The Nottingham Fatigue After Stroke (NotFAST) study: Factors associated with severity of fatigue in stroke patients without depression

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Abstract

Objective. To identify factors associated with post-stroke fatigue in a sample of stroke survivors without depression.

Design. Cross-sectional cohort study.

Setting. Recruitment was from four stroke units in the UK.

Subjects. Participants were assessed within four weeks of first stroke; those with high levels of depressive symptoms (score ≥7 Brief Assessment Schedule Depression Cards) were excluded.

Main measures. Participants were assessed four to six weeks after stroke on the Fatigue Severity Subscale of the Fatigue Assessment Inventory, the Rivermead Mobility Index, Nottingham Extended Activities of Daily Living scale, Beck Anxiety Index, Sleep Hygiene Index, 6m walk test, and measures of cognitive ability.

Results. Of the 371 participants recruited, 103 were excluded and 268 were assessed. Of the latter, the mean age was 67.7 years (SD 13.5) and 168 (63%) were men. The National Institutes of Health Stroke Scale mean score was 4.96 (SD 4.12). Post-stroke fatigue was reported by 115 (43%) of participants, with 71 (62%) reporting this to be a new symptom since their stroke. Multivariate analysis using the Fatigue Severity Scale as the outcome variable found pre-stroke fatigue, having a spouse/partner, lower Rivermead Mobility Index score, and higher scores on both the Brief Assessment Schedule Depression Cards and Beck Anxiety Index were independently associated with post-stroke fatigue, accounting for approximately 47% of the variance in Fatigue Severity Scale scores.

Conclusions. Pre-stroke fatigue, lower mood, and poorer mobility were associated with post-stroke fatigue.

Key words

Stroke, fatigue, correlation, depression, mood

Introduction

Fatigue is one of the most distressing symptoms after stroke and its treatment is an important unmet need for stroke survivors and their carers.[1] Post-stroke fatigue adversely affects daily occupational performance and roles, return to work, participation in rehabilitation programmes, and quality of life. [2-4]

Many studies have highlighted associations between depressive symptoms and fatigue after stroke, leading to the suggestion that post-stroke fatigue is a symptom of depression.[5, 6] However, post-stroke fatigue has also been found independently of low mood.[7, 8] No previous studies have excluded participants with depressive symptoms, allowing fatigue to be investigated independently of this factor. Aside from the link with depression, evidence identifying other factors associated with post-stroke fatigue is limited and often conflicting.

Given the impact of fatigue on outcomes, it is important that post-stroke fatigue is appropriately identified and managed in clinical practice. The aim of the Nottingham Fatigue After Stroke (NotFAST) study was to identify factors associated with post-stroke fatigue in a sample of stroke survivors without depression, in order to inform clinical practice and the development of effective interventions.

Methods

NotFAST was a multi-centre, longitudinal cohort study. Ethical approval was granted by the East Midlands (Nottingham 2) NHS Health Research Authority Research Ethics Committee (13/EM/0187).

Participants were recruited from four UK inpatient stroke services at Nottingham University Hospitals, University Hospitals of Leicester, University College London Hospitals and Salford Royal Hospital.

Recruitment began in September 2013 and took place over an 18-month period. Stroke inpatients were identified by research assistants and by UK Clinical Research Network clinical trials researchers. Those eligible for inclusion had a clinical diagnosis of stroke, were aged ≥18 years, able to give informed consent, and had no previous history of stroke. Potential participants were excluded if they were unable to read or speak English, or had a documented diagnosis of dementia.

Participants were identified within four weeks of stroke and, after obtaining informed consent, screening for dysphasia and depressive symptoms was completed. The Sheffield Screening Test for Acquired Language Disorders was used for dysphasia, and those scoring below the age-recommended thresholds[9] were excluded in order to ensure that subsequent assessments could be completed. Depressive symptoms were assessed using the Brief Assessment

Schedule Depression Cards; those who scored ≥7, consistent with a diagnosis of a depressive disorder,[10] were excluded.

Participants were assessed on the following:

- *Self-reported fatigue* using the nine item Fatigue Severity Subscale of the Fatigue Assessment Inventory[11] (score range 7-49, with higher scores indicative of greater fatigue). Participants were also asked to recall their pre-stroke fatigue level using the Fatigue Severity Subscale. A score >36 was used to indicate clinically significant fatigue, an approach used by others.[12]
- *Mobility and activities of daily living (ADLs)* using the Rivermead Mobility Index[13] (score 0-15), Barthel Index[14] (score 0-20), Nottingham Extended Activities of Daily Living scale[15] (score 0-22), and a timed 6m walk test.[16] Higher Rivermead Mobility Index, Barthel Index and Nottingham Extended Activities of Daily Living scale scores are indicative of greater levels of independence. Participants were also asked to recall their pre-stroke abilities on the Nottingham Extended Activities of Daily Living scale and Rivermead Mobility Index.
- *Sleep* using the Sleep Hygiene Index[17] (score 0-52, with higher scores indicative of poorer sleep practices).

- *Mood and emotional factors* using the Beck Anxiety Inventory[18] (score 0-63) and Impact of Event Scale – Revised.[19] (score 0-88). Higher scores on the Beck Anxiety Inventory and Impact of Event Scale – Revised are indicative of greater anxiety and greater distress arising from traumatic events, respectively.
- *Cognitive abilities* using the Dot cancellation subtest of the Stroke Drivers Screening Assessment (sustained attention),[20] Stroop colour word test (selective attention),[21] and Adult Memory and Information Processing Battery speed of information processing test.[22]

A sample size estimate, based on up to 20 variables in the regression analysis, with 15 participants per variable, would require a sample size of 300.

The data were analysed with IBM SPSS Statistics software version 22. No attempt was made to impute missing data.

The frequency of fatigue was determined pre- and post-stroke and compared using McNemar's test.

Univariate analyses were used to identify factors significantly associated with post-stroke fatigue. Linear regression explored the unadjusted relationships between fatigue (Fatigue Severity Subscale score) and continuous variables, and differences in Fatigue Severity Subscale scores for categorical variables were investigated using one-way ANOVA or t-tests.

The data were examined to check that there were no non-linear associations or extreme outliers using scatter plots, and residuals were computed to test assumptions of normality and constant variance. To determine factors independently associated with fatigue, using the Fatigue Severity Subscale score as the dependent variable, an explanatory model using multivariable linear regression analysis was developed whereby those variables that were statistically significant in univariate analysis ($p \leq 0.05$) were entered into a multivariable model and a step-wise modelling procedure followed to obtain a final model of only statistically significant ($p \leq 0.05$) variables.

Results

Three hundred and seventy-one participants were recruited. After exclusion on screening variables and losses (n=103), further assessments were conducted with 268 participants.

Details of study recruitment and retention are presented in Figure 1.

[Figure 1].

The demographic and clinical characteristics of participants are presented in Table 1. Participants comprised mainly men (63%) and had a mean age of 67.7 years (SD 13.5, range 24 - 94 years). Most (91%) had had an infarction, with a high proportion of lacunar strokes (41%). National Institutes of Health Stroke

Scale (NIHSS)[23] scores indicated mild or/moderate stroke severity[24] (mean 4.96, SD 4.12). The mean days post-stroke at which assessments were completed was 23.61 (SD 13.15), with 164 assessments (61%) completed at home, and the remainder completed in hospital (30%) or in clinic/other settings (9%).

[Table1]

The distributions of scores are shown in Table 2. Mean Fatigue Severity Subscale scores were significantly higher post-stroke than pre-stroke (mean difference 10.4, 95% C.I. 8.7, 12.2, $p < 0.001$).

[Table 2]

The number reporting having had fatigue pre-stroke was 51 (19%), and the number reporting fatigue at assessment was 115 (43%). Of those reporting fatigue after stroke, 44 (38%) had also indicated fatigue pre-stroke, and 71 (62%) had developed new fatigue ($p < 0.001$).

[Table 3]

Factors associated with fatigue

The correlation between fatigue and other variables showed 12 statistically significant associations ($p \leq 0.05$) (Tables 4 and 5). Those with higher Fatigue Severity Subscale scores were younger ($p = 0.01$), had higher pre-stroke

Fatigue Severity Subscale scores ($p < 0.001$), lower pre-stroke ($p = 0.03$) and post-stroke ($p = 0.001$) Rivermead Mobility Index scores, and lower post-stroke Nottingham Extended Activities of Daily Living ($p = 0.004$) and Barthel Index ($p = 0.01$) scores. Higher Fatigue Severity Subscale scores were associated with higher scores on the Brief Assessment Schedule Depression Cards, Beck Anxiety Inventory, Impact of Event Scale, and Sleep Hygiene Index ($p < 0.001$).

For categorical variables, those with high levels of post-stroke fatigue were compared with those with low levels of fatigue. Mean Fatigue Severity Subscale scores were higher in those with a spouse or partner compared to those who were single, widowed or divorced (4.55 95% C.I. 0.42, 8.67, $p = 0.03$). Participants who were in work also reported higher mean Fatigue Severity Subscale scores than those who were retired or not working (4.82, 95% C.I. 0.61, 9.03, $p = 0.03$). No other demographic or clinical characteristics were significantly associated with post-stroke Fatigue Severity Subscale scores.

[Tables 4 and 5]

Factors independently associated with fatigue

Multiple linear regression analysis was conducted, with post-stroke Fatigue Severity Subscale score as the outcome variable, and with the twelve variables which were found to be significantly associated with fatigue in the univariate analyses (Table 6). In the final model, having a spouse or partner, lower

Rivermead Mobility Index, and higher scores on the Brief Assessment Schedule Depression Cards, Beck Anxiety Inventory, and pre-stroke Fatigue Severity Subscale accounted for approximately 47% of the variance (Adjusted R^2= 0.471) in Fatigue Severity Subscale scores. The analyses were repeated with the inclusion of gender, however there was no difference in the resulting overall model. (Adjusted R^2= 0.476).

[Table 6]

Discussion

Fatigue was common at four to six weeks post-stroke in a sample of stroke survivors without depression. Clinically significant levels of fatigue were reported by 43% of participants. Fatigue was associated with self-reported pre-stroke fatigue, being in a relationship, lower levels of functional mobility, and higher levels of anxiety and depressive symptoms.

Our findings on the frequency of fatigue lie within the range of proportions of stroke survivors with fatigue reported by Choi-Kwon et al.,[8] however the large range in frequency of fatigue (23-75%) in the latter review probably reflects the methodological diversity of the included studies. Our figure is considerably higher than that reported by Duncan et al.[25] at one month post-stroke (33%), a study which used a case definition interview, rather than a screening questionnaire, to identify fatigue.

Our sample was relatively unimpaired physically and cognitively, probably due to the predominance of those with lacunar syndrome strokes. The prevalence of fatigue was higher than that reported by Radman et al. (30%)[26], although the assessment of those with minor stroke (NIHSS $\leq$6) in the latter study was conducted rather later, at six months post-stroke. Our findings thus suggest that minor stroke is associated with fatigue frequently, and early, in the recovery process, and therefore has the potential to impact on the early stages of rehabilitation.[3]

The association of post-stroke fatigue and retrospectively reported pre-stroke fatigue has been noted previously.[12, 27, 28] Our sample reported a lower prevalence of pre-stroke fatigue than both Choi-Kwon et al.[27] (38%) and Lerdal et al.[12] (30%), although direct comparison is problematic as fatigue was assessed differently by visual analogue scale and dichotomous question, respectively. Our findings are broadly comparable with those of Chen et al.[28] who also used the Fatigue Severity Subscale to determine the prevalence (22%) of pre-stroke fatigue.

The majority (62%) of those who reported post-stroke fatigue had not experienced fatigue previously, suggesting that the stroke event may be linked to the development of fatigue. However, a high proportion (86%) of our participants who reported fatigue pre-stroke also reported fatigue after stroke, suggesting that some survivors experienced a continuation or exacerbation of pre-existing fatigue following stroke. The causes of pre-stroke fatigue are not clear, and are likely to be multifactorial.[28] Pre-stroke fatigue is, however, difficult to measure accurately, relying on recollection of events prior to stroke, which can result in recall bias.

It has been reported that post-stroke fatigue is more common in single people than in married/cohabiting people,[29] while others have found no significant association with relationship status.[12, 30] In contrast, we found that being in a relationship was significantly associated with fatigue, with higher levels of fatigue reported by those with a spouse or partner compared to those who were single, widowed or divorced, and explained the most variation in Fatigue Severity Subscale scores. However, we did not find an association between fatigue and living arrangements, suggesting that the influence of a personal relationship may be different from the potential availability of practical support at home. The reasons for the differences between these findings are unclear, but may result from heterogeneous samples, chance findings, or a complex interplay of social factors warranting further investigation.

Poorer functional mobility was a significant independent predictor of post-stroke fatigue. Reduced mobility may be a consequence of fatigue, although the direction of this relationship is unclear. However, lower physical activity levels at one month after stroke have been shown to predict fatigue at six and 12 months.[25] This suggests that interventions to promote early activity may have the potential to modify fatigue later in recovery. There is a need for longitudinal intervention studies to explore the effect of early activity levels on the development of fatigue.

The results support the suggestion that fatigue may arise due to several factors. This includes neurophysiological factors, such as corticomotor excitability, physical factors, such as increasing level of disability leading to fatigue, and psychological factors, such as mood leading to increased reports of fatigue. It is not possible to differentiate these factors in people with stroke and, indeed, this multifactorial nature is consistent with fatigue also being a problem in people with other disabling conditions, such as multiple sclerosis[31] and rheumatoid arthritis.[32]

The association between fatigue and depression has been established previously.[5, 6] However, despite having excluded participants with high levels of depressive symptoms, we found that the association between fatigue and depressive symptoms remained. We found a similar association between anxiety symptoms and fatigue. Our findings are consistent with a meta-analysis of psychological factors in relation to fatigue which also found an association between fatigue and mood in those without clinically significant depression or anxiety.[33] Therefore low levels of distress may impact on fatigue, and this would offer justification to address the emotional impact of stroke, even in the absence of clinically significant levels of anxiety or depression.

A limitation of this study is representativeness of the stroke sample. A substantial proportion of participants were recruited from acute stroke wards, where people with more severe strokes were not medically stable, and therefore less likely to participate. This may partially explain the predominance of lacunar syndrome and partial anterior circulation strokes, and the relatively low levels of physical and cognitive impairment in our sample. We also excluded those with aphasia for pragmatic reasons, and accept that our results would more accurately represent the stroke population if these participants had been included.

We had some losses after screening (13%) and participants withdrawing consent or being uncontactable (14%). Not all tests were fully completed, due to interruptions during assessments or participants being unable or declining to complete particular questions or tasks (e.g. 6m walk test, cognitive tests).Diagnosis of stroke classification and NIHSS scores were unavailable in some cases (NIHSS scores available for 203/268 cases (i.e. 76%)), affecting the overall estimation of stroke severity.

We recruited a greater proportion of men (68%) than women, consistent with observations that women are underrepresented in cardiovascular clinical trials.[34] We excluded people with communication problems for pragmatic reasons, but accept that studies investigating fatigue in this population are needed.

One of the key limitations may be our main outcome measure. The Fatigue Severity Subscale is commonly used in stroke research, however there is no validated 'cut-off' score to define clinically significant fatigue after stroke. Nevertheless, the approach we used is consistent with that used in other studies of fatigue in neurological conditions.[12]

Clinical Messages

- Self-reported pre-stroke fatigue, being in a relationship, and poor mobility were all associated with higher levels of fatigue.
- Mood was associated with fatigue, even though those with high levels of depressive symptoms were excluded from the study.
- The factors found to be associated with fatigue require further exploration, but are potential targets for interventions to treat post-stroke fatigue.

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Author contributions

AD, NL, NS, NW, AM, PT and GM were responsible for the study conception and design.

LH was responsible for the co-ordination of the data collection.

AD, NL, LH and EW input and analysed the data.

AD, NL and LH wrote the initial draft of the article and all authors contributed to the revisions.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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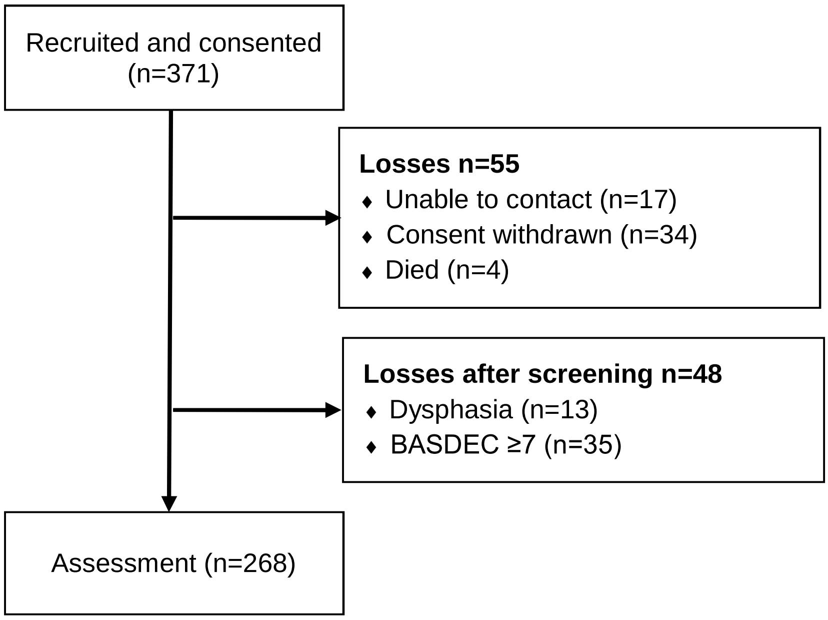
Figures

Figure 1. Recruitment and retention.



Tables

Table 1. Demographic and clinical characteristics (n=268).

	n	**%**
Gender		
Men	168	63
Women	100	37
Living arrangements		
Living with other	184	69
Relationship status		
In a relationship [a]	168	63
Ethnicity		
White	241	90
Other	27	10
Pre-stroke occupation		
Working	91	34
Retired/not working	177	66
Stroke type		
Infarction	243	91
Haemorrhagic	23	9
Missing	2	
Hemisphere		
Left	112	43
Right	141	54
Bilateral	10	4
Missing	5	
Stroke classification		
Total Anterior Circulation Stroke	13	6
Partial Anterior Circulation Stroke	64	30
Lacunar Syndrome	86	41
Posterior Circulation Syndrome	48	23
Missing	57	
Co-existing medical conditions		
Diabetes	41	15
Ischaemic heart disease	25	9
Previous TIA	25	9
Peripheral vascular disease	6	2
Anaemia	10	4
Cancer	14	5
Atrial fibrillation	53	20
Respiratory disease	33	12
Heart failure	6	2
Prescribed statins (n=262)	179	68

[a] defined as having a spouse, partner or civil partner

Table 2. Questionnaire measures and cognitive tests.

	Pre-stroke				Baseline			
	n	**Mean**	**SD**	**Range**	**n**	**Mean**	**SD**	**Range**
Fatigue								
Fatigue Severity Scale	268	21.6	13.4	54	268	32.0	16.7	54
Motor and ADL performance								
Rivermead Mobility Index	267	13.3	1.4	12	267	10.5	4.2	14
Nottingham Extended ADL scale	268	20.5	2.4	17	268	14.5	7.0	22
Barthel Index					266	17.2	4.3	20
6m walk (s)					194	8.3	4.6	37
Emotional factors								
Brief Assessment Schedule Depression Cards					268	3.2	3.0	6
Beck Anxiety Index					263	7.2	6.9	34
Impact of Event Scale –Revised					262	12.2	13.7	77
Sleep								
Sleep Hygiene Index					266	24.0	6.8	41
Cognitive abilities								
Dot cancellation time					244	511.5	183.1	853
Dot cancellation errors					244	30.6	39.2	162
AMIPB adjusted score					253	50.0	18.0	110
Stroop interference					252	22.5	27.0	346

Note: n = number of participants completing each assessment.

Table 3. Comparison of clinically significant fatigue scores pre- and post-stroke.

		Post-stroke fatigue		
		Not fatigued	**Fatigued**	**Total**
Pre-stroke fatigue	**Not fatigued**	146 (95%)	71 (62%)	**217**
	Fatigued	7 (5%)	44 (38%)	**51**
	Total	**153**	**115**	**268**

Table 4. Relationship between fatigue and continuous variables.

Variable	Pearson's correlation co-efficient	Unstandardised regression co-efficient (95% CI)	*p*
Age (per year)	-0.16	-0.19 (-0.34, -0.05)	0.01
Pre-stroke fatigue, motor and ADL performance			
Fatigue Severity Scale	0.55	0.69 (0.56, 0.81)	<0.001
Rivermead Mobility Index	-0.13	-1.56 (-2.96, -0.16)	0.03
Nottingham Extended ADL scale	-0.06	-0.43 (-1.29, 0.43)	0.32
Motor and ADL performance			
Rivermead Mobility Index	-0.20	-0.80 (-1.26, -0.33)	0.001
Nottingham Extended ADL scale	-0.17	-0.41 (-0.70, -0.13)	0.004
Barthel Index	-0.16	-0.63 (-1.09, -0.17)	0.01
Sleep			
Sleep Hygiene Index	0.29	0.71 (0.42, 0.99)	<0.001
Emotional factors			
Brief Assessment Schedule Depression Cards	0.33	3.06 (2.02, 4.11)	<0.001
Beck Anxiety Index	0.50	1.21 (0.95, 1.46)	<0.001
Impact of Event Scale – Revised	0.33	0.41 (0.26, 0.55)	<0.001
Cognitive abilities			
Dot cancellation time	-0.05	-0.01 (-0.02, 0.01)	0.44
Dot cancellation errors	-0.02	-0.01 (-0.06, 0.05)	0.74
AMIPB adjusted score	0.06	0.05 (-0.06, 0.17)	0.37
Stroop interference	-0.01	-0.004 (-0.08, 0.07)	0.91

Table 5. Univariate relationship between fatigue and categorical variables.

Variable	**Category**	**FSS mean(SD)**	**Mean difference (95%CI)**	***p***
Gender	Women	34.45 (15.89)	3.96 (-0.18, 8.09)	0.06
	Men	30.49 (17.04)		
Ethnicity	Other	36.59 (19.27)	5.14 (-1.52, 11.80)	0.13
	White	31.45 (16.35)		
Living arrangements	Alone	29.93 (14.75)	-2.97 (-7.30, 1.35)	0.18
	With other	32.90 (17.48)		
Relationship status	Single	29.12 (14.72)	-4.55 (-8.67, -0.42)	0.03
	In a relationship	33.67 (17.60)		
Occupational status	Working	35.15 (16.93)	4.82 (0.61, 9.03)	0.03
	Retired/not working	30.33 (16.39)		

Table 6. Multiple linear regression model for analysis of relationship between FSS score and other variables.

Variable	**β co-efficient (95% C.I)**	***p***
Marital status: single vs with other	-4.11 (-7.20, -1.01)	0.01
Baseline RMI	-0.46 (-0.82, -0.09)	0.01
BASDEC	1.54 (0.67, 2.42)	0.001
Beck Anxiety Inventory	0.72 (0.47, 0.96)	<0.001
Pre-stroke FSS	0.54 (0.42, 0.65)	<0.001
Adjusted R^2	0.47	