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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

A R T I C L E I N F O

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A B S T R A C T

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).

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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 apprasial 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-