared to patients with normal and high CRF. Although PA measured in steps-per-day was high, MVPA was low, suggesting that stroke patients are slow walkers. Finally, in accordance with the

deconditioning hypothesis, lower CRF was associated with less MVPA and higher fatigue.

Cardiorespiratory fitness

As expected, stroke patients had lower CRF than predicted. This is consistent with previous findings[9] and could be related to inactivity post-stroke or low CRF pre-stroke, as CRF is inversely associated with risk of ischemic stroke.[27] CRF in our study was similar to another Norwegian study,[28] but higher than other European stroke cohorts.[9,10] One reason for the higher CRF compared to other countries might be explained by test modality, treadmill vs. cycling. Cycle ergometry, which is more common in the European studies, is known to yield 10–20% lower VO_{2peak} compared to treadmill-testing, mainly because of early test termination due to quadriceps fatigue rather than maximal cardiopulmonary effort.[29] On the other hand, test modality may not be the sole explanation, as American studies also have reported relatively low VO_{2peak} values (about 15–22 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) one to three months after stroke despite testing their subjects on a treadmill.[30,31] One may suspect that our patients were relatively young and with few disabilities, however the other CRF studies' samples have similar mean age[9,10,31] or lower.[30] Disability levels are harder to compare due to the different measurement methods used, but disability levels, at least in the European studies, are comparable. Sex distribution and mean BMI were also similar across studies. Another explanation may be that we pushed our patients to a higher level of exhaustion during the CPET, as demonstrated by the higher mean peak heart rate[9,31] and higher Borg RPE[10,31] in our study compared to others. This highlights the importance of pushing patients to the maximum during CPET for valid measurements. Finally, aerobic exercise is proven to increase CRF.[13] We believe aerobic exercise should be individually tailored and routinely prescribed after stroke, as CRF is consistently reported to be reduced in stroke patients.

Identifying characteristics of patients with impaired CRF is essential because this allows us to tailor exercise-therapy to specific patients' needs. Overweight and obesity are stroke risk factors[32] and were more prevalent in our impaired versus our non-impaired CRF group, which is consistent with previous studies.[9,33] Any post-stroke weight-gain in our patients is unknown, but stroke patients may be particularly susceptible to weight gain because of impaired mobility, endocrine dysfunction, sleep disturbances, emotional disorders and PSF.[34] Our findings suggest that future studies should investigate whether nutrition and exercise interventions aimed at reducing fat mass and increasing CRF may be especially beneficial for improving overall health and minimizing stroke-recurrence in these patients.

Physical activity

An interesting finding is that mean step count was higher in our sample than in the general population. This is at odds with previous research showing reduced daily step count after stroke[35] and could be related to our sample's relatively low mean age and high functional level. Our results indicate that the included patients walked a lot, but at low intensities. More steps-per-day has been reported to be inversely associated with all-cause and cardiovascular mortality in a recent meta-analysis.[36] Moreover, another study indicated that step-intensity is less important for all-cause mortality than total number of steps taken.[37] This is encouraging for patients who are unable to exercise at higher intensities but can manage walking at lower intensities.

Despite the high number of steps/day in our sample, 49% did not meet WHO's PA recommendations. This is consistent with previous reports of reduced PA levels following stroke[38] and may explain the lower CRF in stroke patients compared to reference values. Our backward regression analysis supports this, showing an association of higher CRF with higher MVPA, but not with more steps-per-day. This underlines the importance of exercising at a certain intensity to improve CRF.[39]

Fatigue and CRF

Fatigue prevalence in our sample was 35%, which falls at the lower range of post-stroke estimates reported in other studies.[1] We speculate that this might be related to the higher CRF in our sample compared to other stroke cohorts. We also

observed a higher prevalence of fatigue in patients with impaired versus non-impaired CRF and found that higher CRF was associated with lower fatigue. For every 4%-point change in VO_{2peak}/kg(%), FSS changed by one point, which is clinically meaningful.[40,41] Furthermore, this association is consistent with both the deconditioning hypothesis and our recent meta-analysis reporting a significant association between physical fitness and fatigue.[11] However, these results should be interpreted with caution as association does not indicate causation. Although there is preliminary evidence of exercise's ability to reduce fatigue,[7] more studies are needed to prove that exercise therapy can reduce fatigue in stroke patients.

Strengths and limitations

This study is robust due to its use of gold standard measurements of CRF and body composition, in combination with objective measurement of PA, and use of the recommended method for assessing PSF.[2] Limiting our cohort to patients with first-ever ischemic stroke enabled us to assess CRF, PA and fatigue levels after stroke without the confounding effect of previous strokes. However, this likely contributed to a relatively low mean age and less disability as patients with previous strokes tend to be older and potentially more severely disabled. Similarly, excluding hemorrhagic strokes likely contributed to lower disability. Consequently, generalization to patients with recurrent or other type of stroke must be done with caution. Evaluating sample representativeness by comparisons with the Norwegian Stroke Registry is another strength. Although, our sample had statistically significant lower age and less disability than patients in the registry, the clinical meaningfulness of the difference in disability is questionable (only 0.3 on the 0–6 mRS scale), and sex distribution was similar.

Certain limitations also need to be considered. Due to small sample size and missing data, we lacked the statistical power to include additional potential confounders in the regression analysis (e.g. fat mass, fat%, leg muscle strength, sleep quality). The small sample size also led to increased risk of type-2 error, especially in comparisons of small groups. Furthermore, we did not consider the potential influence of different sensorimotor phases after stroke in this study (i.e. hypotonic and hypotrophic phase). However, our sample had few physical sequelae after stroke making it less likely that this would have influenced the results, and all patients were in the same phase of recovery. Finally, we may have inadvertently excluded patients with aphasia, as patients unable to complete the study questionnaires were excluded from NORFAST.

Conclusion

First-ever ischemic stroke patients exhibited reduced CRF and MVPA compared to predicted values. Impaired CRF was mainly associated with obesity. However, consistent with the deconditioning hypothesis, lower CRF was also associated with reduced MVPA and greater fatigue after stroke. Future studies should investigate whether an aerobic exercise intervention is effective in improving CRF and reducing fatigue in patients with impaired CRF after stroke.

Acknowledgments

We thank Hege Ihle-Hansen (MD, PhD) at OUS and our research assistants for help with recruitment and data collection, and Associate Professor Einar August Høgestøl (MD, PhD), and Gisle Berg Helland (MD, PhD-student) at OUS for collaboration and help in assessing CT and MR imaging. We thank Professor Milada C. Småstuen for statistical advice. The manuscript originates from the Norwegian Study of Fatigue after Stroke (NORFAST) study group.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The work was funded by Lovisenberg Diaconal Hospital's research fund under Grant: N/A, and the Network for research and innovation to decrease symptom burden and improve quality of life outcomes in patients with chronic medical conditions (NORSMAN) project under Grant: 340113.

ORCID

Petra Larsson http://orcid.org/0000-0003-3866-8287

Data availability statement

Owing to data protection considerations, our dataset is not publicly available in a data repository. For data access, please contact the corresponding author. Any exchange of data is dependent on permission from REK and Lovisenberg Diaconal Hospital's data protection officer.

References

1. Zhan J, Zhang P, Wen H, et al. Global prevalence estimates of poststroke fatigue: a systematic review and meta-analysis. *Int J Stroke*. 2022;18(9):1040–1050. doi:10.1177/17474930221138701.
2. English C, Simpson DB, Billinger SA, et al. A roadmap for research in post-stroke fatigue: consensus-based core recommendations from the third stroke recovery and rehabilitation roundtable. *Int J Stroke*. 2023;19 (2):133–144. doi:10.1177/17474930231189135.
3. Chen W, Jiang T, Huang H, et al. Post-stroke fatigue: a review of development, prevalence, predisposing factors, measurements, and treatments. *Front Neurol*. 2023;14:1298915. doi:10.3389/fneur.2023.1298915.
4. Lerdal A, Gay CL. Fatigue in the acute phase after first stroke predicts poorer physical health 18 months later. *Neurology*. 2013;81(18):1581–7. doi:10.1212/WNL.0b013e3182a9f471.
5. Glader EL, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. *Stroke*. 2002;33(5):1327–33. doi:10.1161/01.STR.0000014248.28711.D6.
6. Duncan F, Kutlubaev MA, Dennis MS, et al. Fatigue after stroke: a systematic review of associations with impaired physical fitness. *Int J Stroke*. 2012;7 (2):157–62. doi:10.1111/j.1747-4949.2011.00741.x.
7. Tai D, Falck RS, Davis JC, et al. Can exercise training promote better sleep and reduced fatigue in people with chronic stroke? A systematic review. *J Sleep Res*. 2022;31(6):e13675. doi:10.1111/jsr.13675.
8. Fan Q, Jia J. Translating research into clinical practice: importance of improving cardiorespiratory fitness in stroke population. *Stroke*. 2020;51(1):361–7. doi:10.1161/STROKEAHA.119.027345.
9. Blokland IJ, Groot FP, Logt NH, et al. Cardiorespiratory fitness in individuals post-stroke: reference values and determinants. *Arch Phys Med Rehabil*. 2023;104 (10):1612–1619. doi:10.1016/j.apmr.2023.03.035.
10. Deijle IA, Van Wegen EE, Van den Berg-Vos RM, Kwakkel G. Is cardiorespiratory fitness independently associated with fatigue in patients with transient ischemic attack or minor stroke? *Brain Sci*. 2023;13 (4):561. doi:10.3390/brainsci13040561.
11. Larsson P, Bidonde J, Olsen U, et al. Association of post-stroke fatigue with physical activity and physical fitness: a systematic review and meta-analysis. *Int J Stroke*. 2023;18(9):1063–70. doi:10.1177/17474930231152132.
12. Thilarajah S, Mentiplay BF, Bower KJ, et al. Factors associated with post-stroke physical activity: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2018;99(9):1876–89. doi:10.1016/j.apmr.2017.09.117.
13. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. *Cochrane Database Syst Rev*. 2020;2020(3). doi:10.1002/14651858.CD003316.pub7.
14. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370 (9596):1453–7. doi:10.1016/S0140-6736(07)61602-X.
15. Edvardsen E, Hansen BH, Holme IM, et al. Reference values for cardiorespiratory response and fitness on the treadmill in a 20-to 85-year-old population. *Chest*. 2013;144(1):241–8. doi:10.1378/chest.12-1458.
16. Borg GA, Noble BJ. Perceived exertion. *Exerc Sport Sci Rev*. 1974;2(1):131–153. doi:10.1249/00003677-197400020-00006.
17. Edvardsen E, Hem E, Anderssen SA, Reddy H. End criteria for reaching maximal oxygen uptake must be strict and adjusted to sex and age: a cross-sectional study. *PLoS One*. 2014;9(1):e85276. doi:10.1371/journal.pone.0085276.
18. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121–1123. doi:10.1001/archneur.1989.00520460115022.
19. Lerdal A, Kottorp A. Psychometric properties of the fatigue severity scale—Rasch analyses of individual responses in a Norwegian stroke cohort. *Int J Nurs Stud*. 2011;48(10):1258–1265. doi:10.1016/j.ijnurstu.2011.02.019.
20. Lerdal A, Bakken LN, Rasmussen EF, et al. Physical impairment, depressive symptoms and pre-stroke fatigue are related to fatigue in the acute phase after stroke. *Disabil Rehabil*. 2011;33(4):334–42. doi:10.3109/09638288.2010.490867.
21. Macek P, Biskup M, Terek-Derszniak M, et al. Optimal cut-off values for anthropometric measures of obesity in screening for cardiometabolic disorders in adults. *Sci Rep*. 2020;10(1):11253. doi:10.1038/s41598-020-68265-y.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67 (6):361–70. doi:10.1111/j.1600-0447.1983.tb09716.x.
23. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007;38(3):1091–6. doi:10.1161/01.STR.0000258355.23810.c6.
24. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26 (2):319–338. doi:10.1183/09031936.05.00034805.

25. Philip HQ, Sanja S, Tim JC, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324. doi:10.1183/09031936.00080312.
26. BH H, Sa JJ, Kolle E, et al. Kartlegging av fysisk aktivitet blant voksne og eldre 2020-22 (Kan3). In: ed. Idrettshøgskole N, Oslo: Folkehelseinstituttet. 2023.
27. Kurl S, Laukkanen JA, Rauramaa R, et al. Cardiorespiratory fitness and the risk for stroke in men. *Arch Intern Med*. 2003;163(14):1682–8. doi:10.1001/archinte.163.14.1682.
28. Gjellesvik TI, Becker F, Tjønna AE, et al. Effects of high-intensity interval training after stroke (the HIIT-stroke study): a multicenter randomized controlled trial. *Arch Phys Med Rehabil*. 2020;101(6):939–47. doi:10.1016/j.apmr.2020.02.006.
29. Arena R, Myers J, Williams MA, et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American heart association committee on exercise, rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation*. 2007;116(3):329–43. doi:10.1161/CIRCULATIONAHA.106.184461.
30. Pereira AS, Aguiar LT, Quintino LF, et al. Effects of detraining on cardiorespiratory fitness of individuals with chronic stroke. *Top*. 2021;28(5):321–330. doi:10.1080/10749357.2020.1816074.
31. MacKay-Lyons M, McDonald A, Matheson J, et al. Dual effects of body-weight supported treadmill training on cardiovascular fitness and walking ability early after stroke: A randomized controlled trial. *Neurorehabil Neural Repair*. 2013;27(7):644–53. doi:10.1177/1545968313484809.
32. Wang X, Huang Y, Chen Y, et al. The relationship between body mass index and stroke: a systemic review and meta-analysis. *J Neurol*. 2022;269(12):6279–89. doi:10.1007/s00415-022-11318-1.
33. Boss HM, Deijle IA, Van Schaik SM, et al. Cardiorespiratory fitness after transient ischemic attack and minor ischemic stroke: baseline data of the MoveIT study. *J Stroke Cerebrovasc Dis*. 2017;26(5):1114–20. doi:10.1016/j.jstrokecerebrovasdis.2016.12.029.
34. Driver S, Douglas M, Reynolds M, et al. A narrative review of biopsychosocial factors which impact overweight and obesity for individuals with acquired brain injury. *Brain Inj*. 2021;35(9):1075–1085. doi:10.1080/02699052.2021.1953596.
35. Fini NA, Holland AE, Keating J, et al. How physically active are people following stroke? Systematic review and quantitative synthesis. *Phys Ther*. 2017;97(7):707–17. doi:10.1093/ptj/pzx038.
36. Banach M, Lewek J, Surma S, et al. The association between daily step count and all-cause and cardiovascular mortality: a meta-analysis. *Eur J Prev Cardiol*. 2023;30(18):1975–1985. doi:10.1093/eurjpc/zwad229.
37. Saint-Maurice PF, Troiano RP, Bassett DR, et al. Association of daily step count and step intensity with mortality among US adults. *JAMA*. 2020;323(12):1151–60. doi:10.1001/jama.2020.1382.
38. English C, Manns PJ, Tucak C, et al. Physical activity and sedentary behaviors in people with stroke living in the community: a systematic review. *Phys Ther*. 2014;94(2):185–96. doi:10.2522/ptj.20130175.
39. Swain DP, Franklin BA. VO2 reserve and the minimal intensity for improving cardiorespiratory fitness. *Med Sci Sports Exerc*. 2002;34(1):152–157. doi:10.1097/00005768-200201000-00023.
40. Keteyian SJ, Brawner CA, Savage PD, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J*. 2008;156(2):292–300. doi:10.1016/j.ahj.2008.03.017.
41. Nordin Å, Taft C, Lundgren-Nilsson Å, et al. Minimal important differences for fatigue patient reported outcome measures—a systematic review. *BMC Med Res Methodol*. 2016;16(1):62. doi:10.1186/s12874-016-0167-6.