Investigating post-stroke fatigue: An individual participant data meta-analysis

Toby B. Cumming[a,b,*], Ai Beng Yeo[c], Jodie Marquez[c], Leonid Churilov[a], Jean-Marie Annoni[d], Umaru Badaru[e], Nastaran Ghotbi[f], Joe Harbison[g], Gert Kwakkel[h], Anners Lerdal[i], Roger Mills[j], Halvor Naess[k], Harald Nyland[l], Arlene Schmid[m], Wai Kwong Tang[n], Benjamin Tseng[o], Ingrid van de Port[p], Gillian Mead[q], Coralie English[b,c]

[a] *Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia*
[b] *Centre of Research Excellence in Stroke Rehabilitation and Brain Recovery, Australia*
[c] *School of Health Sciences and Priority Research Centre for Stroke and Brain Injury, University of Newcastle, Callaghan, Australia*
[d] *Department of Medicine, University of Fribourg, Switzerland*
[e] *Department of Physiotherapy, Bayero University, Kano, Nigeria*
[f] *Department of Physiotherapy, Tehran University of Medical Sciences, Iran*
[g] *Department of Medical Gerontology, Trinity College Dublin, Ireland*
[h] *Department of Rehabilitation Medicine, VU University, Amsterdam, the Netherlands*
[i] *Department of Nursing Science, University of Oslo, Norway*
[j] *Department of Neurology, Royal Preston Hospital, UK*
[k] *Department of Neurology, Haukeland University Hospital, Norway*
[l] *Institute of Clinical Medicine, University of Bergen, Norway*
[m] *Department of Occupational Therapy, Colorado State University, Fort Collins, USA*
[n] *Department of Psychiatry, Chinese University of, Hong Kong*
[o] *Department of Health & Kinesiology, University of Texas, Tyler, USA*
[p] *Revant Rehabilitation Centres, Breda, the Netherlands*
[q] *Centre for Clinical Brain Sciences, University of Edinburgh, UK*

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ABSTRACT

Objective: The prevalence of post-stroke fatigue differs widely across studies, and reasons for such divergence are unclear. We aimed to collate individual data on post-stroke fatigue from multiple studies to facilitate high-powered meta-analysis, thus increasing our understanding of this complex phenomenon.

Methods: We conducted an Individual Participant Data (IPD) meta-analysis on post-stroke fatigue and its associated factors. The starting point was our 2016 systematic review and meta-analysis of post-stroke fatigue prevalence, which included 24 studies that used the Fatigue Severity Scale (FSS). Study authors were asked to provide anonymised raw data on the following pre-identified variables: (i) FSS score, (ii) age, (iii) sex, (iv) time post-stroke, (v) depressive symptoms, (vi) stroke severity, (vii) disability, and (viii) stroke type. Linear regression analyses with FSS total score as the dependent variable, clustered by study, were conducted.

Results: We obtained data from 14 of the 24 studies, and 12 datasets were suitable for IPD meta-analysis (total n = 2102). Higher levels of fatigue were independently associated with female sex (coeff. = 2.13, 95% CI 0.44–3.82, p = 0.023), depressive symptoms (coeff. = 7.90, 95% CI 1.76–14.04, p = 0.021), longer time since stroke (coeff. = 10.38, 95% CI 4.35–16.41, p = 0.007) and greater disability (coeff. = 4.16, 95% CI 1.52–6.81, p = 0.010). While there was no linear association between fatigue and age, a cubic relationship was identified (p < 0.001), with fatigue peaks in mid-life and the oldest old.

Conclusion: Use of IPD meta-analysis gave us the power to identify novel factors associated with fatigue, such as longer time since stroke, as well as a non-linear relationship with age.

* Corresponding author at: 245 Burgundy St, Heidelberg, Victoria 3084, Australia.
  E-mail address: toby.cumming@florey.edu.au (T.B. Cumming).

1. Introduction

Fatigue is very common after stroke and is strongly related to poor quality of life, independent of depression and disability [1,2]. The prevalence of post-stroke fatigue varies widely between studies. Our recent systematic review and meta-analysis identified a pooled fatigue prevalence estimate of 50% (95% CI 43–57%), but with substantial heterogeneity ($I^2 = 94\%$) [3]. All studies included in the meta-analysis used the same instrument (the Fatigue Severity Scale; FSS [4]), so methodological factors alone cannot explain the high variability in prevalence.

Consistent relationships have been found between higher levels of post-stroke fatigue and: female sex [5–8], greater disability [9,10], depression [6,11], and pre-stroke fatigue [6,9]. The relationship with age is unclear, as older age has been associated with greater fatigue [7,8], but so has younger age [12,13], with other studies reporting no link [9,10]. Anxiety has been linked to fatigue after stroke, albeit less strongly than depression [11,14]. Some aspects of cognitive function – sustained attention and executive function [14], processing speed and working memory [15] – relate to post-stroke fatigue, but cognition assessed using the Mini-Mental Status Examination (MMSE [16]) does not [8,10,17]. There are conflicting reports about the role of vascular risk factors and co-morbidities. One study found that leukoaraiosis, diabetes mellitus and myocardial infarction were independently associated with post-stroke fatigue [18], while other large studies failed to identify an association between post-stroke fatigue and diabetes, ischaemic heart disease or hypertension [9,17].

With regard to stroke-specific factors, a history of previous stroke has been linked to greater fatigue [5]. The relationship between stroke severity and fatigue is little studied. Mild stroke does not necessarily mean little fatigue; 3 studies [14,19,20] including only mild stroke survivors all reported fatigue prevalence rates in the expected range (35–72%). Type of stroke and lesion side do not appear to influence post-stroke fatigue [8,17,21], but lesions in the infratentorial region (particularly brainstem) or basal ganglia may increase fatigue risk [22]. Onset of fatigue is typically early after stroke [9], but subsequent time course is unclear. A systematic review of 9 longitudinal studies found that fatigue tended to persist, though it did decline over time in 7 of the studies [23].

The current study follows our recent systematic review and meta-analysis of post-stroke fatigue prevalence [3]. There was striking heterogeneity between studies in fatigue prevalence, and we could not explain this variability using factors such as depressive symptoms and time since stroke. These analyses, though, were highly constrained as they were limited to study-level summary statistics for each variable. Compared to a standard meta-analysis, an individual participant data (IPD) approach can improve the quality of the data and the types of analyses available, producing more reliable results [24]. We therefore aimed to explore factors associated with post-stroke fatigue using IPD meta-analysis, following the PRISMA-IPD guidelines [25]. We hypothesized that fatigue would be independently associated with female sex, depressive symptoms and greater disability, but not with age, stroke type, stroke severity or time since stroke.

2. Methods

2.1. Source studies

Source studies were drawn from our systematic review of post-stroke fatigue prevalence [3], where full details of inclusion criteria, search strategy and quality appraisal can be found. For studies relevant to the current analysis, these details are available in the Supplementary Materials. In our previous review, the initial search (dated September 2014) yielded 921 studies, with 49 included in the review. Across the 49 studies there were 15 different fatigue assessment tools, with the Fatigue Severity Scale (FSS) the most common (N = 24 studies). To maintain methodological consistency, we included only studies that used the FSS. The FSS is a 9-item questionnaire with each item scored on a seven-point Likert scale; higher scores indicate greater fatigue severity [4]. The reliability and precision of the FSS has been demonstrated [26].

2.2. Data collection

Corresponding authors of the 24 eligible studies were contacted via email in February 2016 and invited to share their anonymised raw data on 8 pre-identified variables: (i) FSS score, (ii) age, (iii) sex, (iv) time post-stroke, (v) depressive symptoms, (vi) stroke severity, (vii) disability, and (viii) stroke type. In this email we also requested data on other variables of interest: (i) anxiety, (ii) lesion side, (iii) cognitive impairment, (iv) vascular risk factors, (v) history of depression, and (vi) pre-stroke fatigue. This two-tier approach was taken to simplify participation for study authors, increasing our chances of obtaining the most relevant data. Non-responding authors were emailed a second time in March 2016. All source studies had ethical approval, and we obtained additional ethical approval for our analysis protocol from the University of Newcastle, Australia Human Research Ethics Committee (Ref: H-2016-0201).

2.3. Data collation

In studies with fatigue outcomes collected at multiple times, data from the earliest time point were extracted (maximising available data). For clinical outcomes of depressive symptoms and disability, data were used from the same time point as FSS assessment. One reviewer (ABY) checked for discrepancies in sample size between the datasets received and the original published studies. Two reviewers (CE, ABY) checked variables in the received datasets for consistency with the published reports, noting any missing data. Any inconsistencies were clarified, and finalised data for each study were verified with each corresponding author before being collated into a single database.

2.4. Data classification

Coding of each variable was standardised across studies. No reclassification was required for: fatigue (FSS total score), age (years), sex (male-female), stroke type (ischaemic-haemorrhagic), stroke severity (NIHSS score [27]). Time since stroke was converted into days and then divided into 3 time epochs: < 4 months, 4–12 months, > 12 months. For depressive symptoms, each participant was categorised as 'depressed' or 'not depressed' according to established cut-offs for each assessment scale used. If multiple measures of depression were recorded in the same study, the measure with the fewest missing data was used. The same dichotomisation approach was used to classify disability ('independent' or 'disabled') and anxiety ('anxious' or 'not anxious'). Full details of cut-off scores for depression, anxiety and disability are avaliable in the Supplementary Materials. For other variables of interest, pre-stroke fatigue (yes-no), lesion side (left-right), cognition (MMSE total score), previous stroke (yes-no) and vascular risk factors (yes-no) did not require re-classification. To facilitate additional analysis, categorical variables were created for fatigue status (2 levels, with fatigue defined as FSS total score ≥ 36 [4]) and age (7 levels, by decade).

2.5. Statistical analysis

Statistical analyses were conducted using STATA 14 (College Station, TX: StataCorp LP). The one-stage model for data synthesis was applied, with 'study' included in all regression analyses to preserve clustering within studies; it is inappropriate to analyse individual participant data as if they all came from a single study [24]. First, univariable linear regression analyses were conducted for each pre-
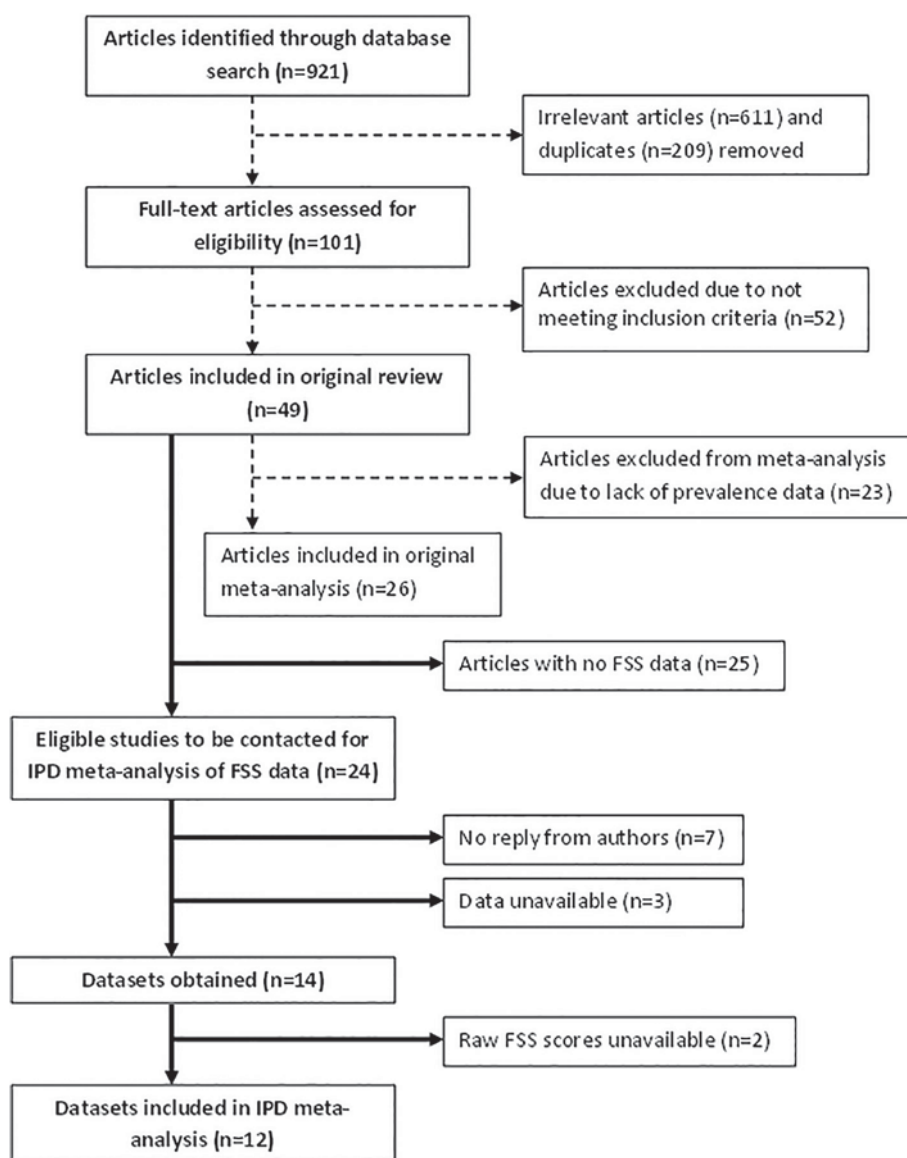
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Fig. 1. Modified PRISMA flowchart: original 2016 systematic review and meta-analysis (dashed arrows) and current IPD meta-analysis (solid arrows).

identified variable except stroke severity (age, sex, depression, stroke type, time since stroke, disability) separately against FSS total score. FSS scores were not normally distributed (Shapiro-Wilk = 0.97, $p < 0.001$); they were not asymmetrical (skewness = 0.06, standard error = 0.05) but there were fewer outliers than normal (kurtosis = -1.04, standard error = 0.11). The same set of univariable analyses were repeated with median regression to confirm results. Next, we ran a multivariable linear regression with all pre-identified variables as independent variables against FSS total score. This was also confirmed with multivariable median regression. These linear and median multivariable regressions were then repeated in the sub-group of participants without depression. Given a previous report of a curvilinear association between age and post-stroke fatigue [28], we investigated non-linear models of this relationship. For the other variables of interest, univariable linear regression analyses were conducted separately against FSS total score. These analyses were repeated with median regression to confirm results. Multivariable analysis of these variables was not conducted due to substantial gaps in the data across studies. To investigate differences in fatigue prevalence, odds ratios for fatigue were calculated for each of the categorical variables.

3. Results

Datasets for 14 of the 24 studies in our previous review were obtained, with 2 then excluded because raw FSS scores were unavailable [29,30]. Fig. 1 portrays the study inclusion flowchart. The 12 included studies provided individual level data for 2141 participants [2,6,10,14,18,31–37]. Three studies had participants with missing FSS data ($n = 14$ (5%) [34]; $n = 24$ (7%) [18]; $n = 1$ ($< 1\%$) [35]), leaving a total of 2102 participants. Mean age was 62.3 (SD = 13.2), 62% were male, and 51% were fatigued (mean FSS score 35.6, SD = 14.9). Time between stroke onset and fatigue assessment ranged from 1 to 5370 days post-stroke (median 193, IQR 105–398). Table 1 summarises participant characteristics.

There was good data availability for pre-specified variables age (N = 12 studies), sex (N = 11), depression (N = 11), stroke type (N = 10), time since stroke (N = 10) and disability (N = 7), but only one study included stroke severity [14]. For the other variables of interest, data were available for lesion side (N = 8 studies), anxiety (N = 6), cognitive function (N = 3), pre-stroke fatigue (N = 2), diabetes (N = 4), hypertension (N = 4), smoking (N = 3), atrial

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Table 1
Participant characteristics.

	N (data available)	N (%) or mean (SD), range
Age, years	2093	62.3 (13.2), *16–97*
Sex, male	2011	1238 (62%)
FSS total score	2102	35.6 (14.9), *9–63*
Fatigued (FSS ≥ 36)	2102	1062 (51%)
Depressed	1984	613 (31%)
Time since stroke (days)	1941	477 (742), *1–5370*
Time epoch		
0–4 months		638 (33%)
4–12 months		699 (36%)
> 12 months		604 (31%)
Stroke type	1870	
Ischaemic		1668 (89%)
Haemorrhagic		202 (11%)
Lesion side	1095	
Right		526 (48%)
Left		569 (52%)
Disability	1392	
Independent		1175 (84%)
Dependent		217 (16%)

fibrillation (N = 3) and previous stroke (N = 3).

Univariable linear regressions indicated that female sex (coeff. = 3.30; 95% CI 2.02–4.58; p < .001), depression (coeff. = 9.44; 95% CI 3.33–15.56; p = .006), longer time since stroke (> 12mth versus < 4mth; coeff. = 7.98; 95% CI 0.27–15.69; p = .044) and disability (coeff. = 6.36; 95% CI 0.97–11.75; p = .028) were each significantly associated with greater fatigue. Age (coeff. = 0.02; 95% CI -0.15-0.19; p = .81) and stroke type (coeff. = 5.77; 95% CI -1.41-12.95; p = .10) were not significantly associated with fatigue. This pattern of results was unchanged in the univariable median regressions. The multivariable linear regression model, with all pre-identified variables except stroke severity included, confirmed independent associations between fatigue and female sex, depression, longer time since stroke and disability (Table 2). The model accounted for 17% of variance in fatigue scores.

Given the complex inter-relationship between depression and fatigue, we analysed whether the same pattern of associations was present in the sub-group without depression (n = 1371). Both the linear and median multivariable regression results were unchanged, with female sex, longer time since stroke and disability all independently associated with greater fatigue (all p < .025), and age and stroke type not significantly associated with fatigue (see Supplementary Materials for full results).

To investigate age further, we computed a range of models, both linear and non-linear. The cubic model was the only one to reach significance [F(3,2089) = 16.9, p < .001]. FSS score by age decade is depicted in Fig. 2.

With regard to the other (not pre-specified) variables of interest, univariable linear regressions indicated that anxiety and not having diabetes were significantly associated with greater fatigue (Table 3). Cognition, lesion side, smoking, hypertension and previous stroke were not associated with fatigue. The relationship between atrial fibrillation and fatigue bordered on significance (p = .077) in the linear model, but was significant in the median regression model (p < .001).

With FSS scores dichotomised into fatigued (≥ 36) or not fatigued, prevalence by sub-group is presented in Table 4. Odds ratios indicated significantly higher likelihood of fatigue in participants who were female, depressed, disabled, anxious, fatigued prior to the stroke, or who had previous stroke. There were borderline relationships between higher fatigue prevalence and haemorrhagic stroke, longer time since stroke, atrial fibrillation, and not having hypertension.

Table 2
Multivariable linear regression model, clustered by study, of each pre-identified variable (excepting stroke severity) against FSS total score.

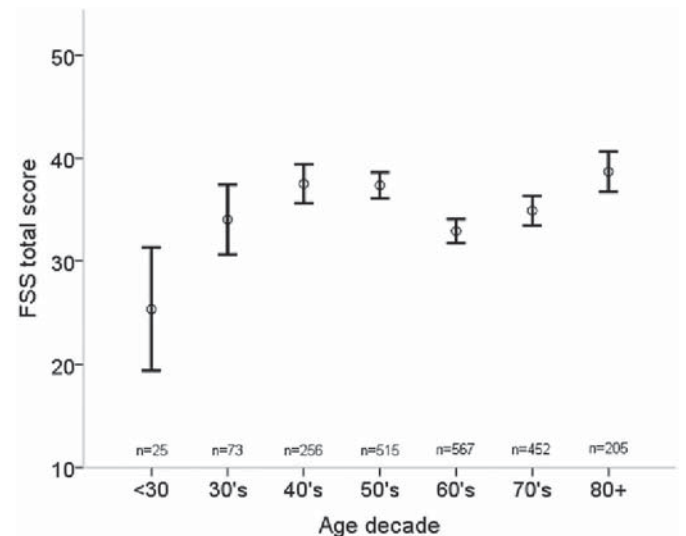|	Coeff.	95% CI	p
Age	0.03	−0.13, 0.18	0.66
Sex	2.13	0.44, 3.82	0.023
Depression	7.90	1.76, 14.04	0.021
Stroke type	3.41	−6.25, 13.07	0.41
Time since stroke: < 4mth vs 4–12mth	6.18	−4.28, 16.64	0.19
Time since stroke: < 4mth vs > 12mth	10.38	4.35, 16.41	0.007
Disability	4.16	1.52, 6.81	0.010

Fig. 2. Means (with 95% CIs) for FSS total score across age decades.

Table 3
Univariable regression models, clustered by study, of other variables of interest against FSS total score.

	Coeff.	95% CI	p
Anxiety	10.96	7.15, 14.76	0.001
Cognition	0.08	−0.17, 0.33	0.31
Lesion side	−0.43	−3.29, 2.43	0.73
Smoking	5.07	−5.67, 15.82	0.18
Diabetes	−2.77	−3.97, −1.56	0.005
Hypertension	−2.19	−5.34, 0.96	0.11
Atrial fibrillation	5.30	−1.42, 12.01	0.077
Previous stroke	2.88	−9.94, 15.70	0.44

4. Discussion

This meta-analysis of individual data revealed significant independent relationships between post-stroke fatigue and female sex, depression, longer time since stroke and disability. The regression model that included all pre-identified variables (except stroke severity) explained only 17% of the variance in fatigue score, indicating that important predictive information was missing. One obvious candidate is level of physical activity, which has been shown to explain a substantial amount of variability in post-stroke fatigue [38]. There was no straightforward linear association between fatigue and age, but there was a cubic relationship, with higher fatigue levels in those aged in their 40s and 50s and those over 80. Post-stroke fatigue was also

Table 4
Fatigue prevalence by sub-group, with odds ratios (clustered by study).

	N	% fatigued	OR	95% CI	p
Male	588/1238	47%			
Female	438/773	57%	1.44	1.18, 1.74	< 0.001
Ischaemic	814/1668	49%			
Haemorrhagic	139/202	69%	1.35	0.97, 1.90	0.076
Not depressed	587/1371	43%			
Depressed	415/613	68%	4.34	3.41, 5.53	< 0.001
0–4 months	256/638	40%			
4–12 months	349/699	50%	1.17	0.86, 1.60	0.32
> 12 months	382/604	63%	1.43	0.96, 2.14	0.080
Independent	516/1175	44%			
Dependent	137/217	63%	2.33	1.67, 3.26	< 0.001
Right lesion	326/526	62%			
Left lesion	350/569	62%	0.99	0.77, 1.27	0.96
Not anxious	384/742	52%			
Anxious	207/262	79%	3.53	2.48, 5.02	< 0.001
No pre-stroke fatigue	116/406	29%			
Pre-stroke fatigue	72/185	39%	1.69	1.16, 2.47	0.007
Not smoking	295/767	38%			
Smoking	118/239	49%	1.01	0.72, 1.42	0.94
No diabetes	352/818	43%			
Diabetes	80/223	36%	1.24	0.88, 1.74	0.22
No hypertension	205/474	43%			
Hypertension	228/568	40%	1.30	0.98, 1.72	0.069
No atrial fibrillation	371/927	40%			
Atrial fibrillation	53/96	55%	1.51	0.96, 2.39	0.077
No previous stroke	359/890	40%			
Previous stroke	62/130	48%	1.49	1.00, 2.21	0.049

significantly associated with anxiety, pre-stroke fatigue and with not having diabetes.

Depression was strongly related to fatigue, with depressed participants scoring 8 points higher on the FSS than non-depressed participants. This finding is consistent with a previous meta-analysis [11] and suggests that our failure to detect such a relationship in the original systematic review and meta-analysis [3] is attributable to having only aggregate study-level summary data available. While depression was closely linked to fatigue, it wasn't all-consuming: adjusting for depression in the multivariable models did not change the pattern of univariable results, and analysis of the sub-group of participants without depression matched the overall analysis. Several source studies had exclusion criteria relating to current or premorbid depression [33,35,36], so prevalence of depression in our dataset may be lower than expected.

The finding of greater fatigue in women than men follows a well-established precedent [5–8]. There are numerous potential explanations for this. Whether the imbalance is reflective of cultural norms (e.g., less acceptable for men to report fatigue-related symptoms), caregiver roles (e.g., women less likely to receive support for household tasks), or a difference in physiology remains unknown. Our finding that higher levels of disability are associated with post-stroke fatigue also supports previous studies [9,10]. There is some evidence that the critical factor here is walking: in a study that included both stroke survivors and controls, variance in fatigue in the stroke group was best accounted for by gait impairments, whereas depression was the predominant factor in explaining fatigue in controls [39].

The research literature on the link between age and post-stroke fatigue is dotted with inconsistent studies [7–10,12,13]. One previous study ($n = 115$) found a curvilinear association between age and post-stroke fatigue [28], with a negative correlation in those under 60 and a positive correlation in those over 75. In our much larger analysis ($n = 2093$ with age and FSS data), we detected a cubic relationship, with people under 40 or in their 60s or 70s being less fatigued than people in their 40s or 50s or over 80. This is a strong finding; when comparing people in their 50s and 60s, the 95% CIs do not overlap (see Fig. 1). Reasons for this result are unclear, but may reflect the heavy demands of family and working life between the ages of 40 and 60, which are not so great between the ages of 60 and 80.

Identifying an association between greater fatigue and longer time since stroke was a surprise. If anything, results of a previous meta-analysis indicated the reverse [23]. While only the comparison between < 4 months and > 12 months was significant, the prevalence results reflect a 'dose-dependent' response: 256/638 (40%) fatigued in the early epoch, 349/699 (50%) fatigued in the middle epoch, and 382/604 (63%) fatigued in the late epoch. The time since stroke results are potentially confounded by age and by study, but the significant association remained (in fact, it became stronger) in multivariable analysis. It is plausible that on-going physical deconditioning and a negative cycle of inactivity may contribute to fatigue levels increasing over time.

The IPD data provided a valuable opportunity to compare fatigue after ischaemic and haemorrhagic stroke. No differences have previously been identified [8,21], but this is unsurprising given the small numbers of haemorrhagic stroke survivors in individual studies. Our regression analyses were consistent with earlier studies, with stroke type not significantly associated with fatigue. However, the comparison of fatigue prevalence indicated a trend ($p = .076$) toward higher fatigue after haemorrhagic stroke (139/202, 69%) than ischaemic stroke (814/1668, 49%).

Of the other variables of interest, anxiety was the most strongly related to fatigue, though the independence of this association was not established (we did not conduct multivariable analysis). Having diabetes was related to lower fatigue, in contrast to other studies that have reported either no association [9,17] or the reverse [18]. This finding is difficult to explain, and may not have survived multivariable adjustment. Lesion side bore no relation to fatigue, nor did cognitive function (as measured by MMSE) or smoking status. When we considered odds ratios, fatigue prevalence was significantly related to pre-stroke fatigue and to previous stroke, and there was some indication of higher rates of fatigue in those with atrial fibrillation and those without hypertension.

An obvious limitation of the current analysis is that it does not directly address the causes of post-stroke fatigue. Several of the important factors identified, such as depression and disability, are very likely to have bi-directional relationships with fatigue. Our sample is not fully representative of the population. We obtained data from 14 of the 24 studies that used the FSS from the original systematic review [3]. This was a good response rate compared to other attempts at obtaining data for re-analysis [40]. At an individual participant level we had data for $n = 2141$, representing 64% of those available for the original meta-analysis. In terms of prevalence patterns, the studies included in IPD meta-analysis (mean prevalence 52%, SD 14) were similar to those from the original review that could not be included in IPD meta-analysis (mean prevalence 49%, SD 16). The original search, conducted in 2014, is now several years old. To check whether there were relevant papers published in the interim, we updated our search, with screening done by two independent reviewers (TBC, CE). Six additional studies were identified that met our inclusion criteria [41–46], but their aggregate sample size was only $n = 269$. We decided that such a small potential increase in numbers was unlikely to alter our findings and did not warrant a renewed round of individual data requests, collation and analysis. Within studies, we were limited by the available data; this was clearest for stroke severity. Lack of commonality in outcome measures across stroke trials is a major issue. To help fix this problem, researchers are urged to follow recently published recommendations on standardisation in outcome measures for stroke recovery trials [47]. While it is a strength that all studies shared the same fatigue scale, the FSS may not be the ideal assessment for post-stroke fatigue. It is more focussed on severity than symptoms (the word 'fatigue' appears in all 9 items) and favours physical over mental fatigue. Any selection bias in the source studies means that our findings may not be fully generalisable to the wider stroke population. Several studies excluded people with substantial cognitive, physical or communication impairments [6,32,34,35,37]. While unfortunate, this is not unusual in clinical stroke research [48].

Given the prevalence and impact of post-stroke fatigue, it is important to determine the major contributing factors. Using individual

participant data from 12 studies, we found that greater fatigue was independently associated with female sex, depression, longer time since stroke and disability. The regression model, however, explained only 17% of the variance in fatigue. There is still much work to be done to understand the genesis of post-stroke fatigue.

Competing interests

The authors have no competing interests to report.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online

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