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ORIGINAL REPORT

EFFECTIVENESS OF SPECIALIZED REHABILITATION AFTER MILD TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: **To determine the effectiveness of specialized rehabilitation in adults with prolonged symptoms, or risk of prolonged symptoms, following mild traumatic brain injury.**

Data sources: **Randomized controlled trials or non-randomized controlled studies published between 1 Jan 2000 and 10 Mar 2019 in Cochrane Controlled Register of Trials, PubMed, EMBASE, CINAHL or PsycINFO. Meta-analyses were performed for studies of similar interventions when identical or comparable outcomes were reported.**

Study selection and data extraction: **Screening, data extraction, and risk of bias assessment were carried out by 2 independent researchers. Quality of evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation.**

Data synthesis: **A total of 9 studies were identified, which were divided into 3 subgroups. Results from meta-analyses implied that problem-solving therapy and cognitive behavioural therapy reduce residual symptoms, improve psychological functioning, decrease depression, increase activity and participation, and improve quality of life, compared with usual care. The meta-analyses also suggested that specialized interdisciplinary rehabilitation reduces residual symptoms.**

Conclusion: **Persons with mild traumatic brain injury who are at risk of, or who experience, prolonged symptoms should be considered for specialist treatment, as they may experience positive effects from cognitive behavioural therapy, problem-solving therapy, or interdisciplinary team rehabilitation. Further research is required to strengthen the evidence.**

Key words: brain injury; traumatic; cognitive behavioural therapy; post-concussion syndrome; problem-solving; rehabilitation; quality of life.

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LAY ABSTRACT

The aim of this study was to determine what type of rehabilitation is most effective for prolonged symptoms in adults following mild traumatic brain injury. The study compared specialized rehabilitation, carried out by healthcare professionals specialized in brain injury rehabilitation, with less specialized rehabilitation, or no rehabilitation at all. Several established databases were searched, yielding 9 relevant studies. There was some evidence that problem-solving therapy and cognitive behavioural therapy reduce symptoms, improve psychological functioning, decrease depression, increase activity and participation, and improve quality of life compared with usual care. There was also some evidence that specialized interdisciplinary rehabilitation reduces residual symptoms. However, few studies assessed the same type of rehabilitation or used the same outcome measures. Further research is therefore required to strengthen the certainty of this evidence.

Mild traumatic brain injury (mTBI) accounts for the majority of all brain injuries worldwide (1). The estimated annual incidence of persons seeking hospital care after traumatic brain injury (TBI) in the European Union (EU) is approximately 490 per 100,000, of which 90% are mTBI (1), and a significant number of persons experience prolonged symptoms for months, and, in many cases, years (2–4). Results from a large European multi-centre study imply that up to 46% of subjects experience persisting symptoms at 3 months after mTBI in complicated cases (presence of intracranial injury on computed tomography (CT) scan), and 35% in uncomplicated cases (5). In a US multi-centre study (TRACK-TBI study), 53% reported functional limitation 12 months after the injury compared with 38% of the orthopaedic controls (6). In the TRACK-TBI study, 23% of the mTBI population had had a previous TBI, which may have affected the high prevalence of prolonged functional limitations (6). Commonly reported symptoms are fatigue, forgetfulness, and slowing of thinking, but also emotional symptoms (5). However, only a minority of patients have abnormal findings on CT after mTBI (7), and several factors contribute to the reports of prolonged symptoms (8).

Development of long-term sequelae is debated, as the outcomes of different studies diverge. This could be due to several factors (9). One important aspect is the ambiguity regarding the definition of mTBI. In the World Health Organization (WHO) Task Force report, 38 different definitions were listed (10). Although most current studies apply the criteria of the American Congress of Rehabilitation Medicine (ACRM) (11) or

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WHO Task Force criteria (10), the definition is broad, making the study population heterogeneous regarding, for example, the degree of severity of mTBI (12). This, in combination with other factors regarding recruitment strategies in studies, such as different inclusion and exclusion criteria, including age, timing, and setting, may contribute to difficulties in comparing studies and explain the diverging results (13, 14).

The choice of measurement instruments could be another factor that contributes to the ambiguity. Self-experienced cognitive symptoms do not always correspond to objective test results (15), results from self-rating instruments often correlate with depression and other inner states (16), and if objective tests are used there is a risk that they may not be sensitive enough to capture the subtle cognitive impairments that result from mild TBI (9). The above-mentioned factors, combined with great individual variation in cognitive function, makes it difficult to predict outcome and contributes to a lack of consensus and limited evidence on how to treat these symptoms.

Taken together, mTBI can lead to a variety of prolonged symptoms, but ambiguities regarding expected symptoms and which treatments are effective can lead to unequal care and sometimes to misdiagnosis (e.g. depression). Although there are many practice guidelines on how to manage prolonged symptoms after mTBI (17), there is a lack of evidence-based treatments, leading to a risk of inappropriate treatments or no treatment at all. A systematic Cochrane review (18) found strong evidence for a good recovery for the majority of patients with mTBI if appropriate information and advice was offered early after injury (18).

To the best of our knowledge, no systematic review has assessed the effectiveness of specialized rehabilitation in adults with prolonged symptoms of mTBI. The objective of this systematic review and meta-analysis was to determine the effectiveness of specialized rehabilitation in adults with prolonged symptoms, or who are at risk of prolonged symptoms following mTBI.

METHODS

This systematic review and meta-analysis was part of a larger project determining the effects of rehabilitation interventions for persons with TBI (mild, moderate, and severe), conducted at the Swedish Agency for Health Technology Assessment and Assessment of Social Services, SBU (19). The project also covered health economics and ethical aspects, as well as persons' experiences of rehabilitation interventions, and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20). A protocol covering the larger project was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=102822). The current study reports the results of rehabilitation following mTBI.

Eligibility criteria

Population. Adults (age ≥ 16 years) with mTBI and prolonged symptoms, or who are at risk of prolonged symptoms. Prolonged was defined as symptoms that persisted, or were at risk of being long-lasting. No lower or upper limit for duration was set, nor for the number of symptoms, as there is no consensus on the definition of prolonged symptoms after mTBI (13). Studies with mixed populations were included if the proportion of mTBI patients was ≥ 50%.

Intervention. Specialized rehabilitation, i.e. rehabilitation carried out by healthcare professionals specialized in brain injury rehabilitation.

Comparison. Less specialized rehabilitation or no rehabilitation.

Outcomes and measures. Post-mTBI symptoms, psychological function (global measure), depression, anxiety, cognitive function, activity and participation, healthcare use, return to work or return to study, quality of life, life satisfaction, and mortality.

It was required that all outcomes should be assessed with validated instruments or methods, at the earliest, 3 months after the start of the intervention. No upper time limit was set for reporting outcomes.

Study design. Randomized controlled trials (RCTs) or non-randomized controlled studies of interventions (NRSI).

Language. English, Swedish, Norwegian, or Danish.

Publication type. Publications in peer-reviewed journals published in the year 2000 or later.

Data sources

The Cochrane Controlled Register of Trials (Central), PubMed (NLM), EMBASE (Elsevier), CINAHL (EBSCO), and PsycINFO (EBSCO) were searched on 2 occasions, covering literature published from 2000 up to 10 March 2019. The detailed search strategy is available as Appendix SI[1]. The reference lists of included studies were also searched for relevant studies.

Study screening and selection

Two persons (KWR and a co-worker) screened the titles and abstracts independently, using the web-based screening tool Rayyan (21). Full-text articles were retrieved if one or both reviewers considered a study potentially eligible. All authors read the full-text articles independently and checked them for eligibility against the pre-stated criteria. Any disagreement was resolved by discussion.

At least 2 authors (from MM, JL, and KWR) independently assessed eligible studies for risk of bias, using the standardized tool developed by Cochrane for randomized controlled studies (22), with the addition of assessments regarding conflicts of interests. Studies were scored as having either: (*i*) high risk of bias, (*ii*) some concern, or (*iii*) low risk of bias, based on risk of bias in the following domains: randomization, adherence, missing outcome, measurement, reporting, and conflicts of interest. Any disagreements were resolved by discussion among all 3 authors.

Data extraction

For all included studies, the following data were extracted: country, patient characteristics such as age, sex, and time after

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2791

injury, description of the rehabilitation and control intervention, method of data collection, length of follow-up, drop-out rate, risk of bias, and outcomes. If several measures were reported for the same outcome, the measure that was considered to best represent the construct of interest was extracted. In some cases, when data were incompletely reported, the authors of the original study were contacted and asked for additional data. The full extracted study data are shown in Appendix SI[1].

Synthesis and statistical analysis

Meta-analyses were performed when identical or comparable outcomes were reported in studies within the same subgroup. Meta-analyses were computed using Review Manager (RevMan) (23), using the Mantel-Haenszel method for continuous and dichotomous outcomes. The random-effects model was used for all analyses, as heterogeneity was present in the included studies, mostly regarding interventions or context. Outcomes were expressed as mean difference (MD), standardized mean difference (SMD), risk difference (RD), and risk ratio (RR) with 95% confidence intervals (95% CI). The degree of statistical heterogeneity was assessed using the I^2 index as guidance. When it was not possible to perform meta-analyses, a narrative approach was used.

Assessment of evidence

The certainty of the evidence was assessed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE), where the certainty of the evidence is expressed as high (++++, moderate (+++o), low (++oo), or very low (+ooo) (24). Each outcome is assessed separately and can be downgraded from the preliminary level, which is considered as high, by the 5 domains in GRADE: overall risk of bias across studies, inconsistency, indirectness, imprecision, and publication bias.

Different approaches can be used to assess the certainty of the evidence of outcomes (25). The current study assessed the certainty that there was a difference between the intervention and the control group (a non-null effect), or alternatively, the certainty that the effect was similar in the 2 groups (null effect).

RESULTS

Search results and study selection

The electronic database search strategy and complementary examinations yielded 4,637 citations, from which 22 articles were examined in full text. A total of 10 articles, describing 9 unique RCTs, met the eligibility criteria (Fig. 1) and were assessed for risk of bias. All studies were scored as having "some concerns" regarding risk of bias, where the most prevailing concern was lack of blinding of study participants and outcome assessors (which in cases of self-assessment were the same persons). Other risks of bias identified

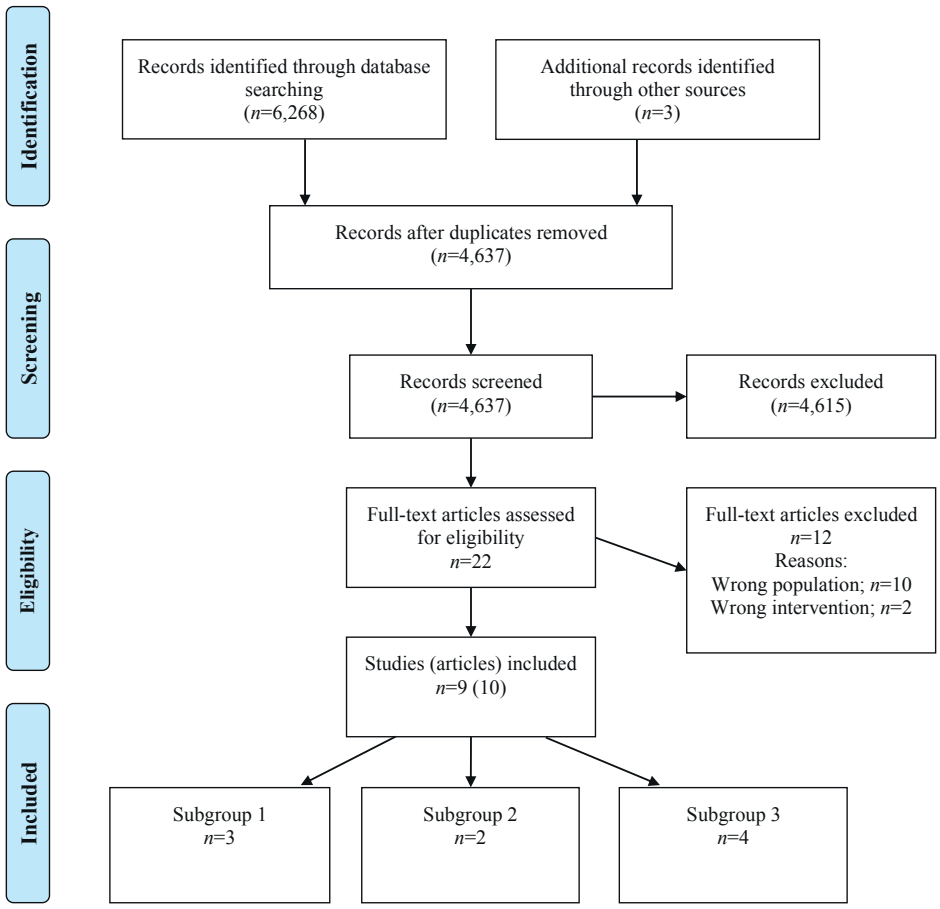


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table I. Characteristics of included studies

Author, Year Country	N	Age, years, and sex	Severity of TBI Time since injury	Setting	Intervention	Control intervention	Follow-up (months post-allocation)	Drop-out rate (%) I; C	Outcome measures extracted
Bell et al. 2017 (29) Richardson et al. 2018 (27) USA[a]	356	Mean age: 29 (range 20–54) Male: 93%	mTBI ≤24 months	Two military medical centres	Telephone-delivered problem-solving treatment, 12 sessions	Usual care (education)	6, 12	22; 7	Post-mTBI symptoms, Psychological function, Depression, AP, Use of healthcare services QoL
Bryant et al. 2003 (30) Australia	24	Mean age: 31 (SD 14) Male: 33%	mTBI ≤2 weeks	PTSD unit	CBT, 5 individual sessions	Supportive counselling, 5 sessions	6	0; 0	Psychological function, Depression, Anxiety
Potter et al. 2016 (28) UK	46	Mean age: 41 (SD 12) Male: 54%	Mild (52%), moderate (28%), severe (20%) >6 months	Two secondary/ tertiary care brain injury clinics	CBT, 12 individual sessions	Waiting list	4	4; 0	Post-mTBI symptoms, Psychological function, Depression, Anxiety, AP, QoL
Rytter et al. 2018 (32) Denmark	89	Age range: 18–65 Male: 34%	mTBI mean 28 months	Specialized post-acute outpatient hospital	Interdisciplinary programme, 22 weeks	Standard care	5, 11	20; 18	Post-mTBI symptoms, Depression, RTW
Scheenen et al. 2017 (31) The Netherlands	91	Mean age: 41 (range 18–66) Male: 45%	mTBI 4–6 weeks	Three level I trauma centres	CBT, 5 group sessions	Telephone counselling, 5 sessions	3, 6, 12	11; 4	Post-mTBI symptoms, Psychological function, Anxiety, Depression, AP, RTW
Silverberg et al. 2013 (26) Canada	28	Mean age: 39 (SD 12) Male: 39%	mTBI 1–6 weeks	Concussion clinic in a tertiary rehabilitation centre	CBT, 6 individual sessions	Usual care (education)	3	13; 15	Post-mTBI symptoms, Anxiety, Depression, AP
Tiersky et al. 2005 (33) USA	29	Mean age: 47 (range 19–62) Male: 45%	Mild (90%) or moderate (10%) mean 6.25 years	Outpatient clinic	CBT + individual cognitive remediation,11 weeks	Waiting list	3	21; 40	Psychological function, Anxiety, Depression, Cognitive function, AP
Twamley et al. 2014 (34) USA	50	Mean age: 32 Male: 96%	Mild to moderate mean 4.5 years	Veterans at the VA San Diego Healthcare System	Cognitive training intervention + supported employment, 12 weeks	Enhanced supported employment	6, 12	16; 16	Post-mTBI symptoms, Cognitive function, RTW, QoL
Vikane et al. 2017 (35) Norway	151	Median age: 32 (range: 16–55) Male: 61%	mTBI 6–8 weeks	Two outpatient rehabilitation clinics	Multidisciplinary programme, 4 weeks	Follow-up by a general practitioner	10	14; 20	Post-mTBI symptoms, Psychological function, Depression, Anxiety, AP, RTW

[a]This study generated two different publications. AP: activity and participation. C: control group; CBT: cognitive behavioural therapy; I: intervention group; mTBI: mild traumatic brain injury; PTSD: post-traumatic stress disorder; TBI: traumatic brain injury; TSI: time since injury; RTW: return to work, QoL: quality of life.

in some studies were missing outcome data and lack of information about the randomization process. The databases were also searched for non-randomized studies with control groups, but no study was identified that fulfilled the eligibility criteria.

Characteristics of included studies and organization into subgroups

The 9 RCTs comprised 864 patients with mTBI and prolonged post-mTBI symptoms, and were designed to investigate specialized brain injury rehabilitation interventions (i.e. interventions carried out by professionals specialized in brain injury rehabilitation) compared with a less specialized intervention (i.e. interventions performed in primary care or other units not specialized in brain injury rehabilitation). As there was heterogeneity across the studies, they were organized into the following 3 subgroups, based on the type of intervention and control group:

- Interventions based on cognitive behavioural therapy (CBT) or problem-solving treatment (PST), compared with usual care; 3 studies comprising a total of 430 persons (26–29).
- CBT compared with counselling; 2 studies comprising a total of 115 persons (30, 31).
- Interdisciplinary rehabilitation, involving at least 2 different professions, compared with usual care; 4 studies comprising a total of 319 persons (32–35).

Although there was some heterogeneity within these subgroups regarding the intervention, population (i.e. the severity degree within the mTBI spectrum varied), and setting (civilians or veterans), it was decided to combine the results within each subgroup, with the ambition to draw conclusions about the effects on a more general level. Data from the included studies are summarized in Table I and shown in more detail in Appendix SI[1].

Interventions based on cognitive behavioural therapy or problem-solving treatment

Three RCTs had assessed the effects of telephone-delivered PST (27, 29) or CBT as individual (26) or group therapy (28). The treatment was delivered by

psychologists, neuropsychologists, or psychiatrists, and the number of treatment sessions ranged from 6 to 12. The control interventions were described as usual care, including some education (26, 29), or being on a waiting list (28).

Effects of cognitive behavioural therapy or problem-solving treatment compared with usual care

The combined effects of CBT or PST compared with usual care are summarized in Table II and Fig. 2. The meta-analyses revealed statistically significant results favouring the intervention group regarding post-mTBI symptoms (MD –3.1; 95% CI –6.0 to –0.1 on Rivermead Post-concussion Questionnaire (RPQ), range 0–64), general psychological function (SMD –0.23; 95% CI –0.45 to –0.02), depression (SMD –0.29; 95% CI –0.50 to –0.08), and activity and participation (SMD –0.22; 95% CI –0.44 to –0.01).

Regarding quality of life, 2 studies reported statistically significant results (28, 29), but the result of the combined meta-analysis was not statistically significant (MD 8.4; 95% CI –0.4 to 17.2 on EQ-5D VAS, range 0–100) ($p = 0.06$). A non-significant result was also retrieved from the meta-analysis of anxiety, (MD –0.4; 95% CI –2.1 to 1.4). One study reported data on healthcare consumption, and no study in this subgroup reported data on cognitive function, return to work, life satisfaction, or mortality.

The certainty of the evidence was rated as "low"' (GRADE ++) regarding post-mTBI symptoms, psychological function, depression, activity and participation, and quality of life, with downgrading one level due to issues with risk of bias in the studies, where the inability to blind study participants was the most important (Table II). Downgrading was also performed based on imprecision, due to the relatively small study population in all the meta-analyses. Some issues regarding the domain inconsistency, indirectness, and publication bias were identified, but they were not considered serious enough to justify additional downgrading of the evidence level. Other results were further downgraded for imprecision, because of the limited number of study participants or because of the imprecise position of the confidence interval, resulting in "very low" (GRADE +ooo) certainty of evidence.

Cognitive behavioural therapy compared with counselling

Two RCTs had assessed the effects of a CBT intervention compared with a counselling intervention (30, 31). One of these studies compared individually given CBT with supportive counselling in trauma survivors with mTBI and acute stress disorder (30), and the other study compared CBT in small groups with telephone counselling in at-risk patients with mTBI and early complaints (31). In this subgroup, both the intervention and comparison groups had received 5 sessions each of an active treatment programme, but the CBT

Table II. Summary of findings regarding cognitive behavioural therapy (CBT) or problem-solving treatment (PST) compared with usual care

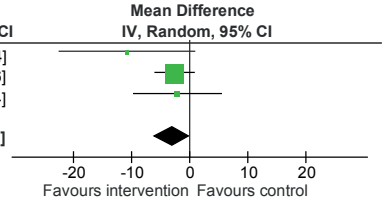
Outcome	No of participants (studies)	Effect (95% CI)	GRADE	Reasons for down-rating
Post-mTBI symptoms (RPQ)	373 (3)	MD –3.1 (–6.0 to –0.1)	Low ++oo	Risk of bias –1 Imprecision –1
Psychological function (IES-R, BSI-18 GSI)	349 (2)	SMD –0.23 (–0.45 to –0.02)	Low ++oo	Risk of bias –1 Imprecision –1
Anxiety (HADS-A)	69 (2)	MD –0.4 (–2.1 to 1.4)	Very low ++oo	Risk of bias –1 Imprecision –2
Depression (HADS-D, PHQ-9)	353 (3)	SMD –0.29 (–0.50 to -0.08)	Low ++oo	Risk of bias –1 Imprecision –1
Cognitive function	-	-	No studies	-
Activity and participation (SDS, Bicro-39, M2PI)	353 (3)	SMD –0.22 (–0.44 to –0.01)	Low ++oo	Risk of bias –1 Imprecision –1
Return to work	–	–	No studies	
Health care use	208 (1)	Healthcare use: RD –0.01 (–0.12 to 0.10); RR 0.98 (0.86 to 1.13) Acute visits: RD 0.10 (0.03 to 0.18); RR 4.9 (1.4 to 17.0) Psychological services: RD –0.06 (–0.20 to 0.07); RR 0.84 (0.59 to 1.20)	Very low +ooo	Risk of bias –1 Imprecision –2
Quality of life (EQ5D-VAS)	328 (2)	MD 8.4 (–0.4 to 17.2)	Low ++oo	Risk of bias –1 Imprecision –1
Life satisfaction	–	–	No studies	
Mortality	–	–	No studies	

BICRO-39: Brain Injury Community Rehabilitation Outcome scale; BSI-18: Behavioural -Symptoms Inventory-18 global score index; EQ5D-VAS: EuroQoL 5 dimensions visual analogue scale; HADS-A: Hospital Anxiety and Depression Scale, anxiety; HADS-D: Hospital Anxiety and Depression Scale, depression; IES-R: Impact of Event Scale Revised; M2PI: Mayo-Portland Adaptability Inventory-4 Participation Index; MD: mean difference; RD: relative difference; RPQ: Rivermead Post-concussion Questionnaire; RR: risk ratio; SDS: Sheehan Disability Scale; SMD: standardized mean difference; 95% CI: 95% confidence interval.

A. Post-concussion symptoms

Study	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Silverberg 2013 (26)	17.9	14.5	13	28.7	14.5	11	6.5%	-10.80 [-22.44, 0.84]
Bell 2017 (29)	22.8	15.3	138	25.4	14.4	166	78.0%	-2.60 [-5.96, 0.76]
Potter 2016 (28)	26	16.4	25	28.1	9	20	15.5%	-2.10 [-9.64, 5.44]
Total (95% CI)			**176**			**197**	**100.0%**	**-3.06 [-6.03, -0.09]**

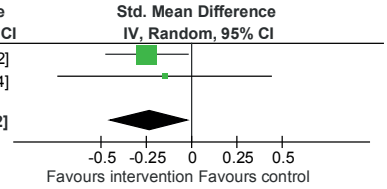
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)



B. Psychological function

Study	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bell 2017 (29)	54.5	12.5	138	57.4	11.1	166	87.1%	-0.25 [-0.47, -0.02]
Potter 2016 (28)	21.48	18.7	25	24.4	19.9	20	12.9%	-0.15 [-0.74, 0.44]
Total (95% CI)			**163**			**186**	**100.0%**	**-0.23 [-0.45, -0.02]**

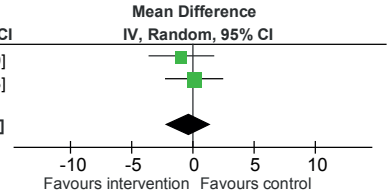
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)



C. Anxiety

Study	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Potter 2016 (28)	9.43	4.9	25	10.37	4.1	20	43.9%	-0.94 [-3.57, 1.69]
Silverberg 2013 (26)	8.5	2.9	13	8.4	2.9	11	56.1%	0.10 [-2.23, 2.43]
Total (95% CI)			**38**			**31**	**100.0%**	**-0.36 [-2.10, 1.39]**

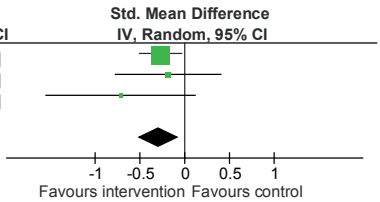
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)



D. Depression

Study	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bell 2017 (29)	7.6	6.2	126	9.2	5.7	158	80.7%	-0.27 [-0.50, -0.03]
Potter 2016 (28)	7.7	5	25	8.6	4.5	20	12.9%	-0.18 [-0.77, 0.40]
Silverberg 2013 (26)	5	3.1	13	7.3	3.1	11	6.4%	-0.72 [-1.55, 0.12]
Total (95% CI)			**164**			**189**	**100.0%**	**-0.29 [-0.50, -0.08]**

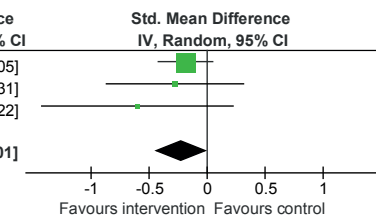
Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.66 (P = 0.008)



E. Activity and participation

Study	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bell 2017 (29)	8	7.6	126	9.4	7.4	158	80.7%	-0.19 [-0.42, 0.05]
Potter 2016 (28)	77.87	24.6	25	83.97	17.3	20	12.7%	-0.28 [-0.87, 0.31]
Silverberg 2013 (26)	6.29	5	13	9.4	5	11	6.5%	-0.60 [-1.42, 0.22]
Total (95% CI)			**164**			**189**	**100.0%**	**-0.22 [-0.44, -0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.09 (P = 0.04)



F. Quality of life

Study	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bell 2017 (29)	73.1	17	126	68.1	18.8	158	63.5%	5.00 [0.83, 9.17]
Potter 2016 (28)	69.93	16.3	24	55.59	18.4	20	36.5%	14.34 [3.97, 24.71]
Total (95% CI)			**150**			**178**	**100.0%**	**8.41 [-0.40, 17.23]**

Heterogeneity: Tau² = 27.35; Chi² = 2.68, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 1.87 (P = 0.06)

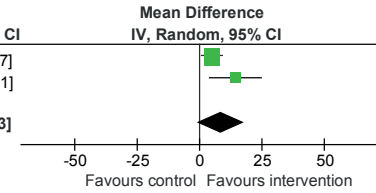


Fig. 2. Meta-analyses of the effects of cognitive behavioural therapy (CBT) or problem-solving therapy (PST) compared with usual care. All outcomes were assessed at 3–6 months after study inclusion. (A) Post-mild traumatic brain injury (mTBI) symptoms (Rivermead Post-concussion Symptoms Questionnaire). (B) Psychological function (Impact of Event Scale revised and Behavioural Symptoms Inventory-18 Global Score Index). (C) Anxiety (Hospital Anxiety and Depression Scale; anxiety subscale). (D) Depression (Hospital Anxiety and Depression Scale; depression subscale and PHQ-9). (E) Activity and participation (Sheehan Disability Scale, Brain Injury Community Rehabilitation Outcome scale 39 and Mayo-Portland Adaptability Inventory-4 Participation Index). (F) Quality of life (EuroQoL 5 dimensions visual analogue scale). SD: standard deviation; 95% CI: 95% confidence interval.

Table III. Summary of findings regarding cognitive behavioural therapy (CBT) compared with counselling

Outcome	Number of participants (studies)	Effect (95% CI)	GRADE	Reasons for down-rating
Post-mTBI symptoms (HISC)	70 (1)	MD 1.8 (0.4 to 3.2)	Very low +ooo	Risk of bias –1 Imprecision –2
Psychological function (IES)	24 (1)	MD –8.92 (–16.73 to –1.11)	Very low +ooo	Risk of bias –1 Imprecision –2
Anxiety (HADS-A, Beck-A)	94 (2)	No meta-analysis[a]	Very low +ooo	Risk of bias –1 Imprecision –1 Inconsistency –1
Depression (HADS-D, Beck-D)	94 (2)	No meta-analysis[a]	Very low +ooo	Risk of bias –1 Imprecision –1 Inconsistency –1
Cognitive function	–	–	No studies	
Activity and participation (GOSE)	91 (1)	RD –0.04 (–0.24 to 0.15) RR 0.88 (0.49 to 1.56)	Very low +ooo	Risk of bias –1 Imprecision –2
Return to work	91 (1)	No data[b]	Very low +ooo	Imprecision –3
Healthcare use	–	–	No studies	
Quality of life (EQ5D-VAS)	–	–	No studies	
Life satisfaction	–	–	No studies	
Mortality	–	–	No studies	

[a]Data incompletely reported in one study.
[b]Data illustrated in figure only.
BECK-D: Beck Depression Inventory; GOSE: Glasgow Outcome Scale Extended HADS-D: Hospital Anxiety and Depression Scale, depression; HISC: Head Injury Symptom Checklist; IES: Impact of Event scale; MD: mean difference; RD: relative difference; RR: risk ratio; HADS-A: Hospital Anxiety and Depression Scale, anxiety; 95% CI: 95% confidence interval.

was regarded as more specialized, based on the content description of the interventions in the studies.

Effects of cognitive behavioural therapy compared with counselling

The effects of CBT compared with counselling are summarized in Table III. It was not possible to combine the results of the meta-analyses for any outcome measure, as data were reported in only one study or, in some cases, reported insufficiently. The certainty of the evidence was rated as "very low" (GRADE +ooo) for all outcomes, due to issues with risk of bias in the studies (lack of blinding), and imprecision (too few study participants and, in some cases, non-significant results).

Interdisciplinary rehabilitation compared with usual care

Four RCTs had assessed the effects of an interdisciplinary rehabilitation programme in comparison with usual care, or care at a level that was distinctively less specialized. The interventions were described as: individual CBT plus cognitive remediation compared with a waiting list (33); Cognitive Symptom Management and Rehabilitation Therapy (CogSMART) plus supported employment compared with usual care plus enhanced supported employment (34); multidisciplinary outpatient rehabilitation compared with follow-up by a general practitioner (35); and specialized, interdisciplinary rehabilitation compared with usual treatment (32). The length of the programmes ranged from 4 to 22 weeks, and the treatment was conducted by at least 2 different professions in all 4 RCTs.

Effects of interdisciplinary rehabilitation compared with usual care

The combined effects of interdisciplinary rehabilitation compared with usual care are summarized in Table IV and Fig. 3. The meta-analysis regarding post-mTBI symptoms revealed a statistically significant result favouring the intervention group (MD –5.0; 95% CI –8.3 to –1.6 on RPQ, range 0–64) no other results were significant. In some cases, meta-analyses could not be undertaken because data were reported in different formats. The certainty of the evidence was rated as "low" (GRADE ++oo) regarding post-mTBI symptoms, where downgrading was performed for issues with risk of bias (lack of blinding) and imprecision (too few study participants). The certainty of evidence regarding all other outcomes was rated as "very low" due to additional problems with imprecision (too few study participants and non-significant results) and, in some cases, inconsistency (large differences in effect sizes between studies).

Regarding cognitive function, the weighing was performed narratively because data were incompletely reported in one of the studies. One study reported data for an attention-demanding test 3 months after inclusion, with a statistically significant difference between groups (33). The second study evaluated cognitive function with several instruments, and reported varying results; the test of memory function was judged

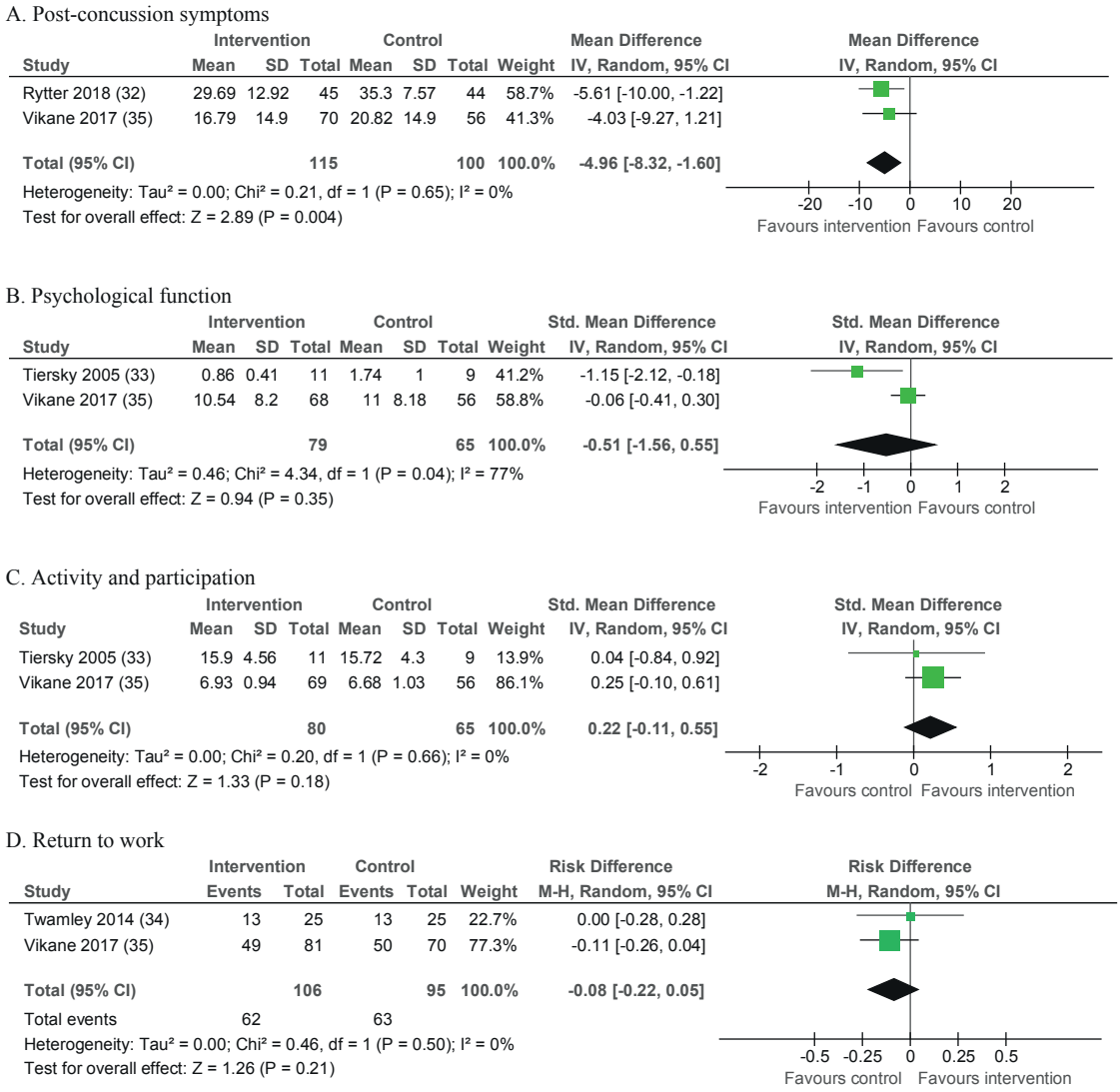


Fig. 3. Meta-analyses of the effects of interdisciplinary rehabilitation compared with usual care. (A) Post-mild traumatic brain injury (mTBI) symptoms, (Rivermead Post-concussion Symptoms Questionnaire) assessed at 10–12 months after study inclusion. (B) Psychological function (Symptom Checklist-90 revised and Hospital Anxiety and Depression Scale; total score) assessed at 3–12 months after study inclusion. (C) Activity and participation (Community integration questionnaire and Glasgow Outcome Scale Extended), assessed at 3–12 months after inclusion. (D) Return to work, assessed at 10–12 months after study inclusion. SD: standard deviation; 95% CI: 95% confidence interval.

to represent the outcome measure best, but with a non-significant effect (34). Therefore, certainty was judged to be very low due to imprecision and inconsistency and it was not possible to assess the effect of interdisciplinary rehabilitation on cognitive functions.

DISCUSSION

This systematic review and meta-analysis synthesized the evidence for the effectiveness of specialized rehabilitation in adults with mTBI, with or at risk of developing prolonged symptoms. The results indicate that there may be positive effects of specialized interventions for people with mTBI with prolonged symptoms, such as CBT or PST, and from team-based interdisciplinary rehabilitation, compared with usual care. For specialized brain injury-oriented rehabilitation consisting of CBT or telephone-based problem solving, there were positive effects on post-mTBI symptoms, general psychological function, depression, activity and participation, and quality of life.

These outcome measures are important for the individuals' health and ability to function in daily life, but there is uncertainty as to whether the estimated effect size corresponds to important clinical differences. Unfortunately, it was not possible to assess the effects on ability to return to work or other employment, as few studies reported this outcome measure as well as for

Table IV. Summary of findings regarding interdisciplinary rehabilitation compared with usual care

Outcome	Number of participants (studies)	Effect (95% CI)	GRADE	Reasons for down-rating
Post-mTBI symptoms (RPQ)	265 (3)	MD −5.0 (−8.3 to −1.6)[a]	Low ++oo	Risk of bias −1 Imprecision −1
Psychological function (SCL-90R, HADS-total)	144 (2)	SMD −0.51 (−1.56 to 0.55)	Very low +ooo	
Anxiety (SCL-90R-A, HADS-A)	163 (2)	No meta-analysis[b]	Very low +ooo	Risk of bias −1 Imprecision −1 Inconsistency −1
Depression (MDI, SCL-90R-D, HADS-D)	252 (3)	No meta-analysis[b]	Very low +ooo	Risk of bias −1 Imprecision −1 Inconsistency −1
Cognitive function (PASAT, CVLT-II)	70 (2)	No meta-analysis[b]	Very low +ooo	Imprecision -3
Activity and participation (CIQ, GOSE)	145 (2)	SMD 0.22 (−0.11 to 0.55)	Very low +ooo	Risk of bias −1 Imprecision −2
Return to work	201 (2)	RD −0.08 (−0.22 to 0.05) RR 0.87 (0.70 to 1.07)	Very low +ooo	Risk of bias −1 Imprecision −1 Inconsistency −1
Healthcare use	–	–	No studies	
Quality of life (QOLI-brief)	50 (1)	SMD −0.19	Very low +ooo	Risk of bias −1 Imprecision −2
Life satisfaction	–	–	No studies	
Mortality	–	–	No studies	

[a]Only 2 studies reported data that could be included in the meta-analysis, but data from the third study supported the result. [b]Data incompletely reported in one study. CVLT-II: California Verbal Learning Test-II; GOSE: Glasgow Outcome Scale Extended; HADS-A: Hospital Anxiety and Depression Scale, anxiety; HADS-D: Hospital Anxiety and Depression Scale, depression; IES-R: Impact of Event Scale revisited; MD: mean difference; MDI: Major Depression Inventory; PASAT: Paced Auditory Serial Addition Task; RCT: randomized controlled trial; RD: relative difference; RR: risk ratio; RPQ: Rivermead Post-concussion Questionnaire; QOLI-brief: The Lehman Quality of Life Interview-Brief; SCL-90R: Symptom Checklist-90 revised; SMD: standardized mean difference; Beck Depression Inventory; 95% CI: 95% confidence interval.

the outcome measure for mortality. As the mortality rate is very low in mTBI, this outcome measure was not expected to be present in many studies, but as the incidences of both depression and emotional sequelae are relatively high (36), we did not want to overlook an increased risk of suicide among those who did not receive psychological treatment.

For interdisciplinary brain injury rehabilitation programmes conducted by at least 2 professions, potentially positive effects were found related to prolonged post-mTBI symptoms. For other outcome measures in this subgroup the certainty of evidence was very low. Two studies reported results for cognitive function, but the results were not consistent. Interdisciplinary rehabilitation is more extensive and, most often, more expensive compared with the individual forms of rehabilitation; this emphasizes the importance of also evaluating rehabilitation in health economic studies.

The control group in the studies of these 2 subgroups received "usual care", which most often did not involve any active intervention except for some general information. The participants in the control groups also had the opportunity to seek help from their regular healthcare providers, usually through primary care. Thus, the control groups' conditions are fairly similar to the conditions that apply to many persons with mTBI with prolonged symptoms in the Nordic countries today.

Several factors contributed to the lack of evidence for many outcome measures. Even though most studies used validated instruments, there was a large variation in the outcome measures reported, resulting in challenges to make a synthesis of the results. For self-rated post-mTBI symptoms, most studies used the Rivermead Post-concussion Questionnaire (RPQ) (37) and therefore, an effect measure could be calculated on this scale. Other outcomes were reported on various instruments and could be combined through calculating SMD when they measured the same construct. However, it was not always considered appropriate to combine outcomes reported on different instruments in meta-analyses because of variations in psychometric properties.

There was a considerable variation in the study populations' time from injury to treatment start. In some studies, treatment occurred relatively early after the mTBI, whereas in others it started up to several years post-injury. It cannot be ruled out that the time from injury can influence the outcome of the treatment, but as for post-mTBI symptoms, both interdisciplinary rehabilitation and CBT seemed to have an effect, regardless of whether it was performed early (26, 35) or late post-TBI (28, 32). In addition, CBT appeared to reduce depression in both early (26) and late (28) stages.

The definition of mTBI also differed between studies. In some studies, it was not clear how the severity of TBI was defined, and the difference between mild and moderate TBI was not always clear. In recent years, there has been an increasing emphasis on the need for improved characterization of the patients (1). However, the true nature of the study population remains unclear.

The settings and regional differences also varied between studies. Thus, intervention research following TBI could be improved by having a higher degree of

rigour and coherence in the choice of methods and definitions (12).

Despite the heterogeneity in the various domains, it was decided to combine results from studies that this study assessed to be fairly comparable in terms of population, intervention, and other variables. Using a meta-analysis approach, it was inevitable that a certain degree of heterogeneity was accepted, regarding, for example, the intensity and content of the interventions, time after injury, and the follow-up time of the study.

One of the major limitations of the included studies was that study participants and staff were not blinded to group affiliation. Blinding is difficult in studies of rehabilitation interventions, for both practical and ethical reasons, with an inevitable risk of bias of the results. In several of the randomized studies, the individuals who evaluated the results had been blinded to the participants' group affiliation, which counteracts the risk of subjective judgment. However, the risk remains that the study participants' outcome may have been influenced by the knowledge of group affiliation, so-called expectancy effects. In addition, many outcome measures had been evaluated with self-reported questionnaires or interviews, which meant that the risk of subjective judgment could not be avoided.

Concerning expectancy effects derived from the study participants' knowledge that they were divided into intervention and control groups; it is likely that this risk was significant as the control group often received "usual care". In many cases this consisted of no or only little effort. Thus, study participants in both the intervention and control groups were probably aware that they received an intervention that was more or less extensive compared with the other group.

The lack of blinding also comprises a risk that people in the control group feel disadvantaged and so, to a greater extent than the intervention group, seek other care or alternative methods. In some of the in-depth studies, the use of interventions have been carefully described and quantified (32, 35), whereas such data are lacking in other studies. A person who receives a more comprehensive multidisciplinary rehabilitation effort is probably less likely to seek other care compared with a person who is only offered a single care contact or information material. This could contribute to insignificant results between the intervention and control group.

Confidence in the results is also affected by the size of the total study population. The heterogeneity of the studies meant that they were divided into smaller groups, which resulted in only a few studies per group. As the studies did not report all outcome measures, the weightings were often even smaller. For all results, downgrading according to GRADE was therefore made for imprecision regarding the number of studies and/or study size.

In some cases, the downgrading for imprecision also applied to the lack of statistical significance of the result. As the purpose was to assess whether there was a difference in effect between the intervention and control groups, a non-significant result usually resulted in very low certainty. In some cases, downgrading for inconsistency was also made because the results from the individual studies showed large differences.

The fact that different studies arrived at different results can be explained by larger or smaller variations in intervention, intensity or extent of the treatment, context or choice of outcome measures. It may also be explained by the fact that the comparison interventions varied, or that the comparison group has, in some studies, sought alternative treatment methods that affected the outcome and thereby reduced the difference in effect between the intervention and control groups.

No downgrading was made for the risk of publication bias. The assessment considered that there are probably no strong commercial incentives or other reasons for refraining from publishing studies with undesirable results in this area. However, the risk of publication bias cannot be completely ruled out and could not be evaluated using funnel plots as the number of studies included in the meta-analysis was small.

In summary, the low level of evidence that emerged in this systematic review can largely be explained by the fact that few studies are evaluating the same interventions with the same outcome measures. The difficulties of blinding study participants and therapists in rehabilitation studies also contribute to the low evidence, which is a general problem when doing this type of evaluations for rehabilitation research.

Given the high number of people with prolonged symptoms or disabilities after mTBI, it is important to offer some clinical guidelines. As both interdisciplinary rehabilitation, PST and CBT may have an effect on subjective symptoms post-mTBI, those who have acquired mTBI and experience, or are at risk of, prolonged symptoms should be given the opportunity to see a specialist team. After our literature search, a study by Caplain et al. was published that also confirmed the beneficial effects of early multidimensional management (psychoeducation and cognitive rehabilitation) for those at risk of development of prolonged symptom (38).

Since CBT also seems to increase the individual's psychological wellbeing and possibilities to engage in an active life, it is possible that this treatment would be rather cost-effective. However, its value from a health economic perspective has not been clarified and needs further study (19).

Future research

There is a need for improved treatment (6) and further research in this area.

- As the mTBI groups are not homogeneous and require differentiated treatments, individualized treatments need to be evaluated.
- Studies with a larger age range are needed. In the current literature review, no study focused on elderly people (over 65 years of age) with TBI, which is particularly important, as older people have a higher incidence of TBI and a higher risk of residual symptoms (1).
- In terms of outcome measures, these need to be sensitive and with good psychometric properties focusing on aspects influenced by mTBI (39). Many of the neuropsychological tests in the TBI Common Data Elements are not sensitive enough to capture subtle changes after mTBI.
- It is important to develop consensus regarding evaluation tools and outcome measures (for example, so-called core outcome sets) to facilitate comparisons. In future research, one also needs to be careful to take into account the variability in this population and study subgroups, and allow different treatments and different instruments for different subgroups in order to capture the heterogeneity of these patients (1). This requires a large population and well-designed multicentre studies.
- Further research is needed, at an early stage, to be able to identify those with an increased risk of long-term symptoms and solid health economic studies are required to evaluate the cost-effectiveness of their treatment.
- It is also necessary to ensure that the treatment intensity or duration of treatment is sufficient to allow for a lasting effect.
- There is a need for studies with a longer follow-up time and with repeated measurements and evaluations over several years.

Conclusion

Persons with mTBI who are at risk of, or who experience, prolonged symptoms should be considered for specialist treatment, as they may receive positive effects of CBT, PST, or interdisciplinary team rehabilitation. Further research is required to strengthen the certainty of evidence.

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