



Prognosis and predictors of fatigue after stroke. An individual patient data meta-analysis from three large multicentre trials of fluoxetine for stroke recovery

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TITLE PAGE

Prognosis and predictors of fatigue after stroke. An individual patient data meta-analysis from three large multicentre trials of fluoxetine for stroke recovery

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Declaration of interests

None

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Data availability

Data will be available to other researchers after further planned analyses have been completed

Key words: Fatigue, cohort, time course, stroke

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Abstract

Background

Fatigue affects about half of stroke survivors, but its natural history and associations are uncertain. We aimed to determine the trajectory of fatigue between 6 and 12 months after stroke, and factors associated with changes in fatigue between 6 and 12 months after stroke, in patients recruited to three large clinical trials.

Methods

We performed three large randomised, placebo-controlled trials of fluoxetine 20mg daily for six months, for stroke recovery. Short Form 36 (SF-36) vitality scores measured post-stroke fatigue at 6 and 12 months. We undertook an individual patient data meta-analysis (IPDM) to explore the proportion of patients with fatigue at 6 months (SF-36 vitality score ≤ 45) who moved to a 'no fatigue' category at 12 months, the proportion with 'no fatigue' at 6 months who moved to a fatigue category, and the proportion experiencing a clinically relevant improvement in fatigue (increase in SF36 vitality of 10 points) from 6 to 12 months. We performed regression analyses to identify which baseline factors and whether the mood (self-assessed combined anxiety/depression) and pain components of EuroQol 5D-5L (EQ 5D-5L) at 6 months influenced fatigue trajectory between 6 and 12 months.

Results

A total of 5907 patients were included. Fatigue (SF-36 vitality scores) was recorded at 6 and 12 months in 5025 (85%) patients. Fatigue (SF-36 vitality ≤ 45) at 6 months was present in 1489 (29.6%, 95%CI: 28.4 to 30.9%) participants, of whom 568 (38.1%, 95%CI: 35.7% to 40.7%) had no fatigue at 12 months. Fatigue at 12 months was present in 1474 (29.3%, 28.0 to 30.6%) participants, of whom 553 (15.6%, 95% CI 14.5% to 16.9%) had no fatigue at 6 months.

Patient consent (rather than proxy consent), being able to lift arms off bed at baseline, and severe/extreme pain at 6 months were independently associated with persistence of fatigue through to 12 months, whereas stroke type (embolic or small vessel disease vs haemorrhagic) at baseline and self-assessed slight anxiety/depression at 6 months were associated with fatigue resolution by 12 months.

Among those without fatigue at 6 months, Asians (compared to whites), and those reporting moderate or severe anxiety/depression problems were less likely to have fatigue at 12 months.

Conclusion

More than a third of patients with fatigue at 6 months experienced a clinically relevant reduction in fatigue between 6 and 12 months, whereas one sixth of patients without fatigue at 6 months developed fatigue at 12 months. Although the individual regression analyses identified statistically significant associations between some independent variables and fatigue at 12 months, there was no consistent pattern across the analyses. Future research should identify factors associated with the development and recovery of fatigue after stroke.

Background

Fatigue affects around half of stroke survivors. It is a research priority [1]. Stroke survivors often ask whether their fatigue will reduce. A 2023 meta-analysis (nine longitudinal studies, 3254 patients) reported that a third of patients experienced a reduction in fatigue; however the studies were heterogeneous in design and of variable quality [2]. A Medline search on 9th July 2025 (from 1st January 2023) using the terms ‘Fatigue AND stroke’ identified 549 citations; of the five cohort studies (1163 patients) fatigue trajectories were highly variable [3-7]. A 2025 systematic review of non-motor stroke symptoms reported no statistically significant change in fatigue over time [8]. This uncertainty about fatigue trajectories makes it difficult for clinicians to counsel patients about fatigue reduction.

There are cross-sectional data showing associations between fatigue and depression, anxiety and pain at a single time point [9] but not over time. Identifying longitudinal associations might provide targets for treatment.

Three large pragmatic randomised controlled clinical trials (FOCUS (fluoxetine or control under supervision), AFFINITY (the Assessment of FluoxetiNe In sTroke recovery) and EFFECTS (Efficacy of Fluoxetine—a randomisEd Controlled Trial in Stroke) compared 6 months of fluoxetine 20mg daily versus placebo for stroke recovery [10-12]. The three trials had the same basic design and data have been combined [13]. All three trials collected data on fatigue (from patient, or proxy if the patient could not answer) at 6 and 12 months using the SF-36 vitality domain (AFFINITY used a different version with an extra response category). The SF-36 vitality score has well established internal consistency, reliability, content validity, construct validity and criterion-related validity for fatigue [14]. Scores range from 0-100 and can be analysed (a) dichotomously, with scores ≤ 45 representing clinically significant fatigue [15] and (b) by a change of at least 10 points representing a clinically meaningful change in fatigue [16]. The three trials also collected EuroQol 5D-5L (EQ 5D-5L) data at 6 months [17]. This self-report tool includes mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

Our aims were to examine

- a) Fatigue trajectories between 6 and 12 months
- b) Whether patient characteristics (at randomisation), and the EQ-5D-5L domains of pain and mood (anxiety/depression) at 6 months, were associated with fatigue trajectories between 6 and 12 months.

Methods

We prepared a statistical analysis plan. We included patients with SF-36 vitality scores at 6 and 12 months.

For the first aim, we described the number (% and 95% confidence intervals (CI)) of patients moving between the two dichotomous fatigue categories from 6 to 12 months [14] and the number who experienced a clinically meaningful reduction in fatigue (i.e. an increase in their vitality scores) from 6 to 12 months [15].

For the second aim, we firstly performed three separate regression analyses. The dependent variables were (a) fatigue (SF-36 vitality ≤ 45) at 12 months in those with fatigue at 6 months (b) fatigue (SF-36 vitality score ≤ 45) at 12 months in those without fatigue at 6 months and c) clinically meaningful reduction in fatigue (≥ 10 point increase in SF-36 vitality between 6 and 12 months) in the entire sample.

Our independent variables included all baseline factors common to the three trials (except for time to enrolment, the probability of being alive and independent at 6-months because the individual components were considered separately, and depression at randomisation due to very small numbers) (table 1). Other independent variables included allocated treatment and the 6-month EQ5D 5DL domains of pain/discomfort and anxiety/depression (self- or proxy-reported). These EQ5D 5L domains are not 'diagnostic' of either pain/discomfort or anxiety/depression. Due to very small numbers in the extreme categories, responses of extreme were combined with 'very' for both domains. The small number with anxiety/depression reflects trial eligibility criteria: patients with current or recent (within the last month) depression requiring SSRI antidepressant treatment were excluded; and AFFINITY also excluded patients currently requiring or receiving any antidepressant therapy.

We constructed initial logistic regression models using factors with a univariable p value of <0.10 . Then using a backwards selection method we removed sequentially variables failing to reach statistical significance until only variables with $p < 0.05$ remained. We did not impute missing data.

We then performed a post-hoc analysis of the factors at baseline associated with fatigue at 6 months, to put the analyses of change in fatigue between 6 and 12 months into context.

Ethical approval had previously been granted for the three trials, and all patients or their proxies provided written consent to participation [10-12]. These current analyses used anonymised data so further ethical approval was not needed.

Results

A total of 5907 patients were included, of whom 5025 had a fatigue (SF-36 vitality) measure at both 6 and 12 months. The remaining 882 patients were not included because of death (n=478), withdrawal of consent (n=40), 6-month fatigue present but 12-month missing (n=192), 12-month fatigue present but missing 6-month (n=47), and fatigue at 6- and 12-month missing (n=125). The source (patient or proxy) of fatigue data appeared similar at 6 and 12 months (appendix 5).

Changes in fatigue from 6 to 12 months

The mean (SD) SF-36 vitality score was 58.6 (23.0) at 6 months and 58.9 (23.8) at 12 months.

Fatigue (SF-36 vitality ≤ 45) at 6 months was present in 1489 (29.6%, 95%CI: 28.4% to 30.9%) participants, of whom 568 (38.1%, 35.7% to 40.7%) had no fatigue at 12 months (figure 1).

Fatigue at 12 months was present in 1474 (29.3%, 28.0 to 30.6%) participants, of whom 553 (15.6%, 95% CI 14.5%, 16.9%) had no fatigue at 6 months (figure 1).

Between 6 and 12 months, SF-36 vitality scores changed by less than 10 points in 2131 (42.4%) participants, increased by ≥ 10 points in 1515 (30.2%) (i.e. fatigue reduced) and fell by ≥ 10 points in 1379 (27.4%) participants (i.e. fatigue worsened).

Fatigue at 12 months in patients with fatigue at 6 months

Table 1 shows the univariable factors.

The initial logistic regression model included the variables reaching statistical significance at <0.1 (table 1). Table 2 shows the final regression model. Stroke type (embolic or small vessel disease vs haemorrhagic); slight problems with anxiety/depression vs no anxiety/depression were associated with resolution of fatigue by 12 months. Being able to lift arms off the bed at baseline, patient consent (rather than proxy consent), severe/extreme pain versus no pain/discomfort were associated with still having fatigue at 12 months.

Fatigue at 12 months in patients without fatigue at 6 months

Univariable analyses are shown in appendix 1 (baseline factors) and in appendix 2 (6 month factors). The final regression model included only ethnicity and anxiety/depression (table 3); Asians were less likely to develop fatigue than whites (24/638 (3.8%) versus 515/2844 (18.1%)), and those reporting moderate or severe anxiety/depression problems were less likely to have fatigue at 12 months (moderate/severe 72/578 (12.5%) compared to 480/2952 (16.3%)).

Factors associated with a clinically relevant reduction in fatigue between 6 and 12 months

The only significant factor was not living at home at 6 months (own/relative's home: 1387/4675 (29.7%) reduced, living in other locations: 127/346 (36.7%) reduced (OR 1.38 95% CI 1.10, 1.73) (appendices 3 and 4).

Post-hoc analysis: factors at baseline associated with fatigue at 6 months (appendix 5)

Being male (OR 1.15, 95% CI 1.01, 1.31), being able to lift arms off the bed (OR 1.22 95% CI 1.07, 1.40) and patient consent (OR 1.42 95% CI 1.18, 1.71) were independently associated with fatigue at 6 months, whilst being Asian rather than white was associated with less fatigue at 6 months (OR 0.29, 95% CI 0.22, 0.38).

Discussion

This IPDM in 5025 patients showed that 38% of those with fatigue at 6 months experienced resolution of fatigue at 12 months, and 16% without fatigue at 6 months developed fatigue at 12 months, demonstrating the dynamic nature of post-stroke fatigue between 6 and 12 months. The overall prevalence did not change over time (figure 1). These descriptive findings alone represent an important contribution to the field.

The regression analyses exploring changes in fatigue between 6 and 12 months identified statistically significant associations with several independent variables, but there was inconsistency between the three models, and some directions of effect were counterintuitive. The pain/discomfort and anxiety/depression domains of the EQ5D 5L at 6 months did not consistently predict changes in fatigue to 12 months.

The regression analyses were pre-specified and conducted in accordance with a statistical analysis plan but were not designed to support definitive causal inference. Accordingly, *statistically* significant associations should be interpreted with caution, as they might not be causal or clinically meaningful. The inconsistency of results across models, including counterintuitive directions of effect, suggest that routinely collected baseline characteristics and the pain/discomfort and anxiety/depression items from the EQ5D 5L at 6 months do not predict individual fatigue trajectories. This may reflect residual confounding and the inherent limitations of measuring complex, overlapping constructs using brief instruments. Post-stroke fatigue is a clinically meaningful and commonly reported symptom [1], but it substantively overlaps with core features of anxiety and depression - indeed, fatigue is itself a recognised symptom within both conditions, and mechanisms such as physiological arousal, hypervigilance, sleep disturbance, and cognitive “fog” are shared across these presentations. Cultural and linguistic differences in symptom perception and expression may also influence reporting across populations. Our analyses reinforce the view that post-stroke fatigue is a multifactorial, transdiagnostic symptom cluster that is currently poorly captured, underscoring the need for more granular phenotyping and longitudinal assessment in future studies.

The strengths of these analyses include the use of a very large dataset generalisable across populations, the application of a validated fatigue measure, and a relatively low proportion of missing data from only 15% of randomised patients, mostly due to death. Furthermore, to our knowledge, this is the first analysis to examine factors predicting changes in fatigue over time rather than fatigue status at a single time point.

There were several limitations. The three trials were not designed a priori to look at changes in fatigue-though we did specify in advance that we would perform this secondary analysis [19]. Although the data were derived from randomised controlled trials, the analysis is an observational design and therefore subject to the limitations inherent to non-experimental designs. The SF-36 vitality score probably did not capture all aspects of fatigue but it would have been impractical to use longer, multidimensional fatigue scales [20]. Correlation and co-linearity of outcome and predictor variables were not checked during the analyses. We used a p value of <0.1 in the univariable analyses to select factors for the regression analyses, there is a risk that this might have missed confounders or predictors. The single mood measure at 6 months was limited to a single EQ5D 5L item that assesses self-reported anxiety and depression concurrently; had we had separate anxiety and depression scores, our analyses might have been more sensitive. We did not collect data on other factors previously implicated in fatigue aetiology e.g. impaired physical fitness. The dynamic psychometric features of the EQ-5D-5L or SF36 after stroke aren't well established. Finally, the use of fluoxetine up until six months could be a confounder because it would be used less commonly in unselected stroke populations, but fluoxetine had no effect in our models.

The clinical implications are that health care professionals can reassure stroke patients with fatigue that reduction in fatigue is common, with approximately one third reporting resolution. For patients who are not fatigued at 6 months, a reasonable approach might be for clinicians to raise the possibility that fatigue can develop later, while emphasising that this occurs in a minority of cases and that support is available if symptoms arise. More generally, further research is needed to find out whether stroke survivors wish to know about the wide range of problems that might develop after stroke-even if the risk is low.

These findings have important implications for research. Substantial gaps remain in our understanding of the aetiology of post-stroke fatigue and the factors that influence its trajectory. Future prognostic studies of post-stroke fatigue should include a wide range of potential predictors including behavioural factors such as illness beliefs, fear avoidance and ‘all or nothing behaviours’ that are associated with fatigue in conditions other than stroke [21]. Improved understanding of the factors associated with fatigue recovery and persistence will help lay the foundations for the development of new treatments to prevent and treat post-stroke fatigue.

Author contributions

All authors were investigators in the three fluoxetine trials. For this IPDM analysis, Catriona Graham performed the analysis, the first draft of the paper was written by Gillian Mead, and all authors commented on drafts.

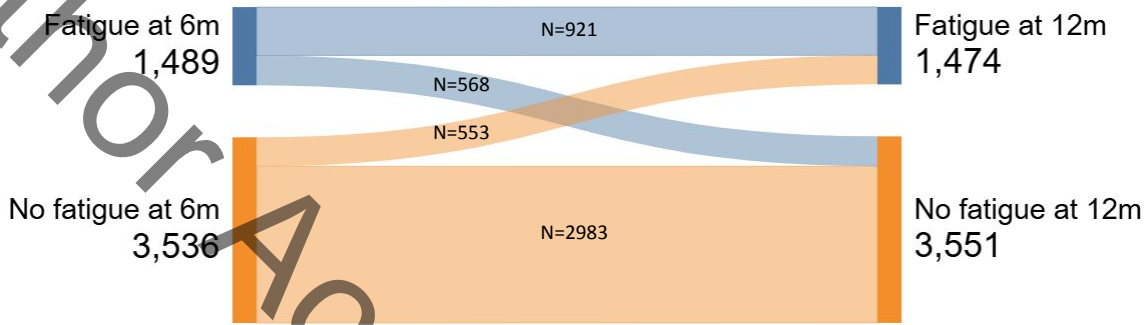
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Figure 1 Sankey plot showing the four different trajectories of fatigue



328 **Table 1**

329 Univariable associations with fatigue at 12 months, in the participants *with* fatigue at 6 months. A
330 higher odds ratio indicates a greater chance of still having fatigue at 12 months

	Fatigue status at 12months				Odds Ratio (95% CI)	P-value
	No fatigue (SF36 vitality >45)		Fatigue (SF 36 vitality <=45)			
	N	%	N	%		
Total number of patients randomised	568	100.00	921	100.00		
Sex						
Female	211	37.2	309	33.6		
Male	357	62.9	612	66.5	1.17 (0.94, 1.46)	0.16
Age group						
<=70 years old	281	49.5	441	47.9		
>70 years old	287	50.5	480	52.1	1.07 (0.89, 1.31)	0.55
Ethnicity						
Asian	36	6.3	37	4.0	0.62 (0.39, 1.00)	
Other	12	2.1	27	2.9	1.38 (0.67, 2.72)	
White	520	91.6	857	93.1		0.09
Marital status						
Divorced	41	7.2	71	7.7	1.22 (0.77, 1.95)	
Married	306	53.9	527	57.2	1.22 (0.90, 1.64)	
Other	7	1.2	12	1.3	1.21 (0.46, 3.19)	
Partner	47	8.3	70	7.6	1.05 (0.67, 1.66)	
Single	73	12.99	108	11.7	1.05 (0.70, 1.56)	
Widowed	94	16.6	133	14.4		0.79
Living arrangements						
Living alone	183	32.2	283	30.7	0.93 (0.75, 1.17)	0.55
Employment status						
Full time	119	21.1	202	21.9		0.49
Other	24	4.2	48	5.2	0.83 (0.51, 1.36)	
Part time	28	4.9	61	6.6	1.28 (0.78, 2.12)	
Retired	387	68.1	610	66.2	0.93 (0.72, 1.20)	
Require assistance with activities of daily living prior to stroke					1.13 (0.70, 1.82)	0.63
	27	4.8	49	5.3		
Previous coronary heart disease	89	15.7	120	13.0	0.81 (0.60, 1.09)	0.15
Previous ischaemic stroke/transient ischaemic attack					0.80 (0.60, 1.06)	0.12
	100	17.6	134	14.6		
Diabetes	107	18.8	185	20.1	1.08 (0.83, 1.4)	0.56
Current or past hyponatraemia	5	0.9	11	1.2	1.36 (0.47, 3.94)	0.57
Previous intracranial bleed	10	1.8	15	1.6	0.92 (0.41, 2.07)	0.85
Previous Upper gastrointestinal bleed					0.69 (0.35, 1.36)	0.28
	16	2.8	18	2.0		
Bone fractures	106	18.7	189	20.5	1.13 (0.86, 1.47)	0.38
Previous depression	37	6.5	71	7.7	1.20 (0.79, 1.81)	0.39
Final diagnosis of stroke						
Missing	7	1.2	19	2.1		
No	.	0.00	3	0.3		
Yes	561	98.8	899	97.6		
Stroke type						
Missing	.	0.00	2	0.22		
Haemorrhagic	52	9.2	106	11.5		
Ischaemic	516	90.9	813	88.3	0.77 (0.55, 1.10)	0.15
Stroke type/Ischaemic classification						
Missing	.	0.00	2	0.2		

Haemorrhagic	52	9.2	106	11.5		0.05
Ischaemic - Large artery disease	84	14.8	147	16.0	0.86 (0.56, 1.32)	
Ischaemic - Small vessel disease	126	22.2	178	19.3	0.69 (0.46, 1.04)	
Ischaemic - Embolism from heart	130	22.9	169	18.6	0.64 (0.43, 0.95)	
Ischaemic - Another cause	9	1.6	29	3.2	1.58 (0.70, 3.58)	
Ischaemic - Unknown/uncertain	167	29.4	290	31.5	0.85 (0.58, 1.25)	
Able to walk (at baseline)	212	37.3	384	41.7	1.20 (0.97, 1.49)	0.10
Able to lift both arms (at baseline)	381	67.1	695	75.5	1.51 (1.20, 1.90)	0.0005
Can talk (at baseline)	465	81.9	770	83.6	1.13 (0.86, 1.49)	0.39
Motor deficit (at baseline)	466	82.0	728	79.0	0.83 (0.63, 1.08)	0.16
Aphasia (at baseline)	124	21.8	183	19.9	0.89 (0.69, 1.15)	0.36
Taking other anti-depressant at baseline	13	2.3	18	2.0		
Mood (Patient health questionnaire) at baseline						
.	5	0.9	3	0.3		
Two 'yes' responses	29	5.1	53	5.8	1.13 (0.71, 1.80)	
One 'yes' response	43	7.6	70	7.6	1.01 (0.68, 1.49)	
Zero 'yes' responses	491	86.4	795	86.3		0.88
Inpatient at baseline	559	98.4	902	97.9	0.76 (0.34, 1.70)	0.51
Who gave consent						
Missing	2	0.3	3	0.3		
Proxy	106	18.7	104	11.3		
Patient	460	81.0	814	88.4	1.80 (1.35, 2.42)	<0.001
Randomised treatment						
Fluoxetine	281	49.5	480	52.1	1.11 (0.90, 1.37)	0.32
Placebo	287	50.5	441	47.9		
National Institute of Health Stroke Scale (baseline) (odd ratio per unit increase in NIHSS)					0.96 (0.94, 0.98)	0.0006
Pain (EQ5 D 5L) at 6 months						
Missing	1	0.2	2	0.2		
No problems	232	40.1	401	43.5		0.0047
Slight problems	175	30.8	246	26.7	0.81 (0.63, 1.05)	
Moderate problems	139	24.5	200	21.7	0.83 (0.64, 1.09)	
Severe/extreme problems	21	3.7	72	7.8	1.98 (1.19, 3.31)	
Anxiety/Depression (EQ5 5DL at 6 months)						
Missing	.	0.0	2	0.2		
No problems	317	55.8	561	60.9		0.0064
Slight problems	184	32.4	224	24.3	0.69 (0.54, 0.84)	
Moderate problems	56	9.9	106	11.5	1.07 (0.75, 1.52)	
Severe/extreme problems	11	1.9	28	3.0	1.44 (0.71, 2.93)	
6 months: living location						
Missing	.	0.0	1	0.1		
Own/relatives/friends home	529	93.1	872	94.7	0.75 (0.48, 1.16)	0.19

Care/nursing home/Long term National health Service Care/In Hospital/Other	39	6.9	48	5.2		
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Table 2

Regression model for the participants *with* fatigue at 6 months, predicting 12 month fatigue. A higher odds ratio indicates higher chance of still having fatigue at 12 months

Odds Ratio				
	Point Estimate	95% Wald Confidence Limits		Pr > ChiSq
Stroke type: Ischaemic - Another cause vs Haemorrhagic	1.33	0.58	3.07	0.01
Stroke type: Ischaemic - Embolism from heart vs Haemorrhagic	0.57	0.38	0.87	
Stroke type: Ischaemic - Large artery disease vs Haemorrhagic	0.77	0.49	1.19	
Stroke type: Ischaemic - Small vessel disease vs Haemorrhagic	0.55	0.36	0.83	
Stroke type: Ischaemic - Unknown/uncertain vs Haemorrhagic	0.75	0.50	1.11	
Able to lift arms from bed: Yes vs No	1.47	1.15	1.88	0.0020
Who gave consent: Patient vs Proxy	1.82	1.34	2.48	0.0002
Pain @ 6 months: Moderate problems vs No problems	0.95	0.71	1.27	0.0059
Pain @ 6 months: Severe/extreme problems vs No problems	2.38	1.38	4.12	
Pain @ 6 months: Slight problems vs No problems	0.90	0.69	1.17	
Anxiety/Depression @ 6 months: Moderate problems vs No problems	1.01	0.69	1.48	0.0028
Anxiety/Depression @ 6 months: Severe/extreme problems vs No problems	1.13	0.53	2.42	
Anxiety/Depression @ 6 months: Slight problems vs No problems	0.63	0.49	0.82	

340 **Table 3**
341 Regression model for participants *without* fatigue at 6 months, predicting 12 month fatigue
342 OR>1.0 indicated greater chance of fatigue at 12 months

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Odds Ratio				Pr > ChiSq
Effect	Point Estimate	95% Wald Confidence Limits		
Ethnicity Asian vs White	0.17	0.11	0.25	<.0001
Ethnicity Other vs White	1.53	0.83	2.84	
Anxiety/Depression @ 6 months: Moderate problems vs No problems	0.69	0.51	0.94	0.0028
Anxiety/Depression @ 6 months: Severe/extreme problems vs No problems	0.41	0.23	0.73	
Anxiety/Depression @ 6 months: Slight problems vs No problems	0.99	0.80	1.22	

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