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REVIEW ARTICLE (META-ANALYSIS)

Factors Associated With Fatigue in People With Spinal Cord Injury: A Systematic Review and Meta-analysis

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Abstract

Objective: To investigate the association between fatigue and clinical and demographic variables in people with spinal cord injury (SCI).

Data Sources: Five databases (MEDLINE, Physiotherapy Evidence Database, Cochrane, Google Scholar, Cumulative Index to Nursing and Allied Health) were searched up to November 2021.

Study Selection: Observational studies that reported the association between fatigue and clinical and demographic variables in English or Spanish were eligible. Reviews, qualitative research studies, and nonoriginal articles were excluded. Twenty-three of the 782 identified studies met the inclusion criteria for the meta-analysis.

Data Extraction: Two researchers independently extracted the data. The strength of the association between each factor and fatigue was determined by the effect size. When the results of the effect size were expressed with different statistics, the correlation coefficient was the preferred estimation. The risk of bias was assessed using the Appraisal Tool for Cross-Sectional Studies and the Newcastle-Ottawa Scale.

Data Summary: A pooled analysis of the associations between fatigue and 17 factors was performed. A direct association was found between fatigue and 9 factors (sorted by effect size): anxiety (r=0.57; 95% CI, 0.29-0.75), stress (r=0.54; 95% confidence interval [CI], 0.26-0.74), depression (r=0.47; 95% CI, 0.44-0.50), pain (r=0.34; 95% CI, 0.16-0.50), analgesic medication (r=0.32; 95% CI, 0.28-0.36), assistive devices (r=0.23; 95% CI, 0.17-0.29), lesion level (r=0.15; 95% CI, 0.07-0.23), incomplete SCI (r=0.13; 95% CI, 0.05-0.22), and medication (r=0.12; 95% CI, 0.01-0.23). An inverse association was found with 3 factors (sorted by effect size): self-efficacy (r=−0.63; 95% CI, −0.81 to −0.35), participation (r=−0.32; 95% CI, −0.58 to −0.001), and physical activity (r=−0.17; 95% CI, −0.28 to −0.05). No association was found with age, sex, educational level, time since injury, and spasticity.

Conclusions: Several factors were associated with fatigue in people with SCI, with those related to mental health showing the strongest associations. These results should be interpreted with caution because of the high heterogeneity observed in some factors.

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Spinal cord injury (SCI) is a condition that can cause dysfunction in movement, sensitivity, or autonomic function,[1] which consequently generates secondary health issues.[2-7] Fatigue is among the most common related symptoms, with a prevalence that ranges between 19.2% to more than 50% [5-10] in the literature depending on the description of the study population and the scales used for measuring it. Fatigue can be present during and after the end of the rehabilitation process of patients,[11] worsening their health problems and disability[12] and negatively affecting their mood,[13] social integration,[5] activities of daily living, rehabilitation process, and quality of life.[14]

Fatigue has been defined as feelings of tiredness, lack of energy, low motivation, and difficulty in concentrating, although a universally accepted definition has not been reached.[11] Studies are highly heterogeneous in the assessment of fatigue given its multidimensional nature, via objective methods such as fatiguing tasks or subjective measures such as self-reports to describe the perception of fatigue. These self-reports also serve to evaluate perceived fatigue intensity or its effect on the participants' lives. The great

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heterogeneity in evaluation methods observed in the scientific literature could explain the existing controversy about the prevalence of fatigue and its association with certain factors.

Fatigue is often undermentioned and/or underestimated during medical interviews in patients with SCI,[4,15] even if these have highlighted fatigue as one of their symptoms where research should be intensified.[16] Gaining a better understanding of which factors are most strongly associated with fatigue is key to designing strategic research lines to determine causality and therefore establish preventive and therapeutic interventions. A qualitative study that questioned people with SCI identified a wide list of factors they linked their fatigue to, including pain, depression, low motivation, anxiety, adverse effects of medication, and sequelae of SCI such as spasticity, among others.[17] A previous study by our research group found fatigue to be associated with the level of injury, depression, pain, and the severity of spasticity.[10] Several studies have investigated the association between perceived fatigue and clinical and demographic factors in people with SCI.[4,8, 9,12,18-22] However, there is no agreement on the association of fatigue with certain demographic factors such as age[9,18] and clinical factors such as spasticity,[4,21] lesion level,[8,22] or medication.[8,9]

In addition to the lack of evidence on which factors are associated with fatigue in people with SCI, the strength of the associations are not clear yet. To our knowledge, there are no systematic reviews with meta-analysis that pooled and summarized the available evidence on factors associated with fatigue. The current disagreements and gaps of knowledge in the literature justify this systematic review with meta-analysis that aimed to analyze and summarize the available evidence on the association between clinical and demographic variables and fatigue in people with SCI.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[23] The protocol for this systematic review and meta-analysis has been registered in PROSPERO (registration no.: CRD42021292875).

Search strategy

To identify eligible studies, a search was conducted of the following electronic bibliographic databases from October 2021 and rerun prior to the final analysis in November 2021: MEDLINE (via PUBMED), Physiotherapy Evidence Database, Cochrane, Google Scholar, and Cumulative Index to Nursing and Allied Health. The search strategy combined the following keywords: “fatigue,” “spinal cord injuries,” “paraplegia,” “quadriplegia,” and “tetraplegia.” The fields were adapted to the search features of each database using identical terms, and the only limit established was the publication language: English or Spanish. The truncation symbol used was *, which allows for all possible word endings.

List of abbreviations:

AXIS	**Appraisal Tool for Cross-Sectional Studies**
CI	**Confidence interval**
NOS	**Newcastle-Ottawa Scale**
OR	**odds ratio**
SCI	**spinal cord injury**

Eligibility criteria

Studies that examined the association between fatigue and other variables in people with SCI were eligible. The inclusion criteria were (1) participants: participants with SCI older than 18 years, (2) measurements: association of fatigue with demographic and/or clinical variables, and (3) publication language: English or Spanish. No limits were imposed in terms of date. Reviews, qualitative studies, nonoriginal articles, abstracts presented at scientific congresses, animal trials, and research on disorders other than SCI or fatigue treatments were excluded.

Study selection and data collection

Two authors (A.O.F., S.F.C.) independently screened the titles and abstracts of the records identified in the search, and the full text of the articles considered potentially eligible was reevaluated. The inclusion of studies was discussed based on the aims and inclusion criteria of the review until reaching a consensus, and a third author (J.A.C.) read the entire article to resolve any discrepancies whenever necessary.

Two researchers (A.O.F., S.F.C.) independently extracted the following data from the included studies using a table created ad hoc: author, year of publication, country, study design, number of participants, years since injury, assessed factors that could be associated with fatigue, and measurement tools for fatigue. Disagreements on data extraction were resolved by consensus with a third author (J.A.C.).

Quality assessment

Two authors (A.O.F., S.F.C.) independently assessed the methodological quality and risk of bias of the included studies. A third author (J.A.C.) was consulted to resolve disagreements when necessary so that the final decision on each assessment was agreed on by all 3 authors.

The Appraisal Tool for Cross-Sectional Studies (AXIS)[24] and the Newcastle-Ottawa Scale (NOS)[25] were used to evaluate the methodological quality of the studies. The AXIS critical appraisal tool addresses the study design and reporting quality, in addition to the risk of bias in cross-sectional studies. It includes 20 items to judge the appropriateness of the study design, selection of participants, response rates, validity of exposure/outcome measures, and potential for introducing bias. Each item is evaluated as either a “yes” or a “no,” and a study is considered to present a high, moderate, or low risk of bias when <60%, 60%-69%, or >70% of the items are rated with a “yes,” respectively.

The NOS modified version for observational studies[25] was used to assess the quality (risk of bias) of the cohort and case-control studies.[26] The domains of the scale comprise the selection of cases and controls, comparability between groups, and measurement of exposure and outcome variables. The scale, which has one section pertinent to case-control studies and another for cohort studies, yields a quality score ranging from 0 (minimum) to 9 (maximum). Studies were categorized as presenting a high, moderate, or low risk of bias when they were rated with <5 points, 5-7 points, or >7 points, respectively.

Data summary and statistical analysis

A pooled data analysis of the association between fatigue and a potential factor was performed whenever 2 or more studies investigated it, and the effect size was used to determine the strength of the associations. When the effect size outcomes were expressed by different statistics (eg, odds ratio [OR], standardized β, correlation coefficient, η^2, and so on), the correlation coefficient (r) was the preferred estimation, with values of 0.1-0.3 being indicative of a small effect size, 0.3-0.5 indicating a moderate effect size, and >0.5 representing a large effect size, as proposed by Cohen.[27] The correlation coefficient was estimated using the online calculator by Lenhard and Lenhard.[28] For cohort studies, the data incorporated into the analysis were selected from the longest available follow-up period and only from non−able-bodied people with SCI. The authors were contacted by email in cases of insufficient reported data. Statistical heterogeneity was explored via the Cochran's Q test and I^2 statistics. Random-effects or fixed-effects analysis models were used when the heterogeneity I^2 was greater or lower than 50%, respectively. The weighted summary correlation coefficient was calculated with the Hedges-Olkin method, either using the Fisher z transformation of correlation coefficients under the fixed-effects model or with the DerSimonian and Laird method under the random-effects model. The weighted pooled OR was estimated using the Mantel-Haenszel method under the fixed-effects model or with the DerSimonian and Laird method under the random-effects model. Egger's test was conducted to evaluate potential publication bias, and P values <.05 were considered to indicate the presence of publication bias. MedCalc[a] and Epidat 3.1[b] were the statistical software tools used for the meta-analysis.

Results

After the removal of duplicates, the systematic search identified 782 potentially eligible studies. After reading the title and abstract, 744 studies were excluded. Finally, after reading the full text, 29 studies were included in the qualitative summary (24 cross-sectional studies,[2-4,6-10,18,19,21,22,29-40] 1 case-control study,[41] 4 cohort studies[11,42-44]) and 23 in the meta-analysis (3 cohort studies,[42-44] 20 cross-sectional studies[2-4,6-10,18,19,21,22,29,31-34,37-39]) (fig 1). Authors were contacted to obtain missing data from 9 of the articles[8,11,18,19,22,30,39,44] to be able to carry out the pooled analysis, of which 5 provided the requested information,[8,19,22,39,44] 3 did not have the data,[7,18,30] and 1 did not respond.[11]

Table 1 shows the outcomes of quality and risk of bias for cross-sectional studies as evaluated with the AXIS scale. Twenty studies[2,4, 6-10,19,21,22,30-32,34-40] were rated as presenting a low risk of bias and 4 studies as moderate risk.[3,18,29,33]

Table 2 shows the risk of bias in the included longitudinal studies as assessed with the NOS. The median quality scores were 6.2 (range, 6-7), 6.0, and 6.3 for the longitudinal, case-control, and cohort studies, respectively.

Table 3 shows the main characteristics of the included studies, which were conducted in 9 different countries from 4 continents (Europe, America, Oceania, Asia) and published between 1995 and 2021. The size of the overall sample was 9425 participants with SCI and 197 able-bodied participants, with sample sizes ranging from 36 participants[33] to 2245 participants.[9] The meta-analysis comprised a sample size of 8380 participants with SCI. With the exception of 1 study that only enrolled men,[18] the samples were composed of both sexes and the number of male participants (6849) was greater than female participants (2544), although 1 study did not specify the proportion of men and women.[3]

The associations between fatigue and a total of 32 factors were investigated in people with SCI (13 factors in separate studies and 19 in 2 or more studies). The most frequently studied factor related to fatigue was age[2,7-11,18,19,22,30,33] (11 studies), followed by depression[2,6, 8,10,19,30,34,38,43,44] and pain[2,4, 6,10,19,21,29,30,43,44] (10 studies), level of lesion[7,8, 10,11,19,22,30,33,42] (9 studies), completeness[4,8, 10,11,19,33,40] (7 studies), medication intake whether analgesics[9,21] or other types of medication[4,7-9,19,21,30] (7 studies), physical activity[2,3, 6,9, 33,37] and sex[8-11,19,22] (6 studies), time since lesion[7,10,19,22,30] (5 studies), anxiety,[8,30,44] participation,[31,36,39] spasticity,[4,10,21] years of education,[7,10,19] and assistive devices[10,21,32] (3 studies), and lastly self-efficacy,[8,19] stress,[8,37] traumatic brain injury,[7,19] and race[9,38] (2 studies).

The most common methods to assess fatigue were the Fatigue Severity Scale[45] in 13 studies (45%)[3,4, 6,10,11,18,21,22,29,33,37,43,44] and the Modified Fatigue Impact Scale 5-item version[46] in 5 studies.[9,11,32,34,38]

Table 4 shows the results of this meta-analysis (additional details can be found in supplemental appendix S1). Of all the factors evaluated in the pooled analysis, no association was found between fatigue and age, educational level, spasticity, and time since injury, although the latter 2 presented high heterogeneity or inconsistency of results. No differences were observed in terms of sex (table 5). Strong associations (r>0.5) were found with anxiety and stress (direct) and with self-efficacy (inverse). However, the associations with these 3 factors presented a possible publication bias (only 2 studies were included for each factor) and high heterogeneity or inconsistency. Fatigue showed an association with a moderate effect size ($0.3<r<0.5$) with depression, pain, and taking analgesic medication (direct) and with participation (inverse). A potential publication bias for analgesic medication and high heterogeneity in pain reports were observed, while the participation outcomes presented both biases. Fatigue showed direct weak associations ($0.1<r<0.3$) with having an incomplete injury, the use of assistive devices, higher levels of injury, and taking medication of any type (including antispasticity, antidepressants, anxiolytics, etc) and an inverse weak association with physical activity. Low heterogeneity was found for these factors except for physical activity.

The certainty of the evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation was low because of the type of research (observational studies) included in this review.

The following 2 factors could not be included in the pooled analysis despite being investigated in more than 1 study: race or ethnicity[9,38] because of the different categorization of races in the 2 studies and traumatic brain injury[7,19] because of insufficient data. Saunders et al,[9] who categorized races as White, Black, and Others, reported that Black participants were less likely to experience fatigue while showing a direct weak association (OR, 3.00; P=.003) for White participants and a moderate effect size (OR, 3.67; P=.003) for other races. Cao et al[38] categorized race and ethnicity into 4 groups: non-Hispanic White, non-Hispanic Black, Hispanic, and Others. Hispanic participants had higher levels of fatigue (7.1±4.9; P<.001) than the rest (non-Hispanic Black [4.1±3.9], non-Hispanic White [4.2±4.1], and Others [4.9±4.5]). On the other hand, no significant association between participants with traumatic brain injury and fatigue was observed ([OR, 2.29; P=.1232][19] and [r=0.15; P>.05][7]).

The factors assessed in only 1 study that showed a direct strong association with fatigue were burnout (r=0.628; P<.05),[37] anger (r=0.59; P<.01),[40] and daytime sleepiness (η^2=0.31; P<.001),[41]

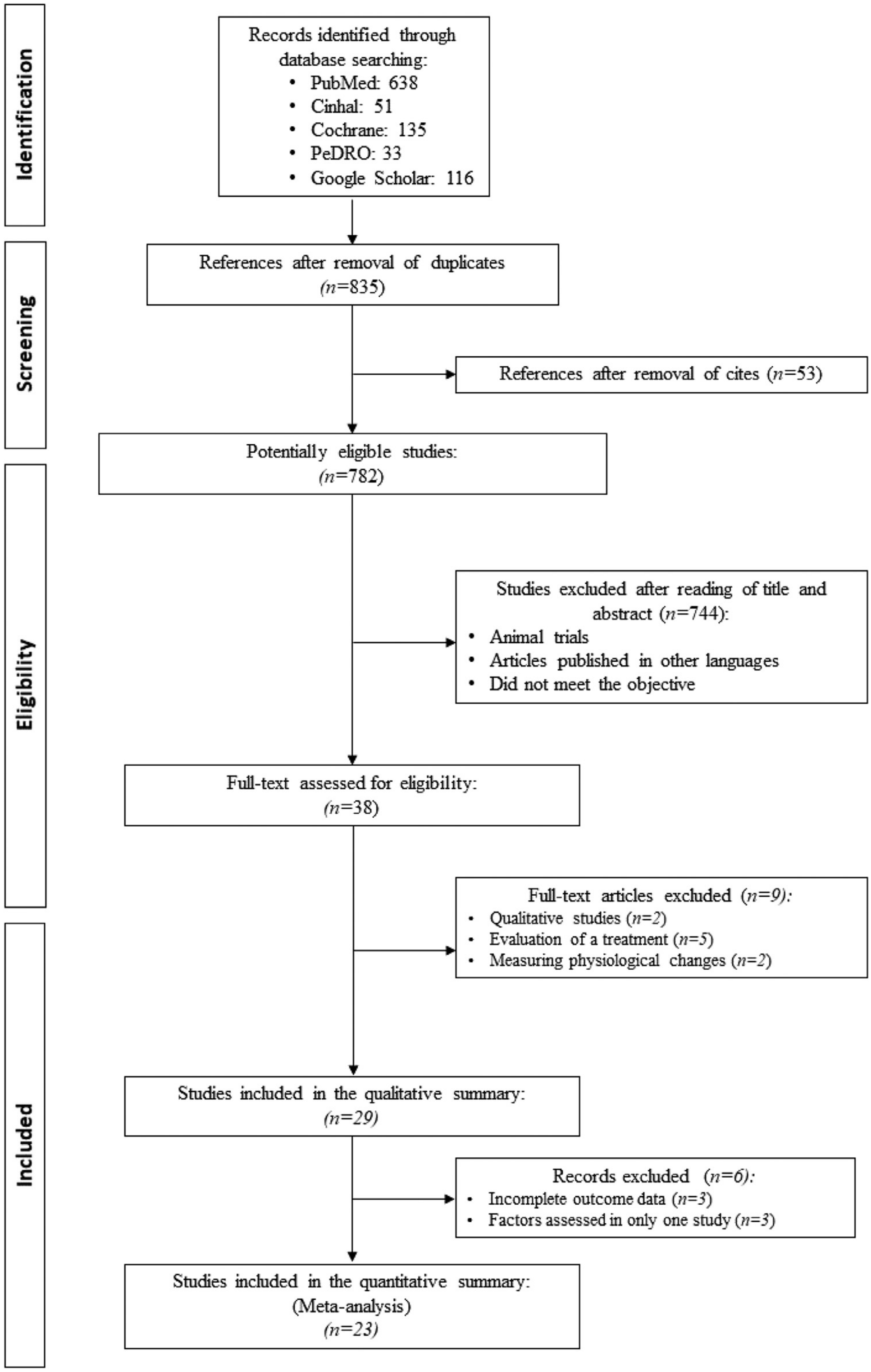

Fig 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram for the systematic review. CINAHL, Cumulative Index to Nursing and Allied Health; PEDro, Physiotherapy Evidence Database.

while an inverse strong association was observed with coping (r=−0.554, P<.05).[37] An inverse association with a moderate to large effect size was found with quality of life as assessed with the 36-Item Short-Form Health Survey, which ranged between r=−0.69 (P<.001) for the vitality domain and r=−0.35 (P<.01) for the mental functioning domain.[7] An association with a moderate effect size (r=−0.37; P<.05) was found with autonomic nervous system dysfunction.[42] Weak associations were observed between fatigue and 6 factors: cause of the lesion (nontraumatic) (OR, 0.731; P>.05),[10] smoking habit (>20 cigarettes/day) (OR, 1.38; 95% confidence interval [CI], 0.78-2.47),[9] alcohol consumption (OR, 1.65; 95% CI, 1.16-2.35),[9] overweight (OR, 1.65; 95%

Table 1 Quality assessment using the AXIS

Author	AXIS Checklist Question																				Risk of Bias
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Alschuler et al[2]	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Low
Craig et al[8]	Y	Y	N	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Craig et al[19]	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Low
Cao et al[38]	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Low
Cudeiro et al[10]	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Low
Dipiro et al[34]	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Low
Fawkes et al[4]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Low
Fernández et al[22]	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Low
Freixes et al[6]	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Low
Hetz et al[35]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Kuzu et al[39]	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Lannem[37]	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Low
Lee et al[21]	Y	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Low
Lidal et al[30]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Lundström et al[36]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Nooijen et al[33]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Moderate
Pentland et al[18]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	Moderate
Saunders et al[9]	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Low
Saunders et al[32]	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Low
Smith et al[31]	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Low
Tawashy et al[3]	Y	Y	N	Y	N	Y	N	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	N	Y	Moderate
Wijesuriya et al[7]	Y	Y	N	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Low
Wijesuriya et al[40]	Y	Y	N	Y	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Low
Zhao et al[29]	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	Y	Y	N	N	N	Y	Y	N	Y	Moderate

Table 2 Quality assessment of included studies by the Newcastle-Ottawa Scale for cohort and case-controls studies

Author	Total Score (%)	Risk of Bias
Anton et al[11]	7 (88)	Low
Craig et al[44]	6 (75)	Moderate
Craig et al[41]	6 (75)	Moderate
Forwell et al[43]	6 (75)	Moderate
Rodrigues et al[42]	6 (75)	Moderate

CI, 1.18-2.33),[35] fair diet (OR, 1.87; 95% CI, 1.28-2.73) or poor diet (OR, 3.13; 95% CI, 1.76-5.90),[9] and cognitive impairment (η^2=0.04; *P*=.06).[44] On the contrary, the participant's occupation did not show an association with fatigue in people with SCI (*P*=.756).[22]

Discussion

The present systematic review and meta-analysis aimed to summarize and analyze the factors that are associated with fatigue in people with SCI. Twenty-nine studies that investigated the associations between fatigue and a total of 32 demographic or clinical factors were included, from which a pooled analysis of 17 factors was performed. A direct association was found between fatigue and the following 9 factors (ranked from largest to smallest effect size): anxiety, stress, depression, pain, analgesic medication intake, use of assistive devices, level of lesion, incomplete SCI, and general medication intake. An inverse association was found between fatigue and 3 factors (from largest to smallest effect size): self-efficacy, participation, and physical activity. No associations were found with the remaining 5 factors: age, sex, educational level, time since injury, and spasticity.

This review found that clinical factors related to mental health (self-efficacy, stress, anxiety, depression) were the ones most strongly associated with fatigue, which could stem from the multidimensional nature of fatigue, which has been shown to have cognitive, emotional, and physical dimensions in people with SCI.[16] Additionally, the prevalence of psychological morbidity is high among this population.[47] Craig et al[8] reported that 51% of people with SCI presented elevated depressive mood (compared with 19% in a control group of able-bodied participants), and around 36% showed poor self-efficacy (compared with 15% in the control group). This greater association with mental health factors compared with physical health components has also been observed in other neurologic conditions such as stroke.[48] A recent meta-analysis revealed that anxiety and depression are factors that affect the appearance of fatigue, with the latter nearly doubling the likelihood of experiencing poststroke fatigue.[49] The reason provided for explaining such a strong association was that fatigue is one of the symptoms of depression. The relevance of the association between fatigue and emotional distress, defined as a negative state of mind including anxiety and depression,[50] has also been highlighted in people with multiple sclerosis. A prospective cohort study showed that fatigue was one of the strongest predictors of depression in this population.[51] However, the present study could not establish the directionality of the association because the majority of the included studies were cross-sectional. On the other hand, a meta-analysis concluded that cognitive-behavioral treatment reduces fatigue in people with multiple sclerosis.[52] These

Table 3 Characteristics of the studies included in the review

Author/Country	Study Design/Sample Size/Years Post Injury, Mean ± SD	Factors Studied Association With Fatigue	Fatigue Measures
Alschuler et al[2]/United States	Cross-sectional/(N=481) 320 men/17.78±11.78	Pain, depressive symptoms, physical functioning, and age	Numeric rating scale
Anton et al[11]/Canada	Cohort/(N=52) 41 men/ 0.12±0.06	Level of lesion, completeness, age, and sex	Fatigue Severity Scale MFIS-SCI
Cao et al[38]/United States	Cross-sectional/(N=1063) 788 men/16.6±14.2	Depressive symptoms and or ethnicity	MFIS-5
Craig et al[8]/Australia	Cross-sectional /(N=82) 41 participants with SCI 39 men and 41 able-bodied 39 men/16.5±14	Depressive symptoms, anxiety, stress, self-efficacy, taking medication, level of lesion, completeness, age, and sex	Iowa Fatigue Scale Chalder Fatigue Scale
Craig et al[19]/Australia	Cross-sectional/(N=70) 63 men/17.4±14	Pain, depressive symptoms, taking medication, completeness, time since injury, self-efficacy, diagnosis of TBI, age, and sex	Chalder Fatigue Scale
Craig et al[44]/Australia	Cohort/(N= 88) 62 men/not reported	Pain, depressive symptoms, anxiety, and cognitive impairment	Fatigue Severity Scale
Craig et al[41]/Australia	Case-controls/(N=89) 45 participants with SCI 38 men and 44 able-bodied 37 men/10.4±12.9	Daytime sleepiness	Iowa Fatigue Scale
Cudeiro et al[10]/Spain	Cross-sectional/(N=253) 163 men/not reported	Pain, depressive symptoms, level of lesion, completeness, spasticity, time since injury, cause of lesion, age, and sex	Fatigue Severity Scale
Dipiro et al[34]/United States	Cross-sectional/(N=652) 459 men/10.5±8.2	Depressive symptoms	MFIS-5
Fawkes et al[4]/Canada	Cross-sectional/(N=76) 49 men/12.68±12.15	Pain, medication, completeness, and spasticity	Fatigue Severity Scale
Fernández et al[22]/Argentina	Cross-sectional/(N=74) 48 men/3.4	Activities of daily life, level of lesion, time since injury, occupation, age, and sex	Fatigue Severity Scale
Forwell et al[43]/Canada	Cohort/(N=52) 41 men/0.12±0.06	Pain and depressive symptoms	Fatigue Severity Scale
Freixes et al[6]/Argentina	Cross-sectional/(N=26) 22 men/2.7	Pain, depressive symptoms, and physical activity	Fatigue Severity Scale
Hetz et al[35]/Canada	Cross-sectional/(N=695) 531 men/15.3±11.1	Overweight	Frequency and effect of fatigue during the past 12 mo
Kuzu et al[39]/United States	Cross-sectional/(N=168) 106 men/20.3±19.5	Participation	PROMIS Fatigue 4a Short

(*continued on next page*)

Table 3 (*Continued*)

Author/Country	Study Design/Sample Size/Years Post Injury, Mean ± SD	Factors Studied Association With Fatigue	Fatigue Measures
Lannem[37]/Norway	Cross-sectional/(N=186) 142 men/15±13	Stress, physical activity, burnout, and coping	Fatigue Severity Scale
Lee et al[21]/Canada	Cross-sectional/(N=136) 105 men/14.06±12.02	Pain, taking medication, spasticity, and assistive devices	Fatigue Severity Scale
Lidal et al[30]/Norway	Cross-sectional/(N=153) 125 men/27.1±4.2	Pain, depressive symptoms, taking medication, level of lesion, time since lesion, anxiety, and age	Fatigue Questionnaire
Lundström et al[36]/Sweden	Cross-sectional/(N=73) 55 men/36.3±9.2	Participation	PARTS-Mv3: how much fatigue limits activity
Nooijen et al[33]/Holland	Cross-sectional/(N=36) 31 men/0.4±0.2	Level of lesion, completeness, physical activity, and age	Fatigue Severity Scale
Pentland et al[18]/Canada	Cross-sectional/(N=83) 83 men/18.3±16.5	Age	Fatigue Severity Scale
Rodrigues et al[42]/Australia	Cohort/(N=99) 45 participants with SCI 38 men and 44 able-bodied 37 men/10.4±12.9	Autonomic nervous system dysfunction	Iowa Fatigue Scale
Saunders et al[9]/United States	Cross-sectional/(N=2245) 1703 men/12.5±9.6	Physical activity, taking medication, race, diet, alcohol consumption, smoke, age, and sex	MFIS-5
Saunders et al[32]/United States	Cross-sectional/(N=783) 556 men/10.5±8.6	Assistive devices	MFIS-5
Smith et al[31]/Canada	Cross-sectional/(N=1549) 1041 men/18.5±14.3	Participation	Frequency of fatigue experienced during the past 12 mo
Tawashy et al[3]/Canada	Cross-sectional/(N=49)/11.8±9.2	Physical activity	Fatigue Severity Scale
Wijesuriya et al[7]/Australia	Cross-sectional/(N=82) 41 SCI participants 39 men and 41 able-bodied 39 men/16±14	Level of lesion, time since lesion, completeness, taking medication, quality of life, diagnosis TBI, and age	Iowa Fatigue Scale
Wijesuriya et al[40]/Australia	Cross-sectional/(N=54) 27 SCI participants 26 men and 27 able-bodied 24 men/20.8±14.59	Anger	Chalder Fatigue Scale
Zhao et al[29]/China	Cross-sectional/(N=200)/135 men/not reported	Pain	Fatigue Severity Scale

Abbreviations: MFIS-5, Modified Fatigue Impact Scale-5 item version; MFIS-SCI, Modified Fatigue Impact Scale for Spinal Cord Injury; PARTS/M-v3, Participation Survey/Mobility version-3; PROMIS, Patient-Reported Outcomes Measurement Information System.

Table 4 Summary of pooled analysis of associations between fatigue and the assessed factors

Factor	Studies (n)	Sample Size (n)	Correlation Coefficient *r* (95% CI)	Fisher *z* Transformation (*P* Value)	Heterogeneity (%) I^2 (*P* Value)	Fixed-/Random-Effects Model	Publication Bias Egger's Test (*P* Value)
Age	8	3250	0.01 (−0.03 to 0.04)	0.5 (.60)	0.0 (.60)	Fixed	0.60 (.11)
Anxiety	2	112	0.57 (0.29 to 0.75)*	3.7 (<.001)*	66.6 (.08)	Random	8.6 (<.001)*
Assistive devices	2	919	0.23 (0.17 to 0.29)*	7.1 (<.001)*	4.0 (.31)	Fixed	−1.9 (<.001)*
Completeness	6	516	0.13 (0.05 to 0.22)*	3.0 (.003)*	0.0 (.52)	Fixed	0.58 (.62)
Depression	9	2709	0.47 (0.44 to 0.50)*	26.3 (<.001)*	46.4 (.06)	Fixed	1.12 (.19)
Level of lesion	7	560	0.15 (0.07 to 0.23)*	3.5 (<.001)*	0.0 (.61)	Fixed	.84 (.39)
Medication: analgesics	2	2381	0.32 (0.28 to 0.36)*	16.2 (<.001)*	0.0 (.40)	Fixed	−1.14 (<.001)*
Medication of any type	6	2609	0.12 (0.01 to 0.23)*	2.1 (.04)*	54.3 (.052)	Random	−1.43 (.09)
Pain	9	1365	0.34 (0.16 to 0.50)*	3.5 (<.001)*	91.3 (<.001)*	Random	−1.07 (<.72)
Participation	2	1718	−0.32 (−0.58 to −0.001)*	−2.0 (.049)	94.2 (<.001)	Random	−6.49 (<.001)*
Physical activity	6	3020	−0.17 (−0.28 to −0.05)*	−2.7 (.006)*	75.5 (.001)*	Random	1.78 (.16)
Self-efficacy	2	111	−0.63 (−0.81 to −0.35)*	−3.8 (<.001)*	73.5 (<.052)	Random	−9.85 (<.001)*
Spasticity	3	462	0.05 (−0.23 to 0.32)	0.3 (.73)	87.4 (<.001)*	Random	2.26 (.84)
Stress	2	227	0.54 (0.26 to 0.74)*	3.5 (<.001)*	74.3 (.048)*	Random	3.98 (<.001)*
Time since injury	4	438	−0.16 (−0.36 to 0.06)	−1.4 (.15)	75.1 (.007)*	Random	2.26 (.84)
Educational level	3	364	0.07 (−0.03 to 0.18)	1.4 (.17)	49.7 (0.14)	Fixed	3.0 (.047)*

* Statistical significance at P<.05.

Table 5 Pooled analysis of the association between sex and fatigue in people with spinal cord injury

Author	Sample Size	Odds Ratio	95% CI	Weight (%) Fixed	Weight (%) Random
Craig et al[8]	41	0.23	0.02-2.3	1.7	1.7
Craig et al[19]	70	0.85	0.2-3.7	4.3	4.3
Cudeiro et al[10]	253	0.65	0.4-1.2	24.2	24.2
Fernández et al[22]	74	0.40	0.1-1.1	8.4	8.4
Saunders et al[9]	2245	0.90	0.6-1.3	61.4	61.4
Total (fixed-effects)	2683	0.75	0.56-1.03	100	100
Total (random-effects)	2683	0.75	0.56-1.03	100	100
Heterogeneity test	Q=3.4, *P*=.49	I^2=0.0%			
Publication bias	Egger's test=−2.0, *P*=.14				

findings highlight the importance of integrating psychological treatment in the rehabilitation process in people with neurologic disorders.

Pain and depression were the factors with the largest number of studies (n=9) that were included in the pooled analysis. The effect size of the association between pain and fatigue was moderate, although this result presented high heterogeneity or inconsistency. A direct association between fatigue and pain was reported in 7 studies, and 1 study found no association, contrary to the study by Lee et al[53] that reported an inverse association with moderate risk of bias. In fact, when the latter study was removed from the pooled analysis, the heterogeneity decreased from 91% to 54% without changing the effect size. Other reasons for this variability could be the heterogeneity in terms of the pain intensity and the different scales used to assess pain. In fact, the studies that evaluated pain with multidimensional scales (short-form McGill Pain Questionnaire,[19] modified Brief Pain Inventory[43]) reported a higher correlation between pain and fatigue than those using scales to quantify the presence or intensity of pain (simple "yes/no" questions,[4,10,21] 0-10 rating scales[2,6, 10,29,44]).

The intake of analgesics showed an association with fatigue with a moderate effect size, whereas the use of any type of medication showed a weak association. This difference in the strength of association could be because fatigue is an adverse effect of certain analgesics, which is not the case for medication in general. Furthermore, Saunders et al[9] investigated the association between fatigue and 3 different types of medication in a sample of 2245 people with SCI and reported a stronger association with the intake of analgesics than with medication for stress and no association with treatments for spasticity. The association of analgesic intake with fatigue could be a confounding factor because pain is also associated with fatigue. Therefore, whether these drugs achieve to control the pain or not should be verified. On the other hand, the use of medication for treating anxiety, depression, or other mental health factors strongly associated with fatigue may also yield positive effects on these clinical components that contribute to fatigue and therefore could help to reduce it.[21] An analysis by subgroups was only possible for painkillers and other types of medication because there were not 2 or more studies that classified other medication families similarly.

High heterogeneity or inconsistency was observed for the outcomes of participation, which showed an association with a moderate effect size with fatigue, and spasticity, which did not show an association. This could be because of the heterogeneity in the scales used to assess both outcomes.[10] In addition, the only study that showed an inverse association between fatigue and spasticity was that by Lee et al,[21] as was the case for the pain factor, and the heterogeneity decreased from 87% to 72% after eliminating it from the analysis, maintaining the absence of association.

The level of injury, completeness, and use of assistive devices showed a weak association with fatigue with low heterogeneity of results. Patients with incomplete lesions, cervical SCI, and greater use of assistive devices for mobility were associated with higher levels of fatigue. Cervical injuries are associated with poorer motor function and greater autonomic nervous system dysfunction. Self-reports of elevated levels of fatigue have been associated with low levels of sympathetic activity.[42] Increased fatigue in participants with incomplete lesions or those using assistive devices could be related to ambulation. Ambulatory people with SCI reported the most disabling fatigue, even after controlling for exercising.[9] Previous research has shown that these individuals, especially dependent ambulatory participants, can have more problems than nonambulatory ones.[54] Severe fatigue has been associated with using a wheelchair 50% of the time or less, and a stronger association has been observed when using a unilateral cane.[32]

People with SCI express a variety of opinions when they are questioned about the association of physical exercise and fatigue, with some believing that it makes them less fatigued while others relate it to greater fatigue.[17] This review found that physical activity was inversely associated with fatigue, with a small effect size and high heterogeneity. This inconsistency was expected given the high heterogeneity in the tools for assessing physical activity, ranging from validated scales such as the Leisure-Time Physical Activity scale by Lannem[37] to simple questioning methods, which include questions such as, "How much exercise do you get compared with other people with spinal cord injury who have about the same severity of injury?" with 3 response options (more, the same, less) used by Saunders et al.[9] A beneficial relationship between exercise and fatigue has been shown in other neurologic disorders, such as a recent meta-analysis reporting that physical exercise reduced fatigue symptoms in people with multiple sclerosis.[55] It seems reasonable to think that physical exercise promotes resistance to fatigue. However, establishing a stronger association may be hindered by the evaluation of fatigue via self-reported scales and not objective measures of motor fatigue. Further research is required with well-defined fatiguing tasks to assess fatigue objectively, even combining objective and subjective measures, to verify whether this is a correct method of determining this association.

The findings of the present meta-analysis showed that fatigue was not associated with the time since injury or any of the analyzed demographic factors (age, sex, educational level). Furthermore, no heterogeneity or inconsistency was observed in the results in terms of demographic factors. The sample size of women included in the analysis (n=667) was much lower than that of men (n=2016), which could reduce the validity of the results obtained for the sex variable. Future studies with sex-balanced samples are necessary to assess the association between fatigue and sex in people with SCI.[56]

Study limitations

Several limitations must be taken into consideration when interpreting the results of the current meta-analysis. First, the heterogeneity or inconsistency in results was high for 35% of the factors included in the pooled analysis, thus reducing the certainty of the evidence for these assessments. High heterogeneity could stem from various factors, such as the use of different scales to assess fatigue, the majority of which measure perceived effect of fatigue on their lives while others evaluate perceived intensity of fatigue. Variations in the study design can also partly explain high heterogeneity, although most of the included studies were cross-sectional. Second, only 2 studies were included for 41% of the factors assessed, both of which showed a risk of publication bias. Third, the analyzed data stemmed from cross-sectional studies, which did not allow for establishing causality between the modifiable factors and fatigue. Finally, most of the data the studies collected were self-reported by the participants, including fatigue, which could result in biases such as recall bias.

Conclusions

In conclusion, clinical factors related to mental health such as stress, anxiety, self-efficacy, or depression showed the strongest association with fatigue in people with SCI. The strength of the association was moderate between fatigue and pain, taking analgesic medication, and participation, while a weak association was observed with physique-related variables such as the use of assistive devices, physical activity, completeness, or level of injury, while no association was found with sociodemographic factors. Large longitudinal studies are necessary to assess the causality direction of the association between these factors and fatigue, especially those factors related to mental health given the potential implications in the rehabilitation process of people with SCI. The results of this study should be interpreted with caution because of the inconsistency of results about the associations between fatigue and certain factors.

Suppliers

a. MedCalc; MedCalc Sofware Ltd. Ostend, Belgium.
b. Epidat 3.1, Servicio Gallego de Salud (SERGAS). Santiago de Compostela, Spain.

Keywords

Association; Fatigue; Meta-analysis; Rehabilitation; Spinal cord injuries

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