Master Thesis:

The involvement of the cervical spine in post-traumatic headache: Mechanisms and management - a systematic review.

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Abstract

Title: The involvement of the cervical spine in post-traumatic headache: Mechanisms and management - a systematic review.

Background: Post-traumatic headache (PTH) is one of the most common secondary headaches, however the evidence for underlying mechanisms and effective management is limited. The cervical spine may be an important part of the pathophysiology and appears to be associated with both acute and persistent PTH. This thesis reviews relevant literature, discuss the rationale of cervical related PTH, with a special focus on management, and finally propose a research protocol.

Study design: Systematic review and a research protocol.

Method: A systematic literature search in MEDLINE/Pub Med, Google Scholar, PEDro, and American Journal of Sport Science was performed. PRISMA was used to structure the search, and JBI to critically appraise each of the articles.

Results: Of the initial 459 articles, 16 articles were identified and included. PTH was associated with cervical pain, stiffness and reduced neuromuscular control, especially in the acute phase. Persistent PTH was associated with previous stress, pain comorbidities and history of headache, mTBI and whiplash injury. Patients with PTH seem to benefit from cervical manual therapy and rehabilitation, although the quality of studies were too weak to make a clear assessment.

Conclusion: The research so far indicates the cervical spine to be involved in acute and persistent PTH. A tailored biopsychosocial approach could be recommended, incorporating reassurance and pain education, manual therapy, and rehabilitation. More research is needed on the pathophysiology and management of PTH in general and the involvement of the cervical spine specifically.

Introduction

Post-traumatic headache (PTH) is one of the most common secondary headache disorders, and accounts for 4% of all symptomatic headaches. PTH can result from both trauma to the head and neck (1). It is the most frequent symptom after concussion (2). After whiplash, neck pain is more prevalent within 7 days of injury (neck pain 84%, headache 60%), but after 12 months, patients report an equal frequency of both headache and neck pain (38%) (3).

The pathophysiology of PTH is not fully understood, and the guidelines consist of treatment recommendations based on sparse scientific evidence. No evidence-based specific treatment for PTH patients exist (4). However, like with other complex pain disorders, a multidisciplinary biopsychosocial approach may be effective in the management of PTH (5, 6).

Impaired central neuromodulation and activation of trigeminal and cervical afferents have been proposed to be parts of the underlying mechanisms behind PTH (4). If this is the case, both the cervical spine and brainstem may be highly relevant in PTH management.

Although whiplash represents the most obvious involvement of the cervical spine, a direct blow to the head may also impact the neck. Both concussion and whiplash results from acceleration/deceleration with energy transferred through the brain and cervical tissues closely related anatomically (7, 8). The symptomatology in concussion and whiplash also has many similarities, including headache, and concussion experts believes the neck to be one of several sources of symptoms (7, 9, 10). The similar symptoms and possible bi-directional involvement of the cervical spine and brain makes it challenging to distinguish the causative mechanisms in many cases (7). The current evidence for the possible connection between the cervical spine and PTH, however, is inadequate.

The overlap of symptoms and limited knowledge of PTH management and mechanisms, forms the background for this thesis. The main objective is to investigate the role of the cervical spine in PTH. A particular focus will be on the non-pharmacologic management options that can have a direct or indirect influence on the cervical spine to relieve PTH. A systematic review will investigate the current evidence for the effect of manual therapy, rehabilitation and strengthening of the cervical spine in reducing PTH symptoms. Articles investigating PTH management in both acute concussion, post-concussion syndrome and

whiplash will be included. Examination findings, prevention, and prognostic factors will also be reviewed.

The thesis contains four parts. The first three consists of method, results, and discussion. Lastly, the thesis will propose a research project that will attempt to investigate the effect of cervical spine management on PTH.

Method

The diagnostic criteria of post-traumatic headache (also called headache attributed to trauma or injury) includes both trauma to the head and neck according to the ICHD-3 (Table 1 and 2). Hence, the articles in this systematic review included research on both areas.

Search strategy

Secondary data was collected through MEDLINE/Pub Med, Google Scholar, PEDro, and American Journal of Sport Science, using the search terms “post-traumatic headache”, “post-concussion syndrome”, “post-commotio syndrome”, “concussion”, “neck”, “cervical”, “whiplash”, “treatment”, “management”, “non-pharmacologic”, “manual therapy”, “mobilization”, “exercise” and “rehabilitation” in both title and text. Some of the terms were combined using “AND”.

Inclusion and exclusion criteria

Literature on PTH covering both cervical dysfunction after a direct head impact, and whiplash without head impact, were included. Some articles focused mostly on persistent concussion symptoms (post-concussion syndrome / disorder (PCD)), where headache is the most common (Table 3). Although it was of interest to review literature on pharmacological interventions, the focus was on the non-pharmacological management of PTH for the purpose of limiting the scope and treatment effect to the cervical spine.

The term “non-pharmacologic” treatment includes every treatment without medication. However, surgical, and invasive treatment were in this review excluded, and treatment typically delivered by physiotherapists and chiropractors (i.e., education, exercise, reassurance, massage, manual therapy, manipulation, mobilization, dry needling, and acupuncture) were included.

Type of publications included were randomized controlled trials, clinical trials, meta-analysis, multicentre studies, and observational studies, while systematic reviews, guidelines and editorials were excluded. The search was limited from 1990 to present date and language was in English.

Table 1: Definition of acute and persistent headache attributed to traumatic injury to the head (ICHD-3) (1).

Acute headache attributed to traumatic injury to the head	**Persistent headache attributed to traumatic injury to the head**
A. Any headache fulfilling criteria C and D B. Traumatic injury to the head[1] has occurred C. Headache is reported to have developed within 7 days after one of the following: 1. the injury to the head 2. regaining of consciousness following the injury to the head 3. discontinuation of medication(s) impairing ability to sense or report headache following the injury to the head D. Either of the following: 1. headache has resolved within 3 months after its onset 2. headache has not yet resolved but 3 months have not yet passed since its onset E. Not better accounted for by another ICHD-3 diagnosis.	A. Any headache fulfilling criteria C and D B. Traumatic injury to the head[1] has occurred C. Headache is reported to have developed within 7 days after one of the following: 1. the injury to the head 2. regaining of consciousness following the injury to the head 3. discontinuation of medication(s) impairing ability to sense or report headache following the injury to the head D. Headache persists for >3 months after its onset E. Not better accounted for by another ICHD-3 diagnosis[2].

Table 2: Definition of acute and persistent headache attributed to whiplash (ICHD-3) (1).

Acute headache attributed to whiplash	**Persistent headache attributed to whiplash**
A. Any headache fulfilling criteria C and D B. Whiplash[1], associated at the time with neck pain and/or headache, has occurred C. Headache has developed within 7 days after the whiplash D. Either of the following: 1. headache has resolved within 3 months after its onset 2. headache has not yet resolved but 3 months have not yet passed since its onset E. Not better accounted for by another ICHD-3 diagnosis.	A. Any headache fulfilling criteria C and D B. Whiplash[1], associated at the time with neck pain and/or headache, has occurred C. Headache developed within 7 days after the whiplash D. Headache persists for >3 months after its onset E. Not better accounted for by another ICHD-3 diagnosis[2].

Table 3: Definitions of persistent concussion symptoms (post-concussion disorder) from ICD-10 and DSM-IV (11).

ICD-10 (International Classification of Diseases 10th edition)	**DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition)**
At least 3 of the following, 4-weeks after injury •Headache •Dizziness •Fatigue •Irritability •Sleep problems •Concentration difficulties •Memory problems •Problems tolerating stress/emotion/alcohol	At least 3 of the following, 3 months after injury Also, person must experience social problems because of it •Headache •Dizziness •Fatigue •Irritability •Sleep Problems •Affect changes, anxiety, or depression •Changes in personality •Apathy

Methods of analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to organize and structure the flow of the search and results. This is presented in diagram 1.

The final articles are analysed using the PICO standard (Population, Intervention, Comparison, Outcome), and included in the extraction forms in the result section (Tables 4, 5, 8, 9 and 10).

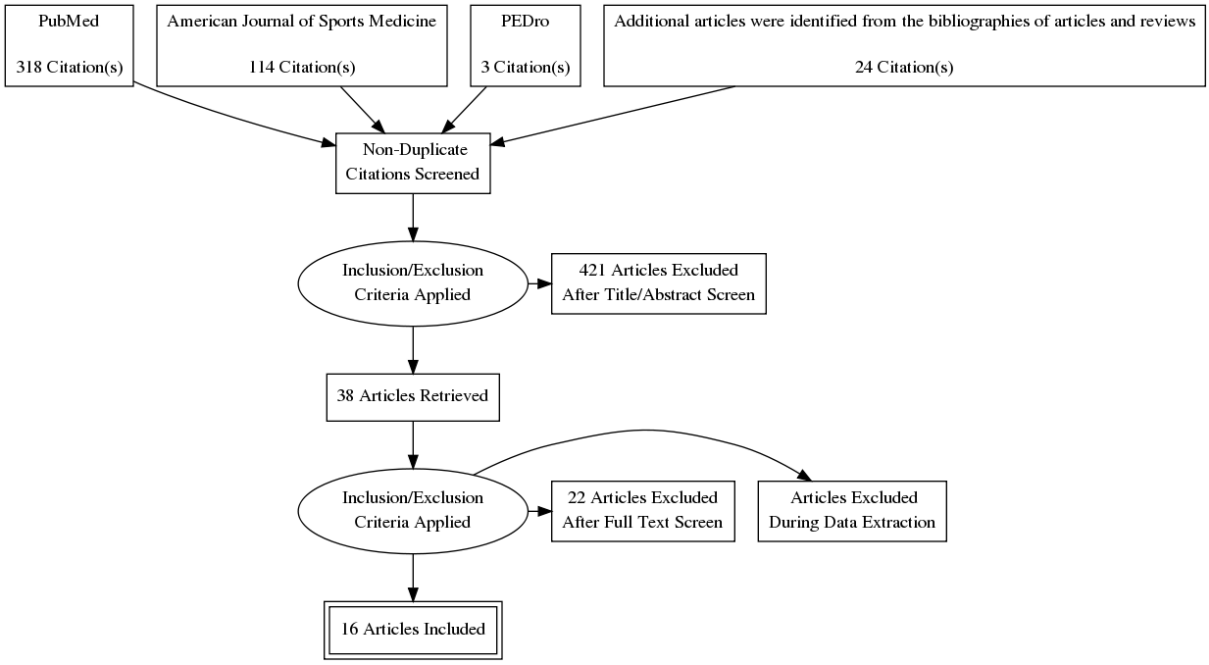
The JBI (Joanna Briggs Institute) Critical Appraisal tool were used to evaluate bias and method quality for each article.

Results

The search resulted in 318 articles from PubMed, 114 from American Journal of Sports Medicine and 3 from PEDro. 21 articles were identified from the bibliographies of reviews and articles.

After reading abstracts of the 459 articles, and applying the inclusion and exclusion criteria, 38 articles were left. These articles were read in full text. The exclusion criteria and 22 articles with lacking relevance finally resulted in 16 included articles. (See diagram 1, PRISMA).

Diagram 1: PRISMA flow chart of the inclusion and exclusion process.



Only 5 studies focused on management through manual therapy or rehabilitation. However, to investigate the association between the cervical spine and post-traumatic headache as thoroughly as possible, it was useful to also include articles describing the correlation through examination procedures, possible prevention strategies and prognostic factors as well. Hence, the results are divided into the following subheadings: Examination, manual therapy, rehabilitation, prevention, and prognosis.

Examination

In a controlled trial, Jensen et al (12) examined 38 people with and without post-traumatic headache with X-ray. Their outcome measurement was reduced segmental motion in PTH patients and relationship between severity of headache and cervical motion. Corrected for age, hypomobility of C1-2 and C5-6 had the most significant correlation to PTH (P <0,05). The hypomobile segment that correlated significantly with associated symptoms was only C5-6 (Spearman's analysis of correlation: r = -0.70, P< 0.01).

Treleaven et al (13) investigated 12 patients with post-concussion headache (PCH), measuring movement, strength, endurance, and tenderness to palpation in the cervical spine. In the PCH group, they found segmental symptomatic joint restriction in C0-1, C1-2, C2-3, and C3-4,

which was absent in the age and gender matched controls. Endurance of deep neck flexors was significantly reduced in the PCH-group compared to the control (P =0.02).

Leddy et al (14) studied if there was a difference in symptoms between 128 patients with a physiological post-concussion disorder (PCD) and a cervicogenic and vestibular PCD (CVG-group). The groups were distinguished using a treadmill test and cervical and vestibular examination. Symptoms were described through a self-reported 22 Post-Concussion Symptom Scale (PCSS). This retrospective review focused more on the general symptoms from a concussion, not solely on headache. No statistically significant difference was found, although there were some differences in headache (P =0.0119, less in CVG group) and sleep (P = 0.0422, more in CVG group).

Drottning and Sjaastad (15) performed a prospective cohort study to search for cervicogenic headache after whiplash injury. 222 headache patients with whiplash were followed for 1 year. They were examined and interviewed at 6 weeks, 6 months and 1 year, and received a questionnaire after 12 months. New cervicogenic headache was present in 8.2% at 6 weeks after injury and declined to 4.4% after 6 months and 3.4% after 1 year. The cohort was compared to a group with previous history of headache, termed as a chronic cervicogenic headache. The chronic group reported higher intensity of headache and neck pain initially- After 1 year, there was also a significant difference to the cohort, with more dominant symptoms of headache, neck pain, neck stiffness and dizziness. The authors described a triad as part of the acute whiplash, with neck pain, neck stiffness and headache. The symptoms, including headache, declined as the neck function improved in the cohort.

In a prospective observational study, Kasch et al (15) compared 141 patients with acute whiplash to 40 patients with acute ankle distortion. One of their aims was to examine the correlation of neck motion with neck pain and headache during the first 6 months post injury. They examined and interviewed both groups at 1 week, and 1, 3 and 6 months after injury. In both groups, neck mobility, neck pain and headache were investigated. The cohort group displayed a significant reduced neck mobility right after the injury but was like the control after 3 months. The result indicate that whiplash does not cause long term reduced neck mobility. Headache and neck pain was inversely related to neck mobility, suggesting that there is a neuroplastic change causing the headache more than the cervical function.

Table 4: Extraction form with articles concerning Examination.

Reference	Study design	Population	Intervention	Comparison	Outcome measurement	Results and conclusions
Drottning et al, 2002 (15)	Prospective cohort study	587 whiplash patients.	Cervical examination and headache and neck questionnaire of 222 patients with new cervicogenic headache Women=49% Men=51%	Patients with chronic cervicogenic headache. N=22 Women: Not found. Men: Not found.	Cervicogenic headache pain intensity and neck range of motion	8% with new CEH at 6 weeks and 3% after 1 year. 65% of chronic CEH, and 41% of cohort had reduced neck ROM. At 1 year, chronic CEH patients had more symptoms than the cohort.
Jensen et al, 1990 (12)	Controlled trial	38 people with and without PTH.	Reduced cervical extension/ flexion in PTH patients on X-ray. N=19. Women=12. Men=7.	Cervical extension/ flexion motion on X-ray in healthy controls. N=19. Women=12. Men=7.	Reduced segmental motion in PTH patients and relationship between severity of headache and neck motion.	Reduced motion in C5-6 and C6-7 was connected to the headache.
Kasch et al, 2001 (15)	Prospective observational study	141 patients with acute whiplash and 40 patients with acute ankle distortion.	Assessment of neck motion, neck pain and headache after 1 wk, 1, 3, and 6 months after injury. N= 40 to match control. Women=21 Men=19	Examination and interview of patients with ankle distortion. N=40. Women=21. Men=19	Pain in the head, neck, shoulder, arm, or low back.	Cervical pain and cervical movement were found to be related inversely to reported headache and cervical mobility.
Leddy et al, 2015 (14)	Retrospective review of symptom reports	128 patients with brain injury and provo- cative treadmill test.	Abnormal cervicogenic/ vestibular physical examination (CVG-group). N=92. Women=43. Men: =49.	Abnormal treadmill exercise test (PCS-group). N=36. Women=16. Men=20.	Self-reported 22-symptom Post-Concussion Symptom scale (PCSS) to distinguish physiologic post-concussion disorder from cervicogenic/vestibular PCD.	No statistically significant difference. However, some difference in headache (less in CVG group) and sleep (more in CVG group).
Treleaven et al, 1994 (13)	Case controlled study	12 patients with post-concussional headache.	Physical examination. N=12. Women=4. Men=8.	Age and gender matched control group. N=12. Women=4. Men=8.	Objective findings in movement, strength, endurance, and palpation.	Symptomatic segmental joint restriction in the PCH group, absent in control group.

Manual therapy

In a prospective clinical controlled trial, Jensen et al (9) compared manual therapy of the cervical spine with cold packs in 23 patients with PTH. The manual therapy consisted of manipulation and mobilization of the cervical and upper thoracic spine, and muscle energy techniques. 4 treatments were spread out over 5 weeks. The cold pack was placed under the neck and shoulders for 15-20 minutes, over 2 treatments. After 5 weeks, the headache severity (VAS-scale) was 43% of the pre-treatment level in the manual therapy group, and a statistically significant difference compared to the cold-pack group (P <0.05). There was no information regarding previous headache history, which is an important risk factor in PTH-patients and may affect the symptom reports. There was also limited information regarding treatment and data.

In a retrospective chart review, Kennedy et al (17) investigated the clinical characteristics and treatment of the cervical spine in patients with persistent post-concussion symptoms. Of the 46 patients, 45 had headache. After physical examination, the patients were divided into groups with or without a cervicogenic component. 21 received treatment, consisting of manual therapy, stability exercises, acupuncture alone or in combination. The treatment group had a 93.5% increase in mean patient specific functional scale (PSFS) and 96.6% reduction in mean numeric pain rating scale (NPRS). The change in PSFS and NPRS was not specifically mentioned for headache but ranged from 55-100 on PSFS and 60-100 on NPRS.

Kennedy et al (18) also looked at how the neck contributes to persistent post-concussion symptoms in a prospective case series. There was a total of 20 patients who all had headache. After a physical examination, neck treatment was given as indicated in 90% of the patients. They found pain, tenderness, and restricted movement in the upper cervical segments. The treatment consisted of manual therapy, soft-tissue techniques, and specific exercises. Some patients also received vestibular-ocular treatment and occupational therapy. There was a reduction in headache frequency, duration and severity after cervical treatment illustrated in a graph, but with no specific numbers.

Table 5: Extraction form with articles concerning Manual therapy.

Reference	Study design	Population	Intervention	Comparison	Outcome measurement	Results and conclusions
Jensen et al, 1990 (9)	Prospective clinical controlled trial	23 patients with post-traumatic headache.	Physical examination and manual therapy. 23 entered and 19 completed. Women=12. Men=7	Cold pack on the neck. W/M not found, but gender matched cohort.	Reduction of headache on visual analogue scale 0-10, reduction of analgesics and reduction of associated symptoms.	43% of headache severity compared to pre-treatment level / 57% reduction at week 5. Statistically significant difference VS cold pack group ($p<0.05$).
Kennedy et al, 2017 (17)	Retro-spective chart review	46 patients with concussion.	Physical examination and physiotherapy on concussion patients **with** cervicogenic component. N= 46. Men=21. Women=25.	Concussion patients **without** a cervicogenic component. N= 46. Men= 21. Women= 25.	Patient specific functional scale (PSFS) and numeric pain rating scale (NPRS).	21 received treatment: PSFS 93.5% increase, NPRS 96.6% decrease. Also: Objective neck pain or stiffness, without subjective neck symptoms, also improved.
Kennedy et al, 2019 (18)	Prospective case series	20 patients with persistent post-concussion symptoms. They all had headache.	Physical examination to evaluate neck injury and neck involvement for the PCS. Neck treatment as indicated. Men=7. Women=13.	No comparison.	Headache frequency, duration, and severity (0-10).	Pain, tenderness, and restricted movement in the upper cervical segments. Reduction in headache frequency, duration, and severity from neck treatment.

Rehabilitation

Ludvigsson et al (19) investigated the effect of neck specific exercises on headache in patients with chronic whiplash associated disorders grade 2 and 3 (see tables 6 and 7). They randomized 188 people into 2 intervention groups and one control group. The first group received neck specific exercises, consisting of deep neck flexor activation, gym exercises and progressive head resistance training. The second group received the same program as the NSE group, in addition to a behavioural approach (NSEB), focusing on positive outcome, pain management and problem solving. The third group was the control that received physical activity prescription (PAP) without specific neck exercises. Outcome measurements were current headache, maximum headache in the preceding week and headache bothersomeness in the last 24 hours on a VAS scale. There was a better outcome for NSEB group compared to the PAP group on all outcome measures (P <0.01, P <0.01 and P <0.001 respectively). Headache bothersomeness and maximum headache was improved significantly in the NSE group (P =0.04 and P <0.12). 51% of the people in the NSE/NSEB group reported a 50% reduction in headache bothersomeness after 1 year, compared to 27% in the PAP group (P <0.05). $P \leq 0.05$ was the significance level. There was no significant difference between the NSE and NSEB groups, indicating a cervicogenic correlation without much psychosocial influence. The study was a second analysis of a RCT, and the initial sample was not based on headache. The results concerning headache were still significant for the NSE/NSEB groups. Limitations were specifically related to recall bias for the maximum headache within the last week. The method of this RCT was still convincing, and results point in the direction that rehabilitation of the cervical spine can reduce headache after whiplash injury.

Table 6: Definition of Whiplash Associated Disorders (20, p. 65)

Whiplash Associated Disorders (WAD)
"The clinical syndrome of whiplash and WAD includes neck pain or stiffness, arm pain and paresthesias, temporomandibular dysfunction, headache, visual disturbances, memory and concentration problems, and psychological distress."

Table 7: Quebec Task Force grading system for Whiplash Associated Disorders (21).

Grade	Clinical presentation of whiplash
0	No complaint about the neck. No physical sign(s).
1	Complaint of neck pain, stiffness, or tenderness only. No physical sign(s).
2	Neck complaint AND musculoskeletal sign(s). Musculoskeletal signs include decreased range of movement and point tenderness.
3	Neck complaint AND neurological sign(s). Neurological signs include decreased or absent tendon reflexes, weakness and sensory deficits.
4	Neck complaint AND fracture or dislocation.

In another RCT, Schneider et al (10) explored 31 young patients with sport-related concussion. The intervention group received cervical spine treatment and rehabilitation as well as vestibular rehabilitation. Treatment of the cervical spine consisted of joint mobilization techniques of the neck and thoracic spine, cervical neuromotor retraining exercises and sensorimotor retraining exercises. Vestibular rehabilitation included habituation, gaze stabilization, adaptation exercises, standing and dynamic balance exercises and canalith repositioning manoeuvres. The control group had postural education, range of motion exercises and general advice. Outcome measures were number of days from treatment initiation to medical clearance to return to sport. The intervention group were 3.91 times more likely to be medically cleared within 8 weeks 8 (P>0.001). The main outcome measurement were days to medical clearance in general for patients with headache, dizziness, and other concussion symptoms. Secondary outcome measures were reduction of symptoms specifically and improvement of function. Headache improvement was only listed in this context and was not the main objective of this study. Nevertheless, one can expect headache, being the most common complaint after concussion, to improve in the treatment group.

Table 8: Extraction form with articles concerning Rehabilitation.

Reference	Study design	Population	Intervention	Comparison	Outcome measurement	Significant result/ conclusions
Ludvigsson et al, 2019 (19)	Randomized controlled trial	188 people with chronic whiplash associated disorders and headache.	Neck specific exercises (NSE) with (N=63, Men=20, Women=43) and without (N=64, Men=11, Women=53) a behavioural approach (NSEB).	Physical activity prescription (PAP) without specific neck exercises. N=61. Men=29. Women=32.	Current headache, maximum headache, and bothersomeness on a VAS scale.	Significantly better outcome for NSE and NSEB groups compared to PAP group.
Schneider et al, 2013 (10)	Randomized controlled trial	31 young patients with sport-related concussion.	Cervical spine treatment and rehabilitation and vestibular rehabilitation. N=15. Men=11. Women=4	Postural education, range of motion exercises and general advice. N= 16. Men=7. Women=9.	Number of days from treatment initiation to medical clearance to return to sport.	The intervention group were 3.91 times more likely to be medically cleared within 8 weeks.

Prevention

Some studies have investigated the effect of cervical strength, endurance, and stiffness in the prevention of head trauma and concussion. Although the articles focused mainly on concussion, and not post-traumatic headache specifically, they are included due to the relevance of cervical function preventing head acceleration/deceleration injury, concussion, whiplash and PTH.

In a longitudinal observational study, Baker et al (22) tested the deep neck flexor endurance (DNFE) of 130 university athletes pre-season and observed if DNFE prevented the concussion incidence in season. They found no significant difference between pre-season DNFE time and concussion incidence, but there was a moderate correlation between DNFE time and concussion recovery. Only 12 sustained a concussion, thus impossible to conclude on a significant correlation with such a small sample.

Schmidt et al (23) did a cohort study of 49 young American football players. They also tested the pre-season cervical strength, as well as muscle size and perturbation, compared with the players in season with mild, moderate, and severe head impacts. For each cervical characteristic, the high and low performers were significantly different ($P<0.01$). Cervical stiffness and reduced angular displacement after perturbation were shown to reduce risk of high magnitude head impact. Stronger and larger neck muscles did not prevent head impact, possibly due to the position and exposure of these strong players. The study had a small sample. They only performed isometric testing; however dynamic testing would be of more realistic value in a play setting.

37 young ice hockey players took part in Mihalik et al's (24) prospective cohort study. Cervical strength in all directions were measured and correlated with linear and rotational head acceleration and head impact telemetry severity profile (HITsp) in play. They found no difference between cervical strength and linear and rotation acceleration. Weak upper trapezius was in fact associated with lower HITsp measures. There was a small sample size, and in this study, and only isometric testing was performed.

Table 9: Extraction form with articles concerning Prevention.

Reference	Study design	Population	Intervention	Comparison	Outcome measurement	Significant result/ conclusions
Baker et al, 2019 (22)	Longitudinal observational study	130 university athletes. Men= 62. Women=68.	Pre-season deep neck flexor endurance (DNFE) VS risk of concussion incidence and recovery in in-season injured athletes. N=12. Men=6. Women=6.	Pre-season deep neck flexor endurance in in-season non-injured athletes. Men/female ratio not found.	Concussion incidence and recovery in-season VS pre-season DNFE time.	No significant difference between pre-season DNFE time and concussion incidence BUT there was a moderate correlation between DNFE time and concussion recovery.
Mihalic et al, 2011 (24)	Prospective cohort study	37 young ice hockey players.	Cervical neck strength in all directions, strong group. Men/female ratio not found.	Cervical neck strength in all directions, moderate and weak group. Men/female ratio not found.	Linear and rotational head acceleration and Head Impact Telemetry severity profile (HITsp).	No difference between cervical strength and linear and rotation acceleration. Weak upper trapezius was in fact associated with lower HITsp measures.
Schmidt et al, 2014 (23)	Cohort study	49 young American football players.	Pre-season cervical strength, muscle size and perturbation in high performance group. Men/female ratio not found.	Pre-season cervical strength, muscle size and perturbation in low performance group. Men/female ratio not found.	Mild, moderate, and severe head impacts VS pre-season cervical strength, muscle size and perturbation.	Cervical stiffness and reduced angular displacement after perturbation reduce risk of high magnitude head impact. Stronger and larger neck muscles do not prevent head impact.

Prognosis

Ellis et al (25) looked at the odds of experiencing delayed recovery with sports-related concussion (SRC) with a cervical spine dysfunction (CSD), compared to patients with no CSD. They had a sample of 266 patients in this retrospective cohort study. 80 patients met the criteria for CSD. These patients were referred to cervical spine physiotherapy, headache neurologist, exercise physiologist for graded aerobic treadmill testing and referral to a vestibular physiotherapist. The odds of experiencing delayed physician-documented clinical recovery time with CSD was 3.95, and 7.93 with both CSD and vestibulo-ocular dysfunction.

In a prospective multicentre cohort study, Coffeng et al (26) explored 922 patients with mild traumatic brain injury (mTBI). The objective was first to describe the course of ANP in relation to mTBI, as well as persistent post-traumatic complaints. The second aim was to establish specific trauma characteristics in ANP patients with incomplete mTBI recovery that could be established at the Emergency Department (ED) or in the subacute phase. The ANP group of 156 patients had more headache (40.8%) at the ED than the non ANP group (32,2%) (*P* =0,06). The non ANP patients had more frequent external head wounds, suggesting more flexion-extension trauma of the cervical spine in the ANP patients. Six months after injury, the ANP patients had poorer functional outcome (55%) compared to the non ANP group (40%) on the Glascow Otucome Scale - Extended (GOSE) (*P* =0,01). The medical charts were incomplete, with lacking information of demographics and symptom correlation. The results still point in the direction that ANP is an important prognostic factor for mTBI recovery.

In 2008, Stovner and Obelieniene (27) published a prospective cohort study where they described the course of 210 patients after rear-end collision. The matched controls were of the same sample size. The headache was significant 2-3 weeks after injury, but not after 2 and 12 months, compared to control. 37 of the cohort patients had neck pain, and 38 had no neck pain after injury. However, they both had the same headache diagnoses, symptoms, and prognosis. This was partly the case also when compared to the control group, where the headache prevalence, diagnoses and prognosis were the same. The authors indicate that the headache reported after the injury is not new, but a primary headache re-induced by the stress of the accident.

Table 10: Extraction form with articles concerning Prognosis.

Reference	Study design	Population	Intervention	Comparison	Outcome measurement	Significant result/ conclusions
Coffeng et al, 2020 (26)	Prospective multicentre cohort study	922 mild traumatic brain injury patients.	156 acute neck pain patients, post-traumatic complaints evaluated. Men=75. Women=81.	766 patients with no acute neck pain. Men=495. Women=271.	Functional outcome related to neck pain and relation to persistent post-traumatic complaints.	More headache in ANP group. ANP regarded as predictor for incomplete recovery after mTBI. Early identification and correct treatment can prevent persistent symptoms.
Ellis et al, 2018 (25)	Retrospective cohort study	266 young patients with sports-related concussion (SRC).	Recovery time following SRC in patients with cervical spine dysfunction (CSD). N=80. Men=46. Women=34.	Recovery time following SRC, without CSD. N=166. Men=126. Women=40.	Odds of experiencing delayed physician-documented clinical recovery time.	Odds of experiencing delayed recovery with and without CSD was 3.95, and 7.93 with both CSD and vestibulo-ocular dysfunction.
Stovner and Obelieniene, 2008 (27)	Prospective cohort study	210 patients with whiplash after rear-end collision.	Questionnaire to assess head and neck pain in patients after whiplash injury. N=210. Women/men ratio not found.	210 non-traumatized controls. Women/men ratio not found.	Head and neck pain 2weeks, 2 and 12 months after the injury (questionnaire).	Headache significant 2-3 weeks after injury, but not after 2 and 12 months, compared to control. Perhaps not new PTH, but rather re-induced primary headache.

JBI Critical appraisal

The JBI critical appraisal tool provided insight into the degree of bias and quality of the research, and all articles had a moderate to high quality score (see appendices 1-16). The level of evidence is valued from 1 to 5, where 1 is the highest, and 5 lowest level of evidence. Of the 16 studies included, 3 had level 4, 9 had level 3, 2 had level 2 and 2 had the top first level of evidence (28).

Table 11: JBI Critical appraisal for each article according to type of study and level of evidence (28), and a column stating if a power calculation was performed (N=No).

Reference	Study design	JBL Critical appraisal tool	Level of evidence	Power calculation
Baker et al, 2019 (22)	Longitudinal observational study	7/11. Moderate quality	3	N
Coffeng et al, 2020 (26)	Prospective multicentre cohort study	6/11. Moderate quality	3	N
Drottning et al, 2002 (15)	Prospective cohort study	6/11. Moderate quality.	3	N
Ellis et al, 2018 (25)	Retrospective cohort study	7/11. Moderate quality	3	N
Jensen et al, 1990 (12)	Controlled trial	7/9. High quality.	2	N
Jensen et al, 1990 (9)	Prospective clinical controlled trial	8/9. High quality.	2	N
Kasch et al, 2001 (16)	Prospective observational study	7/11. Moderate quality.	3	N
Kennedy et al, 2017 (17)	Retrospective chart review	8/10. High quality.	4	N
Kennedy et al, 2019 (17)	Prospective case series	8/10. High quality.	4	N
Leddy et al, 2015 (14)	Retrospective review of symptom reports	7/10. Moderate quality.	4	N
Ludvigsson et al, 2019 (19)	Randomized controlled trial	10/13 points. High quality.	1	N
Mihalik et al, 2011 (24)	Prospective cohort study	5/11. Moderate quality	3	N
Schmidt et al, 2014 (23)	Cohort study	6/11. Moderate quality	3	N
Schneider et al, 2013 (10)	Randomized controlled trial	10/13 points. High quality.	1	N
Stovner and Obelieniene, 2008 (27)	Prospective cohort study	8/11. High quality.	3	N
Treleaven et al, 1994 (13)	Case-controlled study	7/10. Moderate-high quality.	3	N

Discussion

The systematic review indicates that the PTH-patients with cervical involvement may benefit from management directed to the cervical spine, including manual therapy, rehabilitation, and behavioural advice. PTH was associated with cervical pain, stiffness, and reduced neuromuscular control. Patients with persistent PTH (PPTH) had a higher incidence of reduced deep neck flexor endurance, as well as painful cervical segments. PPTH was also associated with stress, pain comorbidities and previous history of headache, mTBI and previous whiplash injury.

Although the results are encouraging, no conclusion can be drawn, due to the methodological limitations described below. Several of the articles also focused on concussion or whiplash in general, more than PTH exclusively. Much is yet to be known regarding PTH in general and the involvement of the cervical spine specifically. In fact, headache associated with trauma may in many cases not even be a new headache, but rather a transitory worsening of a pre-existing primary headache (27). This is important to have in mind when evaluating the causes and prognosis of an acute PTH.

Relevant systematic reviews and guidelines

No systematic reviews concerning PTH, and the association of the cervical spine explicitly have to the author's knowledge been published. However, Argyriou et al performed a systematic review of non-pharmacological management of PTH in general in 2021 (5). PTH patients, especially the persistent, have a complex presentation with cervical pain, cognitive complaints, and psychosocial challenges. According to the authors, PTH is often refractory to pharmacological treatment, possibly due to the multidimensional mechanisms of PTH. Therefore, Argyriou et al suggests a biopsychosocial management of persistent PTH, combining non-pharmacological and pharmacological interventions when indicated.

The research on manual therapy of PTH by Jensen et al (9) and cervicovestibular rehabilitation of sports-related concussion by Schneider et al (10) are the only two manual therapy studies included in the Danish national clinical guideline for non-pharmacological treatment of persistent post-concussion symptom (6). Post-traumatic headache is described as part of the persistent post-concussion symptoms and is not a specific outcome measure. The guidelines indicate that mobilization and manipulation techniques possibly increase the number of patients cleared to return to sports. However, other outcomes like emotional

symptoms, behavioural reactions, quality of life, physical functional level and the collected burden for post-concussion symptoms were not documented.

Methodological limitations

The present systematic review, and previous guidelines and systematic reviews, demonstrates that the amount of research in the field of cervical related post-traumatic headache is inadequate. Especially research of high quality. Due to this fact, and the set inclusion and exclusion criteria, this review included only 16 approved articles (Table 7).

The research methods of the studies included are of fairly good quality overall, according to the JBI critical appraisal tool. This was due to the rating system for each individual study design. Randomized control trials, quasi-experimental studies, case series, case control studies and cohort studies all have different critical appraisals, making it possible to receive a high-quality score within the relevant research design, even though the method and level of evidence is poor. This was a common challenge also in many of the included 16 articles, with small sample sizes, some lacked a control group and the possibility of selection and recall bias was high. There were also very few RCT's, and blinding of the examiner or therapist was impossible for obvious reasons when applying physical non-pharmacological interventions. To evaluate the quality of methods further, the articles were graded by the level of evidence by looking at the study design (see table 7). Although the quality of the research might appear high through the JBL critical appraisal, the level of evidence still only had an average of 2.81, where 5 is the lowest possible score of study design. Therefore, the knowledge drawn from the studies are in my opinion to a large extent inconclusive.

Future directions

Improving the design of previous studies can be a reasonable method to gain higher quality research and possibly approaching results of more conclusive value. Research questions in the articles can be re-used, as the ideas were relevant and important to understand more about the complexity of PTH.

Regardless of possible improvement of previous research, there are still some new insights that can clarify the mechanisms and management of PTH. Based on the results and discussion above, the following is an attempt to outline what areas of research that can enhance the knowledge of cervical related PTH. Future studies should aim to:

1. Investigate anamnestic clues and examination methods that will pinpoint patients who are at risk of developing persistent problems. Cervical dysfunction may be one of the risk factors.
2. Gain a higher understanding of what management is most effective in the acute stage to prevent chronification. Cervical management is suggested to be one of the preventive measures.
3. Explore the various phenotypes of PTH and find the causative factors, including the role of the cervical spine.
4. Study what type of treatment is most effective for each phenotype, including pharmacological and non-pharmacological management in combination and alone.
5. Encourage the education of health professionals involved in patients with mTBI and WAD in examination and management of cervical related PCD and PTH to prevent chronification.

Research proposal

Due to the inadequate conclusive value of the included articles, an important aspect of this thesis is to suggest a future research project. The future directions outlined above give the basis of many important research ideas. Still, the research of interest in this thesis is specifically centred around the management of the cervical spine in PTH.

To design the best possible proposal, important background regarding mechanisms and the cervical involvement of PTH should be outlined first, and in more details than what is described in the result and discussion sections. After a brief introduction, some of the most recognized mechanisms of headache generated from the cervical spine is presented. This provides a rational for the research proposal.

Background

PTH can result from cervical injury with and without objective findings, and in relatively low-force accidents. In a rear-end collision of only 13 km/h, the head accelerates with a force of 5G in less than half a second (29). The sudden impact, especially when it is unexpected, results in an exceeded physiological range of motion of the cervical spine, and increased risk of injury to ligaments, capsules, muscles, and other structures. Still, structural damage that

can be detected objectively (e.g., muscle ruptures, disc herniations, fractures and dislocations) are rare (29). Cervical injury can also occur from mTBI and direct head impact, without a typical whiplash presentation. Between 60 and 160G is necessary to elicit a concussion, while only 4,5G is needed to create sprain/strain in the cervical spine. Any direct head impact is likely to create some load on the neck, especially the upper cervical spine (7). Both mTBI and whiplash results from acceleration/deceleration with energy transferred through the brain and cervical tissues closely related anatomically (8). The symptoms of concussion and whiplash are very similar (see table 12), and some would argue that the two disorders may be difficult to differentiate (8).

In some cases, it may be insignificant to distinguish the two disorders, as the management often is based on symptoms anyway. However, it may be inadequate to term a patient with PTH or PCD as refractory if the cervical spine is left out in the examination and diagnostic triage. Not to forget, evidence of neck pain, neck dysfunction and previous history of pain comorbidities increase the risk of chronification (8, 16, 29). The management of the cervical spine should therefore be addressed as early as possible after the trauma to minimize recovery time. Hopefully, this can prevent acute PTH patients developing persistent symptoms, and reduce the risk of refractory treatment situations.

Table 12: Comparison of symptoms in concussion and whiplash (7, p. 275).

Concussion		**Whiplash**	
• Headache • Pressure in head • Neck pain • Nausea/vomiting • Dizziness • Blurred vision • Balance problems • Sensitivity to light • Sensitivity to noise • Feeling slowed down • Feeling like 'in a fog' • 'Don't feel right'	• Difficulty concentrating • Difficulty remembering • Fatigue or low energy • Confusion • Drowsiness • Trouble falling asleep • More emotional • Irritable • Sadness • Nervous or anxious	• Neck/shoulder pain • Reduced/painful neck movements • Headache • Reduced/painful jaw movements • Numbness, tingling or pain in arm or hand • Numbness, tingling or pain in leg or foot • Dizziness/unsteadiness • Nausea/vomiting • Difficulty swallowing • Ringing in ears	• Memory problems • Problems concentrating • Vision problems • Lower back pain

To plan the management of a PTH-patient with possible cervical involvement, it is important to have a good understanding of how the cervical spine may in fact elicit headache symptoms. What we know so far of the possible cervical causes of post-traumatic headache, are mostly derived from research done on *non-traumatic* cervicogenic headache, migraine, and tension-

type headache. Nevertheless, compared to PTH associated with a concussion or whiplash, one should expect some important differences (29). These differences would again be important to have in mind during the clinical examination and management of PTH, and not the least, what to expect when researching PTH. Therefore, the following paragraphs presents some of the mechanisms in and around the cervical spine known to generate headache symptoms after trauma. A particular attention will be on persistent PTH.

1. Muscles

Myofascial injury is the dominant feature of whiplash, and the typical PTH phenotype from this source is a tension-type headache (30). Even though it is rare, tearing and haemorrhaging of muscles can occur (29), and must be considered in the examination. The most common finding is still increased tension, not injury. Increased muscle activation is in one WAD-review (31) believed to be due to guarding. The guarding may be the result of changes in proprioceptive properties, movement pattern (fear avoidance behaviour), head repositioning and altered cervical function (32). This can lead to local ischaemia, tenderness, and trigger points. Although trigger points are by some considered to be controversial (33), they provide a solid explanation for the referred pain pattern from muscles in the shoulder, neck, and jaw, to various areas of the head (29).

2. Ligaments

The clinical relevance of ligamentous sprains and tears are not convincing, even though structural damage have been discovered on MRI and post-mortem after motor-vehicle accidents (MVA) (31). This has been retested in newer research, and a meta-analysis found the signal changes of alar and transverse ligaments was not believed to be due to a whiplash injury (34). They concluded that the clinical relevance is so far unknown. The topic is subject to an ongoing debate. Patient organizations and some clinicians do on one side believe there is a structural injury in the upper cervical spine causing the whiplash associated symptoms (35), including post-traumatic headache. Solicitors, insurance companies, researchers and radiologists are on the other side not convinced of the association (34, 36). Without solid evidence from a conventional MRI, patients hope the standing positional MRI will find the cause of their symptoms. So far, this is neither a recommended imaging technique for patients with WAD (37). Even though there is so far no convincing evidence for a clinical relevance between structural ligament injury and PTH, the ligaments itself is probably a source of headache, possibly due to stretch or other dysfunction. Ligaments in the upper cervical spine

are innervated by the upper cervical nerve roots and are recognised sources of neck and head pain (38).

3. Zygoapophyseal joint

The zygoapophyseal joint is a source of headache in non-traumatic neck pain patients (38) and in whiplash patients (31). A referred pain pattern to the upper cervical region, occiput, the ear, vertex, forehead, and eye has been observed when injecting contrast media in C2-3. When injecting into C1-2 zygoapophyseal joint, the pain referred behind the ear, mastoid process, and angle of the mandible (39).

Manual therapy of the cervical spine and zygoapophyseal joints in headache patients has a long tradition. Rist et al performed a meta-analysis in 2019 (40) indicating that spinal manipulation may reduce migraine pain and intensity. In a systematic review from 2011, Chaibi (41) suggested that massage, physiotherapy, relaxation, and chiropractic manipulation may have the same effect as propranolol and topiramate as migraine prophylaxis.

Manual therapy, including spinal manipulation, does not seem to influence tension-type headache according to one systematic review (42). In another review the effect seems promising, but not superior to other techniques (43). Krøll et al (44) had a more positive conclusion in the most recent meta-analysis from 2021: Manual therapy may reduce the tension-type headache frequency, pain intensity and stress symptoms, and increase the quality of life. It must be noted that other interventions were also assessed.

In a systematic review on spinal manipulation of cervicogenic headache, Fernandez et al (45) found a short-term effect on pain intensity, frequency, and disability, but not duration of pain. Another review suggests that physiotherapy and spinal manipulation may be effective for cervicogenic headache, but with limited conclusive value as only one study had a control group (46).

Common for all the reviews was research with small samples and poor methodology. In addition, spinal manipulation was in most cases combined with other treatment interventions, making it impossible to evaluate the effect of manipulation of the zygoapophyseal joints alone.

Manual therapy of PTH have already been presented in this review (9, 17, 18). Although the treatment had a positive effect on headache, the manipulation was combined with muscle

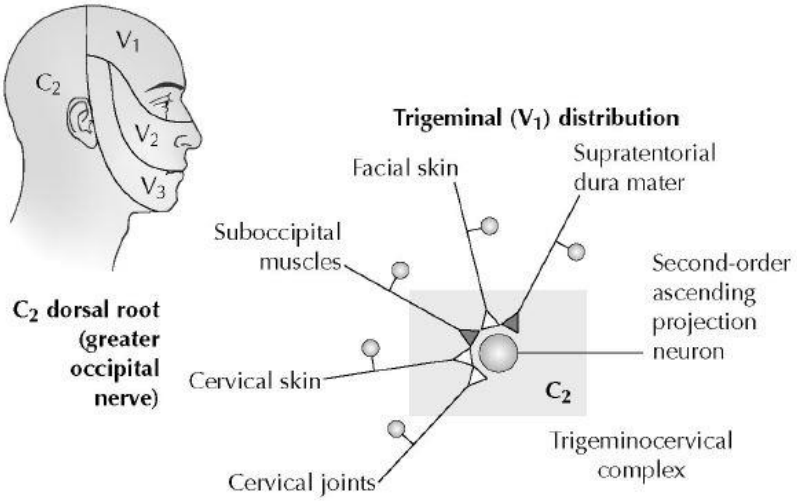
techniques and/or rehabilitation, which challenges the conclusive value of the zygoaphyseal joint as a pain source. The effect is possibly due to the combination of interventions.

4. Referred pain and the trigeminocervical complex

Through the convergence-projection theory, migraine patients may experience neck pain without neck dysfunction, and whiplash patients may experience referred pain to e.g., the forehead. The theory has been confirmed through animal and human studies (7). Stimulation of dura mater produce referred pain in the occiput and may also increase the activation of paraspinal muscles. Similarly, stimulation of the greater occipital nerve creates referred pain to the head, especially in the ophthalmic distribution of the trigeminal nerve (47).

In both primary and secondary headache disorders, there is a convergence of nociceptive dural afferents and cervical afferents in the greater occipital nerve on to neurons in the trigeminocervical complex (38). The trigeminocervical complex extends anatomically from the trigeminal nucleus caudalis to C2-3 segments (see figure 1). The trigeminal neurons are dural sensitive and display convergence from other sensory areas of the head, including facial and corneal receptive fields. The upper cervical roots are also involved in sensory input, including occipital and suboccipital structures, dura mater and vessels in the posterior fossa, zygoapophyseal joints, ligaments, and deep neck muscles. The convergence and referred pain pattern of no specific anatomical pain source may explain why neck pain and headache can be difficult to localize (38).

Figure 1: The Trigeminocervical complex (38, p. 373).



5. Sensitization and chronification mechanisms

The development of chronic headache in general, also including PPTH, depends on several mechanisms. The three main theories presented here are central sensitization, descending inhibition, and sensitization through biopsychosocial mechanisms. They all involve the cervical spine, directly or indirectly.

5.1. Central sensitization

Neck and headache patients tend to become hypersensitized as part of the chronification process. Long-lasting stimulation of afferents from visceral and deep somatic tissues like muscles and joints produce a higher degree of central sensitization than cutaneous input. The afferents in the spinal cord are hypersensitized from the release of neuropeptides, like calcitonin gene-related peptide (CGRP), glutamate and action of the receptor N-methyl-D-aspartate (38). CGRP may activate the trigeminovascular system and induce neurogenic inflammation and vasodilation of dural and pial arteries (5). This sequence is most likely responsible for migraine attacks.

5.2. Descending inhibition

The sensitization may also result from reduced pain inhibition on a cervical spinal level (38). Descending pain modulatory systems link several sites in the brain and neuronal pathways. Disruption of the modulatory system and descending control of pain can lead to chronification and can be implicated in the pathophysiology of PTH (4).

5.3. The biopsychosocial model and risk for chronification

There is an increased risk of developing persistent PTH (PPTH) if the patient has a previous history of primary headache, post-traumatic stress disorder (PTSD), anxiety, depression and other pain-comorbidities like neck and low back pain. Even without any objective findings, the shock from the unexpected mild head trauma or whiplash injury, with the following anxiety and stress response, may be enough to sensitize and disinhibit pain signals, with resulting headache (27). Post-traumatic headache is likely to evolve in conjunction with cognitive deficits and psychiatric symptoms as part of a neurobehavioural spectrum. 40% of patients with persistent PTH (PPTH) are depressed. 25% have anxiety disorders (48). Compared to migraine patients, the frequency of depression and anxiety is higher in patients with PPTH (4). Anxiety is linked to cognitive impairment, sleep disorders and fatigue. The

latter two are predictive of PTH severity. 30% of PPTH patients also have post-traumatic stress disorders (PTSD), with associated functional impairment (48).

Psychosocial factors are often viewed as reactions to pain rather than contributing to pain. However, the link is bidirectional. Depression, anxiety, and distress are established risk factors for the development of chronic pain in general. The psychological processes influence neurological and biological pathways as epigenetic processes, cellular priming, and changes in brain networks related to motivation, reward, learning and descending modulation. The pain sensitization precipitated by the psychosocial factors may occur both centrally and peripherally (49).

The biopsychosocial model facilitates the planning of chronic pain management. The patients can benefit from a multidisciplinary approach, with e.g., pain education, cognitive behavioural therapy, rehabilitation, manual therapy. This is also the case for patients presenting with PPTH, PCD and WAD (5, 6). Combining non-pharmacological with pharmacological management may also be helpful (5).

The biopsychosocial model has however been criticized to leave out the biological aspect when there is no objective structural finding, resulting in too much focus on the psychosocial factors (49). Even though the objective biological causative factors are yet to be found in many chronic pain patients, there is still a matter of continuing developing research to explain the complexity of the pain process. Spontaneous Intracranial Hypotension headache (SIH) due to CSF leak, commonly in the cervico-thoracic junction, has for instance appeared to be the biological cause of headache of some patients originally being diagnosed with chronic migraine, new daily persistent headache and PPTH. It is believed that the SIH headache is underdiagnosed, and correct management with blood patch may help these patients that initially have been labelled to have a psychiatric diagnosis or other non-objective causes contributing to the headache (50).

6. Whiplash associated disorders and headache

Whiplash is, as the name indicates, a whip-lash, flexion/extension, S-movement of the neck, due to unexpected and fast acceleration/deceleration of the head and neck (8). In 1995, the Quebec Task Force graded WAD into 5 categories, based on the clinical presentation, where 0 is no signs and symptoms, and 4 is neck fracture and dislocation (21).

Whiplash associated disorders (WAD) is the persistent symptoms of a whiplash injury, and includes cervical pain or stiffness, arm pain, upper extremity paraesthesias, temporomandibular joint dysfunction, headache, visual disturbances, memory and concentration difficulties, and psychological distress (20). Most WAD-patients fall into grade 2 with signs and symptoms of neck stiffness, but no neurological findings (8).

Prevalence of symptoms in WAD varies between studies, but as much as 80% with headache symptoms is reported VS. 60% with neck pain (8). Cervical findings related to symptoms are commonly functional, not structural. In both whiplash and concussion patients with upper cervical dysfunction, cervical stiffness and reduced endurance of deep neck flexors can lead to tension-type headache. Proprioception deficits, on the other hand, is more related to dizziness (7).

In patients with diagnosed whiplash and no direct head impact, diffusion tensor tractography have shown diffuse axonal lesions consistent with the symptoms described. However, the authors suggest that it is a secondary appearance of axonal swelling, not due to the mechanical trauma (7). In SPECT (Single Photon Emission Computed Tomography), WAD patients have presented with parieto-occipital hypoperfusion. Altered cerebral blood flow is a common cause of concussion symptoms and PTH, especially related to increased pulse during exercise. SPECT is used to examine cerebral blood flow in mTBI patients. Even though hypoperfusion is displayed and may explain the symptomatology, the same findings are evident in WAD-patients and other chronic patients without neck or head trauma, like low back pain, depression, and chronic fatigue syndrome (7). The findings of altered cerebral blood flow may in other words represent a chronification process, rather than trauma-related damage.

Since 1995, newer research claims that the grading system fails to address risk factors of chronic WAD, since psychosocial distress is not included (16, 51). Kasch et al observed association between neck stiffness and symptoms only the first 3 months (15). As mentioned previously, neck stiffness and pain were related inversely to headache and neck stiffness after 6 months. The research paved way for a risk assessment tool for acute whiplash patients to predict outcome. The Risk Assessment Score reflects biopsychosocial factors, as opposed to the grading system of The Quebec Task Force (52) (See table 13). The system can segment acute whiplash patients into different risk strata based on signs and symptoms of prognostic value. It is also helpful in assessing work disability (53).

The late whiplash syndrome experienced after 6 months is in other words not explained by physical findings alone but is a complex biopsychosocial phenomenon (16). History of previous neck pain and a high degree of emotional distress at the time of injury increases the risk of developing chronic neck pain 1 year after the accident by a tenfold (51).

Table 13: Risk Assessment Score. Total risk points are based on three risk factors: Neck mobility, present score of pain or by number of nonpainful complaints. (52, p. 265).

Points	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
CROM	>280		261-280		241-260		221-240		200-220		<200
Neck / Head VAS (0-10)	0-2	3-4			5-8		9-10				
Number of non-pain symptoms	0-2	3-5		6-11							
Risk strata 1-7	Stratum 1= 0 points; Stratum 2=1-3 points; Stratum 3=4-6 points; Stratum 4=7-9 points; Stratum 5=10-12 points; Stratum 6=13-15 points; Statum 7=16-19 points										

Although the persistent WAD is associated with psychosocial risk factors and distress, and objective findings are rare, there may be biological explanations that influence symptoms of pain and headache. Future research will hopefully clarify this.

Summary of cervical related post-traumatic headache

The research and reviews discussed, indicates a bi-directional relationship between neurobehavioral mechanisms in the brain and the cervical spine. In the acute stage of whiplash and brain trauma, cervical joints, ligaments, muscles, and the brain may become affected due to shearing forces and inflammation alone or in combination with the shock of the unexpected trauma, distress and catastrophising thoughts. The post-traumatic headache may result from referred pain from the neck, via convergence of dural and cervical afferents in the greater occipital nerve on to neurons in the trigeminocervical complex. Guarding of cervical muscles may also lead to trigger points with referred pain patterns.

Some patients are at risk of developing persistent PTH after 3 months. This includes females, patients with a previous history of headache, head trauma, psychosocial distress, and other pain-comorbidities. The chronification mechanisms can be due to central sensitization and changes in the descending pain control system.

Relevance of mechanisms when designing the research proposal

After reviewing the literature, the complexity of the PTH-patients needs clarification and stratification. Sub-grouping the patients into symptom-categories and phenotypes, can facilitate the understanding of the pathophysiology as well as tailoring the treatment to each patient category. The cervical spine may be an area of importance and should be included in the examination before targeted therapy, both for acute and persistent PTH. The persistent PTH-patients represents the most complex group, and may benefit from a biopsychosocial management, combining both pharmacological and non-pharmacological treatment interventions. This will be prioritized in the present research proposal.

Although all phenotypes of PTH are interesting to explore, choosing only one is beneficial for the sake of cost, organization, and methods. Investigating one phenotype, may also limit the scope of mechanisms of PTH and how the cervical spine can be involved. The most interesting phenotype to start with is in my opinion tension-type headache. It is the second most common phenotype of PTH and is the subject of a possible complex pathophysiology with limited knowledge and can be refractory to pharmacological treatment. Although the migraine phenotype is more common and would provide more subjects, standardization of treatment may be more feasible for tension-type headache (TTH). TTH is also clearer to distinguish from the physiological concussion sequala, due to the difference in activity exacerbation. Migraine, in comparison, is worsened by physical activity, like any physiological concussion with PTH (7, 14, 25).

Research proposal

With the background above, I propose the following research project:

Title

The effect of manual therapy VS. pain education on persistent post-traumatic headache with tension-type headache phenotype. A randomized controlled trial.

Objectives:

1. To compare the effect of non-pharmacological interventions, specifically manual therapy, and pain education, on persistent PTH with tension-type headache phenotype.
2. To explore what relevance the cervical spine has on tension-type headache phenotype.

The suggested research question is as follows:

In patients with a tension-type headache phenotype of persistent post-traumatic headache and a cervical involvement, is there a significant effect difference between manual therapy and pain education?

Methods

Study design: Prospective, multicentre, single-blinded, 3-arm, randomized controlled trial evaluating treatment over 3 months, and follow up 6 months, 1 and 2 years from baseline.

Inclusion criteria: 1) PTH patients with TTH phenotypes with onset related to direct head trauma or whiplash, lasting for more than 3 months. 2) Patients with trauma related subjective neck pain or neck stiffness for the last 3 months. Both criteria need to be fulfilled for inclusion.

Exclusion criteria: 1) Patients with structural cervical injury from the trauma, diagnosed on X-ray or MRI related. 2) Patients with contraindications to manual therapy of the cervical spine. 3) Patients with clinically diagnosed psychiatric disorder before the onset of trauma. (A history of previous headache or neck pain, other pain-comorbidities and common psychosocial distress related to the trauma is accepted, and can be of interest, but need to be recorded for the results.) 3) Patients with Occipital neuralgia and Trigeminal Autonomic Cephalgia's are excluded. One criterion may be sufficient for exclusion.

Setting: 2 tertiary hospitals with a multidisciplinary headache unit, 2 private neurology clinics with headache specialists and chiropractors and 3 private multidisciplinary physiotherapy and chiropractic clinics with specialists in concussion, WAD, and headache. Qualified clinicians will ensure proper examination and diagnosis. It will also secure the intended quality of treatment alone and in combination, and a better chance of reaching the desired sample size.

Randomization: All patients are 1 month before first consultation asked to complete a post-concussion symptoms scale questionnaire (22 symptoms, grade 0-6) (54), Risk Assessment Score of WAD (52), and every day for 1 month, complete a headache diary. The clinicians diagnose the patients based on diary, questionnaires, validated anamnestic relevant questions and a validated cervical examination. All participating clinicians are carefully selected and

trained in diagnostic skills of PTH phenotypes, as well as examination methods of the cervical spine. Validated SOAP notes are saved in electronic medical records. The patients are carefully placed in the TTH phenotype specific group by the clinicians. Then, patients are block randomized into interventions and comparison groups (see below).

Blinding: Participants draw a sealed lot with the random 3 study arms. After each treatment, they fill out a questionnaire whether they believed real treatment was received. The randomization of sealed lots and questionnaires are administered by an external party for each clinic and department participating.

Population: A minimum of 150 patients with persistent TTH-type PTH headache.

Interventions: Intervention groups consist of 1) Real manual therapy and rehabilitation of the cervical spine and 2) Pain education, based on the Explain Pain education model (55). The last group intends to rule out the direct biomechanical mechanisms of the cervical spine and explore the biopsychosocial aspect of persistent PTH. However, the pain mechanisms of the cervical spine are not possible to exclude completely and will most likely be affected through pain education and activity to some degree. See table 14 for intervention descriptions.

Comparisons: Sham manual therapy and rehabilitation of the cervical spine. The sham procedure with thrust of the scapula is also utilized by Chaibi et al (56) in a RCT investigating the effect of manipulation on migraine-patients.

Table 14: Interventions and description in the RCT

Interventions	Description
Manual therapy	Manipulation, mobilization, and soft tissue work of the cervical spine as indicated performed by chiropractors or physiotherapists.
Sham manual therapy	Low velocity thrust to areas other than the spine, e.g., edge of scapula.
Rehabilitation	Deep neck flexor endurance exercise, extensor exercise and cervical mobilization techniques, performed by chiropractors or physiotherapists.
Sham rehabilitation	For the cervical spine, rehabilitation not effecting the cervical spine directly. For instance, squats.
Education	Patients are educated on their tension-type headache phenotype and post-traumatic mechanisms, and given self-efficacy advice, reassurance, and advice on normal activities of daily living. The education model is based on Explain Pain, by Moseley and Butler (2015).

Outcome: Headache and neck pain intensity and frequency, using a validated diary, filled out every day for the whole period to avoid recall bias. At longer intervals, headache, neck pain and 20 other important concussion related questions are filled out in the PCSS-scoring system. This is measured at baseline, after 3 months, 6 months, 1 and 2 years. The Risk Assessment Score filled out in the beginning is to evaluate the risk for developing chronic neck pain and is not needed in the follow up.

Limitations

Many PTH-patients have more than one phenotype, which may propose a challenge in the triage before randomization. The best solution for this problem is yet to be solved. Without this clarification, sufficient recruitment into the TTH PTH group can be challenging.

The JBI Critical Appraisal Checklist for randomized controlled trials will not be able to obtain a full score, due to question 5 ("Were those delivering treatment blind to treatment assignment?", see appendix). This is the major challenge with RCT for non-pharmacological therapies, especially manual therapy. Blinding is only possible in the randomization process and when evaluating outcome, not to the clinician delivering the treatment.

The proposed RCT with 3 arms is also a meticulous and expensive design and may lead to dropout of both patients and clinicians. However, it is worth considering the method, due to the possible significance of indispensable results helping clinicians to manage PTH-patients in a more proficient manner.

The study may, if effectuated, gives extremely valuable insight into PTH prognosis and effect of cervical interventions, and can clarify the involvement of the cervical spine in PTH. It will also provide valuable information not only on PTH-development, but also parameters related to PCD, whiplash and chronic pain, as the questionnaires covers all aspects.

Conclusion

The main objective of this systematic review was to investigate the involvement of the cervical spine in PTH, with a particular focus on non-pharmacological management.

The research indicates that manual therapy and rehabilitation may be effective interventions in the treatment of PTH. As early as possible after the injury, consider signs and symptoms significant for the development of persistent symptoms, including acute neck pain, previous

history of head or neck trauma and psychosocial challenges. A tailored biopsychosocial approach could be recommended, incorporating reassurance and pain education, manual therapy, and rehabilitation.

Due to methodological shortcomings, the articles have restricted conclusive value and more high-quality research is required. Future research may benefit from sub-grouping the patients into symptom-categories and phenotypes. This can improve the understanding of the pathophysiology and facilitate tailored treatment to each patient category. The cervical spine may be an area of importance and should be included in the examination before triaging patients into targeted therapy, both for acute and persistent PTH.

The author suggests a future RCT to clarify some of these indications, titled: “The effect of manual therapy VS. pain education on persistent post-traumatic headache with tension-type headache phenotype. A randomized controlled trial”.

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Appendices:

1-16: Checklists of articles included in the review, according to the JBI Critical appraisal (28).

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Baker et al Year 2019 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☒	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☒	☐
5. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☒	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☒	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☒	☐
11. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Coffeng et al Year 2020 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☒	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☒	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☒	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☒	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☒	☐
11. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Drottning et al Year 2002 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☒	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☒	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☒	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☒	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☒	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☒	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☒	☐
11. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Ellis et al Year 2018 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☒	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☒	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☒	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☒	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☒	☐	☐
11. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

THE JOANNA BRIGGS INSTITUTE

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer_____ Date_____

Author Jensen et al Year 1990 Record Number_____

		Yes	No	Unclear	Not applicable
1.	Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☒	☐	☐	☐
2.	Were the participants included in any comparisons similar?	☒	☐	☐	☐
3.	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☒	☐
4.	Was there a control group?	☒	☐	☐	☐
5.	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☒	☐	☐	☐
6.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☒	☐	☐	☐
7.	Were the outcomes of participants included in any comparisons measured in the same way?	☒	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☒	☐	☐	☐
9.	Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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THE JOANNA BRIGGS INSTITUTE

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer_____ Date_____

Author Jensen et al Year 1990 Record Number_____

		Yes	No	Unclear	Not applicable
1.	Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☒	☐	☐	☐
2.	Were the participants included in any comparisons similar?	☒	☐	☐	☐
3.	Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☒	☐	☐
4.	Was there a control group?	☒	☐	☐	☐
5.	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☒	☐	☐
6.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☒	☐	☐	☐
7.	Were the outcomes of participants included in any comparisons measured in the same way?	☒	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☒	☐	☐	☐
9.	Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Kasch et al Year 2001 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☒	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☒	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☒	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☒	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☒	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☒	☐
11. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Case Series

Reviewer_____ Date_____

Author Kennedy et al Year 2017 Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	☒	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	☒	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	☒	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☒	☐	☐	☐
• Did the case series have complete inclusion of participants?	☐	☐	☒	☐
• Was there clear reporting of the demographics of the participants in the study?	☒	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	☒	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	☒	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☒	☐
• Was statistical analysis appropriate?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Case Series

Reviewer_____ Date_____

Author Kennedy et al Year 2019 Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	☒	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	☒	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	☒	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☒	☐	☐	☐
• Did the case series have complete inclusion of participants?	☐	☐	☒	☐
• Was there clear reporting of the demographics of the participants in the study?	☒	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	☒	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	☒	☐	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☒	☐	☐	☐
• Was statistical analysis appropriate?	☐	☐	☒	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Case Series

Reviewer_____ Date_____

Author Leddy et al Year 2013 Record Number_____

	Yes	No	Unclear	Not applicable
• Were there clear criteria for inclusion in the case series?	☒	☐	☐	☐
• Was the condition measured in a standard, reliable way for all participants included in the case series?	☒	☐	☐	☐
• Were valid methods used for identification of the condition for all participants included in the case series?	☒	☐	☐	☐
• Did the case series have consecutive inclusion of participants?	☒	☐	☐	☐
• Did the case series have complete inclusion of participants?	☐	☐	☒	☐
• Was there clear reporting of the demographics of the participants in the study?	☒	☐	☐	☐
• Was there clear reporting of clinical information of the participants?	☒	☐	☐	☐
• Were the outcomes or follow up results of cases clearly reported?	☐	☒	☐	☐
• Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☒	☐
• Was statistical analysis appropriate?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR RANDOMIZED CONTROLLED TRIALS

Reviewer_____ Date_____

Author Ludvigsen et al Year 2019 Record Number_____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment groups?	☒	☐	☐	☐
2.	Was allocation to treatment groups concealed?	☒	☐	☐	☐
3.	Were treatment groups similar at the baseline?	☒	☐	☐	☐
4.	Were participants blind to treatment assignment?	☐	☒	☐	☐
5.	Were those delivering treatment blind to treatment assignment?	☐	☒	☐	☐
6.	Were outcomes assessors blind to treatment assignment?	☐	☐	☒	☐
7.	Were treatment groups treated identically other than the intervention of interest?	☒	☐	☐	☐
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☒	☐	☐	☐
9.	Were participants analyzed in the groups to which they were randomized?	☒	☐	☐	☐
10.	Were outcomes measured in the same way for treatment groups?	☒	☐	☐	☐
11.	Were outcomes measured in a reliable way?	☒	☐	☐	☐
12.	Was appropriate statistical analysis used?	☒	☐	☐	☐
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Mihalic et al Year 2011 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☒	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☐	☒	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☒	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☒	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☒	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☒	☐	☐
11. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Schmidt et al Year 2014 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	X			
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X			
3. Was the exposure measured in a valid and reliable way?	X			
4. Were confounding factors identified?		X		
5. Were strategies to deal with confounding factors stated?		X		
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	X			
7. Were the outcomes measured in a valid and reliable way?	X			
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?		X		
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?			X	
10. Were strategies to address incomplete follow up utilized?		X		
11. Was appropriate statistical analysis used?	X			

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR RANDOMIZED CONTROLLED TRIALS

Reviewer_____ Date_____

Author Schneider et al Year 2014 Record Number_____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment groups?	☒	☐	☐	☐
2.	Was allocation to treatment groups concealed?	☒	☐	☐	☐
3.	Were treatment groups similar at the baseline?	☒	☐	☐	☐
4.	Were participants blind to treatment assignment?	☐	☒	☐	☐
5.	Were those delivering treatment blind to treatment assignment?	☐	☒	☐	☐
6.	Were outcomes assessors blind to treatment assignment?	☐	☐	☒	☐
7.	Were treatment groups treated identically other than the intervention of interest?	☒	☐	☐	☐
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☒	☐	☐	☐
9.	Were participants analyzed in the groups to which they were randomized?	☒	☐	☐	☐
10.	Were outcomes measured in the same way for treatment groups?	☒	☐	☐	☐
11.	Were outcomes measured in a reliable way?	☒	☐	☐	☐
12.	Was appropriate statistical analysis used?	☒	☐	☐	☐
13.	Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____ Date_____

Author Stovner and Obelieniene Year 2008 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☒	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☒	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☒	☐	☐	☐
4. Were confounding factors identified?	☒	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☒	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☒	☐
7. Were the outcomes measured in a valid and reliable way?	☒	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☒	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☒	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☒	☐
11. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI CRITICAL APPRAISAL CHECKLIST FOR CASE CONTROL STUDIES

Reviewer_____ Date_____

Author Treleaven et al Year 1994 Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	☒	☐	☐	☐
2. Were cases and controls matched appropriately?	☒	☐	☐	☐
3. Were the same criteria used for identification of cases and controls?	☒	☐	☐	☐
4. Was exposure measured in a standard, valid and reliable way?	☒	☐	☐	☐
5. Was exposure measured in the same way for cases and controls?	☒	☐	☐	☐
6. Were confounding factors identified?	☐	☒	☐	☐
7. Were strategies to deal with confounding factors stated?	☐	☒	☐	☐
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	☒	☐	☐	☐
9. Was the exposure period of interest long enough to be meaningful?	☐	☐	☒	☐
10. Was appropriate statistical analysis used?	☒	☐	☐	☐

Overall appraisal: Include ☒ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)