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Review Article

Prevalence and experience of fatigue in survivors of critical illness: a mixed-methods systematic review

3 1 S. Bench,¹ L. Stayt,² A. Shah,³ P. Dhiman⁴ and W. Czuber-Dochan⁵

1 Professor, School of Health and Social Care, London South Bank University, London, UK

2 Senior Lecturer, Oxford Brookes University, Oxford, UK

3 NIHR Doctoral Research Fellow, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

4 Senior Statistician, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

5 Senior Lecturer and Associate Dean, Florence Nightingale School of Nursing, Midwifery and Palliative Care, King's College London, London, UK

Summary

We conducted a mixed methods systematic review to investigate the prevalence, experience and management of fatigue in survivors of critical illness. We identified 76 studies investigating fatigue or vitality in adults discharged from an intensive care unit and split the data we extracted into three datasets: vitality scores from the Short Form Health Survey-36 ($n = 54$); other quantitative data ($n = 19$); and qualitative data ($n = 9$). We assessed methodological quality using critical appraisal skills programme tools. We adopted a segregated approach to mixed-methods synthesis. In a final step, we attributed combined results to one of four qualitative themes: prevalence and severity; contributing factors; impacts on quality of life; and assessment and management. Prevalence of fatigue ranged from 13.8 to 80.9%. Short Form Health Survey-36 vitality scores were commonly used as a marker of fatigue. Vitality scores reached a nadir approximately 1 month following ICU discharge (mean (SD) 56.44 (32.30); 95%CI 52.92–59.97). They improved over time, but seldom reached reference population scores. Associated biological, disease-related and psychological factors included age, poor pre-morbid status, sleep and psychological disturbance. Qualitative data highlight the profound negative impact of fatigue on survivors' quality of life. Survivors seldom had any information provided on the potential impact of fatigue. No fatigue assessment tools specific to critical illness or evidence-based interventions were reported. Fatigue is highly prevalent in survivors of critical illness, and negatively impacts recovery. Further research on developing fatigue assessment tools specifically for critically ill patients and evaluating the impact of pharmacological and non-pharmacology interventions is needed.

Correspondence to: S. Bench

Email: benches@lsbu.ac.uk

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2 Twitter: @szbench; @LouiseStayt; @DocAShah

Introduction

Every year, more than 130,000 patients survive an episode of critical illness in the UK [1]. Survivors commonly report

long-lasting physical, cognitive and psychosocial problems impacting their quality of life, a combination termed post-intensive care syndrome [2, 3]. Post-intensive care

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syndrome can also impact on the family members of survivors [4]. A cardinal symptom of post-intensive care syndrome is fatigue [5], which is defined as an overwhelming, sustained sense of exhaustion, typically unrelieved by sleep, with decreased capacity for physical and mental work at a usual level [6, 7].

Recent data suggest that fatigue is an important, but under-recognised and under-researched problem in survivors of critical illness [8–10]. In a qualitative study by Nedergaard et al., former patients ranked fatigue as one of three outcomes most important to them [11]. International advisory panels also highlight the need for research investigating the prevalence, severity and underlying mechanisms of fatigue and the design of strategies to optimise support during patients' recovery [12, 13]. Moreover, although the long-term consequences of COVID-19 are unknown, preliminary reports suggest that fatigue is the most prominent symptom for many survivors [14].

Previous reviews have evaluated overall health-related quality of life (HRQoL) following critical illness, and reported some data on fatigue, for example, by Hashem et al. [5] Two narrative reviews that included data on the assessment and management of fatigue in the intensive care unit (ICU) have also been published [15, 16]. In this mixed-methods systematic review we aimed to identify the prevalence, experience, risk-factors for and management of fatigue in adult critical illness survivors following ICU discharge.

Methods

We conducted this systematic review according to a study protocol pre-registered on PROSPERO. We report our findings in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [17]. We undertook a mixed-methods approach, combining studies from different research methodologies in accordance with best practice guidance [18].

We considered primary research of any methodology published in English. We included studies investigating fatigue in adult patients who had been in ICU. We excluded studies that focused on fatigue secondary to a solitary pathological process (e.g. brain injury) and those on a different, but parallel topic (e.g. sleepiness). We also excluded studies reporting data collected while the patient was still in the ICU. Due to the extensive number of studies reporting Medical Outcomes Study 36-item Short Form Health Survey (SF-36) data as part of overall HRQoL, we included only papers published after 2000 and which reported raw vitality data as a measure of fatigue.

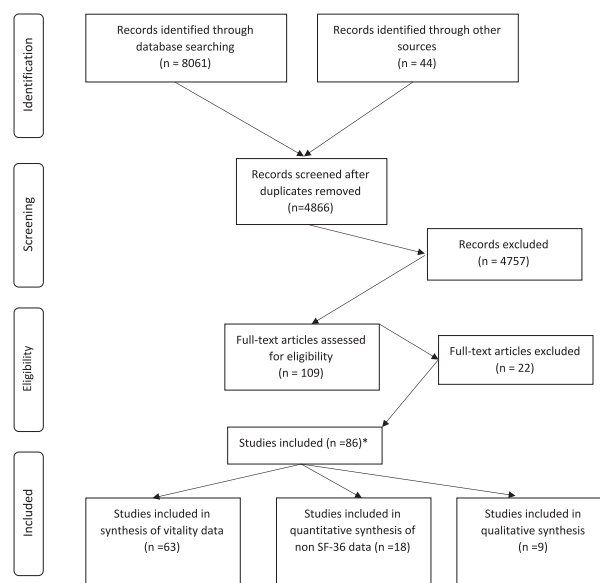
We searched seven databases from 1 January 1946 until 28 February 2018: CINAHL®, MEDLINE®, EMBASE®,

PsycINFO®, OVID® Emcare, British Nursing Index and the Web of Science™. An updated search was conducted on 14 May 2020. The search strategy can be found in online Supporting Information Table S1. We also contacted known experts and searched professional websites using the terms fatigue and vitality. We performed forward and backward citation searches on all studies that met the inclusion criteria.

A single reviewer screened all titles and abstracts, and two authors independently reviewed the full text of selected studies against the eligibility criteria. We resolved any discrepancies through discussion and consensus. Figure 1 presents results of the search and sifting process.

We collated the extracted data onto pre-piloted forms. We assessed methodological quality using the critical appraisal skills programme tools [19]. No study was excluded on the basis of its methodological quality, but we assigned each included study a grade (green, amber, red) based on the quality and strength of the evidence reported (Table 1). Consensus agreements by the whole team determined final decisions.

We adopted a segregated approach to mixed-methods synthesis [18]. We split extracted data into three datasets for analysis: data from the vitality domain of the SF-36 (dataset A); other quantitative data (dataset B); and qualitative data (dataset C). In a final step, we merged all datasets, attributing all results to one of the identified qualitative themes.



*Some studies included data relevant to more than one synthesis approach

Figure 1 Study flow diagram.

Table 1 Included studies and their methodological quality rating.

Study	Dataset	Type of study	Quality rating	Study	Dataset	Type of study	Quality rating
Abelha et al. [21]	A	Cohort	Green	Kaarlola et al. [58]	A	Cohort	Green
Ågård et al. [22]	C	Qualitative	Green	Kang and Jeong [59]	C	Qualitative	Green
Agren et al. [23]	A	RCT ^a	Red	Kayambu et al. [60]	A	RCT ^a	Green
Aitken et al. [24]	A	Cohort	Green	Kelly & McKinley [61]	A	Cohort	Red
Bäckman et al. [25]	A	Cohort	Amber	Khoudri et al. [62]	A	Cohort	Green
Bakhru et al. [26]	A	Cohort	Red	König et al. [63]	C	Qualitative	Green
Bapat et al. [27]	A	Cohort	Green	Kowalik et al. [64]	A	Cohort	Green
Baranyi et al. [28]	A	Cohort	Amber	Kress et al. [65]	A	RCT ^a	Green
Battle et al. [29]	A	Cohort	Green	Kvale & Flaatten [66]	A	Cohort	Amber
Bocci et al. [30]	B	Cohort	Amber	Lagercrantz et al. [67]	A	Cohort	Red
Boyle et al. [31]	A	Cohort	Amber	Langerud et al. [68]	B	Cohort	Green
Chaboyer et al. [32]	A	Cohort	Amber	Lasocki et al. [69]	B	Cohort	Red
Choi et al. [8]	B	Cohort	Green	Maley et al. [70]	C	Mixed ^b	Green
Choi et al. [33]	C	Qualitative	Green	Needham et al. [71]	B	Cohort	Green
Colman et al. [34]	B & C	Mixed ^b	Green	Nessler et al. [72]	A	Cohort	Green
Combes et al. [35]	A	Cohort	Green	Orwelius et al. [73]	A	Cohort	Amber
Contou et al. [36]	A	Cohort	Amber	Pettilä et al. [74]	A	Cohort	Green
Cuthbertson et al. [37]	A	Cohort	Green	Raggi et al. [75]	B	Cohort	Red
Cuthbertson et al. [38]	A	Cohort	Green	Roll et al. [76]	A	Cohort	Amber
Daffurn et al. [39]	B	Cohort	Green	Rosendahl et al. [77]	B	Cohort	Green
Das Neves et al. [40]	B	Cohort	Green	Rothenhäusler et al. [78]	A	Cohort	Amber
Deja et al. [41]	A	Cohort	Amber	Schandl et al. [79]	A	Cohort	Amber
Denehy et al. [42]	A	RCT ^a	Green	Schneiderman [80]	A	Cohort	Amber
Eakin et al. [43]	C	Qualitative	Green	Skinner et al. [81]	A	Cohort	Amber
Eddleston et al. [44]	A & B	Cohort	Amber	Spadaro et al. [9]	B	Cohort	Green
Elliott et al. [45]	A	Cohort	Amber	Steenbergen et al. [82]	A & B	Cohort	Green
Elliott et al. [46]	A	RCT ^a	Green	Strahan et al. [83]	C	Qualitative	Green
Elliott et al. [47]	B & C	Mixed ^b	Red	Stricker et al. [84]	A	Cohort	Red
Ferrand et al. [48]	A	Cohort	Green	Su et al. [85]	A	Cohort	Amber
Flaatten and Kvale [49]	A	Cohort	Green	Svenningsen et al. [86]	A	Cohort	Amber

 RCT, randomised controlled trial.

Mean SF-36 vitality domain scores, SD and sample size were extracted for each reported time-point. Mean vitality scores were combined to produce a weighted mean score. Indication of ICU admission type was categorised as unselected general cohort, sepsis or surgery. Weighted mean vitality score, SD and 95%CI were collated for each study design. Studies presenting median SF-36 vitality score were not included in this analysis. Although both mean and median vitality scores were presented in included studies, access to the raw data was not always available to confirm their normality assumption. We assumed that where means were presented, data were normally distributed, and where median was presented, data were not normally

distributed. Due to both mean and median values being presented, we were unable to combine all scores, and so only present the summary of the mean vitality scores at each time-point. We used STATA (Version 15; StataCorp, College Station, TX, USA) for analysis of dataset A.

Pooling of results from other quantitative data (dataset B) was not possible due to the heterogeneity of assessment tools used to measure fatigue; results are thus presented narratively. Qualitative data (dataset C) were subjected to a standard process of thematic analysis [20]. A single researcher manually coded extracted data and identified initial themes. These were reviewed by a second researcher and a consensus approach involving the whole team used to determine final decisions.

Results

We included 76 studies (Fig. 1). Full details of included quantitative and qualitative studies can be found in online Supporting Information Tables S2 and S3, respectively. Sixty-one of the 76 included studies were observational, 6 were randomised controlled trials (RCTs), 6 were qualitative and 3 were mixed methods studies [8–11, 21–92]. Forty-four studies were conducted in Europe, 13 in Australasia, 7 in North America and 8 in other parts of the world (Argentina, China, Iran, Morocco, South Africa, South Korea). Most studies ($n = 53$ (73%)) were single centre; and were investigating a general/unselected ICU patient cohort ($n = 45$ (62%)).

The majority of quantitative studies ($n = 54$) used SF-36 vitality scores as a marker of fatigue; however, 19 studies used a specific fatigue assessment tool. Only one of the qualitative studies focused specifically on fatigue [34], while all others evaluated fatigue as part of a wider focus on HRQoL after critical illness. Two of the qualitative studies also reported data from the perspective of relatives [22, 23].

Follow-up assessments were most commonly evaluated 6–12 months after ICU or hospital discharge (online Supporting Information Table S4). Nine studies evaluated outcomes at 2 or more years following hospital discharge. Only two studies collected pre-ICU/hospital admission vitality data and eight collected vitality data at the point of ICU discharge.

Studies were generally of adequate quality, defined by a subjective rating of amber or green (Table 1). Follow-up rates for SF-36 studies exceeded 70% in 25 (52%) studies, with a median (IQR [range]) response rate of 71.5% (48.7–82.3 [14.2–100]). Response rates in dataset B ranged from 35% to 100%. Response rates were higher in studies that used face-to-face assessment, or a combination of methodologies (online Supporting Information Table S4). However, vitality or fatigue was commonly a secondary outcome measure, and few of the observational studies adequately identified and considered all confounding factors. Several qualitative studies also provided insufficient data to allow a full judgement of quality. Regardless of methodological quality ratings, all data were treated equally during analysis.

Synthesised results are reported under the four identified qualitative themes: prevalence and severity; contributing factors; impacts on quality of life; and assessment and management.

The reported prevalence of fatigue ranged from 13.8% at 1 year to 80.9% 4 months post-ICU discharge [8, 32, 51, 68, 70]. Vitality scores reached a nadir at 1 month following

ICU discharge and slowly improved over time (Table 2; Fig. 2) but remained worse than the reference population in most studies until follow-up was complete. Vitality scores obtained from RCT data were lower than those from cohort studies (Fig. 2).

Qualitative findings support fatigue as a commonly experienced symptom post ICU discharge, with people describing it as a complex symptom rather than simple muscle weakness [59]. Fatigue was particularly prevalent in the early period after ICU discharge [22, 34, 83] and, for many people, fatigue symptoms and vitality improved over time [43, 63]. Fatigue was generally viewed as an expected and integral part of recovery; *"I just think of it as getting over what I've been through"* [34]. However, recovery took time and survivors were surprised by this; *"... I am similarly stunned at the time it's taken to get to the point where I am at"* [47].

A range of factors were reported to be contributors, and were associated with fatigue following ICU discharge; these are summarised in Table 3. However, they were not consistently observed across all studies.

Fatigue was reported to have a profound impact on quality of life, including cognitive, physical and social dimensions of an individual's functioning [34]. Fatigue was also associated with a significantly lower Barthel Index at discharge [10] and was a commonly cited cause of reduced physical function [61], as described by one person who said; *"I can't walk very far. I've just got no energy"* [47]. This affected peoples' independence with regard to their personal care, as described by a participant in a study by Strahan et al.; *"... somebody has to take me for a shower and that exhausts me"* [83]. Fatigue also impacted on wider activities, highlighted in the following quote; *"I can only do one thing a day. If I had two appointments, I couldn't make it because I would be exhausted even before I finished the first one"* [59]. Long-term iron deficiency was also reported to impact fatigue preventing a return to pre-ICU admission daily activities [82].

Fatigue was linked to a greater risk of being diagnosed with depression [11]. Survivors also reported losing their identity and their self-worth, because they were unable to look after themselves or to perform their normal social roles, such as being a parent or partner [22, 34]. Fatigue affected both employed and retired participants' ability to return to their previous level of activity [51] and had a financial impact; *"I'd lost the business, ... we were in debt to the bank. ... We had no money coming in, we couldn't pay the mortgage. ... Just all those money worries"* [34]. Being unable to work also impacted on people's status within the family, making them feel a burden [59].

Table 2 SF-36 Vitality scores of included studies over time. Values are mean (SD) with 95% CIs.

Study design (n = no. of studies)	Baseline (n = no. of study participants providing vitality data)	1 month	3 months	6 months	9 months	12 months	24 months	60 months
Cohort (n = 38)	49.71 (25.75) [48.44–50.98] (n = 1586)	46.18 (22.80) [44.48–47.88] (n = 690)	53.56 (22.72) [52.36–54.76] (n = 1370)	55.40 (24.05) [54.39–56.41] (n = 2194)	UA ^b	53.78 (24.07) [52.83–54.73] (n = 2464)	55.69 (22.13) [54.61–56.77] (n = 1610)	57.02 (22.29) [54.79–59.25] (n = 387)
RCT ^a (n = 5)	38.91 (12.99) [36.43–41.39] (n = 108)	UA ^b	42.80 (12.02) [40.44–45.16] (n = 102)	43.45 (13.92) [41.17–45.73] (n = 145)	UA ^b	45.65 (12.91) [42.70–48.38] (n = 82)	UA ^b	UA ^b
Cross-sectional (n = 8)	UA ^b	56.44 (32.3) [52.92–59.97] (n = 325)	50 (18.5) [46.96–53.04] (n = 145)	UA ^b	UA ^b	54.66 (16.1) [52.83–56.49] (n = 299)	UA ^b	UA ^b
Case-control (n = 2)	UA ^b	UA ^b	UA ^b	UA ^b	UA ^b	71.63 (18.86) [67.29–75.97] (n = 75)	UA ^b	UA ^{b,c}
Before-and-after (n = 1)	UA ^b	UA ^b	UA ^b	UA ^b	10.08 (n = 19)	UA ^b	UA ^b	UA ^b

^a RCT, randomised controlled trial; ^b UA, Unavailable (insufficient data on mean or SD).

Survivors often had little energy for social activities such as interaction with friends and family [22]. The social impact was made worse by what was described as ‘cognitive fatigue’, leaving people with difficulties with concentration, memory and thought processing; *“I would think, oh, I wish this was over. I want to go home and have a sleep... things like laughing and being humorous... that’s not really important when you’re trying to do the basics of having a conversation”* [34].

In addition to the SF-36, 11 tools were used, either in their original form or as a modified version, to measure the presence, severity or impact of fatigue (Table 4).

Tools varied in length from 40 items (Fatigue Impact Scale (FIS)) to 20 or 18 items (Multidimensional Fatigue Inventory-20 (MFI-20) and Lee Fatigue Scale (LFS) respectively), down to 13, 9 or 8 items (Functional Assessment of Chronic Illness Therapy for Fatigue (FACIT-F), Fatigue Severity Scale-9 (FSS-9), Checklist individual strength-fatigue (CIF-F)), with some being just a single item (e.g. visual analogue scale (VAS)).

Some tools were designed solely to measure fatigue, while others had a sub-section or one question designated to assess fatigue, or related constructs. Different scales provided different information on fatigue. This ranged from a simple ‘yes/no’ answer such as on the Symptom Assessment Tool, or a rating of severity using, for example, a VAS numerical scale. Some tools used more discrete severity scores for different fatigue domains such as general

fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity or cognitive, physical and psychosocial impact of fatigue.

Causes of fatigue were assessed in only two studies using the FSS-9 [47, 75] and only three studies used one of two tools (FIS and FSS-9) to measure the impact of fatigue [34, 47, 75]. None of the tools were developed with critical illness survivors and only two, the FACIT-F scale and MFI-20, were validated in former ICU patients. Spadaro et al. stated that the reliability and construct validity data they collected suggested that the FACIT-F scale grasped the negative aspects of fatigue better than the vitality dimension of SF-36, while Wintermann et al. reported the MFI-20 to have a Cronbach’s α of 0.91 [9, 10].

People reported using a range of strategies to mitigate and manage their fatigue. As well as trying to eat well and taking regular naps to avoid feeling ‘wiped out’ [22, 34, 43], exercise was seen as beneficial; *“any tiredness I had after that [exercise] I felt was a natural tiredness, not just a tiredness from being unwell”* [34]. This included trying to exercise the brain by doing things like puzzles, although the ability to do this was limited by the fatigue itself; *“When I play it [Sudoku] and the time it takes for me to do it is all related to the fatigue factor and the concentration factor so if I am fatigued it takes forever to do it and I just have to put it down”* [47].

Survivors also reported pacing activities and prioritising as useful strategies [34, 47, 59]. Planning ahead

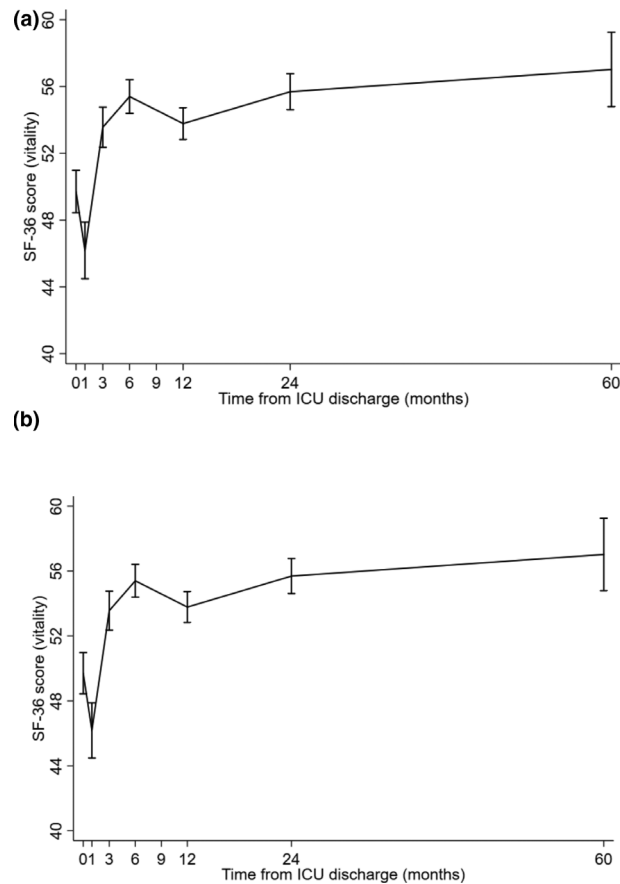


Figure 2 Mean (95%CI) SF-36 vitality scores over time for data from (a) observational cohort studies and (b) randomised controlled trials.

and being organised helped people to continue with their daily activities; *"I do have to write on the calendar... I had the whole week planned... and I had to write it all down to make sure I knew exactly what I was doing"* [43].

Finally, education and information about fatigue, its impacts and how to manage it was considered important, but difficult to obtain; *"Nobody forewarned us about anything... Even if a doctor sat you down and said to you 'you can expect to be very tired for the next two years. You're going to get fatigue... Expect this', while another said 'The fatigue part of it has never been broached. Never'"* [34].

Discussion

In this most comprehensive review to date, we have demonstrated the following: fatigue is common in critical illness survivors with a prevalence ranging from 13.8 to 80.9%; fatigue severity reaches its nadir at approximately 1 month post-ICU discharge, improves over time but seldom reaches reference population scores; there is no critical illness-specific tool to assess fatigue in ICU survivors; and there is a paucity of evidence-based interventions for

managing fatigue, despite it having a profound negative impact on survivors' quality of life. Our findings support systematic reviews published on other long-term conditions including cancer [94], inflammatory bowel disease [95] and chronic kidney disease [96], highlighting fatigue as a commonly experienced symptom of ill health.

Fatigue is multifaceted and multifactorial, and related to a variety of modifiable and non-modifiable factors. The variety of scales used to assess fatigue make it difficult to compare severity, types and impact between studies and across patient populations. We recommend the development of a critical illness-specific fatigue assessment tool. Tools used to assess fatigue to date have been developed for other population groups, for example, cancer, chronic fatigue, inflammatory bowel disease and stroke [97–100]. Two fatigue assessment tools have been validated in a critical care population [9, 10]; however, none have been developed with or for ICU survivors.

The prevalence of fatigue reported in studies included in our review was extremely wide (13.8 to 80.9%). This is likely due to the heterogeneity of methodologies

Table 3 Factors associated with fatigue in ICU survivors. Data are number of studies.

Negative impact	Positive impact
Patient / baseline characteristics <ul style="list-style-type: none"> Female sex (n = 3)[21, 44, 50] Age – both increasing age [10, 48, 50, 57, 92] and young age, especially in men (n = 5)[21] Poor pre-morbid vitality/quality of life scores (n = 3)[10, 37, 51, 75] High pre-existing comorbidity (n = 2)[10, 73] Admission/ICU-related <ul style="list-style-type: none"> High ICU admission illness severity scores (n = 3)[48, 50, 62] Multiple organ dysfunction (n = 1)[74] Severe sepsis/septic shock (n = 2)[29, 93] Prolonged ventilation (n = 2)[48, 92] ICU length of stay (n = 2)[27, 50] Hydroxyethyl starch fluid resuscitation (n = 1)[91] Traumatic brain injury (n = 1)[50] Cognitive impairment (n = 1)[78] Muscle weakness (n = 4)[8,30,53,69] Iron deficiency (n = 1)[69] Psychological/constitutional <ul style="list-style-type: none"> Pain (n = 5)[8,30,31,39,68] Sleep disturbance (n = 6)[8,30,39,44,47,68] Depression and/or anxiety (n = 4)[10,30,68,75] PTSD or PTSS (n = 2)[10,68] Breathlessness / dyspnoea (n = 1)[9] Weight loss (n = 1)[53] Social <ul style="list-style-type: none"> Lack of social support (n = 1)[10] Discharged home following ICU (n = 1)[8] Unable to return to employment (n = 1)[53] 	<ul style="list-style-type: none"> Psycho-educational (n = 1)[23] Increased 6-min walking distance (n = 1)[24] ICU diaries (n = 1)[25] Mild therapeutic hypothermia (following out of hospital cardiac arrest)(n = 1)[64]

ICU, intensive care unit; PTSD, post-traumatic stress disorder; PTSS, post-traumatic stress symptoms.

employed, the range of tools used for assessment and the different time-points at which researchers measured outcomes. Fatigue severity reaches a nadir at 1-month post-ICU discharge and demonstrates the greatest improvement in the first year after discharge. Interventions to treat fatigue may, therefore, be most effective in this time period.

To address its multidimensional nature, fatigue management requires a complex intervention. Findings of our review and those with other population groups suggest a tailored, multifaceted approach with recommendations for nutrition, exercise, pacing activities and education/information [101–105]. Outside of critical care, non-pharmacological interventions have proved effective in community-dwelling older adults [106]. Alternative therapies [107] and pharmacological interventions such as iron, modafinil and doxepin have also been evaluated, with the latter two proving effective in patients with Parkinson's disease [108].

The estimates in this review can be used to inform power calculations for future long-term trials, which should

include collection of pre-ICU fatigue/vitality data for comparison where possible. Conducting long-term outcome research in critical illness survivors is challenging, however, more than half of included studies in our review had follow-up rates of greater than 70%.

Further qualitative study is needed to better understand critical illness fatigue, from the perspective of patients and their family members. The impact of critical illness on family members' fatigue remains an unexplored area and is a strong recommendation for future research. Despite Choi et al. reporting that fatigue is also experienced by family members [33], our original search failed to uncover enough data to review further.

Employing a mixed-methods approach enabled us to produce a comprehensive review of all available evidence, with estimates that can inform power calculations for future studies (Table 2). Our review also identifies factors that may increase or mitigate against fatigue (Table 3), which researchers might find useful in the future when designing interventional studies. Our review has limitations.

Table 4 Assessment tools used to evaluate fatigue.

Tool	Item measured	Tool description	Version	Study reference
Fatigue Severity Scale (FSS-9)	Cause/ Presence/Severity/ Impact	Nine items using 7-point scale. Higher score indicates greater impact of fatigue.	Original	Raggi et al. [75]; Elliott et al. [47]
Fatigue Impact Scale (FIS)	Functional impact	40-item questionnaire. Likert-like scale of 0-4, with a sub-score calculated for each dimension of fatigue (cognitive, physical and social) occurring in the preceding 4 weeks.	Original	Colman et al. [34]
Functional Assessment of Chronic Illness Therapy for Fatigue (FACIT-F) scale	Presence/Severity	13 items referring to the previous 7 days. Final score ranges from 0 to 52; higher scores represent less fatigue.	Original	Needham et al. [71]; Spadaro et al. [9]
Lee Fatigue Scale (LFS)	Presence/Severity	18-item – 13 fatigue and five energy scale (no symptoms (0) to very high symptoms (10)). Total score calculated as mean.	Original	Langerud et al. [68]
Checklist individual strength-fatigue (CIS-fatigue) scale	Severity/Impact	8 questions scoring on a 7-point Likert scale, (range 8–56).	Dutch Version	van Vliet et al. [88]
Multidimensional Fatigue Inventory-20 (MFI-20)	Presence/ Severity/ Type	20-item self-report measure covering five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity. Minimum score 4 (absence of fatigue) and maximum of 20 for each subscale.	French version Original	Lasocki et al. [69] Wintermann et al. [10]
Symptom Assessment Tool	Presence	Fatigue 1 of 10 symptoms on which people self-report (Yes/No)	Modified version	Choi et al. [8]
Giessen Subjective Complaints List	Presence/Severity	Four subscales, one of which is exhaustion, rated on 5-point scale from 0 (not at all) to 4 (very much)	Original	Rosendhal et al. [77]
WHOQOL-BREF	Presence	One of 26 questions (subset of Physical health domain); <i>"Do you have enough energy for everyday life?"</i>	Original	König et al. [63]
Visual/numerical analogue scale	Presence/Severity	Measure of global fatigue/11-point (0 = worst fatigue possible, 10 = normal)	Part of FSS-9	Elliott et al. [47]
		0 (not tired) to 10 (exhausted).	Own version	Lasocki et al. [69]
		Range, 0 (no symptoms) to 10 (worst symptoms)	Own version	Walsh et al. [90]
		3-point scale	Own version	Eddleston et al. [44]
Local questionnaire	Presence	15-item questionnaire regarding ICU complications including fatigue	Own version	Steenbergen et al. [82]
	Presence	14-item questionnaire, one question on fatigue; <i>"Currently, do you feel more fatigue than before the ICU stay"</i> Yes/No	Own version	Granja et al. [51]
	Presence/Severity	One question asking whether fatigue was absent, mild, moderate or severe	Own version	Bocci et al. [30]

Meta-analysis of the vitality data was not possible due to the degree of heterogeneity. Additionally, alongside fatigue often being studied as a secondary outcome measure, differences in study design, patient populations, fatigue measurement tools, follow-up time-points and response rates of the studies included in our review make it difficult to provide one overall conclusion.

In summary, this mixed method review shows that fatigue is highly prevalent in critical illness survivors, negatively impacting their recovery after discharge. To date, no critical illness-specific fatigue assessment tool or targeted intervention has been specifically designed to manage this symptom. Our review identifies factors that may increase or mitigate against fatigue, along with potential management strategies, which should be used to inform future research and practice.

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References

- Intensive Care National Audit and Research Centre (ICNARC). Key Statistics from the Case Mix Programme-Adult, General Critical Care Units. 2019. <https://onlinereports.icnarc.org> (accessed 14/05/2020).
- Brown SM, Bose S, Banner-Goodspeed V, et al. Approaches to addressing post-intensive care syndrome among intensive care unit survivors. A narrative review. *Annals of the American Thoracic Society* 2019; **16**: 947–56.
- McPeake J, Hirshberg EL, Christie LM, et al. Models of peer support to remediate post-Intensive care syndrome: a report developed by the Society of Critical Care Medicine Thrive International Peer Support Collaborative. *Critical Care Medicine* 2019; **47**: E21–E27.
- Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: Postintensive care syndrome-family. *Critical Care Medicine* 2012; **40**: 618–24.
- Hashem MD, Nallagangula A, Nalamalapu S, et al. Patient outcomes after critical illness: a systematic review of qualitative studies following hospital discharge. *Critical Care* 2016; **20**: 345.
- Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *Journal of Psychosomatic Research* 2004; **56**: 157–70.
- NANDA International. *Nursing Diagnoses: Definitions and Classification 2018–2020*. Eleventh edition. New York: Thieme Publishers, 2018.
- Choi J, Hoffman LA, Schulz R, et al. Self-reported physical symptoms in intensive care unit (ICU) survivors: pilot exploration over four months post-ICU discharge. *Journal of Pain and Symptom Management* 2014; **47**: 257–70.
- Spadaro S, Capuzzo M, Valpiani G, et al. Fatigue in intensive care survivors one year after discharge. *Health and Quality of Life Outcomes* 2016; **14**: 1–9.
- Wintermann GB, Rosendahl J, Weidner K, Strauss B, Hinz A, Petrowski K. Self-reported fatigue following intensive care of chronically critically ill patients: a prospective cohort study. *Journal of Intensive Care* 2018; **6**: 1–12.
- Nedergaard HK, Haberlandt T, Reichmann PD, Toft P, Jensen HI. Patients' opinions on outcomes following critical illness. *Acta Anaesthesiologica Scandinavica* 2018; **62**(4): 531–9.
- Latronico N, Herridge M, Hopkins RO, et al. The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Medicine* 2017; **43**: 1270–81.
- Reay H, Arulkumaran N, Brett SJ. Priorities for future intensive care research in the UK: results of a James Lind Alliance priority setting partnership. *Journal of the Intensive Care Society* 2014; **15**: 288–96.
- Carfi A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *Journal of the American Medical Association* 2020; **324**: 603–5.
- Cajanding R. Causes, assessment and management of fatigue in critically ill patients. *British Journal of Nursing* 2017; **26**: 1176–81.
- Matthews EE. Sleep disturbances and fatigue in critically ill patients. *American Association of Critical Care Nurses Advanced Critical Care* 2011; **22**: 204–24.
- Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009; **62**: 1006–12.
- Pearson A, White H, Bath-Hextall F, Salmond S, Apostolo J, Kirkpatrick P. A mixed-methods approach to systematic reviews. *International Journal of Evidence Based Healthcare* 2015; **13**: 121–31.
- Critical Appraisal Skills Programme (CASP). CASP Checklists 2020. <https://casp-uk.net/casp-tools-checklists> (accessed 10/02/2020).
- Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006; **3**: 77–101.
- Abelha FJ, Luís C, Veiga D, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. *Critical Care* 2013; **17**: 257.
- Ågård AS, Egerod I, Tønnesen E. Struggling for independence: A grounded theory study on convalescence of ICU survivors 12 months post ICU discharge. *Intensive and Critical Care Nursing* 2012; **28**: 105–13.
- Ågren S, Berg S, Svedjeholm R, Strömberg A. Psychoeducational support to post cardiac surgery heart failure patients and their partners—a randomised pilot study. *Intensive and Critical Care Nursing* 2015; **31**: 10–8.
- Aitken LM, Burmeister E, McKinley S, et al. Physical recovery in intensive care unit survivors: a cohort analysis. *American Journal of Critical Care* 2015; **24**: 33–40.
- Bäckman CG, Orwelius L, Sjöberg F, Fredrickson M, Walther SM. Long-term effect of the ICU-diary concept on quality of life after critical illness. *Acta Anaesthesiologica Scandinavica* 2010; **54**: 736–43.
- Bakhru RN, Davidson JF, Bookstaver RE, et al. Physical function impairment in survivors of critical illness in an ICU Recovery Clinic. *Journal of Critical Care* 2018; **45**: 163–9.
- Bapat V, Allen D, Young C, Roxburgh J, Ibrahim M. Survival and quality of life after cardiac surgery complicated by prolonged intensive care. *Journal of Cardiac Surgery* 2005; **20**: 212–7.

28. Baranyi A, Krauseneck T, Rothenhäusler HB. Posttraumatic stress symptoms after solid-organ transplantation: preoperative risk factors and the impact on health-related quality of life and life satisfaction. *Health Quality of Life Outcomes* 2013; **11**: 111.
29. Battle CE, Davies G, Evans PA. Long term health-related quality of life in survivors of sepsis in South West Wales: an epidemiological study. *Public Library of Science One* 2014; **9**: e116304.
30. Bocci MG, Grieco DL, Lochi S, et al. Defining needs and goals of post-ICU care for trauma patients: preliminary study. *Minerva Anestesiologica* 2016; **82**: 22–9.
31. Boyle M, Murgo M, Adamson H, et al. The effect of chronic pain on health-related quality of life amongst intensive care survivors. *Australian Critical Care* 2004; **17**(104–106): 108–13.
32. Chaboyer W, Foster M, Creamer J. Health status of ICU survivors: a pilot study. *Australian Critical Care* 2002; **15**: 21–6.
33. Choi JY, Lingler JH, Donahoe MP, Happ MB, Hoffman LA, Tate JA. Home discharge following critical illness: a qualitative analysis of family caregiver experience. *Heart and Lung* 2018; **47**: 401–7.
34. Colman ZE, Johnston CL, Ashby S, Mackney JH. Experiences of fatigue following critical illness: a mixed methods study. *Physiotherapy* 2015; **101**: e258–e259.
35. Combes A, Leprince P, Luyt CE, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Critical Care Medicine* 2008; **36**: 1404–11.
36. Contou D, Canoui-Poitine F, Coudroy R, et al. Long-term quality of life in adult patients surviving Purpura Fulminans: an exposed-unexposed multicenter cohort study. *Clinical Infectious Diseases* 2019; **69**: 332–40.
37. Cuthbertson BH, Scott J, Strachan M, et al. Quality of life before and after intensive care. *Anaesthesia* 2005; **60**: 332–9.
38. Cuthbertson BH, Roughton S, Jenkinson D, MacLennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. *Critical Care* 2010; **14**: R6.
39. Daffurn K, Bishop GF, Hillman KM, Bauman A. Problems following discharge after intensive care. *Intensive and Critical Care Nursing* 1994; **10**: 244–51.
40. Das Neves AV, Vasquez DN, Loudet CI, et al. Symptom burden and health-related quality of life among intensive care unit survivors in Argentina: a prospective cohort study. *Journal of Critical Care* 2015; **30**: 1049–54.
41. Deja M, Denke C, Weber-Carstens S, et al. Social support during intensive care unit stay might reduce the risk for the development of posttraumatic stress disorder and consequently improve health related quality of life in survivors of acute respiratory distress syndrome. *Critical Care* 2006; **10**: R147.
42. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Critical Care* 2013; **17**: R156.
43. Eakin BMN, Patel Y, Mendez-Tellez P, Dingals VD, Needham DM, Turnbull A. Patients' outcomes after acute respiratory failure: a qualitative study with the PROMIS framework. *American Journal of Critical Care* 2017; **26**: 456–66.
44. Eddleston JM, White P, Guthrie E. Survival, morbidity, and quality of life after discharge from intensive care. *Critical Care Medicine* 2000; **28**: 2293–9.
45. Elliott D, Mudaliar Y, Kim C. Examining discharge outcomes and health status of critically ill patients: some practical considerations. *Intensive and Critical Care Nursing* 2004; **20**: 366–77.
46. Elliott D, Mckinley S, Alison J, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. *Critical Care* 2011; **15**: R142.
47. Elliott R, Yarad E, Webb S, et al. Cognitive impairment in intensive care unit patients: a pilot mixed-methods feasibility study exploring incidence and experiences for recovering patients. *Australian Critical Care* 2019; **32**: 131–8.
48. Ferrand N, Zaouter C, Chastel B, et al. Health related quality of life and predictive factors six months after intensive care unit discharge. *Anaesthesia, Critical Care and Pain Medicine* 2019; **38**: 137–41.
49. Flaatten H, Kvåle R. Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. *Intensive Care Medicine* 2001; **27**: 1005–11.
50. Fu XY, Chen M, Yu T, Liu XK. Health-related quality of life of trauma patients after intensive care: a 2-year follow-up study. *European Journal of Trauma and Emergency Surgery* 2011; **37**: 629–33.
51. Granja C, Lopes A, Moreira S, Dias C, Costa-Pereira A, Carneiro A; for the JMIP Study Group. Patients' recollections of experiences in the intensive care unit may affect their quality of life. *Critical Care* 2005; **9**: 96–109.
52. Haines KJ, Berney S, Warrillow S, Denehey L. Long-term recovery following critical illness in an Australian cohort. *Journal of Intensive Care* 2018; **6**: 1–10.
53. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *New England Journal of Medicine* 2003; **348**: 683–93.
54. Heyland DK, Hopman W, Coo H, Tranmer J, McColl MA. Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. *Critical Care Medicine* 2000; **28**: 3599–605.
55. Hofhuis JGM, Spronk PE, Van Stel HF, et al. The impact of severe sepsis on health-related quality of life: a long-term follow-up study. *Anesthesia and Analgesia* 2008; **107**: 1957–64.
56. Hofhuis JGM, van Stel HF, Schrijvers AJP, Rommes JH, Spronk PE. ICU survivors show no decline in health-related quality of life after 5 years. *Intensive Care Medicine* 2015; **41**: 495–504.
57. Jeitziner MM, Zwahlen SM, Bürgin R, Hantikainen V, Hamers JP. Changes in health-related quality of life in older patients one year after an intensive care unit stay. *Journal of Clinical Nursing* 2015; **24**: 3107–17.
58. Kaarlola A, Pettit V, Kekki P. Quality of life six years after intensive care. *Intensive Care Medicine* 2003; **29**: 1294–9.
59. Kang J, Jeong YJ. Embracing the new vulnerable self: a grounded theory approach on critical care survivors' post-intensive care syndrome. *Intensive and Critical Care Nursing* 2018; **49**: 44–50.
60. Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Medicine* 2015; **41**: 865–74.
61. Kelly MA, McKinley S. Patients' recovery after critical illness at early follow-up. *Journal of Clinical Nursing* 2010; **19**: 691–700.
62. Khoudri I, Ali Zeggwagh A, Abidi K, Madani N, Abouqal R. Measurement properties of the Short Form 36 and health-related quality of life after intensive care in Morocco. *Acta Anaesthesiologica Scandinavica* 2007; **51**: 189–97.
63. König C, Matt B, Kortgen A, Turnbull A, Hartog CS. What matters most to sepsis survivors: a qualitative analysis to identify specific health-related quality of life domains. *Quality of Life Research* 2019; **28**: 637–47.
64. Kowalik R, Szczerba E, Kołtowski Ł, et al. Cardiac arrest survivors treated with or without mild therapeutic hypothermia: performance status and quality of life assessment. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2014; **22**: 76.
65. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative

- interruption on critically ill patients. *American Journal of Respiratory and Critical Care Medicine* 2003; **168**: 1457–61.
66. Kvale R, Flaatten H. Changes in health-related quality of life from 6 months to 2 years after discharge from intensive care. *Health Quality of Life Outcomes* 2003; **1**: 2.
 67. Lagercrantz E, Lindblom D, Sartipy U. Survival and quality of life in cardiac surgery patients with prolonged intensive care. *Annals of Thoracic Surgery* 2010; **89**: 490–5.
 68. Langerud AK, Rusteén T, Småstuen MC, Kongsgaard U, Stubhaug A. Intensive care survivor-reported symptoms: a longitudinal study of survivors' symptoms. *Nursing in Critical Care* 2018; **23**: 48–54.
 69. Lasocki S, Chudeau N, Papet T, et al. Prevalence of iron deficiency on ICU discharge and its relation with fatigue: a multicenter prospective study. *Critical Care* 2014; **18**: 1–9.
 70. Maley JH, Brewster I, Mayoral I, et al. Resilience in survivors of critical illness in the context of the survivors' experience and recovery. *Annals of the American Thoracic Society* 2016; **13**: 1351–60.
 71. Needham DM, Dinglas VD, Bienvenu OJ, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. *British Medical Journal* 2013; **346**: 1–12.
 72. Nesseler N, Defontaine A, Launey Y, Morcet J, Mallédant Y, Seguin P. Long-term mortality and quality of life after septic shock: a follow-up observational study. *Intensive Care Medicine* 2013; **39**: 881–8.
 73. Orwelius L, Nordlund A, Nordlund P, et al. Pre-existing disease: the most important factor for health-related quality of life long-term after critical illness: a prospective, longitudinal, multicentre trial. *Critical Care* 2010; **14**: R67.
 74. Pettilä V, Kaarlola A, Mäkeläinen A. Health-related quality of life of multiple organ dysfunction patients one year after intensive care. *Intensive Care Medicine* 2000; **26**: 1473–9.
 75. Raggi M. Long-term outcomes in lung transplant patients requiring prolonged mechanical ventilation and their family caregivers. 2013. https://tspace.library.utoronto.ca/bitstream/1807/70025/3/raggi_marco_201311_MSc_Thesis.pdf (accessed 14/05/2020).
 76. Roll MA, Kuys S, Walsh JR, Tronstad O, Ziegenfuss MD, Mullany DV. Long-term survival and health-related quality of life in adults after extra corporeal membrane oxygenation. *Heart Lung & Circulation* 2019; **28**: 1090–8.
 77. Rosendahl J, Brunkhorst FM, Jaenichen D, Bl S. Physical and mental health in patients and spouses after intensive care of severe sepsis: a dyadic perspective on long-term sequelae testing the actor-partner interdependence model. *Critical Care Medicine* 2013; **41**: 69–75.
 78. Rothenhäusler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *General Hospital Psychiatry* 2001; **23**: 90–6.
 79. Schandl AR, Brattström OR, Svensson-Raskh A, Hellgren EM, Falkenhalv MD, Sackey PV. Screening and treatment of problems after intensive care: a descriptive study of multidisciplinary follow-up. *Intensive and Critical Care Nursing* 2011; **27**: 94–101.
 80. Schneiderman J. The health-related quality of life of survivors of critical illness as measured with the SF-36 and EQ-5D questionnaires at six months after discharge. 2011. <https://core.ac.uk/download/pdf/39670009.pdf> (accessed 14/05/2020).
 81. Skinner EH, Haines KJ, Howe B, et al. Health-related quality of life in Australasian survivors of H1N1 influenza undergoing mechanical ventilation a multicenter cohort study. *Annals of the American Thoracic Society* 2015; **12**: 895–903.
 82. Steenbergen S, Rijkenberg S, Adonis T, Kroeze G, van Stijn I, Endeman H. Long-term treated intensive care patients' outcomes: The one-year mortality rate, quality of life, health care use and long-term complications as reported by general practitioners. *BMC Anesthesiology* 2015; **15**: 1–8.
 83. Strahan EHE, Brown RJ. A qualitative study of the experiences of patients following transfer from intensive care. *Intensive and Critical Care Nursing* 2005; **21**: 160–71.
 84. Stricker KH, Cavegn R, Takala J, Rothen HI. Does ICU length of stay influence quality of life? *Acta Anaesthesiologica Scandinavica* 2005; **49**: 975–83.
 85. Su YX, Xu L, Gao XJ, Wang ZY, Lu X, Yin CF. Long-term quality of life after sepsis and predictors of quality of life in survivors with sepsis. *Chinese Journal of Traumatology* 2018; **21**: 216–23.
 86. Svenningsen H, Tønnesen EK, Videbech P, Frydenberg M, Christensen D, Egerod I. Intensive care delirium - effect on memories and health-related quality of life - a follow-up study. *Journal of Clinical Nursing* 2014; **23**: 634–44.
 87. van Den Boogaard M, Schoonhoven L, Evers AWM, et al. Delirium in critically ill Patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Medicine* 2012; **40**: 112–8.
 88. van Vliet M, van Den Boogaard M, Donnelly PJ, Evers AWM, Blijlevens NMA, Pickkers P. Long-term health related quality of life following intensive care during treatment for haematological malignancies. *PLoS One* 2014; **9**: 1–7.
 89. Vogel G, Forinder U, Sandgren A, Svenson C, Joelsson-Alm E. Health-related quality of life after general surgical intensive care. *Acta Anaesthesiologica Scandinavica* 2018; **62**: 1112–9.
 90. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. *Journal of the American Medical Association Internal Medicine* 2015; **175**: 901–10.
 91. Wittbrodt P, Haase N, Butowska D, Windig R, Poulsen JB, Perner A; the 6S trial group and the Scandinavian Critical Care Trials Group. Quality of life and pruritus in patients with severe sepsis resuscitated with hydroxyethyl starch long-term follow-up of a randomised trial. *Critical Care* 2013; **17**: R58.
 92. Zaheri A, Sadat Z, Abasian M, et al. Quality of life and related factors among patients discharged from critical care units. *Critical Care Nursing Journal* 2017; **10**: 62148.
 93. Zhang K, Mao X, Fang Q, et al. Impaired long-term quality of life in survivors of severe sepsis: Chinese multicenter study over 6 years. *Anaesthetist* 2013; **62**: 995–1002.
 94. Abrahams HJG, Gielissen MFM, Schmits IC, Verhagen CAHHVM, Rovers MM, Knoop H. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Annals of Oncology* 2016; **27**: 965–74.
 95. Czuber-Dochan W, Ream E, Norton C. Review article: description and management of fatigue in inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics* 2013; **37**: 505–16.
 96. Ju A, Unruh ML, Davison SN, et al. Patient-reported outcome measures for fatigue in patients on hemodialysis: a systematic review. *American Journal of Kidney Disease* 2018; **71**: 327–43.
 97. Czuber-Dochan W, Norton C, Bassett P, et al. Development and psychometric testing of inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale. *Journal of Crohn's and Colitis* 2014; **8**: 1398–406.
 98. Lerdal A, Johansson S, Kottorp A, von Koch L. Psychometric properties of the Fatigue Severity scale: Rasch analyses of responses in a Norwegian and a Swedish MS cohort. *Multiple Sclerosis* 2010; **16**: 733–41.

99. Miaskowski C, Paul SM, Cooper BA, et al. Trajectories of fatigue in men with prostate cancer before, during, and after radiation therapy. *Journal of Pain and Symptom Management* 2008; **35**: 632–43.
100. Theander K, Cliffordson C, Torstensson O, Jakobsson P, Unosson M. Fatigue Impact Scale: its validation in patients with chronic obstructive pulmonary disease. *Psychology, Health & Medicine* 2007; **12**: 470–84.
101. Meneses-Echávez J, González-Jiménez E, Ramírez-Vélez R. Supervised exercise reduces cancer-related fatigue: a systematic review. *Journal of Physiotherapy* 2015; **61**: 3–9.
102. Abonie US, Sandercock GRH, Heesterbeek M, Hettinga FJ. Effects of activity pacing in patients with chronic conditions associated with fatigue complaints: a meta-analysis. *Disability and Rehabilitation* 2020; **42**: 613–22.
103. Artom M, Czuber-Dochan W, Sturt J, Norton C. Targets for health interventions for inflammatory bowel disease-fatigue. *Journal of Crohn's and Colitis* 2016; **10**: 860–9.
104. Baguley BJ, Bolam KA, Wright ORL, Skinner TL. The effect of nutrition therapy and exercise on cancer-related fatigue and quality of life in men with prostate cancer: a systematic review. *Nutrients* 2017; **12**: E1003.
105. Wendebourg MJ, Heesen C, Finlayson M, Meyer B, Pöttgen J, Köpke S. Patient education for people with multiple sclerosis-associated fatigue: a systematic review. *PLoS One* 2017; **12**: e0173025.
106. Ho LYW, Ng SSM. Non-pharmacological interventions for fatigue in older adults: a systematic review and meta-analysis. *Age and Ageing* 2020; **49**: 341–51.
107. Tao W, Luo X, Cui B, et al. Practice of traditional Chinese medicine for psycho-behavioral intervention improves quality of life in cancer patients: a systematic review and meta-analysis. *Oncotarget* 2015; **6**: 39725–39.
108. Elbers RG, Berendse HW, Kwakkel G. Treatment of fatigue in Parkinson disease. *Journal of the American Medical Association* 2016; **315**: 2340–1.

Supporting Information

Additional supporting information may be found online via the journal website.

Table S1. Search strategy terms.

Table S2. Study characteristics of included quantitative studies.

Table S3. Study characteristics of included qualitative studies.

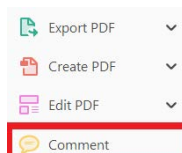
Table S4. Follow-up methods, duration of follow-up and response rate.

Required software to e-Annotate PDFs: **Adobe Acrobat Professional** or **Adobe Reader** (version 11 or above). (Note that this document uses screenshots from **Adobe Reader DC**.)

The latest version of Acrobat Reader can be downloaded for free at: <http://get.adobe.com/reader/>

Once you have Acrobat Reader open on your computer, click on the **Comment** tab (right-hand panel or under the Tools menu).

This will open up a ribbon panel at the top of the document. Using a tool will place a comment in the right-hand panel. The tools you will use for annotating your proof are shown below:




1. Replace (Ins) Tool – for replacing text.



Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it:

- Highlight a word or sentence.
- Click on .
- Type the replacement text into the blue box that appears.

... of nutritional conditions, and landmark events are monitored in populations of relatively homogeneous single n of *Saccharomyces*, and is initiated after carbon source [1]. Str are referred to as mei n of meiosis-specific g *revisiae* depends on th inducer of meiosis) [3]. I functions as a repre reposition, the genes pression) and *RGR1* at rise II mediator subor osome density [8]. SIM irectly or indirectly re

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
05/05/2017 15:32 Post

2. Strikethrough (Del) Tool – for deleting text.



Strikes a red line through text that is to be deleted.

How to use it:

- Highlight a word or sentence.
- Click on .
- The text will be struck out in red.

... experimental data if available. For ORFs to be had to meet all of the following criteria:



1. Small size (35-250 amino acids).
2. Absence of similarity to known proteins.
3. Absence of functional data which could not the real overlapping gene.
4. Greater than 25% overlap at the N-termin terminus with another coding feature; over both ends; or ORF containing a tRNA.


3. Commenting Tool – for highlighting a section to be changed to bold or italic or for general comments.



Use these 2 tools to highlight the text where a comment is then made.

How to use it:

- Click on .
- Click and drag over the text you need to highlight for the comment you will add.
- Click on .
- Click close to the text you just highlighted.
- Type any instructions regarding the text to be altered into the box that appears.

... nformal invariance:  r
A: Math. Gen., Vol. 12, N

... lified theory for a matrix
'ol. 8, 1984, pp. 305-323

... d manuscript, 1984.
... ching fractions for $D_0 \rightarrow K+K$
... lation in D_0 decays' Phys

jstaddon Reply X

This needs to be bold


16/05/2017 15:40 Post

4. Insert Tool – for inserting missing text at specific points in the text.



Marks an insertion point in the text and opens up a text box where comments can be entered.

How to use it:

- Click on .
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the box that appears.

Meiosis has a central role in the sexual reproduction of nearly all eukaryotes. *Saccharom* analysis of meiosis, esp by a simple change of n conveniently monitored cells. Sporulation of *Sae* cell, the a/a cell, and is of a fermentable carbon sporulation and are refe [2b]. Transcription of me meiosis, in *S. cerevisiae* activator, *IME1* (inducer of the gene *RME1* funct Rme1p to exert repress of *GAL1* gene expression) and *RGR1* are required [1, 2, 3, 4]. These ge for RNA polymerase II and RNA polymerase I (RNA polymerase I) which are

jstaddon Reply X

Yeast.

05/05/2017 15:57 Post

5. Attach File Tool – for inserting large amounts of text or replacement figures.



Inserts an icon linking to the attached file in the appropriate place in the text.

How to use it:

- Click on .
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

The attachment appears in the right-hand panel.

chondrial preparator
ative damage injury
re extent of membra
malondialdehyde (TBARS) formation.
used by high perform

6. Add stamp Tool – for approving a proof if no corrections are required.



Inserts a selected stamp onto an appropriate place in the proof.

How to use it:

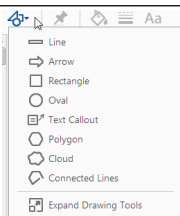
- Click on .
- Select the stamp you want to use. (The [Approved](#) stamp is usually available directly in the menu that appears. Others are shown under *Dynamic*, *Sign Here*, *Standard Business*).
- Fill in any details and then click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).

of the business cycle, starting with the
on perfect competition, constant ret
production. In this environment goods
extra costs are incurred to make marks
he total cost of production is deter
etermined by the model. The New-Key
otaki (1987), has introduced produc
general equilibrium models with nomin
and supply shocks. Most of this litera

APPROVED



Drawing tools available on comment ribbon

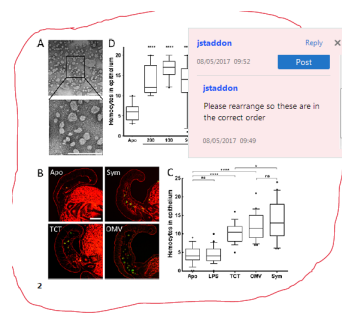


7. Drawing Markups Tools – for drawing shapes, lines, and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines, and freeform annotations to be drawn on proofs and for comments to be made on these marks.

How to use it:

- Click on one of the shapes in the [Drawing Markups](#) section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, right-click on shape and select *Open Pop-up Note*.
- Type any text in the red box that appears.



For further information on how to annotate proofs, click on the [Help](#) menu to reveal a list of further options:

