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Early Mobilization in Patients with Stroke

Early Sitting in Ischemic Stroke Patients (SEVEL): A Randomized Controlled Trial

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Abstract

Background

Extended immobility has been associated with medical complications during hospitalization. However no clear recommendations are available for mobilization of ischemic stroke patients.

Objective

As early mobilization has been shown to be feasible and safe, we tested the hypothesis that early sitting could be beneficial to stroke patient outcome.

Methods

This prospective multicenter study tested two sitting procedures at the acute phase of ischemic stroke, in a randomized controlled fashion (clinicaltrials.org registration number NCT01573299). Patients were eligible if they were above 18 years of age and showed no sign of massive infarction or any contra-indication for sitting. In the early-sitting group, patients were seated out of bed at the earliest possible time but no later than one calendar day after stroke onset, whereas the progressively-sitting group was first seated out of bed on the third calendar day after stroke onset. Primary outcome measure was the proportion of patients with a modified Rankin score [0–2] at 3 months post stroke. Secondary outcome measures were a.) prevalence of medical complications, b.) length of hospital stay, and c.) tolerance to the procedure.

Results

One hundred sixty seven patients were included in the study, of which 29 were excluded after randomization. Data from 138 patients, 63 in the early-sitting group and 75 in the progressively-sitting group were analyzed. There was no difference regarding outcome of

people with stroke, with a proportion of Rankin [0–2] score at 3 months of 76.2% and 77.3% of patients in the early- and progressive-sitting groups, respectively (p = 0.52). There was also no difference between groups for secondary outcome measures, and the procedure was well tolerated in both arms.

Conclusion

Due to a slow enrollment, fewer patients than anticipated were available for analysis. As a result, we can only detect beneficial/detrimental effects of +/- 15% of the early sitting procedure on stroke outcome with a realized 37% power. However, enrollment was sufficient to rule out effect sizes greater than 25% with 80% power, indicating that early sitting is unlikely to have an extreme effect in either direction on stroke outcome. Additionally, we were not able to provide a blinded assessment of the primary outcome. Taking these limitations into account, our results may help guide the development of more effective acute stroke rehabilitation strategies, and the design of future acute stroke trials involving out of bed activities and other mobilization regimens.

Trial Registration

ClinicalTrials.gov NCT01573299

Introduction

With an estimated 17 million cases worldwide, of which 70% result from an ischemic injury, stroke has a deep socio-economic impact [1]. Patients' outcomes depend on the initial severity of the cerebral infarction, comorbidities and subsequent medical complications, often due to prolonged immobility [2,3]. In the context of the acute stroke phase, starting out-of-bed mobilization can be a challenging clinical decision to make. Indeed, the inability of the cerebral circulation to adapt to hemodynamic changes, and the dysfunction of the cardiac baroreceptor sensitivity may be expected to limit the use of early upright positioning [4]. Under physiologic conditions, compensatory mechanisms (known as cerebral auto-regulation) prevent the cerebral blood flow (CBF) from varying with systemic blood pressure. During acute stroke, cerebral auto-regulation mechanisms are impaired and any fluctuation in blood pressure can affect the CBF directly [5]. When a change in the position of the body occurs, such as from lying to sitting, a potential drop in the systemic blood pressure could then theoretically translate in a decrease of the CBF. In view of a potential neurological worsening due to a change in the body position, protocols to lead the patient towards an upright position progressively may then be indicated during the acute stroke stage. Clinicians therefore have to weigh potentially beneficial out-of-bed activities in the prevention of complications, against the potential aggravation of neurological deficits, with very little guidance available [6–8].

The hypothesis that early out-of-bed mobilization (sitting or standing within 24h of stroke onset) would improve outcome of people with stroke has first been tested in pilot trials [9,10]. Combined analysis of two pilots studies, AVERT (n = 71 patients) and VERITAS (n = 32 patients), which were respectively conducted in Australia and UK, showed that early out-of-bed mobilization increased the probability for the patient to be independent (modified Rankin score 0–2) at 3 months, and decreased the risk of developing complications during hospitalization [11]. Nevertheless, the recently published international trial AVERT, which enrolled 2104

patients randomized in "usual care" and "very early mobilization" (VEM) arms, the latter with higher frequency and duration of out-of-bed activities, wasn't able to confirm a more favorable effect of the VEM procedure [12]. Because both groups were mobilized relatively early after stroke onset (median 18.5 vs. 22.4 in VEM and control groups, respectively), the increased frequency (median 6.5 vs. 3 times per day) and duration (median 31 vs. 10 min), may actually serve as stronger discriminators between treatment arms than mobilization onset.

In this study, we explored the hypothesis that upright positioning (out of bed) within 24 hours of stroke onset would be beneficial to patient outcome at 3 months, as compared to a more progressive upright positioning protocol over 3 days, which would minimize acute cerebral hemodynamic changes. To answer this question, we designed a prospective randomized control study in which the two protocols were tested.

Materials and Methods

Study design and sample size calculation

The study design was a prospective multicenter, randomized control trial in parallel groups with equal randomization. Patients were enrolled and randomized after screening for inclusion/exclusion criteria and obtaining informed consent. Randomization between early and progressively sitting was performed via numbered sealed envelopes that the investigator would draw from in consecutive fashion (with blocks of 4 in 1:1 ratio, stratified by center) each time a patient was enrolled in the study. The random sequence was generated by our statistician (C. V.) using the SAS software. Data was reported online using a server dedicated to the study.

Sample size was estimated from a previous study in which data from 2 individual trials testing early mobilization within 36h of stroke onset were grouped [11]. Calculation was performed based on a type I error risk of 5% and a power of 80%, in a two-sided approach and with a Fisher exact test. A total of 183 patients per group was calculated as necessary to show a difference of 15% in the prevalence of patients showing a Rankin score [0–2] at three month after stroke onset: 35% in the progressive-sitting group versus 50% in the early-sitting group. Additional risk of low tolerance for early sitting was estimated at 9% (from our own observations) so the sample size has been adjusted to a total of 200 patients per group.

Protocol approval, registration and patients consent

The SEVEL (Stroke and Early VErticaL positioning) study was approved by the Ethics Committee at the Nantes University Hospital in France (approved September 06th 2011). The authors confirm that all on going and related trials for this intervention are registered. This study was registered at clinicaltrials.org (registration number NCT01573299), with a delay. Indeed it has been registered as a "usual care" study at the level of the Institutional research board, and a miscommunication between our team and the clinical research department caused the delay, which was not sufficiently problematic to force a study restart. Informed and written consent was obtained from all patients.

Patients, inclusion and exclusion criteria

Patients were recruited from 11 centers located in the North West region of France. Ischemic stroke was diagnosed by a neurologist and defined by the sudden onset of a persistent neurological deficit without sign of bleeding on the CT scan, or MRI. Patients were eligible to participate in the study if they were above 18 year old, exhibited neurological deficits at the inclusion time, were kept in bed (30° maximum) until inclusion time, and if they were enrolled in a healthcare plan (French social security). Patients had to be included at the earliest possible

time, and no later than one calendar day after stroke onset. Exclusion criteria were based on 1. stroke severity (malignant infarction, NIHSS > 22, alteration of consciousness with a Glasgow Coma Score < 13), 2. fluctuation of the neurological signs before admission (history of worsening linked to an upright positioning), 3. known intra-cranial stenosis > 50%, symptomatic of the current episode, 4. minor neurological deficit (isolated facial palsy, isolated hemianopia, isolated sensory impairment), 5. iterative vomiting or difficulty in breathing, 6. contra-indication for sitting, e.g. deep vein thrombosis (diagnosed or suspicion) or lower limb fracture, 7. Pre-admission Rankin score [3–6] 8. anticipated difficult follow up (e.g. not speaking French, living in another region), 9. pregnant women, and 10. enrollment in another trial or refusal to participate.

Intervention

In this study we aimed to test two different protocols for sitting in acute ischemic stroke patients: early and progressive. In the early sitting arm, patients would be seated out of bed at the earliest time possible, but no later that the calendar day after stroke onset. The progressive sitting arm started the day of stroke onset (day 0) when the patient would be positioned in bed at 30°, 45° the day after (day 1) and 60° at day 2 and sitting out of bed at day 3 (which corresponds to the first sitting in this group). Those angles reflect the position of the upper body relative to the bed (and floor). For both protocols, minimal duration of the first sitting was 15 minutes. The procedure could be continued depending on patient fatigue and tolerance (60 minutes maximum). The physiotherapist or the nurses were in charge of collecting the data (blood pressure, tolerance. . .) related to it. Sitting posture (legs dangling or feet positioned on a foot rest), was done as usual in keeping with each unit's protocol. The use of a lifter, when necessary, was allowed. Close monitoring of the blood pressure and heart rate was performed: before the sitting procedure, immediately after and 5 minutes after. While sitting, patients showing any sign of low tolerance, defined by neurological worsening (of current or new neurological deficits), vagal reaction (bradycardia or nausea), a greater than 40 mmHg increase of blood pressure topping 180/100mmHg, or a symptomatic decrease in blood pressure, would be put back in bed.

Sitting was repeated on a daily basis according to initial tolerance of the procedure, as approved by the physician in charge. Physiotherapy and deep vein thrombosis prevention by low molecular weight heparin were performed as usual in each unit.

Outcome measures

Evaluations were made during the intermediate time point at 7 days (or the day of discharge, if before 7 days) and at 3-month after stroke, by a neurologist from the same stroke unit, aware of the study and unblinded to the patient group assignment. The primary outcome measure was the proportion of modified Rankin score [0–2] at three months visit after stroke onset. Patients with major deviation to the protocol or serious adverse event that were enrolled but couldn't continue the study were assigned a Rankin score in the category [3–6].

Secondary outcomes were assessed during the hospital stay at an intermediate time point at 7 days (or the day of discharge, if before 7 days), and also during the 3-month follow-up. At the intermediate evaluation time point, NIHSS and Rankin scores were evaluated. The Rankin, NIHSS and Barthel scores were provided to the study staff from the NINDS or Internet stroke center websites. Data about the tolerance of the sitting positioning (including prevalence of side effects that forced termination of the procedure) was also collected. A final review of the complications that occurred during hospital stay was also performed at 3 months using a multiple-choice list, and based on both patient interview and medical records. The presence of

fatigue (question about the presence or not of an abnormal sensation of being tired, which would impact patient's activity) was assessed at 3 months only. The duration of sitting out of bed was calculated from the recorded time at which the patient was positioned seated out of bed to the time at which the patient would be put back in bed. The observer would directly write on the case report both first sitting time and sitting duration through specific sections. Length of hospitalization was also recorded for each patient.

Analyses

Analyses were performed on all data available from patients whose primary outcome was assessed. Continuous variables were presented with mean and standard deviation. Categorical data were expressed as number and percentages (calculated on the number of available data from each group). Primary and secondary outcomes were compared between groups with Chi square test, Student test, Wilcoxon test or generalized linear mixed models (taking into account randomization stratified by center and baseline NIHSS measure for continuous variable). Linear mixed models included baseline NIHSS as fixed effect and center as random effect. Statistical tests were two-sided, and significance has been set at 0.05. Analyses were conducted using the SAS ® 9.3 software.

Results

Enrollment period was conducted between November 2011 and April 2014. The study ended prematurely as it became unviable due to degradation of recruitment rate. One hundred sixty seven patients were enrolled, of whom 29 were excluded (19 in the early sitting group, 10 in the progressive sitting group): for 17 patients the 3 month visit was not performed (6 patients not were not scheduled, 6 patients failed to attend the appointment and for 5 patients no reason was provided), 6 patients lacked evaluation of the Rankin score at 3 months, one patient withdrew his consent and 5 patients subsequently matched exclusion criteria (1 was enrolled in another study, two patients without written consent, two patients misdiagnosed for stroke), Fig 1. One hundred and thirty eight patients were therefore available for analysis. Sixty-three

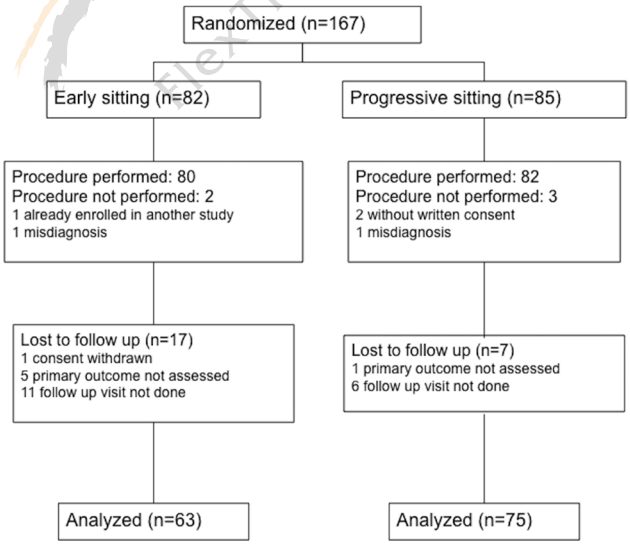

Fig 1. Flow chart of the study.

patients were analyzed in the early sitting procedure and 75 in the progressive sitting procedure.

A description of the sample is given in Table 1. The two groups were similar regarding age, gender, stroke etiology and severity. Stroke to the first sitting time was 1.1 ±0.2 days in the early sitting group versus 3 ±0.2 days in the progressive group, reflecting good adherence to protocol for both groups.

First sitting lasts significantly longer in the progressive group compared to the early group: 83.7 ±94.7 minutes versus 56.6 ±41.7 minutes respectively ($p<0.05$). Tolerance of the sitting procedure was the same in the early and progressive sitting groups, with a prevalence of side effects of 14.5% and 13.7%, respectively (Table 2). Only one patient showed a worsening of the neurological state (early sitting group). Systolic and diastolic blood pressure, as well as heart rate, did not significantly vary between baseline, acute measurement right after being seated, and 5 minutes later (Table 2). Sitting was continued daily for both groups during hospitalization in 96% of cases.

While both groups improved over the first week, there was a significant difference in the NIHS scores at one week: 3.7±3.7 NIHSS in the early sitting group versus 2.6±3.7 in the progressive arm ($p<0.05$, Table 3). Nevertheless, outcome at 3 months was comparable between the two groups, with a prevalence of Rankin [0–2] score of 76.2% in the early sitting group and 77.3% in the progressive sitting group ($p = 0.52$, Table 3). About the same proportion of patients in both groups were living at home at the 3 month visit (86% in the early sitting group and 91% in the progressively sitting group, $p = 0.41$). Nine deaths were recorded: 3 in the early sitting group (4.84% of the sample) and 6 in the progressively sitting group (8.33%). For five patients (two in the early sitting group, 3 in the progressive sitting group) the Rankin score was assigned. For two patients, a complication that led to the abortion of the sitting procedure occurred ($n = 1$ in each group, imputed to the [3–6] class). For two others in the "progressive sitting" group, a deviation to the protocol was noted: one was seated at day one, and one was not monitored properly during the first sitting (both imputed to the [3–6] class). One patient had a Rankin score imputed at 5 at 3 months in the "early sitting" group for a recurrent stroke (two months after the qualifying event). Regarding independence in activities of daily living, there was a slight, but significant difference in the Barthel index at 3 months, as patients included in the early sitting procedure would show a higher ($p = 0.05$) Barthel index (96.7±8.1) than the progressive group (90.5±22.3). Absolute difference for that parameter is 6.1 with a 95% confidence interval of [0.09–12.11]. Fatigue prevalence at 3 months was not different in the two groups: 43.1% in the early sitting group versus 48.5% in the progressive sitting group, respectively, $p = 0.81$.

No significant difference in the prevalence of medical complications was observed between the early and progressive sitting groups (Table 4). Overall prevalence of medical complications was 28.4%, of which the most frequent were urinary retention (16.4%) followed by constipation (12.7%). Eight percent of our sample showed infectious complication (50% pulmonary and 50% urinary), one patient who had both. Deep vein thrombosis was observed in one case (0.75%). Early sitting didn't significantly shorten the hospital length of stay, which averaged approximately 10 days in each group (Table 4), or the proportion of patients who were discharged and at home at the time of the visit at 3 months (about 60% in each group).

Discussion

In this study, we did not observe a significant beneficial or detrimental effect of early sitting, starting as early as possible but no later than the calendar day after stroke onset, compared to a progressive sitting procedure over 3 days post-stroke onset. Our primary endpoint at 3 months

Table 1. Description of the population.

	Early sitting	Progressive sitting
Analyzed patients	n = 63	n = 75
Age (mean ±SD)	68.1 ±13.7	71.2 ±13.3
Age Median (Q1-Q3)	70.8 [60.9–78.5]	73.6 [62.1–81]
Male (n,%)	48 (76.2)	41 (54.7)
Pre admission Rankin score 0 (n, %)	58 (93.6)	65 (89)
At home before hospitalization (n,%)	62 (98.4)	73 (97.3)
Cardiovascular risk factors	56 (88.9)	64 (85.3)
High blood pressure (n,%)	39 (61.9)	48 (64)
Diabetes (n,%)	5 (7.9)	15 (20)
Dyslipidemia (n,%)	31 (49.2)	34 (45.3)
Current or past smoking (n,%)	20 (31.8)	6 (8)
BMI>30 (n,%)	11 (18.3)	12 (17.7)
Cardiovascular comorbidity		
Arteritis (n,%)	1 (1.6)	4 (5.3)
Coronaropathy (n,%)	9 (14.3)	10 (13.3)
Qualifying event		
Admission NIHSS (mean ±SD)	7.2±3.9	7.8±5.6
Median (Q1-Q3)	7 [4–9]	6 [3–10]
Hemiplegia (n,%)	15 (23.8)	13 (17.3)
Aphasia (n,%)	18 (28.6)	25 (33.3)
Admission Rankin score (n,%)		
Available data	61	73
0	0 (0)	3 (4.11)
1	8 (13.11)	9 (12.33)
2	11 (18.03)	11 (15.07)
3	13 (21.31)	21 (28.77)
4	23 (37.7)	22 (30.14)
5	6 (9.84)	7 (9.59)
Rankin score [0–2] (n,%)	19 (31.1)	23 (31.5)
Stroke etiology		
Available data	62	73
Athero-thrombotic (n,%)	16 (25.8)	25 (34.2)
Carotid symptomatic stenosis >50%	3 (4.8)	8 (11)
Cardio embolic (n,%)	22 (35.5)	24 (32.9)
Atrial fibrillation	17 (27.4)	18 (24.7)
Dissection (n,%)	1 (1.16)	1 (1.33)
Lacunar (n,%)	10 (16.1)	5 (6.8)
Cryptogenic (n,%)	12 (19.4)	16 (21.9)
Other (n,%)	1 (1.6)	2 (2.7)
Symptomatic intra cranial stenosis	3 (4.8)	1 (1.3)
First sitting parameters		
Calculated time to first sitting (day)		
Available data	51	55
Mean ±SD	1.08 ±0.26	2.97.±0.26
Median [Q1-Q3]	1.08 [0.91–1.24]	2.98 [2.78–3.08]
First sitting duration (min)		
Available data	59	61

(*Continued*)

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Table 1. (*Continued*)

	Early sitting	Progressive sitting
Mean ±SD	56.6±41.7	83.7 ± 94.76
Median [Q1-Q3]	55 [30–60]	0 [60–90]

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was the proportion of each group matching a modified Rankin [0–2]. We reported a significant but slight difference (6.1) in the Barthel index favoring the early sitting group, which may only have border-line clinical relevance. No significant difference was noted regarding medical complications during hospitalization, and tolerance to first sitting was similar in the two procedures.

However, given that the original recruitment goal was set at 200 patients per group, the achieved power to detect a 15% difference between groups was reduced to 37% as opposed the targeted 80% power. As a result, effects of early sitting on recovery, and associated complications, may have been missed. The study is actually sufficiently sensitive to detect a difference of 25% between groups, with a power of 80% and unchanged modified Rankin score proportion of [0–2]. The odds ratio in favor of the intervention "early sitting" effect was calculated at 1.33, with a confidence interval of [0.55–3.19]. We therefore consider the effect of early sitting on

Table 2. Tolerance in early and progressive sitting procedures.

Analyzed patients	Early sitting (n = 63)	Progressive sitting (n = 75)	
Physiological parameters during first sitting procedure			
Available data			
Before	n = 59	n = 69	
Right after	n = 58	n = 68	
5 minutes after	n = 59	n = 66	
Systolic blood pressure (mmHg, mean ±SD)			
Before	145.5 ±18.6	141 ±21	
Right after	146.8 ±22.3	142.8 ±23.2	
5 minutes after	145 ±21.7	140.4 ±24	
Diastolic blood pressure (mmHg, mean ±SD)			
Before	82.8 ±15.1	80.6 ±14.2	
Right after	84 ±17.4	83.6 ±14	
5 minutes after	84.2 ±15.3	80.1 ±16.3	
Heart rate (bpm)			
Before	75.6 ±13.9	71.9 ±14.5	
Right after	79.2 ±15.6	76.7 ±17.2	
5 minutes after	77.1 ±14.6	74.7 ±15.8	
Adverse events			
Available data	n = 62	n = 73	p
Adverse events, total (n,%)	9 (14.52)	10 (13.7)	0.89
Neurological worsening (n,%)	1 (1.61)	0	
Headache (n,%)	0	1 (1.37)	
Vagal reaction (n,%)	1 (3.22)	2 (2.74)	
Symptomatic hypotension (n,%)	1 (1.61)	1 (1.37)	
Blood pressure increase > 180/100mmHg or more than 40 mmHg from baseline (n,%)	2 (3.23)	2 (2.74)	
Fall (n,%)	1 (1.61)	1 (1.37)	
Other (n,%)	3 (4.84)	3 (4.11)	

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Table 3. Outcome of patients in early and progressive sitting procedures.

	Early sitting (n = 63)		Progressive sitting (n = 75)		
		Available data		Available data	P
Day 7 or discharge NIHSS mean (±SD)	3.68±3.71	62	2.64±3.71	72	0.03**
Median [Q1-Q3]	2.5 [1–5]		2 [1–3]		
3 month NIHS score (mean ±SD)	1.75±2.44	57	1.71±2.52	66	0.9**
Median [Q1-Q3]	1 [0–3]		1 [0–2]		
Day 7 or discharge Rankin score (mean ±SD)	2.1±1.5	62	1.75±1.32	72	0.07**
Median [Q1-Q3]	2 [1–4]		1.5 [1–3]		
Day 7 or discharge detailed Rankin score(n,%)		62		72	
0	11 (17.74)		12 (16.67)		
1	13 (20.97)		24(33.33)		
2	15 (24.19)		17 (23.61)		
3	7 (11.29)		10 (13.89)		
4	14 (22.58)		7 (9.72)		
5	2 (3.23)		2 (2.78)		
3 month Rankin [0–2] (n,%)	48 (76.19)	63	58 (77.33)	75	0.52**
3 month detailed Rankin score (n,%)		62		72	
0	19 (30.65)		18 (25)		
1	20 (32.26)		23 (31.94)		
2	9 (14.52)		17 (23.61)		
3	8 (12.9)		4 (5.56)		
4	2 (3.23)		3 (4.17)		
5	1 (1.61)		1 (1.39)		
6	3 (4.84)		6 (8.33)		
3 month Barthel Index (mean ±SD)	96.67±8.09	57	90.53±22.28	66	0.05**
Median [Q1-Q3]	100 [100–100]		100 [95–100]		
Discharge destination (n,%)		58		67	0.27
Transitional care hospital	2 (3.45)		5 (7.46)		
Another hospital	0		3 (4.48)		
Rehabilitation	21 (36.21)		18 (26.87)		
Home	35 (60.34)		41 (61.19)		
Patients living at home at 3 months (n,%)	49 (84.5)	58	60 (90.9)	66	0.41
3 month Fatigue (n,%)	25 (43.1)	58	32 (48.48)	66	0.81**
Days since stroke onset at Day 7 or discharge visit (days, mean ±SD)	6.5±1.51	62	6.78 ±1.13	72	0.27*
Median [Q1-Q3]	7 [6–7]		7 [6–7]		
Days since stroke onset at 3 month visit (days, mean ±SD)	99.95±17.58	58	95.61±11.95	66	0.13*
Median [Q1-Q3]	97.5 [91–107]		95 [90–104]		

* test adjusted on center

**test adjusted on center and baseline NIHSS

stroke outcome, in comparison to the progressive sitting procedure, to be unlikely to be extreme. Also, 17% (n = 29) of the patients that have been randomized were excluded from the study. This does not comply fully with the intention-to-treat principle, but resembles a per protocol analysis. For 23, the primary endpoint of the study was missing (the 3 month visit was not performed, or was performed without this assessment), 5 subsequently matched exclusion

Table 4. Medical complication prevalence in early and progressive sitting procedures.

	Early sitting (n = 63)		Progressive sitting (n = 75)		
		Available data		Available data	P
Length of stay (days, mean ±SD)	9.78±4.85	58	10.53±6.11	66	0.27*
Patient with at least one medical complication during hospitalization (n,%)	15 (24.19)	62	23 (31.94)	72	0.33
Pulmonary infection (n,%)	2 (3.23)	62	4 (5.56)	72	0.69
Urinary tract infection (n,%)	2 (3.23)	62	4 (5.56)	72	0.69
Dysphagia (n,%)	3 (4.84)	62	5 (6.94)	72	0.72
Constipation (n,%)	10 (16.13)	62	7 (9.72)	72	0.27
Urinary retention (n,%)	7 (11.29)	62	15 (20.83)	72	0.14
Deep vein thrombosis (n,%)	1 (1.61)	62	0	72	0.46
Pressure ulcer (n,%)	0	62	0	72	

*test adjusted on center and baseline NIHSS

criteria and 1 withdrew his consent. We considered these patients to generally match the study population (description of this population is provided as supplementary material).

Rehabilitation strategies at the acute stroke phase (within 24–48 hours) raise significant interest among clinicians. Previously restricted to pilot studies, a major effort by the international AVERT trial reported the results of 2104 patients assigned to an out-of-bed "very early mobilization" (VEM) arm compared to the "usual care" arm. However, VEM was characterized not only by early mobilization starting within 24 hours of stroke onset, but also significantly higher frequency and duration of mobilization. In contrast to the pilot studies, the analysis of the AVERT trial actually revealed a more favorable outcome for patients in the "usual care" arm, as defined by a modified Rankin score [0–2] at 3 months. Because the level of activity during first out-of-bed activities differed greatly between the treatment arms, and may impact outcome and complications independently, the optimal timing of first mobilization still remained to be individually addressed.

In our study, the initial level of activity was set at a minimum of 15 minutes of sitting, and the staff in charge (physicians, nurses or physiotherapists) decided about the total duration of the procedure, according to patient tolerance and comfort. A maximum of 60 minutes for the first sitting was recommended, but not respected in most cases, probably because of the overall good tolerance of the procedure. In the progressive sitting group, a longer first mobilization was performed, but adjusting by this factor did not change the significance of primary outcome at 3 months. We did not record the time spent out of bed in the following days after the day of the first sitting, hence we cannot compare this parameter between groups. However, we did collect information about whether the first-sitting procedure was continued subsequently. In almost all patients, and regardless their group affiliation, the sitting procedure was continued at least once a day afterwards.

For the early sitting group, recommendations were given to sit the patient out of bed at the earliest possible time. Our median time to first mobilization in the early sitting group is 25.9 hours, which is longer than the 22.4h of the usual care group of the AVERT study. Twenty out of the 51 patients (39%) for whom we calculated an exact time to mobilization in the early seating group, were mobilized within 24 hours after stroke onset, all of them in the 12–24 hour interval. These first 24 hours may be critical to stroke expansion. Other strategies will be explored at this stage by the on-going clinical study Headpost, which compares a lying flat position with a 30 degrees in-bed position, within the first 24 hours after stroke onset [13]. In

both arms, the duration of first sitting (30–60 IQR) was longer than in the AVERT trial (16.5–50.5 IQR), which could indicate that the detrimental effects of the VEM protocol in the AVERT trial may not stem from the duration of out-of-bed activities. Instead, the frequency of out-of-bed activities may emerge as a possible predictor of less favorable outcomes in the AVERT study: VEM and usual-care groups differed significantly in daily frequency of mobilization (median 6.5 vs. 3 per day). In contrast, our study did not specifically modify frequency of mobilization between early and progressive mobilization groups but deferred to each center's standard care practice, which was applied equally to both groups. Repeated challenge of the cerebral auto regulation through more frequent upright positioning during the acute stroke phase may explain this observation. Future studies together with further analyses of the AVERT dataset would be needed to characterize and analyze this parameter in isolation.

Medical complication rate was lower than in previously published work about acute stroke [3,11]. Other studies testing early mobilization during acute stroke phase also showed a comparable rate of medical complications between groups mobilized in different fashion [14]. While reflecting a typical hospital-based population, most of our patients showed relatively mild neurological deficits, and thus were less likely to develop medical complications based on previous reports [2,15]. This parameter [16,17] may also explain the comparable length of stay between the two groups in our study. However, it is also possible that stroke exploration tests (e.g. carotid ultrasounds, cardiac echography) have artificially increased the patient stay when the neurological deficit was mild.

Our study was limited by slow recruitment and the loss to follow-up rate (about 10% of the initial cohort), which reflects difficulties inherent to conducting intervention studies in the acute phase of stroke. Even though centers were selected based on the number of people with stroke admission per year, several parameters reduced the recruitment rate: 1.) work load of the physicians, which limited time available to clinical research, 2.) high proportion of emergency room admissions, where high staff turnover may have limited enrollments, and 3.) patients' perceptions of clinical trials, which led several to refuse participation. Future trials for acute stroke procedures may require dedicated resources for greater pre-trial sensitization and training of the staff of the emergency room, and additional communication with patients to relate information about the clinical trial. Finally, we were not able to implement a blinded evaluation of the primary outcome at 3 months, which may allow for some bias from the physician assessing the Rankin score at follow-up.

Taken together our results indicate that there is no extreme effect of the early sitting procedure in comparison to a progressive sitting procedure in either direction after ischemic stroke. As early mobilization may enable more treatment possibilities in the rehabilitation process, with an earlier start for out-of-bed activities and a shortened hospitalization, future research efforts on this question are warranted. Our study provides more data about the timing of the first out-of bed activity after stroke, it may contribute to future meta analyses, and improve design of future studies in this area.

Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial

Summary

Background Early mobilisation after stroke is thought to contribute to the effects of stroke-unit care; however, the intervention is poorly defined and not underpinned by strong evidence. We aimed to compare the effectiveness of frequent, higher dose, very early mobilisation with usual care after stroke.

Methods We did this parallel-group, single-blind, randomised controlled trial at 56 acute stroke units in five countries. Patients (aged ≥18 years) with ischaemic or haemorrhagic stroke, first or recurrent, who met physiological criteria were randomly assigned (1:1), via a web-based computer generated block randomisation procedure (block size of six), to receive usual stroke-unit care alone or very early mobilisation in addition to usual care. Treatment with recombinant tissue plasminogen activator was allowed. Randomisation was stratified by study site and stroke severity. Patients, outcome assessors, and investigators involved in trial and data management were masked to treatment allocation. The primary outcome was a favourable outcome 3 months after stroke, defined as a modified Rankin Scale score of 0–2. We did analysis on an intention-to-treat basis. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12606000185561.

Findings Between July 18, 2006, and Oct 16, 2014, we randomly assigned 2104 patients to receive either very early mobilisation (n=1054) or usual care (n=1050); 2083 (99%) patients were included in the 3 month follow-up assessment. 965 (92%) patients were mobilised within 24 h in the very early mobilisation group compared with 623 (59%) patients in the usual care group. Fewer patients in the very early mobilisation group had a favourable outcome than those in the usual care group (n=480 [46%] *vs* n=525 [50%]; adjusted odds ratio [OR] 0·73, 95% CI 0·59–0·90; p=0·004). 88 (8%) patients died in the very early mobilisation group compared with 72 (7%) patients in the usual care group (OR 1·34, 95% CI 0·93–1·93, p=0·113). 201 (19%) patients in the very early mobilisation group and 208 (20%) of those in the usual care group had a non-fatal serious adverse event, with no reduction in immobility-related complications with very early mobilisation.

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Introduction

Early mobilisation after stroke, comprising out-of-bed sitting, standing, and walking, is thought to contribute to the powerful effect of stroke-unit care[1,2] and is recommended in many guidelines; however, it is poorly defined and not underpinned by strong evidence.[3] The biological rationale underlying the potential for early out-of-bed training centres around three arguments: (1) that bed rest negatively affects the musculoskeletal, cardiovascular, respiratory, and immune systems,[4] and might slow recovery; (2) that immobility-related complications are common early after stroke[5] at a time when patients are very inactive;[6] and (3) that there might be a narrow window of opportunity for brain plasticity and repair,[7] and the optimum period for change could be early after stroke.[8] Prompt start and more episodes of out-of-bed activity might therefore improve outcome. However, early mobilisation also has a plausible potential for harm, particularly within the first 24 h of stroke onset.[9] Harms could include damage to the ischaemic penumbra associated with reduced cerebral blood flow when the head position is raised,[10] or increased blood pressure associated with activity that might also worsen outcome.[11] Out-of-bed activity could also result in more falls with injury. Concerns about early start of mobilisation appear even more pronounced in the case of intracerebral haemorrhage[9] and in patients with ischaemic stroke treated with thrombolysis. These concerns are largely driven by clinical concerns about the risk of bleeding in the absence of any clear evidence.

Research in context

Evidence before this study

Early mobilisation after stroke is recommended in many clinical practice guidelines worldwide. In our 2015 review of 30 guidelines, early mobilisation was recommended in 22 examples, but the timing and prescription of the mobilisation intervention is scarcely specified. Early mobilisation is most often recommended as a method to reduce the risk of post-stroke complications, with subsequent improvements in favourable outcome expected. Our early Cochrane review identified no evidence of benefit, but included only one small randomised controlled trial (AVERT phase 2, n=71). A systematic review and meta-analysis by Lynch and colleagues identified three randomised controlled trials (n=159) in which a protocol of mobilisation starting within 24 h of stroke was compared with usual care. In this review, the investigators reported improved, albeit non-significant, odds of a favourable outcome with early mobilisation (Barthel index odds ratio [OR] 1·20, 95% CI −0·77 to 3·18; p=0·23; OR 1·16, 95% CI 0·61–2·18; p=0·66, with significant heterogeneity I^2=66%). The odds of having no complications in the first 3 months after stroke did not differ significantly between groups (OR 0·92, 95% CI 0·46–1·87, p=0·82). Fewer patients had died by 3 months after stroke in the usual care group (n=6) than in the early mobilisation group (n=15; OR 2·58, 95% CI 0·98–6·79; p=0·06), but this finding was not significant. When data on deaths from this meta-analysis are combined with data from the present trial, with both fixed-effects and random-effects meta-analysis, the findings are not appreciably changed (fixed-effects OR 1·35, 95% CI 0·99–1·83; p=0.06; random-effects OR 1·61, 0·82–3·14; p=0·17, I^2=26%). This meta-analysis represents the most recent systematic review of the topic.

Added value of this study

Before AVERT, evidence in trials came from three studies including 159 patients. We now have more robust evidence to inform practice. We believe that the results of AVERT are very generalisable. We have also shown that large, international, high-quality trials of complex interventions in stroke care, trials that are led by physiotherapists and nurses, are possible.

Interpretation

Very early mobilisation was associated with a significant reduction in the odds of little or no disability at 3 months after stroke, with no evidence of accelerated walking recovery; however, the number of patients who died or had serious adverse events at 3 months after stroke did not differ significantly between groups. Our data show that an early, lower dose out-of-bed activity regimen is preferable to very early, frequent, higher dose intervention, but clinical recommendations should be informed by the future prespecified, detailed analysis of the dose–response association.

This background of clinical uncertainty prompted us to plan and undertake the AVERT trial.

The phase 2 study of AVERT provided preliminary evidence that very early mobilisation started within 24 h of stroke onset and continued frequently thereafter was feasible, likely to be safe[12] with promising improvements in walking recovery,[13] and could be cost effective.[14] In 2009, AVERT phase 2 was the only completed mobilisation trial in which intervention started within 48 h of stroke onset.[15]

We did the present study to investigate the relative efficacy of a protocol intended to start earlier than usual care, with frequent out-of-bed activity (very early mobilisation), compared with usual care, traditionally started later (>24 h), with less frequent and lower intensity out-of-bed activity. Our clinical hypotheses were that more intensive, early out-of-bed activity would improve functional outcome at 3 months, reduce immobility-related complications, and accelerate walking recovery with no increase in neurological complications. We also postulated that very early mobilisation would result in an improvement in quality of life at 12 months and would be cost effective. We aimed to undertake this large, pragmatic trial in a range of stroke units—small and large, urban and regional—with existing clinical staff as the intervention teams. We wanted to recruit a broad sample of patients, including those with intracerebral haemorrhage and those receiving recombinant tissue plasminogen activator, to increase external validity and clinical relevance.

Methods

Study design and participants

We did this pragmatic, parallel-group, single-blind, multicentre, international, randomised controlled trial at 56 stroke units in five countries: Australia, New Zealand, Malaysia, Singapore, and the UK (England, Scotland, Northern Ireland, and Wales). Full details of the study rationale, design, and statistical analysis have been published elsewhere.[16]

Eligible patients were aged 18 years or older, had confirmed first (or recurrent) stroke (infarct or intracerebral haemorrhage), and were admitted to a stroke unit within 24 h of stroke onset. Treatment with recombinant tissue plasminogen activator was allowed. Exclusion criteria were clinically significant pre-morbid levels of disability (modified Rankin Scale score >2), early deterioration, direct admission to the intensive-care unit, documented palliative treatment, immediate surgery, another serious medical illness or unstable coronary condition, no response to voice, systolic blood pressure lower than 110 mm Hg or higher than 220 mm Hg, oxygen saturation lower than 92% with

oxygen supplementation, resting heart rate of less than 40 beats per min or more than 110 beats per min, temperature greater than 38·5°C, or enrolment in another intervention trial. Patients with subarachnoid haemorrhage were not eligible for the trial.

Institutional review boards at all sites approved the study. Eligible patients were invited to participate in a trial testing "different types of rehabilitation", but were given no specific information about the two approaches.[16] Informed consent was obtained from all patients or their nominated representative.

Randomisation and masking

Patients were randomly assigned (1:1), with a secure, remote, web-based computer-generated block randomisation procedure (block size of six), to receive usual stroke-unit care alone or very early mobilisation in addition to usual care. Randomisation was stratified by study site and stroke severity on the basis of baseline National Institutes of Health Stroke Scale (NIHSS) score: mild (NIHSS 1–7), moderate (8–16), and severe (>16).[17] Intervention staff were masked to treatment allocation. To reduce the risk of contamination of usual care intervention, staff were trained to conceal the mobilisation protocol and group allocation, patients were unaware of their treatment group, and outcome assessors and investigators involved in trial and data management were masked to group assignment.

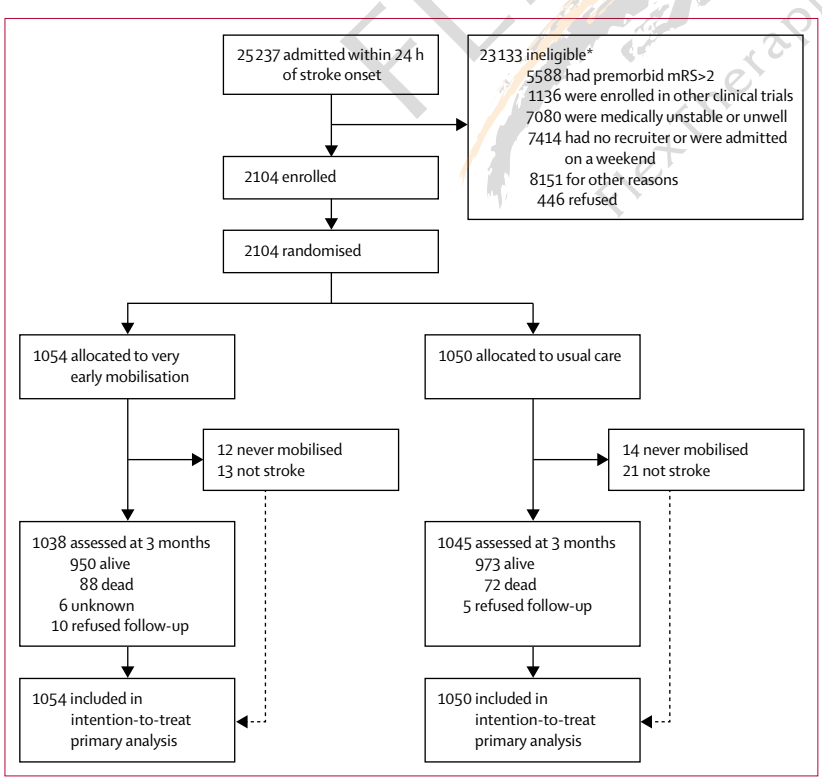

***Figure 1*: Trial profile**
mRS=modified Rankin Scale. *More than one reason possible per patient.

Procedures

Components of usual care, including physical therapies, were at the discretion of individual sites. The very early mobilisation intervention included three crucial elements: (1) begin within 24 h of stroke onset; (2) focus on sitting, standing, and walking (ie, out-of-bed) activity; and (3) result in at least three additional out-of-bed sessions to usual care. Patients assigned to very early mobilisation were assisted by physiotherapy and nursing staff trained in study procedures to continue out-of-bed activity at a dose guided by a detailed intervention protocol. The task-specific intervention targeted recovery of standing and walking. Functional ability dictated intervention dose, with four levels specified, and dose was adjusted in line with recovery (titrated). We applied a strict protocol in the case of a patient's first time out of bed, with mobilisation out of bed only if the patient's blood pressure did not drop by more than 30 mm Hg on achievement of an upright position. The intervention period lasted 14 days or until discharge from stroke-unit care, whichever was sooner. Therapy and nursing input in both groups was recorded online. Very early mobilisation interventions were not recorded in medical records. Throughout the trial, intervention staff received feedback from an external monitor about intervention compliance per patient, and received quarterly compliance summaries. These summaries were reviewed regularly by the Data Safety and Monitoring Committee.

Outcomes

The primary outcome was a favourable outcome at 3 months after stroke, measured with the modified Rankin Scale.[18] The modified Rankin Scale is an ordinal scale ranging from 0 (no disability) to 5 (severe disability), with a score of 6 allocated to those who die. We defined a favourable outcome as modified Rankin Scale scores of 0–2 (no or minimum disability) and a poor outcome as scores of 3–6 (moderate or severe disability, or death).

Major secondary outcomes included an assumption-free ordinal shift[19,20] of the modified Rankin score across the entire range of the scale; time taken to achieve unassisted walking over 50 m and the proportion of patients achieving unassisted walking by 3 months; and deaths and the number of non-fatal serious adverse events at 3 months. All serious adverse events were reported according to standard definitions. Important medical events were events most relevant to the time period (acute stroke) and intervention, and included stroke progression, recurrent strokes, falls, angina, myocardial infarctions, deep-vein thromboses, pulmonary emboli, pressure sores, chest infections, urinary tract infections, and depression. All deaths and serious adverse events were independently adjudicated by an outcome committee masked to treatment allocation, including a review of source data when necessary. We classified complications as immobility related or neurological, and examined each class of complication separately. Serious

	Very early mobilisation (n=1054)	Usual care (n=1050)
Recruitment region		
Australia and New Zealand	617 (59%)	626 (60%)
Asia	126 (12%)	125 (12%)
UK	311 (29%)	299 (28%)
Age (years)	72·3 (62·3–80·3)	72·7 (63·4–80·4)
<65	331 (31%)	298 (28%)
65–80	448 (43%)	481 (46%)
>80	275 (26%)	271 (26%)
Sex		
Female	411 (39%)	407 (39%)
Male	643 (61%)	643 (61%)
Risk factors		
Hypertension	707 (67%)	717 (68%)
Ischaemic heart disease	235 (22%)	251 (24%)
Hypercholesterolaemia	419 (40%)	423 (40%)
Diabetes mellitus	239 (23%)	228 (21%)
Smoking		
Never smoked	454 (43%)	491 (47%)
Smoker*	227 (22%)	204 (19%)
Ex-smoker*	352 (33%)	341 (33%)
Unknown	21 (2%)	14 (1%)
Atrial fibrillation	229 (22%)	237 (23%)
Premorbid history		
Premorbid modified Rankin Scale		
0	799 (76%)	786 (75%)
1	145 (14%)	158 (15%)
2	110 (10%)	106 (10%)
Living arrangement at time of admission		
Home alone	257 (25%)	275 (26%)
Home with someone	781 (74%)	761 (73%)
Supported accommodation	16 (1%)	14 (1%)
Independent walking		
Without aid	908 (86%)	925 (88%)
With aid	146 (14%)	125 (12%)
Time to randomisation (h)	18·2 (12·1–21·8)	18·2 (12·5–21·8)
Stroke history		
First stroke	878 (83%)	843 (80%)
NIHSS score	7 (4–12)	7 (4–12)
Mild (1–7)	592 (56%)	578 (55%)
Moderate (8–16)	315 (30%)	328 (31%)
Severe (>16)	147 (14%)	144 (14%)
Stroke type (Oxfordshire Stroke Classification)		
Total anterior circulation infarct	224 (21%)	232 (22%)
Partial anterior circulation infarct	340 (32%)	328 (31%)
Posterior circulation infarct	93 (9%)	106 (10%)
Lacunar infarct	255 (24%)	268 (26%)
Intracerebral haemorrhage	142 (14%)	116 (11%)
rtPA treatment		
Yes	247 (23%)	260 (25%)
Baseline walking (Mobility Scale for Acute Stroke walking score)		
Independent	439 (42%)	416 (40%)
Supervised or assisted	522 (49%)	538 (51%)
Unable to walk	91 (9%)	96 (9%)
Unknown	2 (<1%)	0 (0%)

(Table 1 continues in next column)

(Continued from previous column)

Data are n (%) or median (IQR). NIHSS=National Institutes of Health Stroke Scale. rtPA=recombinant tissue plasminogen activator. *We defined a smoker as a current smoker or a participant who had quit smoking in the past 2 years, and an ex-smoker as a participant who had quit smoking more than 2 years ago.

***Table 1*: Baseline characteristics of the intention-to-treat population**

complications were categorised into immobility related (pulmonary embolism, deep-vein thrombosis, urinary tract infection, pressure sores, and pneumonia) or neurological (stroke progression and recurrent stroke). Assessments were done in person or, if necessary, by telephone by a trained assessor remote from the hospital ward and masked to treatment allocation.

Because very early mobilisation was a complex intervention, we prespecified exploration of dose and subgroup analyses for age, stroke severity, stroke subtype (infarct or haemorrhage), treatment with recombinant tissue plasminogen activator, and time to mobilisation on 3 month outcome.

Statistical analysis

We powered the study to detect an absolute risk reduction of a poor outcome of 7·1% or greater, on the basis of two rationales: (1) consensus among investigators and international advisers that an absolute risk reduction of this magnitude would represent a clinically meaningful effect size; and (2) 3 month data for death and institutionalisation from a hospital that has practised early mobilisation for many years showing 9·1% better outcome than in a similar Australian dataset, with early mobilisation estimated to account for 78% of the benefit,[1] giving a final absolute difference of 7·1%. A sample of 2104 patients (1052 per group) was estimated to provide 80% power to detect a significant intervention effect (two sided, p=0·05) with adjustments for 5% drop-in and 10% drop-out. We prespecified our statistical analysis plan[16] and used STATA IC (version 13) for all analyses.

We did primary efficacy analysis on an intention-to-treat basis, with an assumption for the main analysis that data were missing at random.[21] We explored the sensitivity of the

	Very early mobilisation (n=1054)	Usual care (n=1050)	p value	Median shift (95% CI)
Time to first mobilisation (h)	18·5 (12·8–22·3; n=1042*)	22·4 (16·5–29·3; n=1036*)	<0·0001	4·8 (4·1–5·7)
Frequency per person†	6·5 (4·0–9·5)	3 (2·0–4·5)	<0·0001	3 (3–3·5)
Daily amount per person (min)‡	31 (16·5–50·5)	10 (0–18)	<0·0001	21·0 (20–22·5)
Total amount per person (min)§	201·5 (108–340)	70 (32–130)	<0·0001	117 (107–128)

Data are median (IQR) or median (IQR; n), unless otherwise indicated. Dose data for very early mobilisation includes components of both usual care and very early mobilisation. Frequency is derived from nursing and therapist data. Amount (min) is derived from physiotherapist data only. Median estimates include days when time or number of out-of-bed sessions were zero—ie, the patient was recorded as not getting up on that day or for that session. *12 patients were missing from the very early mobilisation group and 14 patients were missing from the usual care group. Missing patients were never mobilised, either because of an early serious adverse event, decision to palliate, or early death or transfer from the stroke unit. For these patients, therapy and nurse recording forms were completed throughout their stroke-unit stay, with zero time and zero sessions. †Daily sessions of out-of-bed activity. ‡Min per day spent in out-of-bed activity. §Total amount is over the length of stay or until 14 days after stroke (whichever took place first).

***Table 2*: Intervention summary**

	Very early mobilisation (n=1038*)	Usual care (n=1045*)	Adjusted analysis		Unadjusted analysis	
			OR, generalised OR, or HR† (95% CI)	p value	OR generalised OR, or HR† (95% CI)	p value
Primary						
Favourable outcome‡	480 (46%)	525 (50%)	0·73 (0·59–0·90)	0·004	0·85 (0·72–1·0)	0·068
Secondary						
mRS category	..	..	0·94 (0·85–1·03)	0·193	0·94 (0·85–1·03)	0·202
0	90 (9%)	96 (9%)	..	..	..	..
1	200 (19%)	204 (19%)	..	..	..	..
2	190 (18%)	225 (22%)	..	..	..	..
3	238 (23%)	218 (21%)	..	..	..	..
4	140 (14%)	127 (12%)	..	..	..	..
5	92 (9%)	103 (10%)	..	..	..	..
6	88 (8%)	72 (7%)	..	..	..	..
Walking 50 m unassisted§	6 (5–7; n=1051)	7 (6–8; n=1049)	1·04 (0·94–1·15)	0·459	1·05 (0·95–1·16)	0·331

Data are n (%) or median (IQR; n), unless otherwise indicated. All analyses are adjusted for baseline National Institutes of Health Stroke Scale score and age. OR=odds ratio. HR=hazard ratio. mRS=modified Rankin Scale. *16 patients were missing from the very early mobilisation group and five patients were missing from the usual care group. These 21 patients declined follow-up or could not be found. Missing data were analysed according to our intention-to-treat strategy assuming missing at random. The appendix shows results of the sensitivity analysis. †Point estimates are ORs for the primary outcome, generalised ORs for the secondary outcome of mRS category, and HRs for the secondary outcome of walking unassisted. ‡mRS 0–2. §Time at which 50% of participants walked. The number walking unassisted includes all patients who were recorded as having walked 50 m unassisted in the first 3 months. This number might include patients for whom we were unable to obtain 3 month mRS.

***Table 3*: Outcomes at 3 months**

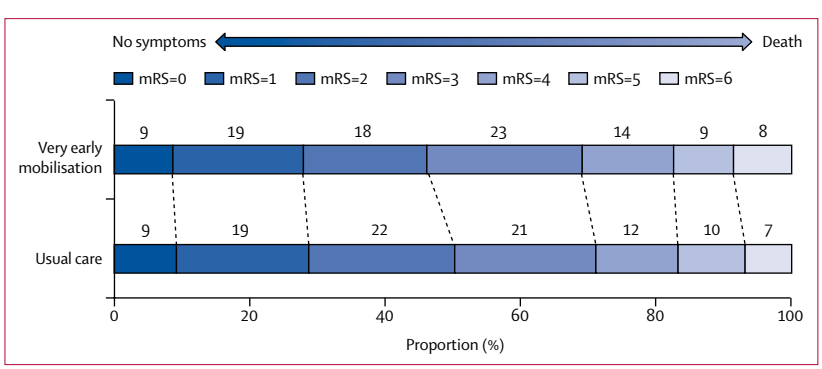

***Figure 2*: Patients achieving each mRS score at 3 months**
mRS=modified Rankin Scale.

results to plausible departures from the missing-at-random assumption as part of our intention-to-treat analysis, with use of both a selection model (modelling of the missing data mechanism) and a pattern mixture model (modelling of the differences between missing and observed data). Assumptions about the missing data were expressed via a parameter that measures the degree of departure from the missing-at-random assumption. The results were graphed over a range of assumptions (appendix).

We did the primary efficacy analysis with the binary logistic regression model, with treatment group as an independent variable and the 3 month modified Rankin Scale outcome (dichotomised into scores of 0–2 as favourable outcome, and scores of 3–6 as poor outcome) as the dependent variable, including baseline stroke

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severity (NIHSS) and age as treatment covariates for adjustment purposes.

Additional efficacy analyses of primary outcome included exploratory analyses of age (<65; 65–79; >80); stroke severity (mild: NIHSS<7; moderate: 8–16; and severe: >16); stroke type (ischaemic *vs* haemorrhagic); treatment with recombinant tissue plasminogen activator; time to first mobilisation (<12 h; 12–24 h; >24 h); and geographical region (Australia and New Zealand *vs* Asia *vs* UK), with adjustment for age and stroke severity when relevant.

We estimated the treatment effect for ordinal analysis of the modified Rankin Scale (across the full scale) at 3 months with the assumption-free Wilcoxon-Mann-Whitney generalised odds ratio approach,[19,20] providing a measure of effect size with confidence intervals. The analysis was again stratified by age and stroke severity.

To examine time taken to achieve unassisted walking 50 m within the first 3 months of stroke, we used a Cox regression model with treatment group as the independent variable, the time to unassisted walking (censored at 3 months) as the dependent variable, and baseline NIHSS and age as treatment covariates. We present the estimated effect size as a hazard ratio (HR) with corresponding 95% CI. We analysed walking status (yes or no) with a binary logistic model, with treatment group as the independent variable and walking status as the dependent variable.

We analysed mortality outcomes with the binary logistic regression model, with treatment group as the independent variable and death at 3 months (modified Rankin Scale score of 6) as the dependent variable, and stroke severity and age as treatment covariates. We used negative binomial regression to compare the expected counts of serious complications between groups at 3 months. We report the estimated effect sizes and corresponding 95% CI as incidence rate ratios adjusted for age and stroke severity.

To determine whether practice shifted over the course of this trial, we tested the association between the treatment effect and the time since the beginning of the trial by inclusion of an appropriate interaction term into the logistic regression model used for the primary outcome analysis. To further examine the possible effects of time on the intervention delivered, we did an exploratory analysis in which we examined the effect of time since the beginning of the trial on differences in individual dose characteristics between the two groups with appropriate regression models (ie, a median regression model for time to first mobilisation and median session frequency, and negative binomial regression for median daily minutes per session and total min over the intervention period) with an interaction term for treatment by time since the trial began.

This trial was registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12606000185561 and the protocol is available online.

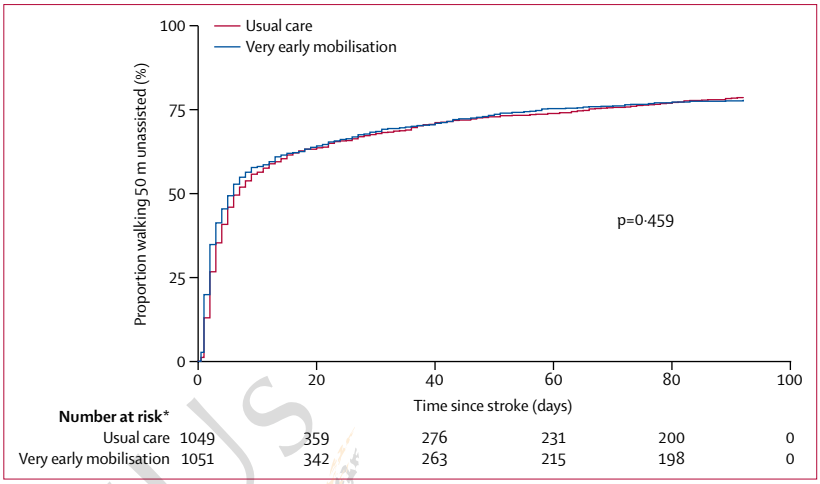

***Figure 3*: Time to walking unassisted 50 m by 3 months**
*Number of patients who had not achieved walking.

	Very early mobilisation (n=1054)	Usual care (n=1050)	OR or IRR* (95% CI)	p value
Death	88/1048 (8%)†	72 (7%)	1·34 (0·93–1·93)	0·113
Non-fatal serious adverse events			0·88 (0·72–1·07)	0·194
0	853 (81%)	842 (80%)	..	..
1	157 (15%)	146 (14%)	..	..
2	32 (3%)	41 (4%)	..	..
3	10 (1%)	16 (2%)	..	..
4	2 (<1%)	4 (<1%)	..	..
5	0	1 (<1%)	..	..
Immobility serious adverse events‡			0·92 (0·62–1·35)	0·665
0	1000 (95%)	997 (95%)	..	..
1	50 (5%)	46 (4%)	..	..
2	4 (<1%)	5 (1%)	..	..
3	0	2 (<1%)	..	..
4	0	0	..	..
5	0	0	..	..
Neurological serious adverse events‡			1·26 (0·95–1·66)	0·108
0	947 (90%)	967 (92%)	..	..
1	104 (10%)	78 (7%)	..	..
2	3 (<1%)	4 (<1%)	..	..
3	0	1 (<1%)	..	..
4	0	0	..	..

Data are n/N (%) or n (%), unless otherwise indicated. We did IRR analysis with event counts per person. All analyses are adjusted for age and baseline National Institutes of Health Stroke Scale score. OR=odds ratio. IRR=incidence rate ratio. *Point estimates are OR for death and IRRs for all adverse events. †The 3 month outcome was missing (unknown) for six patients in the very early mobilisation group. Missing data were analysed according to our intention-to-treat strategy assuming missing at random. The results remain stable over the range of possible violations of this assumption. ‡Immobility-related and neurological serious adverse events include both fatal and non-fatal complications; immobility-related events include pulmonary embolism, deep-vein thrombosis, urinary tract infection, pressure sores, pneumonia; and neurological events include stroke progression and recurrent stroke.

***Table 4*: Deaths and serious complications at 3 months**

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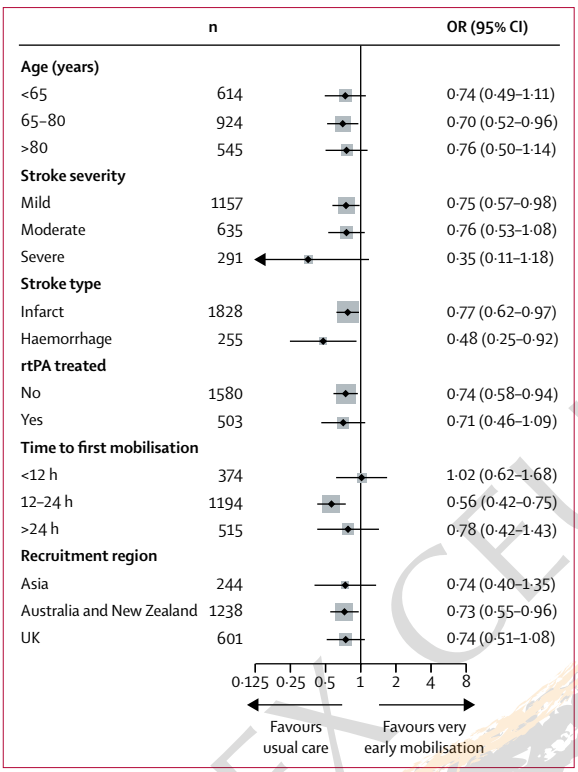

***Figure 4*: Prespecified subgroup analyses**
None of the individual subgroup analyses had significant treatment-by-subgroup interactions (all p>0·05). OR=odds ratio. rtPA=recombinant tissue plasminogen activator.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and, with support of the management committee, had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between July 18, 2006, and Oct 16, 2014, we randomly assigned 2104 patients to receive either very early mobilisation (n=1054) or usual care (n=1050), with 2083 (99%) patients included in the 3 month follow-up assessment (figure 1). Baseline characteristics were similar between study groups (table 1). Median time to randomisation was 18 h after stroke in both groups (table 1). For more than 80% of patients, this stroke was their first; 45% of patients were classified as having moderate to severe stroke (NIHSS >7) at time of recruitment, 26% of all patients were older than 80 years, and 24% of patients had received recombinant tissue plasminogen activator (table 1).

The three crucial elements of the very early mobilisation protocol were achieved (table 2). Patients in the very early mobilisation group began mobilising soon after randomisation, at a median of 18·5 h after stroke (table 2). The median time to mobilisation in the usual care group was also within 24 h of stroke onset, but the median difference was almost 5 h later than in patients in the very early mobilisation group (table 2). In the very early mobilisation group, 241 (23%) patients had mobilised within 12 h of stroke, 965 (92%) patients had mobilised within 24 h, and 1038 (98%) patients had mobilised within 48 h; the corresponding numbers in the usual care group were 148 (14%), 623 (59%), and 977 (93%) patients, respectively. Patients in the very early mobilisation group received more frequent out-of-bed sessions than did those in the usual care group (table 2). The median time to first mobilisation in the usual care group reduced by 28 min per year (95% CI 11·3–44·6, p=0·001) over the study period, with no significant change in the very early mobilisation group. This finding resulted in a significant interaction between time since the beginning of the trial and time to first mobilisation (p=0·017). We detected no significant change in either the daily frequency or daily minutes of out-of-bed intervention, or total intervention time, in either group over the study period (data not shown).

More patients in the usual care group than in the very early mobilisation group had a favourable outcome at 3 months after stroke (table 3), resulting in a significant difference between the groups in the analyses adjusted for baseline age and NIHSS (table 3, figure 2). We noted similar results in sensitivity analyses (appendix). This treatment effect showed no interaction with time since the start of the trial (data not shown). The assumption-free ordinal analysis did not show a significant difference between groups across the entire modified Rankin Scale (scores 0–6).

50% of patients were able to walk unassisted by roughly 7 days after stroke, and 75% were walking by 3 months (n=796 in the usual care group and n=784 in the very early mobilisation group; adjusted OR 0·83, 95% CI 0·64–1·07; p=0·143). Time to walking unassisted did not differ significantly between groups (table 3, figure 3); however, the proportional hazards assumption was violated.

The overall case fatality by 3 months was 8% (95% CI 6·5–8·8). 72 (7%) patients died in the usual care group and 88 (8%) patients died in the very early mobilisation group (table 4). The main causes of death, accounting for 64% of all deaths, were stroke progression (n=19 in the usual care group *vs* n=31 in the very early mobilisation group), pneumonia (n=15 *vs* n=19), and recurrent stroke (n=7 *vs* n=11). Most patients did not have a serious adverse event in the first 3 months (table 4). The proportion of patients who had non-fatal serious adverse events did not differ significantly between groups (table 4). When complications were examined by prespecified category (immobility *vs* neurological), fewer than 6% of patients in either group had a fatal or non-fatal serious complication related to immobility (table 4). Fewer than 12% of patients in either group had a serious neurological complication (table 4), with no significant between-group differences.

Stroke progression was the most common serious neurological complication, recorded in 128 (6%) patients (n=56 in the usual care group *vs* n=72 in the very early mobilisation group). Only one staff injury was reported in the very early mobilisation group.

In the prespecified subgroup analyses we noted a more favourable outcome for the usual care intervention than for the very early mobilisation intervention (figure 4). The point estimate showed a stronger effect in patients with severe stroke and with intracerebral haemorrhage (estimated with lower precision). However, within each individual subgroup analysis, no significant interactions were recorded (all p>0·05; figure 4). The appendix shows dose characteristics by subgroup and the subgroup analysis for death at 3 months. Although the effect of very early mobilisation on patients with intracerebral haemorrhage seemed to be strong, again, no significant interactions were recorded in this analysis (all p>0·05; appendix).

The median length of hospital stay for acute care and rehabilitation was 16 days (IQR 5–44) for patients in the very early mobilisation group and 18 days (6–43) for those in the usual care group. The number of patients moving on to inpatient rehabilitation was 492 (46%) in the very early mobilisation group and 523 (49%) in the usual care group. Median length of stay for acute care alone was 7 days (IQR 4–13) for patients receiving very early mobilisation and 7 days (4–13) for those receiving usual care; the corresponding times for rehabilitation length of stay were 28 days (15–49) and 30 days (16–51), respectively.

Discussion

Our very early mobilisation protocol was effectively delivered, leading to an earlier, more frequent, and higher dose of out-of-bed sitting, standing, and walking activity than usual care. The very early mobilisation intervention significantly reduced the odds of a favourable outcome 3 months after stroke compared with lower dose usual care starting, on average, 5 h later. This outcome of very early mobilisation was recorded against a background of favourable overall prognosis, with almost 50% of patients having a favourable outcome and fewer than 8% dying at 3 months, despite more than 25% of participants being older than 80 years, and more than 45% having had a moderate or severe stroke. Although the case-fatality rate at 3 months was higher in the very early mobilisation group, no significant difference was recorded between groups. The prespecified subgroup analyses of efficacy might provide a signal that patients with severe stroke and those with intracerebral haemorrhage had reduced odds of a favourable outcome by 3 months if treated with the very early mobilisation protocol. Additional exploration of death in the subgroups also suggested that patients with intracerebral haemorrhage might be more susceptible to harm. However, these groups were small with wide confidence intervals. Although biologically plausible explanations could be made about the differential effect of a more frequent, higher dose intervention on the odds of a favourable or unfavourable outcome in these subgroups, there was no evidence of any interaction and the results should be interpreted with caution. This study was not powered to detect differences between these subgroups; however, such signals of potential harm could be clinically important and warrant further exploration. We also noted that outcomes for patients receiving recombinant tissue plasminogen activator were no different to outcomes for those who did not receive that treatment. Hence, there is no evidence that early mobilisation in this subgroup is harmful.

We were intrigued by these results, partly because our pilot work suggested that the early, frequent, higher dose very early mobilisation protocol increased the odds of a favourable outcome (OR 4·1, 95% CI 0·99–16·89; p=0·05),[12] as did an individual patient meta-analysis, which included two small early mobilisation trials.[22] Conversely, another small trial comparing very early (<24 h) versus later (>24 h) mobilisation, with an unspecified training dose, reported higher, but non-significant odds, of an unfavourable outcome in the earlier mobilised group.[23] Because the AVERT trial is more than ten times the size of the total sample of all previous mobilisation trials, we believe that our results add precision. The low rates of adverse events overall and, in particular, the low proportion of immobility-related complications in both groups was surprising. Our clinical hypothesis was that very early mobilisation would lead to fewer immobility-related complications, but we noted no difference between groups. The shift in practice over time to earlier onset intervention in usual care (a median 28 min earlier each year) might explain this result. One of the striking differences between previous studies and the present trial is that median time to first mobilisation in usual care has decreased from more than 30 h,[22] to 22 h in this trial. Only 7% of patients in our usual care group stayed in bed for more than 48 h after stroke onset. Unfortunately, no directly comparable data are available from other acute stroke trials. AVERT is the first large rehabilitation trial recruiting patients within 24 h of stroke onset, and although the inclusion criteria were broad, the included patients were a selected population. Modern, high quality stroke-unit care in the participating hospitals, which did include out-of-bed mobilisation within 24 h of stroke onset in 75% of cases, could explain the low rate of immobility-related complications.

This study represents the largest acute stroke rehabilitation trial ever done with a complex intervention directed by existing physiotherapy and nursing staff. We aimed to design and undertake a trial that met the same quality standards expected of drug or device trials, so that effect sizes could be sensibly compared. We have achieved this aim, with fewer than 1% of patients missing from the primary endpoint calculation, proven delivery of the intervention protocol, careful characterisation of usual

care and adjudicated safety outcomes, and provision of precise estimates of the efficacy and safety of the intervention. The external validity of the trial has been enhanced by embedding it fully within routine hospital care across five countries. In view of these design considerations, we believe that these results are robust and provide clinicians with important new evidence.

Our trial has several limitations. A consequence of doing large trials is the small amount of information that can be obtained about potential confounding factors (such as physiological variables), and about each staff–patient interaction. This limitation will restrict, but not prevent, further detailed analyses of the effect of patient and practice variables on outcome. Being a pragmatic trial, we were not prescriptive about usual care mobilisation practices, which changed significantly during the trial. Independent monitoring, reporting, and feedback about usual care and very early mobilisation did not prevent change in usual care. Usual care clinicians started mobilisation earlier each year, with the result that roughly 60% of patients receiving usual care had started out-of-bed therapy within 24 h of stroke onset. Whether this result was a consequence of contamination from the trial protocol, a response to changes in attitudes to early mobilisation over time as reflected in recent clinical guidelines, or both, is uncertain.

The results of our trial should affect clinical practice by changing present clinical practice guidelines. In our review of 30 guidelines, early mobilisation was recommended in 22 examples,[3] but with little, or more often no, information about the protocol that should be used. The obvious implication of our results is that start of a high-dose, frequent mobilisation protocol within 24 h of stroke onset is not better than usual care. However, because the usual care protocol also represents a complex intervention package that in most cases started early, to advise that patients are provided with usual care is too simplistic. Components of our intervention are already part of routine clinical care; therefore, understanding of which components might affect outcome is a priority. By further exploration of this rich dataset, our trial provides the best opportunity yet to develop evidence-based guidelines for patients with stroke about the timing, frequency, and amount of out-of-bed activity to improve outcome (or prevent harm). Consequently, as outlined in our published statistical analysis plan,[16] our next priority will be to undertake a dose–response analysis to establish the effect of dose of rehabilitation (rather than group) on efficacy and safety outcomes.

The results of AVERT raise several important research questions. First, when is the best time to start rehabilitation after stroke? Whereas some early studies in stroke-affected rodents suggested that early, intensive exercise increased lesion volume, more recent systematic reviews and meta-analyses have shown a strong positive effect for exercise after stroke, including a positive association between better outcome and reduced time to starting exercise.[24,25] An improved understanding is needed of the molecular mechanisms induced by early physical activity on ischaemic tissue to provide a biological rationale for choice of time windows for intervention. Indeed, this question remains one of the most important questions for the entire timescale after stroke. Second, what should training consist of, and who should we target early? We have shown that the common adage of more is better does not apply to the early post-stroke period. Furthermore, our data signal that some patients might respond better to more conservative treatment protocols. A deep understanding of who responds to treatment, who does not, and why, is missing in the specialty of rehabilitation and should be a research priority.

Contributors

JB conceived the study. JB, JC, HD, GD, RIL, MM, AGT, and FE designed the study. JB, JC, HD, GD, RL, MM, AGT, and FE wrote the protocol. JB is the Principal Investigator. PL is the Chief Investigator for the UK. LC is the study statistician who prepared the analyses. JB wrote the first draft and all authors provided input and approved the final version.

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Prevalence of fatigue in patients 3 months after stroke and association with early motor activity: a prospective study comparing stroke patients with a matched general population cohort

Abstract

Background: Fatigue is a common complaint after stroke. Reasons for higher prevalence are still unclear. This study aimed to determine if fatigue prevalence in stroke patients is different to that of age and gender matched general population controls, and to explore whether early motor activity was associated with reduced likelihood of fatigue three months after stroke.

Methods: This was a prospective multicenter cohort study of stroke patients admitted to eleven regional Norwegian hospitals, within 14 days after stroke. Stroke patients ($n = 257$) were age and gender matched to participants in a general population health survey (HUNT3-survey) carried out in a regional county of central Norway. The single-item fatigue questionnaire from the HUNT3-survey was administered to both groups to compare prevalence. The association between early motor activity (*time in bed, time sitting out of bed*, and *time upright)* and fatigue at three months after stroke (Fatigue Severity Scale) was tested with logistic regression. Simple models including each activity outcome, with adjustment for stroke severity and pre-stroke function, were tested, as well as a comprehensive model that included additional independent variables of depression, pain, pre-stroke fatigue, age and gender.

Results: Prevalence was higher after stroke compared with the general population: 31.1 % versus 10.9 %. In the simple regression models, none of the early motor activity categories were associated with fatigue three months after stroke. In the comprehensive model, depression, pain and pre-stroke fatigue were significantly associated with post-stroke fatigue. Time in bed through the daytime during hospital stay approached statistical significance ($p = 0.058$) with an odds ratio for experiencing fatigue of 1.02 (95 % CI 1.00-1.04) for each additional 5.4 minutes in bed.

Conclusions: Stroke patients had higher prevalence of fatigue three months after stroke than the age and gender matched general population sample, which may be partly explained by the stroke population being in poorer health overall. The relationship between early motor activity (and inactivity) and fatigue remains unclear. Further research, which may help drive development of new treatments to target this challenging condition, is needed.

Keywords: Stroke, Fatigue, Physical activity, Early mobilization, HUNT

Background

Fatigue is described as a "constant weariness unrelated to previous exertion levels and not usually ameliorated by rest" [1]. Perceptions of fatigue are a common complaint among older people and for those with a range of chronic diseases including stroke. The prevalence of fatigue in the general population has been variably reported from 5 to 47 %, depending on the population studied, the questionnaire used, and the threshold score used to differentiate those with fatigue from those without [2–5]. Prevalence appears to increase with the number of chronic diseases [6, 7], and is higher in women [8], but findings are inconsistent for age [3, 9].

Prevalence is elevated even further following stroke, ranging from 35 to 92 % [10], again depending on the tool used to measure fatigue, but also depending on the time since stroke and sample selection strategies [10–13]. Post-stroke fatigue (PSF) is distressing and debilitating. It is associated with higher levels of dependency [14, 15] and poorer quality of life [16]. It also independently predicts institutionalization and mortality after stroke [17, 18]. Fatigue is rarely assessed in clinical practice and poorly managed, largely because strong evidence supporting effectiveness of fatigue-reducing interventions, either for fatigue in general, or for fatigue unique to stroke patients, is lacking.

Fatigue after stroke is complex, and while fatigue can be experienced secondary to medications, sleep disorders and/or medical complications [19], it is probable that PSF also relates to the brain injury itself [14, 17, 20–22]. Ongoing fatigue may be compounded by reduced activity and subsequent deconditioning, particularly in the sub-acute phase, perhaps in combination with the increased energy cost of movement due to impairment [22–25]. Our current understanding of the biology of fatigue is limited. Understanding how PSF may differ from other fatigue is clinically important as unique management options may be required. If deconditioning and movement inefficiency play a crucial role in the experience of fatigue later after stroke, increased physical activity opportunities and movement training may be further endorsed as a treatment approach.

Several previous studies have investigated risk factors for PSF. Evidence suggests the main predictors for fatigue in the sub-acute phase are depression [11, 26], pre-stroke fatigue [26–28], and pain [29, 30]. Recent evidence suggests that activity early after stroke (step count at one month) predicts fatigue later after stroke (six and 12 months) [31]. However, knowledge is limited on the role of physical activity on fatigue levels for stroke patients, especially in the early phase after stroke.

Previous prevalence studies have often had restricted sample selection of stroke patients leading to subpopulation analyses, and not controlling for age and gender in comparison populations [32–34]. The present study firstly aimed to determine the prevalence among a less selective stroke population three months after stroke, and to directly compare prevalence with an age and gender matched general population sample from a similar region. We hypothesized that the fatigue prevalence would be higher in the stroke sample. The second aim of this study was to investigate the relationship between motor activity early after stroke and PSF. Because some evidence exists supporting the positive impact of physical activity on fatigue, we hypothesized that patients engaged in more motor activity early after stroke would have reduced likelihood of fatigue at three months, after adjustment for stroke severity and pre-stroke function, and independent of depression, pain, pre-stroke fatigue, age and gender. A reversed causal pathway was also considered possible as the reduced activity early after stroke may be caused by fatigue which then persists three months after stroke [13].

Methods

Study design and settings

This was a prospective observational study including patients admitted to eleven Norwegian hospitals [35]. An age and gender matched control group was derived from a population-based study in the county of Nord-Trøndelag [36], were two of the eleven hospitals were located.

Study participants

From 1st December 2011 to 11th June 2013, all consecutive acute first ever or recurrent stroke patients (except those with subarachnoid haemorrhages) admitted to the eleven stroke units were invited to participate, provided they were over 18 years of age, understood Norwegian and were not on palliative treatment. Stroke was defined according to the World Health Organisation definition. Recruitment was within 14 days after stroke onset. In keeping with Norwegian consent procedures, for patients unable to sign informed consent, verbal consent to participate was obtained from their next of kin. Further details of the study methods can be found in a prior publication [35]. Patients alive at three months, were contacted either in person or by telephone interview for assessment of perceptions of fatigue, depression, and pain.

Community-dwelling controls came from the Nord-Trøndelag population Health Survey3 (HUNT3-survey) [36]. The HUNT3-survey is a population-based study of the Norwegian county of Nord-Trøndelag. Two of the eleven hospitals in the stroke study were located in Nord-Trøndelag. Data were collected from October 2006 to June 2008. All adult residents aged ≥ 20 years were invited to participate in the study. The HUNT3-

survey included several priority public health issues, and questionnaires included fatigue [37, 38], as outlined below. Of 93,860 eligible adults, 50,807 (54.1 %) returned the questionnaire and written consent. Participation was highest among people 60–69 years (71 %) decreasing to 18 % in the oldest age group 90–96 years. There was a selection bias toward more healthy individuals and higher socioeconomic status [39].

Ethics

The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study and storage of data on behalf of all participating hospitals and also the use of data from the HUNT3-survey (REC numbers 2011/1428 and 2012/675 respectively).

Baseline assessment of stroke patients

Baseline characteristics of the stroke participants measured at inclusion included age, gender, pre-stroke function measured by modified Rankin scale (mRS) [40], stroke severity measured using National Institutes of Health Stroke Scale (NIHSS) [41], stroke type by Oxford classification [42], co-morbidities and pre-stroke fatigue. Pre-stroke fatigue was estimated from the following two items: 'Did you experience fatigue before you had your stroke' (yes/no), and, 'If yes, how long did you experience fatigue' (less than a week, less than three months, 3–6 months and more than six months). Patients who reported fatigue lasting longer than three months before the stroke were classified as having pre-stroke fatigue [11].

For the early motor activity outcomes, participants were observed every 10th minute during a working day from 8.00 am to 5.00 pm using the method of *behavioural mapping*. Motor activity was defined as the proportions of the daytime spent (i) *in bed*, (ii) *sitting out of bed* and (iii) *upright.* The procedure was reported in detail in a previous publication [43].

Data extracted from the HUNT3-survey

Age and gender were used to select the general population sample from HUNT3-survey participants and data collected from the matched participants included co-morbidities and fatigue.

Outcome measures

Stroke patients were assessed three months after the stroke. Fatigue was measured in both samples (stroke and controls) using a simple fatigue questionnaire from the HUNT3-survey. This was a single question about weariness/fatigue: "Do you feel, for the most part, strong and fit or tired and worn out?". There were seven response categories which ranged from "1 = very fit and healthy" to "7 = very tired and worn out", with the middle option as neutral. Fatigue was defined as a score ≥ 5. In the stroke group, a second fatigue questionnaire, the Fatigue Severity Scale (FSS) was also administered. The 9-item FSS is the most commonly used scale to measure fatigue in stroke patients [16, 28, 44]. The shorter 7-item version of the FSS, FSS-7, was shown to have better psychometric properties in patients with stroke than the original 9-item version [2]. The FSS-7 was therefore chosen for this study.

Pain was assessed by a simple question 'Did you experience new pain after stroke? (yes/no)'. Depression was assessed by Hospital Anxiety and Depression Scale (HADS) [45]. HADS is a self-report questionnaire which comprises two subscales HADS-anxiety and HADS-depression (HADS-D), each with seven items scored from zero to three. The scores are summed to give a total score for each subscale ranging from 0 to 21.

Data management and analysis

Stroke patients were matched by age (up to a maximum of 2 years difference) and gender to respondents from the HUNT3-survey [36] who had all the outcome measures of interest to this study and no history of previous stroke. The HUNT participant of the same gender with the closest age (in 0.1 year increments) to each stroke participant was selected, with the matching procedure carried out blinded to any other outcome measure. The number of participants with available data determined the sample size for the study.

FSS scores from the 7-point Likert scale response options were averaged to yield a score from 1.0 to 7.0. Higher scores indicate higher fatigue levels. Most studies recommend a cut-off score of ≥ 4.0 as indicative of fatigue [33, 46]. The FSS-7 and HADS-D questionnaires were excluded if less than four items were answered. Up to three missing items were imputed with the average of the answered items.

Fatigue prevalence was examined in both groups using the HUNT3-survey questionnaire. The proportion of participants from each group reporting fatigue ≥ 5 on this questionnaire was compared using the chi-square test. Fatigue prevalence among the stroke patients was also reported using the FSS-7 with cut off of ≥ 4.0.

The association between early motor activity and PSF was tested using logistic regression models with fatigue dichotomised using FSS-7 score ≥ 4.0. Proportion of daytime *in bed*, *sitting out of bed* and *upright* were each tested in separate simple models. Stroke severity (NIHSS score) and pre-stroke function (mRS) were included as covariates. A single comprehensive multivariable logistic regression model also including HADS-D score, pain, pre-stroke fatigue, age and gender as additional independent variables was also examined. In this model both *time in bed* and *time upright* were included but *time sitting out of bed* was excluded as it is co-dependent on the

other two activity categories. This model was designed to determine whether early motor activity or inactivity were independently associated with fatigue at 3 months.

Results

Two hundred and fifty-seven stroke participants were age and gender matched to HUNT3-survey participants for the prevalence study, and 199 stroke participants had the outcome measures needed for inclusion in the regression models (Fig. 1). Four patients had missing items on the FSS-7 questionnaire (one had three items missing and three had one item missing) and had the missing data imputed. There was a mean of 4.2 (SD 2.8) days from admission to the stroke unit to the day of inclusion in the study and behavioural mapping. Table 1 shows the descriptive data and fatigue prevalence for the age-gender-matched cohort. Data were available in both groups for several co-morbid diseases. These were hypertension, heart failure, myocardial infarct, lung disease (including asthma and COPD), kidney disease, diabetes mellitus, cancer and connective tissue disease (including rheumatoid arthritis and spondylitis). Thirty-four percent of the HUNT3-survey cohort had none of these diseases, while only 16 % of the stroke patients had none. Twenty-five percent of the stroke patients had three or more of the diseases, compared with only 11 % in the general population. Most patients were classified as PACI (40 %) according to the Oxford Classification, with only 7 % as TACI. Prevalence of fatigue ranged from 24 to 41 % across the different classification groups using the HUNT3 survey fatigue question, and ranged from 35 to 44 % using FSS-7.

Chi-square test indicated a significant difference in fatigue prevalence between the groups (31.1 % among stroke versus 10.9 % among healthy controls, $p < 0.001$). Odds of a stroke patient experiencing fatigue three months after stroke were 3.7 times the odds for the general population. The prevalence of fatigue was broadly similar if using the FSS-7 scale with a cut off of ≥ 4.0 for

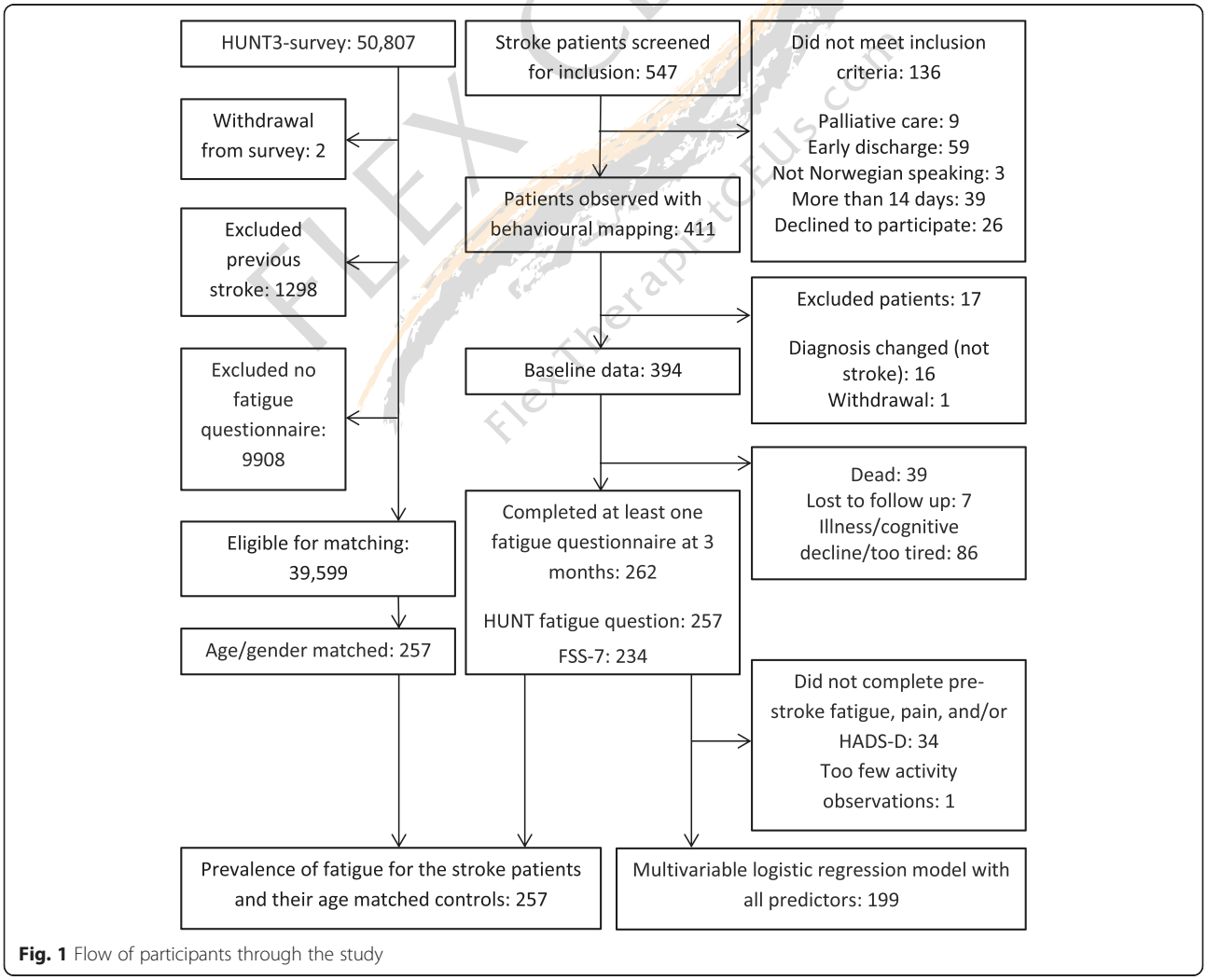

Fig. 1 Flow of participants through the study

Table 1 Descriptive data and prevalence

			Stroke	HUNT3-survey
Gender, % female			46.3 %	46.3 %
Age, mean (SD, range)			74.8 (11.4, 30.7–91.7)	74.8 (11.5, 30.7–92.5)
HUNT3 fatigue question (Do you feel, for the most part, strong and fit or tired and worn out?), n (%)	1. Very strong and fit		6 (2.3 %)	11 (4.3 %)
	2. Strong and fit		29 (11.3 %)	42 (16.3 %)
	3. Somewhat strong and fit		60 (23.3 %)	88 (34.2 %)
	4. Somewhat in between		82 (31.9 %)	88 (34.2 %)
	5. Somewhat tired and worn out		42 (16.3 %)	21 (8.2 %)
	6. Tired and worn out		20 (7.8 %)	6 (2.3 %)
	7. Very tired and worn out		18 (7.0 %)	1 (0.4 %)
Fatigue (HUNT3), % score ≥ 5			31.1 %	10.9 %
Fatigue (FSS-7), % score ≥ 4.0			34.6 %	-
Early motor activity, mean (SD)	% of day in bed		36.6 (23.4)	-
	% of day sitting out of bed		47.4 (19.9)	-
	% of day upright		10.9 (9.2)	-
	% of day not observed		5.1 (7.9)	-
Stroke severity (NIHSS), mean (SD)			5.0 (5.0)	
Function at inclusion (mRS), median, mean (SD)			3, 3.2 (1.1)	-
Function at 3 months (mRS), median, mean (SD)			2, 2.5 (1.2)	-
		n (% of cohort)	% reporting fatigue with HUNT3, FSS-7	
Oxford stroke classification groups	TACI	17 (7 %)	41 %, 38 %	-
	PACI	103 (40 %)	34 %, 40 %	-
	LACI	58 (23 %)	24 %, 35 %	-
	POCI	47 (18 %)	30 %, 44 %	-
	Haemorrhagic	32 (13 %)	31 %, 35 %	-
Co-morbidities, % of cohort	Hypertension		68 %	48 %
	Heart failure		10 %	7 %
	Myocardial infarct		19 %	14 %
	Lung disease (including asthma and COPD)		12 %	14 %
	Kidney disease		3 %	2 %
	Diabetes mellitus		15 %	11 %
	Cancer		18 %	9 %
	Connective tissue disease (including rheumatoid arthritis and spondylitis		8 %	8 %

Descriptive data, prevalence of fatigue and early motor activity data are provided for the stroke patients ($n = 257$) and their age/gender-matched counterparts ($n = 257$) from HUNT3-Survey

FSS-7 7-item Fatigue Severity Scale, *mRS* modified Rankin Scale (range of scores 0–5), *NIHSS* National Institutes of Health Stroke Scale (range of scores 0–42), *COPD* chronic obstructive pulmonary disease

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fatigue or using the HUNT3-survey fatigue question with cut off of ≥ 5 (34.6 and 31.1 % respectively).

The simple regression models testing the association of each of the early motor activity variables with fatigue (controlling for pre-stroke function and stroke severity) showed no association: proportion of *time in bed* OR 95 % CI 0.99–1.02 ($p = 0.14$), *time sitting out of bed* OR 95 % CI 0.98–1.01 ($p = 0.21$), and *time upright* OR 95 % CI 0.96–1.03 ($p = 0.58$). In the comprehensive model, which included the independent variables in the simple models plus age, gender, pre-stroke fatigue, depression, and pain, only pre-stroke fatigue, depression and pain were significantly associated with fatigue at three months (Table 2). Proportion of *time in bed* approached significance ($p = 0.058$). If the point estimate for *time in*

Table 2 Descriptive data and results of comprehensive multiple variable regression model

Independent variables		B	OR (95 % CI)
Gender, n (%) female	91 (45.7 %)	−0.58	0.56 (0.26–1.21)
Age, mean (SD, range)	73.8 (11.7, 30.7–91.3)	−0.002	1.00 (0.97–1.03)
Pre-stroke fatigue, n (%) yes	53 (26.6 %)	1.30*	3.67 (1.62–8.31)
Depression (HADS-D), mean (SD)	3.8 (3.8)	0.27*	1.31 (1.17–1.47)
Pain (new since stroke), n (%) yes	38 (19.1 %)	1.51*	4.55 (1.82–11.34)
Pre-stroke function (mRS), mean (SD)	1.4 (1.1)	0.04	1.04 (0.70–1.54)
Stroke severity (NIHSS), mean (SD)	4.0 (3.7)	0.07	1.08 (0.97–1.19)
Early motor activity:			
% of day in bed, mean (SD)	35.0 (22.8)	0.02*	1.02 (1.00–1.04)
% of day upright, mean (SD)	11.8 (9.3)	0.03	1.03 (0.98–1.07)

$N = 199$, dependent variable fatigue (FSS-7 score ≥ 4.0), *significant at $p < 0.05$, *significant at $p < 0.10$ (trend). 77 participants (38.7 %) had fatigue
HADS-D Hospital Anxiety & Depression Scale – Depression subscale (range of scores 0–21), *mRS* modified Rankin Scale (range of scores 0–5), *NIHSS* National Institutes of Health Stroke Scale (range of scores 0–42)

bed of B = 0.02 was correct, then for every additional 1 % of the daytime (approximately 5.4 min) spent in bed, there was 2 % greater odds of experiencing fatigue at three months, holding all other variables constant.

Pre-stroke fatigue was one of the strongest independent predictors of PSF in our model (OR 3.7, 95 % CI 1.6–8.3, $p = 0.002$). The percentage of stroke patients that reported pre-stroke fatigue (had experienced fatigue prior to their stroke lasting at least three months) was 27 %, which was much higher than fatigue in the general population (11 %), although different measurement questionnaires were used. Of the 53 stroke participants reporting pre-stroke fatigue, 30 (57 %), reported fatigue at three months. However, about a third (32 %) of the 146 without pre-stroke fatigue reported fatigue three months after stroke.

Discussion

The main finding from the study was, a higher prevalence of fatigue in stroke patients even after careful matching with a general population sample. Prevalence of fatigue three months after stroke was around one third, using either FSS-7 with a cut off ≥ 4.0, or using the HUNT3-survey questionnaire with a cut off ≥ 5. The prevalence is lower than most previous studies where prevalence was most often reported in the range of 50 %. There are several possible reasons for this difference. Most obviously, use of different questionnaires and different cut-offs to define fatigue will affect prevalence findings. However, a further possible explanation may be the older patient population in our study compared with other studies. Younger patients may be more aware of fatigue due to increased likelihood of wanting to return to work, more social activities, and higher activity levels [9, 12, 47]. We did not find compelling support for our hypothesis that more early motor activity would be associated with decreased likelihood of PSF. Our analysis confirms previous findings that pre-stoke fatigue, depression and pain are important predictors. *Time in bed* almost reached statistical significance in the model, with 95 % CI for OR ranging from 1.00 (no association) to 1.04 (4 % greater odds of having fatigue for every 5.4 min of extra bed rest).

The stroke patients were about three times more likely to report fatigue than their community-living counterparts who had not experienced stroke. Our results also showed that the stroke patients had more than double the likelihood of having at least one other disease prior to their stroke compared to the general population, and more than double the likelihood of having three or more other diseases. This finding suggests that the higher prevalence of PSF may be at least in part related to the stroke population being in poorer health even before they had a stroke. The previous literature on the association between pre-stroke co-morbidities and fatigue is not clear. A study in young patients found an association between PSF and both diabetes mellitus and myocardial infarction [32], while two other studies found no such association [14, 15]. PSF is a serious problem which clearly warrants better monitoring and management. Our findings suggest that pre-stroke health is an important factor in development of PSF.

Our findings hint at the possibility that early inactivity may be associated with fatigue at three months. This may be similar to the finding that more time in bed, but not less time in higher level activities, was predictive of worse functional outcome three months after stroke [48]. Previous bed rest studies have shown bed rest in general is not a benign treatment, but harmful to health [49, 50]. One possible mechanism by which bed rest could lead to higher levels of fatigue is the loss of cardiorespiratory fitness (CRF). CRF declines rapidly with bed rest [51], and is related to fatigue scores [52]. However, a recent review of cross-sectional studies found neither current physical activity levels nor CRF explained the level of fatigue experienced by people after stroke [53]. The risk of immobility-related complications increases with increased amounts of bed rest [54] suggesting that an association between fatigue and time in bed might also be explained by an increased prevalence of post-stroke complications. The reverse causal pathway is also

plausible, whereby early activity is dependent on the absence of fatigue. Despite our non-significant finding, we argue that further research is still needed to investigate how early fatigue and early inactivity are related to the problem of debilitating PSF.

A recent study found that patients with stroke, who had more effortful movement as determined by movement velocity during a timed hand movement task, were found to have increased likelihood of fatigue [22]. The authors proposed that the relationship could be due to either a simple effort-fatigue relationship or because both fatigue and reduced movement speed may result from an alteration in motor cortex excitability. With this finding in mind alongside our own results, PSF may be largely explained by a combination of poor pre-stroke health, effects of the brain injury (including early inflammatory effects), issues secondary to stroke during the acute phase (including medications, sleep problems and complications), depression, pain, the harmful consequences of too much inactivity, and increased effort of movement related to motor impairment.

Strengths of our study of PSF prevalence are the largely unselected stroke sample and the appropriate and well-matched control group. The main limitations of our study are that important confounding variables may be missing from the regression models such as cognitive function, medications and sleep disorders [19]. However, all models were adjusted for the most common and significant predicting variables after stroke. Secondly, there may be bias introduced because participants excluded due to lost to follow-up ($n = 7$), illness/cognitive decline/too tired ($n = 86$), or failure to complete pre-stroke fatigue, pain or depression questionnaires ($n = 34$) was potentially non-random. This group was likely to include the least healthy among the cohort. Thirdly, our measures of activity early after stroke may not adequately represent activity, or inactivity, of importance in preventing the development of PSF. All studies of PSF are limited by the multidimensional nature of fatigue and the inadequacies of the fatigue measurement tools used. Pre-stroke fatigue was measured with a different questionnaire to PSF, which may compromise our study, and early PSF was not measured. Finally, as the stroke units were all in Norway where national guidelines strongly recommend promotion of early out of bed activity, there may not have been sufficient between-individual spread of inactivity/activity levels for the role of early motor activity in predicting PSF to be revealed. The likelihood that the amount of bedrest is closely related to stroke severity and pre-stroke function also poses a challenge in this and future studies. Carefully controlling for these confounders as in the present study, using pre-stroke mRS and NIHSS in the models, is helpful but may still be inadequate. These limitations may have resulted in the lack of support for our second hypothesis.

Some previous research supports there being a difference between mental and physical fatigue, particularly after stroke. The impact of a stroke (irrespective of whether ischemic or haemorrhagic) taxes the central nervous system and increases the level of cognitive strain, which may be interpreted as fatigue. Stroke patients may be physically capable of participating in rehabilitation exercises or physical activity, but feel unable to engage in the activity due a depletion of cognitive reserves or higher vascular burden. Global increases in allostatic load coupled with negative affect may further compound this problem. Drawing a distinction between mental and physical fatigue is currently difficult and controversial and was not attempted in our study. However, we suggest further research along these lines may yield important knowledge and facilitate management of the problem of PSF in the future.

PSF presents management challenges with few options currently available with proven effectiveness [55]. A combined cognitive therapy and graded exercise program has shown promise in alleviating fatigue, as well as cognitive therapy alone [56, 57]. However these trials are small and more research is needed on the effect of multifactorial approaches including exercise programs. It is apparent from the results of observational studies that improvement of general health and management of depression, sleep and pain should all help alleviate PSF. We also suggest that determining the appropriate amount of time spent on bed-rest versus out of bed activities early after stroke warrants urgent further investigation in relation to fatigue [31].

Conclusions

Despite the lower prevalence of PSF in this relatively unselected stroke population than typically previously reported, this study confirms a higher prevalence than in those without stroke and further highlights the problem of PSF. Pre-stroke health appears to be an important factor, as does post-stroke depression and pain. The role of early motor activity in the development of fatigue following stroke remains unclear.

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