

**The Nottingham Fatigue After Stroke (NotFAST) Study: Results from follow-up
six months after stroke**

1 **Abstract**

2 **Background:** Post-stroke fatigue is common and disabling.

3 **Objectives:** The aim of NotFAST was to examine factors associated with fatigue in stroke
4 survivors without depression, six months after stroke.

5 **Methods:** Participants were recruited from four UK stroke units. Those with high levels of
6 depressive symptoms (score ≥ 7 on Brief Assessment Schedule Depression Cards) or aphasia
7 were excluded. Follow-up assessment was conducted at six months after stroke. They were
8 assessed on the Fatigue Severity Scale, Rivermead Mobility Index, Nottingham Extended
9 Activities of Daily Living scale, Barthel Index, Beck Anxiety Index, Brief Assessment
10 Schedule Depression Cards, Impact of Event Scale-Revised, and Sleep Hygiene Index.

11 **Results:** Of the 371 participants recruited, 263 (71%) were contacted at six months after
12 stroke and 213 (57%) returned questionnaires. Approximately half (n=109, 51%) reported
13 fatigue at six months. Of those reporting fatigue initially (n=88), 61 (69%) continued to
14 report fatigue. *De novo* fatigue was reported by 48 (38%) of those not fatigued initially.
15 Lower Nottingham Extended Activities of Daily Living scores and higher Beck Anxiety
16 Index scores were independently associated with fatigue at six months.

17 **Conclusions:** Half the stroke survivors reported fatigue at six months post-stroke. Reduced
18 independence in activities of daily living and higher anxiety levels were associated with the
19 level of fatigue. Persistent and delayed onset fatigue may affect independence and
20 participation in rehabilitation, and these findings should be used to inform the development of
21 appropriate interventions.

22

23 **Keywords**

24 CVA; fatigue; follow-up; mood; rehabilitation; stroke; anxiety.

25 **Introduction**

26 Post-stroke fatigue (PSF) is common and adversely affects participation in rehabilitation,
27 daily occupational performance, return to work, and quality of life (1-3). In a survey of unmet
28 needs after stroke, 43% of respondents reported that they had inadequate support to manage
29 their fatigue (4). Yet, despite being an important clinical issue, there is a dearth of evidence-
30 based recommendations for the prevention, treatment and management of PSF (5).

31 The course of fatigue for individual stroke survivors may vary. A recent review reported that
32 approximately one third of participants who reported PSF early after stroke (within the first
33 three months) experienced fatigue resolution by 12 months. However, some (12-58%) of
34 those without PSF in the early stages of recovery subsequently developed fatigue during the
35 following 12 months (6). For some stroke survivors, fatigue remained a persistent problem, in
36 excess of 36 months post-stroke (7).

37 The association between depressive symptoms and fatigue has been established (7, 8), but
38 evidence for other factors associated with PSF is often conflicting. Therefore, the overall aim
39 of the Nottingham Fatigue After Stroke (NotFAST) study was to identify factors associated
40 with fatigue, in a sample of stroke survivors without depression.

41 In our previous study, we investigated the factors affecting fatigue at four to six weeks
42 following stroke onset (n=268), these results have been reported in detail elsewhere (9). In
43 summary, 115 (43%) participants reported fatigue, of whom 71 (62%) identified this as a
44 post-stroke symptom. Multivariate analysis, using the Fatigue Severity Scale as the outcome
45 variable, found that pre-stroke fatigue, having a spouse/partner, lower Rivermead Mobility
46 Index score, higher Brief Assessment Schedule Depression Cards score, and higher Beck
47 Anxiety Index scores were independently associated with post-stroke fatigue.

48 The aim of the study was to investigate factors associated with fatigue at six months post-
49 stroke.

50 **Materials and methods**

51 Ethical approval was obtained (NHS Health Research Authority Research Ethics Committee
52 13/EM/0187) and all procedures followed were in accordance with their guidelines.

53 NotFAST was a multi-centre, longitudinal cohort study; the methodology has been reported
54 previously (9). Participants were recruited from four UK inpatient stroke services
55 (Nottingham University Hospitals, University Hospitals of Leicester, University College
56 London Hospitals and Salford Royal Hospital) over an 18-month period. Eligible participants
57 had a clinical diagnosis of first stroke, were aged 18 years or over, and gave written consent.
58 Participants were ineligible if they were unable to read or speak English sufficient to
59 complete questionnaires or had a documented diagnosis of dementia.

60 Participants were screened for dysphasia using the Sheffield Screening Test for Acquired
61 Language Disorders (10), and for depressive symptoms using the Brief Assessment Schedule
62 Depression Cards (BASDEC) (11). Where there was significant dysphasia, i.e. those scoring
63 below the age-recommended thresholds (10), or a BASDEC score consistent with a diagnosis
64 of depression (≥ 7) (11), participants were excluded.

65 Remaining participants were assessed on the following measures, four to six weeks following
66 stroke onset, and again by postal questionnaire at six months after stroke:

67 The Fatigue Severity Scale (FSS) of the Fatigue Assessment Inventory – nine item version
68 (12) was used to assess the severity of fatigue. Scores range from 7 to 63, with higher scores
69 indicative of greater fatigue. A score >36 was used to indicate clinically significant fatigue,
70 based on previous research. (13)

71 Mobility was assessed using the Rivermead Mobility Index (14) (score 0-15), and
72 independence in activities of daily living (ADLs) using the Barthel Index (15) (score 0-20)
73 for personal care, and the Nottingham Extended Activities of Daily Living scale (16) (score
74 0-22) for instrumental activities of daily living. Sleep was assessed using the Sleep Hygiene
75 Index (17) (score 0-52), with higher scores indicative of poorer sleep practices. Mood and
76 emotional factors were assessed using the Brief Assessment Schedule Depression Cards
77 (BASDEC) (11) (score 0 to 21) to detect depressive symptoms, Beck Anxiety Inventory (18)
78 (score 0-63) to measure anxiety, and the Impact of Event Scale – Revised (19) (score 0-88) to
79 detect post-traumatic stress. Higher scores are indicative of greater depression, greater anxiety
80 and greater distress arising from traumatic events, respectively.

81

82 In order to maximise return of six-month postal questionnaires, the research team; checked
83 with each participant's general practitioner that they were still alive and at the same address;
84 provided stamped addressed return envelopes; undertook follow-up telephone calls to prompt
85 participants (if questionnaires were not returned within three weeks); and offered telephone
86 or face-to-face support to aid questionnaire completion. Where returned questionnaires were
87 incomplete, participants were contacted by telephone to collect any missing information.

88 *Statistical analysis*

89 Data analyses were undertaken using IBM SPSS Statistics software version 22. Where $\leq 10\%$
90 of data was missing for a measure, and participants were not contactable, the missing values
91 were assigned the mean score of items that they had completed on the measure. If $>10\%$ of
92 answers for a measure were missing, this item was omitted from the analyses.

93 Pearson's chi-square (using Yates' Correction for Continuity where applicable) and t-tests
94 were used to compare the characteristics of participants who completed questionnaires with

95 those who did not. An explanatory model was developed whereby those variables that were
96 statistically significant in univariate analyses ($p \leq 0.05$) were entered into a multivariable
97 linear regression model. A step-wise modelling procedure was followed to obtain a final
98 model including only statistically significant ($p \leq 0.05$) variables.

99 **Results**

100 Of the 371 participants recruited to the NotFAST study, 263 (71%) were sent questionnaires
101 at six months post-stroke (Figure 1). Two hundred and thirteen (57%) questionnaires were
102 returned; 50 (13%) withdrew or did not respond. The mean number of days post-stroke at
103 which questionnaires were completed was 198 (SD 29.69, range 162 to 430).

104 [Figure 1: Study recruitment and retention]

105 Demographic and clinical characteristics of participants and those who did not return six-
106 month follow-up questionnaires are presented in Table 1.

107 [Table 1: Demographic and clinical characteristics of participants who completed, and those
108 who did not complete, six-month follow-up questionnaires]

109 The characteristics of those who completed follow-up were comparable to those who did not,
110 except for age. Participants who completed follow-up were significantly older (68.8 years,
111 SD 12.36) than non-respondents (62.8 years, SD 17.2) ($p=0.03$).

112 The results of the completed questionnaire measures at initial assessment and at six months
113 are shown in Table 2. NEADL and RMI scores were significantly higher at six months
114 ($p < 0.001$) than at four to six weeks post-stroke. Mood and sleep hygiene measure scores at
115 six months did not differ significantly from those at four to six weeks after stroke.

116 [Table 2: Distribution of questionnaire scores for participants who completed six-month
117 follow-up]

118 Mean FSS scores were significantly higher at six months post-stroke than at four to six weeks
119 ($p=0.002$). However, the proportion of participants reporting significant fatigue at six months
120 was 51% ($n=109$), which was not significantly different ($p=0.07$) from the proportion at four
121 to six weeks ($n=115$, 43%). Of those who reported fatigue initially ($n=88$), 61 (69%)
122 continued to report fatigue. A further 48 (38%) of those who were not fatigued previously
123 ($n=125$) reported ‘*de novo*’ (new) fatigue at six months ($p=0.02$).

124 ***Factors associated with fatigue at six months after stroke***

125 Univariate analysis found higher FSS scores at six months to be associated with lower scores
126 on the RMI, NEADL and BI ($p < 0.001$) and with higher scores on the BASDEC, BAI, IES-R
127 and SHI ($p < 0.001$) (Tables 3 and 4). No other demographic or clinical characteristics were
128 significantly associated with FSS scores at six months.

129 [Table 3: Relationship between fatigue and continuous variables at six-month follow-up]

130 [Table 4: Relationship between fatigue and categorical variables at six-month follow-up]

131 ***Factors independently associated with fatigue at six months after stroke***

132 Multiple linear regression analysis was conducted using FSS score as the dependent variable,
133 and variables found to be significantly associated with fatigue in the univariate analyses as
134 independent variables.

135 In the final model (Table 5), 33% of the variance in FSS scores at six months was accounted
136 for by lower NEADL scale scores and higher BAI scores at six months. There was no
137 difference in the overall model when repeated with *a priori* factors (age and gender).

138 [Tables 5: Multiple linear regression model for analysis of relationship between FSS score
139 and other variables at six-month follow-up]

140 **Discussion**

141 We found that fatigue was common at six months post-stroke (51%), but less so than reported
142 by Schepers *et al.* (20) (64%) and by van de Port *et al.* (3) (68%). Both of these studies were
143 conducted in rehabilitation settings and , both assessed fatigue at six months post-stroke using
144 the FSS. However, neither of these studies excluded participants with high levels of
145 depressive symptoms, which may account for the greater proportions of fatigue reported.
146 Furthermore, Schepers *et al.* (20) also reported a higher proportion of participants with
147 fatigue at study commencement (52%) compared with those in our cohort when assessed four
148 to six weeks after stroke (43%) (9).

149 The prevalence of fatigue at six months was also greater in our study than reported by
150 Duncan *et al.* (21) (22%) and by Radman *et al.* (22) (30%). This is likely to be due to
151 methodological differences. Duncan and colleagues used a case definition interview to define
152 clinically significant fatigue, rather than a multi-item scale, and Radman *et al.* included
153 people with less severe strokes (NIHSS score ≤ 3) than in our sample.

154 Whilst we found the severity of fatigue to be greater at six months than at four to six weeks
155 (9), the frequency of clinically significant fatigue was not significantly greater. A high
156 proportion (69%) of those fatigued in the early stages of recovery remained fatigued at six
157 months. New cases of fatigue (n=48) were reported, which is consistent with previous
158 research (7). Our findings are broadly consistent with the time course of fatigue suggested by
159 Wu *et al.* (6). Fatigue early in recovery may be a consequence of stroke-related biological
160 factors, which have the potential to resolve, whilst longer-term fatigue may arise from
161 chronic neurological deficit (6, 23).

162 A lower level of independence in ADLs was a significant independent predictor of fatigue in
163 the multivariate analysis, despite generally low levels of impairment overall. This finding
164 differs from that reported by Van de Port *et al.* (3), who found no significant association
165 between instrumental ADLs and fatigue at six months after stroke, after controlling for the
166 influence of depression and impaired motor function. It may be that instrumental ADLs (e.g.
167 shopping and social activities) have greater energy demands, and are more affected by
168 fatigue, than basic ADLs (e.g. washing and dressing) (3). Although we excluded participants
169 with symptoms consistent with a diagnosis of depression, it may be that even low levels of
170 depressive symptoms, along with environmental and behavioural factors, contribute to
171 reduced activity and participation in ADLs (24).

172 A strong statistical association was found between higher levels of anxiety symptoms and
173 fatigue, which remained significant in the multivariate analysis. Other studies have reported a
174 similar association between PSF and anxiety (22, 25, 26). A recent meta-analysis of
175 psychological associations with PSF identified a trend towards an association between fatigue
176 and anxiety, but noted that, due to their co-morbid relationship, the presence of depressive
177 symptoms may confound the reporting of anxiety (27). Psychosocial and behavioural factors
178 may also play an important role in sustaining and mediating responses to fatigue (6, 21).

179 Further studies to investigate factors which may underpin or sustain fatigue are required.

180 Our follow-up questionnaire return rate (81%) was comparable to that of other studies using
181 similar approaches (1, 28), although not all outcome measures were fully completed.

182 However, where possible, the impact of this was mitigated by contacting the participants for
183 clarification of missing data. There was an accidental omission of the BAI from eight
184 questionnaire packs. Another limitation was that the study was not sufficiently powered to
185 enable all possible factors related to fatigue to be investigated.

186 Our choice of outcome measures for fatigue and anxiety may also be a limitation. The FSS is
187 commonly used in stroke research, however there is no validated ‘cut-off’ score to define
188 clinically significant fatigue after stroke. Yet the approach we used to define significant
189 fatigue is consistent with other studies. Whilst it is possible that the association between
190 fatigue and anxiety symptoms reflects the overlap between stroke symptoms and descriptions
191 of physiological anxiety symptoms used in the BAI, our findings regarding anxiety are
192 nonetheless consistent with those reported by others.

193

194 **Conclusions**

195 At six months after stroke, fatigue was common in those who had experienced minor to
196 moderate stroke. In some cases, this persisted from the early stages of recovery, whilst for
197 others it was new *de novo* fatigue. Fatigue was associated with reduced independence in
198 ADLs and higher levels of anxiety symptoms. The persistence of fatigue at six months, and
199 the potential for delayed onset of fatigue, has important clinical implications for participation
200 and the recovery of stroke survivors in the long-term. These findings indicate that levels of
201 fatigue should be reviewed and interventions to address fatigue should be considered. Future
202 research should conduct further validation studies on the FSS as a measure of clinically
203 significant fatigue after stroke. In addition, research is needed to identify whether treatments
204 to reduce depression and anxiety and increase levels of independence in activities of daily
205 living have an effect on levels of fatigue.

206

207 **Acknowledgements**

208 We acknowledge the assistance of Emily Birks, Ella Clark, Christodouli Lagogianni, Holly
209 Milligan, Caroline Watchurst and Anne Worthington and also the support of the National
210 Institute of Health Research Clinical Research Network (NIHR CRN). We gratefully
211 acknowledge the input of our Steering Group, which comprised the authors, Dr Allison
212 Cooper, Mr Martin Kelly, Dr Peter Knapp, Professor Gillian Mead, Mr Ciaran Morgan, and
213 Dr Alex Pollock and the input of Dr Andrea Venn who provided statistical advice.

214

215 **Declaration of interest statement**

216 *Disclosure of interest*

217 The authors report no conflicts of interest.

218

219 **Funding details**

220 This research was supported by the Stroke Association under Grant TSA 2012/04.

221

222 **Word count:** 3,170

223 **References**

- 224 1. Andersen G, Christensen D, Kirkevold M, Johnsen S. Post-stroke fatigue and return to
225 work: a 2-year follow-up. *Acta neurologica Scandinavica*. 2012;125:248-53.
- 226 2. Morley W, Jackson K, Mead G. Post-stroke fatigue: an important yet neglected
227 symptom. *Age and Ageing* 2005;34(3):313.
- 228 3. van de Port I, Kwakkel G, Schepers V, Heinemans C, Lindeman E. Is fatigue an
229 independent factor associated with activities of daily living, instrumental activities of
230 daily living and health related quality of life in chronic stroke? *Cerebrovasc Dis*.
231 2007;23:40-5.
- 232 4. McKeivitt C, Fudge N, Redfern J, et al. Self-Reported Long-Term Needs After Stroke.
233 *Stroke*. 2011;42:1398-403.
- 234 5. Wu S, Kutlubaev M, Chun H, et al. Interventions for post-stroke fatigue. *Cochrane*
235 *Database of Systematic Reviews* 2015(7).
- 236 6. Wu S, Mead G, Macleod M, Chalder T. Model of Understanding Fatigue After Stroke.
237 *Stroke*. 2015;46(3):893-8.
- 238 7. Duncan F, Wu S, Mead G. Frequency and natural history of fatigue after stroke: a
239 systematic review of longitudinal studies. *J Psychosom Res*. 2012;73:18-27.
- 240 8. Lerdal A, Bakken L, Kouwenhoven S, et al. Poststroke fatigue – a review. *J Pain*
241 *Symptom Manage*. 2009;38:928-49.
- 242 9. Drummond A, Hawkins L, Sprigg N, et al. The Nottingham Fatigue After Stroke
243 (NotFAST) Study: Factors associated with severity of fatigue in stroke patients without
244 depression. *Clinical Rehabilitation*. First published 1st March 2017.
245 [10.1177/0269215517695857](https://doi.org/10.1177/0269215517695857)
- 246 10. Synder D, Body R, Parker M, Boddy M. *Sheffield Screening Test for Acquired*
247 *Language Disorders (Manual)*. Windsor: NFER Nelson; 1993.
- 248 11. Adsheed F, Day Cody D, Pitt B. BASDEC : a novel screening instrument for
249 depression in elderly medical inpatients. *BMJ*. 1992;305:397.
- 250 12. Schwartz J, Jandorf L, Krupp L. The measurement of fatigue: A new instrument. *J*
251 *Psychosom Res*. 1993;37(7):753-62. Lerdal A, Bakken LN, Rasmussen EF, et al.
252 Physical impairment, depressive symptoms and pre-stroke fatigue are related to fatigue
253 in the acute phase after stroke. ; (). *Disabil Rehabil*. 2011;33 (4):334-42.
254
- 255 14. Collen F, Wade D, Robb G, Bradshaw C. The Rivermead Mobility Index: a further
256 development of the Rivermead Motor Assessment. *Int Disabil Stud*. 1991;13:50-4.

- 257 15. Wade D, Collin C. The Barthel ADL index: a standard measure of physical disability.
258 Int Disabil Stud. 1988;11:89-92.
- 259 16. Nouri F, Lincoln N. An extended activities of daily living scale for stroke patients. Clin
260 Rehabil. 1987;1:301-5.
- 261 17. Mastin D, Bryson J, Corwyn R. Assessing sleep hygiene using the sleep hygiene index.
262 J Behav Med. 2006;29(3):223-363.
- 263 18. Beck A, Steer R. Beck Anxiety Inventory (BAI) Manual. Oxford: Pearson; 1990.
- 264 19. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective
265 stress. Psychosom Med. 1979;41:209-18.
- 266 20. Schepers V, Visser-Meily A, Ketelaar M, Lindeman E. Poststroke Fatigue: Course and
267 Its Relation to Personal and Stroke-Related Factors. Arch Phys Med Rehabil.
268 2006;87(2):184-8.
- 269 21. Duncan F, Lewis S, Greig C, et al. Exploratory Longitudinal Cohort Study of
270 Associations of Fatigue After Stroke. Stroke. 2015;46:1052-8.
- 271 22. Radman N, Staub F, Aboulaflia-Brakha T, Berney A, Bogousslavsky J, Annoni J.
272 Poststroke fatigue following minor infarcts: a prospective study. Neurology.
273 2012;79(14):1422-7.
- 274 23. Kuppuswamy A, Rothwell J, Ward N. A model of poststroke fatigue based on
275 sensorimotor deficits. Current opinion in neurology. 2015;28(6):582-6.
- 276 24. Barak S, Duncan PW. Issues in selecting outcome measures to assess functional
277 recovery after stroke. NeuroRx: the journal of the American Society for Experimental
278 NeuroTherapeutics 2006;3(4):505-24.
- 279 25. Glader E, Stegmayr B, Asplund K. Poststroke Fatigue: A 2-Year Follow-Up Study of
280 Stroke Patients in Sweden. Stroke. 2002;33(5):1327-33.
- 281 26. Snaphaan L, van der Werf S, de Leeuw F. Time course and risk factors of post-stroke
282 fatigue: a prospective cohort study. European journal of neurology. 2011;18(4):611-7.
- 283 27. Wu S, Barugh A, Mcleoad M, Mead G. Psychological associations of poststroke
284 fatigue: a systematic review and meta-analysis. Stroke. 2014;45:893-8.
- 285 28. Parker C, Dewey M. Assessing research outcomes by postal questionnaire with
286 telephone follow-up. Int J Epidemiol. 2000;29(6):1065-9.

287