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# Chronic pain and posttraumatic stress disorder – a systematic review.

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**Grado de Psicología**

Any acadèmic 2017-18

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S'autoritza la Universitat a incloure aquest treball en el Repositori Institucional per a la seva consulta en accés obert i difusió en línia, amb finalitats exclusivament acadèmiques i d'investigació	Autor		Tutor	
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chronic pain, posttraumatic stress disorder

## Abstract

The purpose of this paper is to provide an overview of the most recent body of research regarding the comorbid condition of chronic pain (CP) and posttraumatic stress disorder (PTSD). To meet this end, ten selected studies were systematically reviewed.

Theoretical components and the findings of the studies were then synthesized into a more holistic framework in order to make the attempt to understand the complexity of overlapping CP and PTSD. This paper concludes with an outlook for further research to address the emotional dimensions of anger, impulsivity, and aggression in PTSD and CP.

Key words: chronic pain, posttraumatic stress disorder

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## ABBREVIATIONS

e.g.           exempli gratia

et al.         et alii

i.e.           id est

CONSORT     Consolidated Standards of Reporting Trials

STROBE      Strengthening the Reporting of Observational Studies in Epidemiology

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## CHAPTER I: RESEARCH OBJECTIVE

### Introduction

CP is one of the most frequent conditions for people to seek medical consultation (Pereira, França, de Paiva, Andrade, & Viana, 2017). It is considered to be a public health problem causing impairment in social and physical functioning, and emotional regulation (Pereira et al., 2017). Patients may experience disruption in sleeping pattern, loss of energy, appetite, and libido, increased irritability, and “decreased interest in family, social, and professional activities” (Kreling, Cruz, & Pimenta, 2006). In a cross-cultural study including 19 countries, Viana et al. (2018) found that (especially earlier-onset) mental disorders were strong predictors of subsequent chronic neck and back pain. PTSD is one of the mental disorders most strongly linked to CP (McWilliams, Cox, & Enns, 2003). Although there is a great amount of studies investigating PTSD and pain, only few study this comorbidity from the view of the affected population seeking treatment (Siqueland, Ruud, & Hauff, 2017).

In this paper, the relationship between PTSD and (self-) reported pain in CP patients is analyzed. Based on previous research, it is hypothesized that

- (1) there would be a high comorbidity between any type of CP and PTSD,
- (2) the prevalence of PTSD in CP patients would be higher than in the general population,
- (3) CP patients with a PTSD diagnosis would report more severe pain,
- (4) there would be a gender difference regarding the prevalence, severity, and number of pain locations, women outnumbering men.

## Definitions

### Chronic pain

Pain, a complex phenomenon, is an unpleasant sensory and emotional experience linked to actual or potential tissue damage, or described in terms of such damage. Often, pain serves as a symptom or warning of a medical condition or an injury. Treatment of the lesion not always resolves the pain, so that it may persist (IASP Taxonomy Working Group, 2011). Within the concept of pain, the discrimination between the conditions of acute pain and CP is made. CP is pain that lasts or recurs for longer than three months. Such pain can become the sole or principal clinical problem in some individuals (Bonica, 1953; Treede et al., 2015). In June 2017 the WHO proposed a new definition of the term. Supported by the IASP, the new classification for the 11<sup>th</sup> ICD catalogue has been developed (The Societal Impact of Pain, 2017). This reference work comprises seven CP categories: (1) chronic primary pain, (2) chronic cancer pain, (3) chronic post-traumatic and post-surgical pain, (4) chronic neuropathic pain, (5) chronic headache and orofacial pain, (6) chronic visceral pain, and (7) chronic musculoskeletal pain (Treede et al., 2015).

CP is a frequent condition, affecting approximately 20% of people worldwide (Breivik, Collet, Ventafridda, Cohen, & Gallacher, 2006; Goldberg & McGee, 2011; Gureje, 2008). It is among the most prevalent and expensive health problems in the West (Siqueland, Hussain, Lindstrøm, Ruud, & Hauff, 2017). Within the population of individuals suffering from CP, two-thirds describe their pain intensity as moderate and one-third as severe (Breivik et al., 2006). And there is a sex difference - more women than men announce to suffer from CP. Mental disorders, such as anxiety disorders and depression, are more prevalent among individuals with CP compared to the general population (Breivik et al., 2006). Mental illnesses are linked to more functional impairment in people with CP and therefore may impede recovery (McWilliams et al., 2003; Tunks, Crook, & Weir, 2008). ). It is considered that anxiety disorders could be even more strongly linked to painful chronic conditions than depression (McWilliams, Goodwin, & Cox, 2004). Understanding the nature of this interrelation is indispensable in order to improve treatment and to ensure high quality care for those who are affected.

## Posttraumatic stress disorder

PTSD is a relatively common anxiety disorder that develops in some individuals who have experienced or witnessed a shocking, dangerous, or life-threatening event.

According to Levine (1997), people are often traumatized by apparently ordinary experiences. Symptoms of PTSD usually begin within three months of the traumatic incident, but its onset can also be delayed (National Institute of Mental Health, 2017).

Psychophysiological assessment has shown a heightened autonomic (heart rate, skin conductance) and facial EMG reactivity to trauma-related cues, where reactivity correlates with PTSD severity (Pitman, Orr, Foa, & Claiborn, 1987; Blanchard et al., 1996; Kleim, Ehring, & Ehlers, 2012), exaggerated startle, impaired extinction, and increased sensitivity to stimulation (Pitman et al., 2012). In sum, the characteristics in individuals who suffer from posttraumatic stress are widespread (Van der Kolk, 1994). Among these are psychophysiological changes (e.g. extreme autonomic responses to stimuli reminiscent of the trauma and non-habituation to startle stimuli), abnormalities in neurotransmitter activity (e.g. down-regulation of adrenergic receptors, decreased serotonin activity), disruption in the HPA axis (e.g. decreased glucocorticoid response to stress) and memory functioning (e.g. amnesia, hypermnnesia, sensorimotor memories rather than semantic), and traumatic nightmares (Van der Kolk, 1994). It has been shown that the hippocampus and the amygdala as well as cortical regions including the anterior cingulate, the insula, and the orbitofrontal region are altered in patients with PTSD (Rauch, Shin, & Phelps, 2006). These interconnected areas form a neural circuit that mediates, among other functions, adaptation to stress and fear conditioning (Rauch et al., 2006). Changes in these circuits have been proposed to have a direct link to the development of PTSD (Rauch et al., 2006).

Psychologically, three main features are characteristic for the posttraumatic reaction: (1) reminders of the exposure (including flashbacks, intrusive thoughts, nightmares); (2) activation (including hyperarousal, insomnia, agitation, irritability, impulsivity and anger); and (3) deactivation (including numbing, avoidance, withdrawal, confusion, derealization, dissociation, and depression) (Sherin & Nemeroff, 2011). However, the (long-term) response of a person to trauma depends not only on stressor characteristics, but also on factors specific to the person itself (LeDoux, 2007). Although of great importance for the comprehension of this complex condition, it goes beyond the scope of this paper to discuss this aspect more profoundly. However, I will come back to it at the end of this review.

As reported, the 12-month PTSD prevalence in the general population is 3.6% (USA) and 1.1% (Europe) (Darves-Bornoz et al., 2008). Women are at greater risk to develop PTSD than men (Neria, Nandi, & Galea, 2008) and more women than men suffer from PTSD (McLean, Asnaani, Litz, & Hofmann, 2011). Noteworthy in this context is a study of female veterans that revealed that pregnancy increases the risk of PTSD above that for non-pregnant females (Mattocks, Skanderson, & Goulet, 2010).

## CHAPTER II: RELATED LITERATURE

### Theoretical paradigm and conceptual framework

#### The neurobiological integration of pain and stress

Shifting from an acute to a chronic state of pain, the individual's psychological state of being and his mind are altered (Simons, Elman, & Borsook, 2014). It has been described that physical and emotional pain exists on the same continuum (Borsook, 2007; Elman, Zubieta, & Borsook, 2011) with common brain networks involved (Bendelow & Williams, 2008). As human beings we are in constant interaction with our environment. Physical and psychological stressors can elicit adaptive or maladaptive neural and hormonal responses (Abdallah & Geha, 2017). Acute stress activates the hypothalamic-pituitary-adrenal axis (HPA) leading to the release of steroid hormones (glucocorticoids) that are produced by the adrenal gland (McEwan, 2007). These glucocorticoids have receptors concentrated in the limbic brain including the amygdala, hypothalamus, hippocampus, and prefrontal cortex (PFC) (Sanchez, Young, Plotsky, & Insel, 2000). In the limbic system, these corticosteroid hormones act as transcription factors, which are proteins that help turn specific genes "on" or "off" by binding to nearby DNA (Abdalla & Geha, 2017). Glucocorticoids can thus have long-lasting effects on the brain's cellular functioning (Abdallah & Geha, 2017). Perceived stress is integrated in the limbic brain with past experiences (i.e. memory), the current physiological state (e.g. hunger/satiety), and decision-making. According to this process, emotional states are updated (e.g. increased or decreased anxiety, anger etc.) which leads to a behavioral action, the so-called fight-or-flight (or freeze) reaction (Abdallah & Geha, 2017). Functional magnetic resonance imaging studies in response



to stress or pain reveal noticeable spatial overlap in the amygdala, hippocampus and other brain structures (Sinha, Lacadie, Constable, & Seo, 2016).

As part of the limbic system, the amygdala plays a crucial role in emotional processing, neuropsychiatric disorders, the emotional-affective dimension of pain, and in pain modulation (Thompson & Neugebauer, 2017). The amygdala is critical in the expression of fear (Phelps & LeDoux, 2015) and active during response to threats, such as angry faces (Whalen et al., 2001). Neuroimaging studies indicate not only hyperactivity of the amygdala in individuals with diagnosed CP such as IBS, migraine, and fibromyalgia (Simons et al., 2014), but also in patients with PTSD (Hashmi et al., 2013). Former research revealed the bidirectional relationship between physical pain and psychological states (Simons et al., 2013, see Figure 3). On the one hand, experiencing pain can set off a cascade of neurological (originally sensory) events that lead to an altered psychological condition (Elman et al., 2013; Goldberg et al., 1999; Nicolson et al., 2010; see Figure 2). On the other hand, previous psychological conditions can create a heightened risk for pain chronicity due to greater vulnerability by initiating the process of cross-sensitization (Elman, Borsook, & Volkow, 2013). That is when former exposure to stressful events results in greater sensitivity to other apparently unrelated stimuli in the present (e.g. childhood trauma) (Elman et al., 2013).

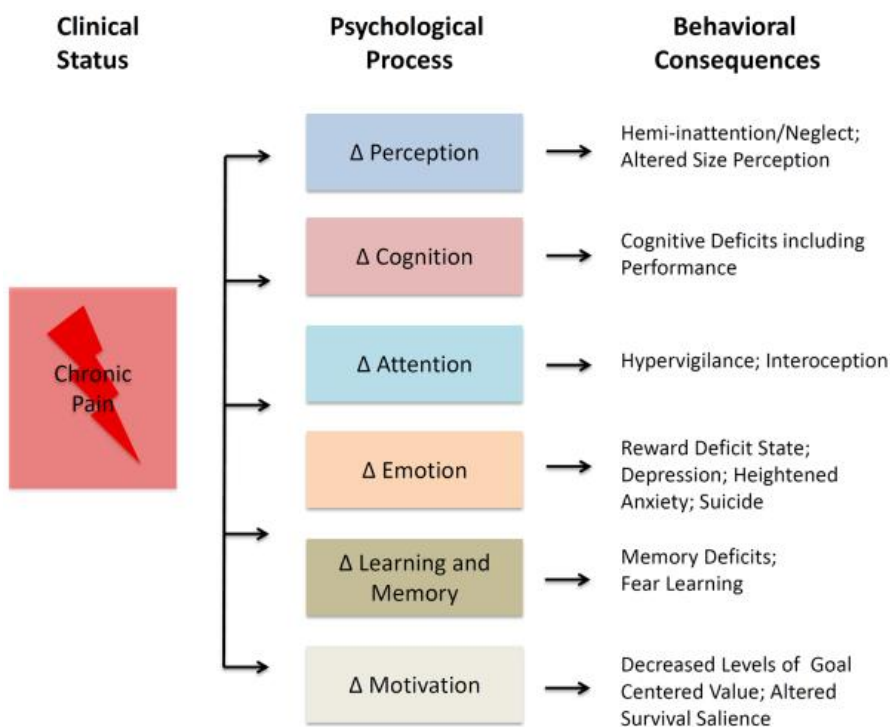


Figure 1. Pain, psychological processes, and behavior (Simons et al., 2014).

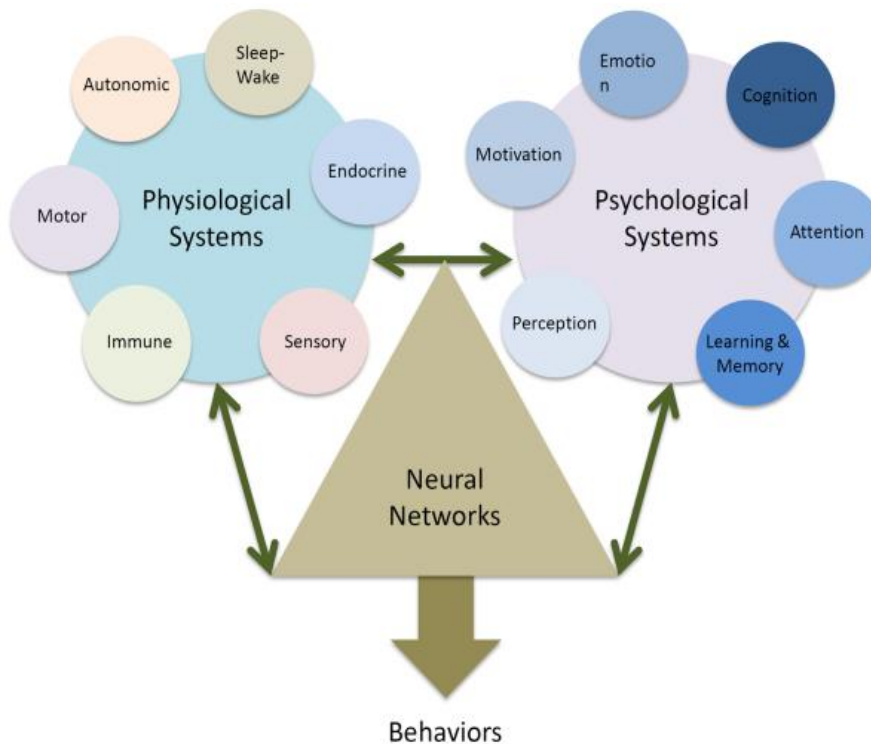


Figure 2. Integration of pain behaviors – physiological and psychological systems involved (Simons et al., 2013).

Psychological models try to explain possible mechanisms of how CP and PTSD may relate to, and maintain each other. To give an overview, without the claim to be complete, some of these models are described briefly below.

*Mutual Maintenance Model* by Sharp and Harvey (2001)

According to this model, there are seven specific factors by which mutual maintenance of CP and PTSD may occur: (1) attentional bias regarding threatening / painful stimuli, (2) anxiety sensitivity leads to catastrophizing, (3) pain acts as a trigger and reminder of trauma and causes arousal, (4) avoidance serves as coping strategy to minimize pain and disturbing thoughts, (5) dimensions of depression may contribute to the maintenance, (6) general anxiety is another factor of contribution, and (7) cognitive overload from CP and PTSD prevent / limit the use of adaptive coping strategies.

*Shared Vulnerability Model* by Asmundson, Coons, Taylor, & Katz (2002)

According to this model, anxiety sensitivity is a predisposing factor contributing to the development of both, CP and PTSD. It says that individuals with high anxiety-sensitivity are physically and emotionally more reactive to any kind of stressors, leaving

them more vulnerable to pain and traumatic stressors compared to those with low-anxiety sensitivity. Regarding CP, anxiety sensitivity intensifies fear and avoidance of activities that may induce pain, which leads to a maintenance of pain. To summarize, the model's hypothesis is that anxiety sensitivity represents a vulnerability factor in the development and maintenance of PTSD and CP.

*Fear-Avoidance Model* by Norton and Asmundson (2003)

Norton and Asmundson (2003) propose that avoidance is a shared feature in both, CP and PTSD. According to the authors, physical symptoms and / or physical arousal (e.g. muscle tension, increased heart rate) may lead to pain sensations and dysfunctional cognitions (e.g. catastrophizing). Avoidance behavior increases when fears and negative cognitions are confirmed. In CP, fear and avoidance generally refer to the avoidance of movements such as exercise or work, for apprehension of causing increased pain or injury. In PTSD, commonly, individuals avoid everything that reminds them of the traumatic event, trying to prevent themselves from re-experiencing disturbing thoughts and feelings. Avoidance and fear can lead to the maintenance of PTSD symptoms, hindering adaptation.

*Triple Vulnerability Model* by Keane and Barlow (2000)

In order to develop an anxiety disorder, a set of vulnerabilities needs to be present: (1) a generalized biological vulnerability, (2) a generalized psychological vulnerability based on early experiences of control over salient events, and (3) a specific psychological vulnerability in which focusing anxiety on specific situations has been learned (Keane & Barlow, 2002). According to the authors, PTSD may develop when negative affect and a sense of uncontrollability emerges during exposure to potential traumatic events.

## CHAPTER III: METHODS

### Material and methods

#### Search strategies and selection of studies

Ensuring accuracy, the PICOS criteria were formulated a priori in the protocol of the systematic review. The PICOS is an approach to develop a research question (Liberati et al., 2009) defining the characteristics of the participants, interventions, comparators, the type of outcomes and the study designs to be included. Additionally, a search was conducted on PROSPERO. As an international database of prospectively registered systematic reviews in health related topics, PROSPERO records and maintains key features from existing review protocols as a permanent record (PROSPERO, 2017). The last update was made on November 24<sup>th</sup>, 2017, and no (ongoing) review referring to the present subject was found.

This review followed the quality standards for systematic reviews as presented in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses-PRISMA) statement (Liberati et al., 2009), which is attached in the Appendix. Data collection took place between September 2017 and November 2017 by searching in *PubMed Central* database using the following criteria for eligibility: a) human population over the age of 18 years, with CP of any origin, lasting for at least three months; b) PTSD lasting for at least three months; c) observational studies with primary and secondary outcomes, or clinical trials; d) studies from 2012 until 2017. Migraine was considered as CP, assuming that it is a chronic disorder, despite the episodic presentation of acute symptoms (Bigal & Lipton, 2008). The period of the last five years was chosen to gain an overview over the most recent body of research on this subject. The search descriptors in the database were “chronic pain” AND “ptsd”. Exclusion criteria were mere case studies, diagnosed obsessive-compulsive disorder, attention-deficit-/hyperactivity disorder or attention-deficit disorder, respectively; history of / or current psychotic or bipolar disorder, current intake of antipsychotics, and acute suicidality.

### Data extraction

Initially, titles and abstracts of the filtered articles were screened. Studies using non-structured assessments only (e.g. informal clinical interviews) or assessments that did not represent sufficiently the diagnostic criteria for either PTSD or CP were removed. Additionally, all reference lists of the studies included were hand searched for further relevant publications. Any doubts or disagreements relating to inclusion eligibility were resolved through discussion with my supervisor Prof. Pedro Montoya. After selecting the filtered studies based on inclusion and exclusion criteria, full texts were retrieved for analyses. The following items were manually extracted, tabulated, and described:

1. Study quality scores by using the STROBE and CONSORT standards for observational studies and clinical trials (Table 1).
2. Clinical and demographic characteristics, including number of participants per group, age, sex, studied conditions, diagnostic criteria, and control group (Table 2).
3. Study design, data collection and findings, including used protocols, study merits, and limitations (Table 3).

*Table 1. Results of the quality assessment of studies and risk of bias using the STROBE and CONSORT criteria.*

Source	Criteria for patient selection	Quality criteria STROBE & CONSORT scale; Level of Quality			Total score (max. 8 points)
		Low	Moderate	High	
Siqveland et al., 2017	Study specific inclusion/ exclusion criteria			x	7
Häuser et al., 2015	ACR <sup>1</sup> criteria			x	8
Karşıkaya et al., 2013	Study specific inclusion/ exclusion criteria			x	7
Friedman et al., 2017	Study specific inclusion/ exclusion criteria			x	7
Balaban et al., 2012	Study specific inclusion/ exclusion criteria			x	8
Roper et al., 2017	Study specific inclusion/ exclusion criteria			x	7
Iorio et al., 2014	Study specific inclusion/ exclusion criteria			x	7
Åkerblom et al., 2017	Study specific inclusion/ exclusion criteria			x	7
Morasco et al., 2013	Study specific inclusion/ exclusion criteria			x	8
Teodorescu et al., 2015	Study specific inclusion/ exclusion criteria		x		6

<sup>1</sup>American College of Rheumatology

*Table 2. Study design, demographic and clinical characteristics of subjects from the included studies.*

Source	Study design	Studied conditions	Diagnostic criteria	Patients with CP n (w,m)	Mean age in years (SD)/ min-max	Patients with PTSD n (w,m)	N	Control
Siqveland et al. 2017	Cross sectional	PTSD, CP	LEC <sup>1</sup> , MINI <sup>2</sup> , VAS <sup>3</sup> , DSM-IV <sup>4</sup> , BD <sup>5</sup> , medical records	63 (40,23)	44.9 (10.5)/ 24-66	20 (-)	63	+
Häuser et al., 2015	Cross-sectional	PTSD Fibro- myalgia	PSDS <sup>6</sup> , PHQ-4 <sup>7</sup> , PDI <sup>8</sup> , CTQ <sup>9</sup> , M-CIDI <sup>10</sup> , PDS <sup>11</sup> , DSM-IV	71 (68,3)	51.2 (10.2)	24* (-)	142	+
Karşıkaya et al., 2013	Cross-sectional	PTSD Migraine Alexi- thymia	SCID-I/CV <sup>12</sup> , CAPS <sup>13</sup> , TAS-20 <sup>14</sup> , VAS	60 (44,16)	33.4 (8)	17 (-)	60	+
Friedman et al., 2017	Cross-sectional	PTSD Migraine Depression	ICHD-III <sup>15</sup> , PCL-C <sup>16</sup> , PHQ-9 <sup>17</sup>	366 (366,-)	27.76 (6.27)	232 (232,-)	2922	-
Balaban et al., 2012	Cross-sectional	PTSD Migraine Alexi- thymia	IHS <sup>18</sup> , TAS-20, VAS, PCL-C, MIDAS <sup>19</sup> , SCID-I, ID Migraine <sup>20</sup>	31 (25,6)	20.9 (1.7)	7 (-)	246	+
Roper et al., 2017	Cross-sectional	PTSD, TBI <sup>21</sup> Headache disability	HIT-6 <sup>22</sup> , PCL-C	86 (21,65)	45 (20)	35 (-)	86	-

Ioro et al., 2014	Cross-sectional	PTSD, IBS <sup>23</sup>	PDS, HADS <sup>24</sup> , SF <sup>25</sup> , PDS, HADS, MPI-V2 <sup>26</sup> , NRS <sup>27</sup> , TSK <sup>28</sup>	1,748 (1,430; 318)	- / 39.9-52.8	919 (-)	21,264**	-
Åkerblom et al., 2017	Cross-sectional	CP, PTSD	PDS, HADS, NRS, MPI, SF-36, TSK	439 (334,129)	41.1 (11.3) / 18-67	127 (-)	463	-
Morasco et al., 2013	Cross-sectional	PTSD, CP Depression SUD <sup>***</sup>	CPCI <sup>29</sup> , PCL-C, MPI <sup>30</sup> , BDI-II <sup>31</sup> , SCID, TLFB <sup>32</sup> , ICD-9-CM <sup>33</sup> LEC, SCID-PTSD,	201 (16,85)	54.9 (7.6)	65	201	+
Teodorescu et al., 2015	Cross-sectional	PTSD, CP	SIDES <sup>34</sup> , M.I.N.I. <sup>35</sup> , IES-R <sup>36</sup> , HSCL-25 <sup>37</sup>	40 (17,23)	43 (8.2)	50 (-)	61 (25,36)	-

Explanation of abbreviations of diagnostic criteria, see Table 2. Appendix

\* probable PTSD

\*\* weighted sample size (factual sample size: 419)

\*\*\* substance use disorder



### Risk of bias and study quality

Due to the heterogeneous symptoms and diagnoses, risk of bias was considered. The analysis of exclusion criteria, patient selection, and validity of assessment instruments and statistical analysis was conducted in accordance to the following parameters

1. Did inclusion and exclusion criteria follow the recommendations of the International Association for the study of Pain (IASP)? Or alternatively, did the study present a detailed and consistent description of inclusion and exclusion criteria for participants with CP and PTSD, and controls?
2. Were standardized assessment instruments used to determine PTSD, CP, and the characteristics of these conditions (intensity, duration, time of onset etc.)?
3. Did the study provide detailed information about possible confounders, distorting the association between the variables?

Study quality was quantified using the STROBE & CONSORT quality review criteria as an instrument. These criteria assess the quality of randomized clinical trials as well as non-randomized studies. The rating categories of the scale are divided into three quality levels: low, moderate, and high with a minimum of 0 and a maximum score of 8. A range of 1 to 3 points represents low quality evidence, moderate quality level is given when 4 to 6 criteria are met, and high quality evidence exists when 7 to 8 criteria are met (see Table A in the Appendix). Since all selected studies were descriptive studies, comparison groups and baseline measurements were treated as “control groups”.

## CHAPTER IV: RESULTS

### Selected studies

The following search criteria were applied in *PubMed Central* using the builder to create the search in *Body – All words: (Chronic pain) AND ptsd*. The publication date served as a filter ranging from **2012/01/01 to 2017/11/24**. Initially, 890 items were found. The main reasons for exclusion were animal studies, studied sample under 18 years of age, narrative reviews, posters and conference papers, single case studies, assessments and comparisons of diagnostic instruments, healthcare programs, policies and law implementation, theoretical frameworks and concepts, ethical issues and genome studies, meta-analyses and other health conditions. Of these, 25 studies were selected for further screening after reading the titles.

Another 15 studies were excluded, due to the presence of exclusion criteria after reading the abstracts and / or the full text. The reasons for exclusion were the following: absence of either PTSD or CP diagnosis, synopsis of possible underlying mechanisms, and studied sample under the age of 18 years. (see Figure 1. for eligibility criteria).

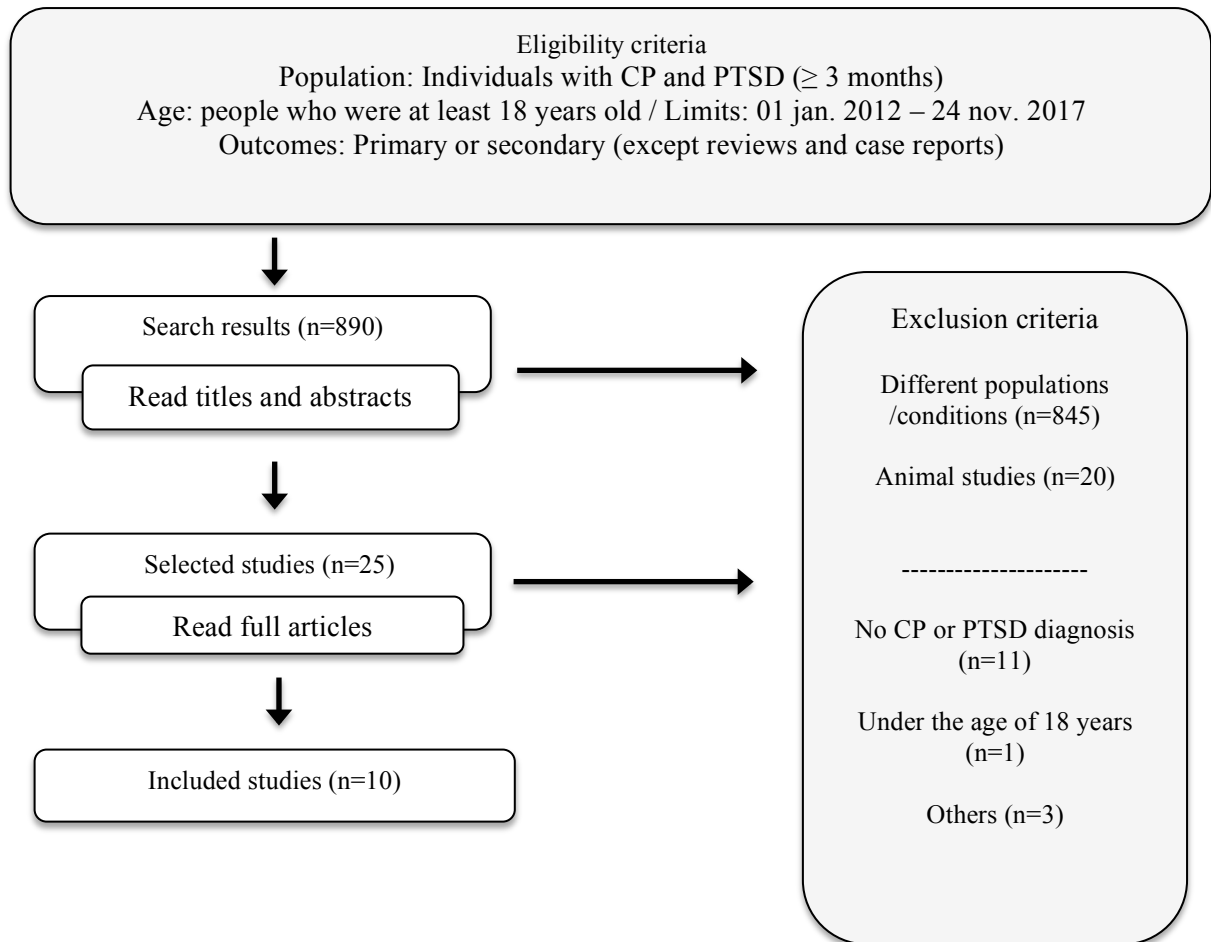
#### Quality assessment

The assessment of the study quality was performed using the STROBE and CONSORT criteria (Von Elm et al., 2014). Data analysis was conducted with findings organized in relation to the key issues of quantity and quality of the evidence base. To increase clarity of the final results, the final studies included in the qualitative synthesis were arranged into three main categories of evidence (see Table C in Appendix). Categories A and B correspond to evidence that is expected to be of high to moderate quality. Given the general much weaker value of evidence in category C, extracted data from studies classified as category C are limited to the existence of the study alone. The risk of bias was assessed using an 8-item scale (range 0-8; STROBE criteria for observational studies; see Table A in Appendix). These scales combine various criteria for evaluating sources of bias, e.g. the definition of inclusion and exclusion criteria and the existence of a comparison group. One point for each criterion met was given to each study, with the categories of low quality evidence (scores ranging from 0-3 points) indicating a high risk of bias, moderate quality evidence (4-6 points), and high quality evidence (7-8 points) indicating a moderate and low risk of bias, respectively.

Table 1. visualizes the results of the quality assessment and risk of bias of the 10 studies included in this review. The quality scores in this review ranged from 6 to 8. Detailed information about the scores of each study is provided in Table B (Appendix).

Classification of CP as established by the American College of Rheumatology was used as inclusion criteria in one study. No study provided information about the medication status, nor description of medication / drug use by its participants. Therefore, measures to control possible bias resulting from medication use were not provided. To summarize, nine of the ten studies corresponded to category A, and one study was found to be of moderate quality and was placed into category B. There was no low quality study.

Figure 3. Flow chart of selection process for eligible studies



## Study design, demographic, and clinical characteristics

### Study design

All studies used a cross-sectional design (n = 10).

### Patients' profile

In total, 25.508\* individuals were evaluated of whom 3.105 were diagnosed with CP and 1.496 were diagnosed with PTSD. Five out of the ten studies included comparison groups with a total of 19.823 individuals. The factual sample sizes of the patient groups ranged from 31 to 419\*\* (weighted sample sizes ranged from 31 to 21,264) individuals. Within the sample of CP patients, women outnumbered men with a percentage of 76%. The age of participants, when identifiable, ranged from 18 to 67 years. Seven out of the ten studies evaluated the differences between the participants on traumatic exposure using minimally three different (sub-) categories: emotional, physical, and sexual abuse. One study investigated CP and PTSD after any kind of accident leading to traumatic brain injury (TBI). Two studies did not refer to the nature of traumatic exposure. The Life Event Scale, the PTSD-Civil Version, and the DSM-IV were the most frequently used instruments to assess PTSD. The Pain Disability Index was used in two studies to measure the degree to which aspects of participants' lives were disrupted by CP. The most frequent comorbid conditions were alexithymia, fibromyalgia, migraine, and affective disorders (Table 2).

\*includes weighted sample, factual sample size= 419 (Ioro et al., 2014)

\*\*effective, not weighted

### Diagnosis

Participants in the included studies suffered from generalized pain, neuropathic pain, (low) back pain, pain related to head or cervical pain, chest pain, neck or joint pain, CP of any origin, rheumatism/arthritis, fibromyalgia, migraine with and without aura, irritable bowel syndrome, alexithymia, panic disorder, specific phobia, kinesiophobia, anxiety, depression, TBI, alcohol and substance abuse. Participants with PTSD were exposed to different traumatic events, e.g. natural disaster, fire or explosion, transportation accident, serious accident at work or at home, exposure to toxic substance, physical assault, assault with weapon, sexual assault or other unwanted sexual experience, combat or exposure to a war-zone, captivity, life-threatening illness

or injury, severe human suffering, witnessing sudden, violent death, witnessing sudden, unexpected death of someone close to them, serious injury, harm, or death the participants caused to someone else, and other stressful event or experience. All studies used standardized, validated and specific diagnostic criteria for CP and PTSD (Table 2).

#### CP assessment

The most frequently used instruments to assess CP and its severity were the Visual Analogue Scale, the Pain Disability Index, the International Classification of Headache Disorders, and the Multidimensional Pain Inventory.

#### PTSD assessment

The most frequently used instruments to assess trauma exposure and PTSD were the Life Events Checklist, the Munich Composite International Diagnostic Interview, the Childhood Trauma Questionnaire, the DSM-IV, the Post-traumatic Diagnostic Scale, the Post-traumatic Stress Disorder Scale, and the PTSD Checklist.

#### Findings

The most frequently analyzed subject was the prevalence of PTSD in CP patients, pain severity and the overall impact of functioning. Overall, the studies found a significantly higher prevalence of PTSD in patients suffering from any CP condition, compared to non-CP patients or healthy individuals (Åkerblom, Perrin, Fischer, & McCracken, 2017; Siqueland, Ruud, et al., 2017). One study found that nearly one-third of its participants with CP also were diagnosed with PTSD, and that PTSD was associated with poorer functioning and greater treatment needs (Åkerblom et al., 2017). One study assessed the difference between intentional and non-intentional traumatic events and PTSD on CP (Siqueland, Ruud, et al., 2017). The authors found that exposure to intentional traumatic events, as well as PTSD was significantly associated with more severe pain. PTSD significantly moderated the relationship between trauma exposure and pain in CP patients (Siqueland, Ruud et al., 2017).

Two studies examined the relationship between PTSD, migraine, and alexithymia. The major relevant findings from these studies were that the prevalence of co-morbid PTSD and alexithymia are higher in individuals with current migraine than in the comparison group (Karşıkaya, Kavakçı, Kuğu, & Güler, 2013; Balaban et al., 2012). One study was designed to assess the relationship between PTSD, depression, and migraine in a cohort of pregnant women (Friedman et al., 2017). The prevalence of PTSD was increased in those women who suffered from migraine, irrespective of the presence or absence of depression. Another study investigated the mediating role of depression and coping strategies in patients with CP and PTSD (Morasco et al., 2013). The researchers found that illness-focused pain coping (e.g. guarding, resting, asking for assistance) and depressive symptoms jointly mediated the relationship between PTSD and both, pain interference and pain severity (Morasco et al., 2013). Transcultural robustness regarding the significantly heightened prevalence between adults with CP and childhood maltreatment, lifelong traumatic experiences, and PTSD were found by three studies (Häuser et al., 2015; Iorio, Makipour, Palit, & Friedenber, 2014; Teodorescu et al., 2015). All studies revealed a gender difference regarding CP and PTSD, with more women than men suffering from CP and PTSD (e.g. Teodorescu et al., 2015; Iorio et al., 2014). The evaluation of a sample of African Americans indicated that PTSD was independently associated with IBS (Iorio et al., 2014). One study showed that increased severity of PTSD-type symptoms was significantly associated with increased disability in patients with chronic posttraumatic headache after traumatic brain injury (Roper et al., 2017). Teodorescu et al., (2017) revealed that in a sample of refugee psychiatric outpatients, CP at clinical levels was present in 66%. And 88% of the sample fulfilled the criteria of a current PTSD diagnosis. Comorbid CP and PTSD were found in more than half of these outpatients (57%).

#### Overview over included papers

A brief description of major findings reported by the selected studies is provided as following:

Siqveland, Ruud, et al., (2017) assessed 63 patients from a specialized pain clinic, regarding pain severity and localization, trauma exposure and psychiatric disorders. Additionally the treatment outcome was analyzed in a follow-up assessment with 42 of the initially 63 patients present. The most common pain conditions was generalized pain with 26 participants suffering from it, 21 had neuropathic pain, 9 had pain related to head or cervical pain and 7 had back or low back pain. The participants reported being exposed to an average of four potentially traumatizing events (PTEs) with significantly more women than men reporting exposure to sexual abuse, war, and the death of a close one. Exposure to 4 of the 16 PTEs (assault with a weapon, war zone experience, sexual abuse, and sudden death) was significantly related to PTSD. As for mental disorders, depression was most common – 42% of the participants had a current major depressive disorder. About a third (32.3%) of the participants had PTSD, and PTSD was significantly more common among women than among men. Of those with PTSD, 55% were diagnosed with depression. Other mental disorders were less frequent: 21% had any anxiety disorder (excluding PTSD) and 6% had an alcohol or substance abuse disorder. Overall trauma exposure was significantly related to PTSD. With trauma exposure divided into intentional and non-intentional events, only exposure to the intentional events was significantly related to PTSD and to pain severity. Participants with PTSD reported more severe pain than those without PTSD, and PTSD was related to pain severity with a medium-to-large effect size. PTSD, but not exposure to trauma, came out as the only significant predictor of CP explaining 13% of the variance in pain. There were no significant differences in treatment effects between persons with and without PTSD. The authors suggest that clinicians treating pain patients should pay attention to a history of trauma and evaluate their patients' PTSD status.

Häuser, et al. (2015) examined the association between Fibromyalgia Syndrome (FMS), childhood maltreatment, lifetime psychological traumas, and potential differences between countries adjusting for psychological distress, in a transcultural study. Seventy-one age- and sex-matched US- and German FMS outpatients were compared. There were differences found regarding FMS severity, probable anxiety, depression, and posttraumatic stress between the groups. When adjusted for psychological distress, statistical differences between the cohorts emerged. These statistical differences were fully accounted for by psychological distress with small effect for emotional and medium effects for sexual abuse, emotional neglect and physical neglect.

In summary, US- and German patients did not significantly differ in the amount of self-reported childhood maltreatment (emotional, physical and sexual abuse or neglect) or in the frequency of lifetime traumatic experiences. No differences in the frequency of potential anxiety, depression, and PTSD were observed. Psychological distress fully accounted for group differences in emotional and sexual abuse, and emotional and physical neglect. Findings between the examined samples were robust. The authors argue that abuse and trauma are potential risk factors for developing FMS across different cultures. Further, FMS outcome is negatively influenced by mental disorders. Therefore they recommend the screening for mental disorders in these patients.

Karşıkaya et al. (2013) evaluated the prevalence of PTSD and alexithymia in migraine patients. Sixty patients with migraine and 60 healthy volunteers without a diagnosis of migraine were included in the study. The rates of history of witnessing trauma were statistically significantly higher in the migraine group compared to the control group. When the two groups were compared in terms of a diagnosis of current and lifelong PTSD, the rate of PTSD was found to be significantly higher in migraine patients. A diagnosis of PTSD was made in 28.3% of the subjects in the migraine group, compared to 8.3% of the subjects in the control group. The number of individuals who were found to have alexithymia was statistically significantly higher in the migraine group compared to the control group. Regarding the time of onset of migraine in individuals diagnosed with PTSD, 94% stated that headache started after a traumatic experience. When the groups with and without PTSD in the migraine group were compared in terms of sexual abuse, accident and tendency to trauma, no statistically significant difference was found. When they were compared in terms of physical abuse, the rate of physical abuse was significantly higher in the individuals with PTSD compared to those without PTSD. The number of participants who were exposed to a traumatic event was significantly higher in those with PTSD in the migraine group compared to those without PTSD. The researchers suggest the realization of further studies with large sample sizes to generalize the results of their investigation.



Friedman et al. (2017) studied the relationship between migraine, depression, and PTSD in a cohort of 2922 pregnant women. In summary, migraine in pregnant Peruvian women was associated with increased odds of PTSD. After adjusting for confounders including antepartum depression, women who reported any migraine had a 1.97-fold increased odds of PTSD (95% CI: 1.64–2.37) compared to women with no history of migraine. The authors call for additional research on the relationship between migraine and PTSD (in pregnant women), as well as for further research to assess treatment implications of this comorbidity.

Balaban et al. (2012) investigated the prevalence of migraine, alexithymia, and PTSD in a sample of 250 Turkish medical students. PTSD and alexithymia were found to be significantly higher in students with migraine compared to the control group. Students with migraine had significantly higher rates of alexithymia. The authors advocate that the detection and treatment of PTSD and alexithymia may improve pain levels and migraine-related function impairment in medical students.

Roper et al. (2017) studied the relationship between posttraumatic headache (PTH) after TBI and PTSD. They found that PTSD was significantly correlated with headache disability (HD). PTSD was highly associated with HD, with a prevalence rate of 40%. In sum, (1) patients with chronic PTH had greater HD if they also had PTSD, (2) younger patients with loss of consciousness at the time of injury had the greatest disability from chronic PTH, and (3) in patients with chronic PTH and PTSD, HD might be improved if PTSD is actively managed alongside headache management. The researchers propose future research to address these issues.

Iorio et al. (2014) found IBS in African Americans (AA) to be prevalent with 8.2%. The prevalence of PTSD and harmful alcohol use was far higher in those with IBS than in those without. Women outnumbered men regarding PTSD (70.4%). PTSD was associated with depression, anxiety, harmful drinking, and substance abuse. The study found a strong relationship between PTSD and moderately severe to severe depression as well as anti-depressant use. AA with IBS were twice as likely to suffer from PTSD. PTSD was associated with adverse lifestyle choices (e.g. drug and alcohol misuse) and had a substantial impact on quality of life, both in the physical and psychological domains.

Åkerblom, et al. (2017) investigated the prevalence of traumatic experiences, trauma types, and PTSD in a sample of patients seeking treatment for CP. The researchers examined how indices of pain-related functioning varied with a history of traumatic exposure and PTSD diagnostic status. Out of 439, 71.8% reported experiencing at least one previous trauma(s) and 28.9% fulfilled criteria for PTSD diagnosis. For patients reporting a history of traumatic exposure no significant differences were observed regarding the reported types of traumas. When patients were asked to identify their most upsetting traumatic event, most of them were *other traumatic events* (27.9%) followed by *serious accident* (23.8%), *life-threatening illness* (8.3%), *sexual assault by someone you know* (7.6%), *sexual assault by a stranger* (4.4%), and *non-sexual assault by a stranger* (4.1%). Additionally, 14.6% of the patients were unable to identify their most upsetting traumatic event and instead re-reported multiple traumas. The study revealed that (1) those fulfilling PTSD (group 1) criteria had significantly higher levels of pain interference, kinesiophobia, anxiety, and depression and a significantly lower level of life control when compared to those exposed to trauma, but not fulfilling PTSD criteria (group 2) and those with no history of traumatic exposure (group 3); (2) those with PTSD had significantly higher pain intensity and lower physical functioning compared to group 2 as well as worse general health and more pain sites compared to group 3. No significant differences on any of the variables were found between groups 2 and 3. The authors conclude that routine screening for PTSD in CP patients is needed. They suggest using the PDS as a low-cost screening instrument.

Morasco et al. (2013) studied the mediating role of pain-related coping and depressive symptoms in PTSD and CP in US military veterans. Thirty-two percent of all veterans who suffered from CP had comorbid PTSD. Participants with PTSD reported more severe pain, poorer pain-related function, displayed more symptoms of depression, and were more likely to meet diagnostic criteria for a current alcohol or substance use disorder. Participants with PTSD were more likely to be diagnosed with chronic back pain (79% versus 55%), but did not differ from participants without PTSD on other pain diagnoses.

Participants with PTSD used both illness-focused (i.e., guarding, resting) and wellness-focused (i.e., relaxation, exercise/stretching, coping self-statements) pain coping strategies to a greater extent than those without PTSD. Results suggest that an illness-focused pain coping mediates the relationship of PTSD with pain interference and pain severity. PTSD symptoms, particularly avoidance, may predispose individuals to use analogous CP coping strategies (e.g.) guarding and resting. The authors propose that treatment should target depression symptoms and illness-focused coping styles.

Teodorescu et al. (2015) examined CP in multi-traumatized refugee outpatients in Norway. The researchers found 65.6% of their sample reporting CP at clinical levels. The most frequent CP location was in the head. Outpatients with CP had significantly more posttraumatic symptoms, and more psychiatric comorbidity than outpatients without CP. The study found that CP was highly comorbid with PTSD, (57%). The authors call for further investigation regarding the comorbidity with somatic disorders and psychiatric conditions, respectively.

*Table 4. Description of findings, strengths, and limitations of the included studies.*

Source	Condition	Cultural / ethnic background of sample	Results	Merit	Limitations
Siqveland et al. 2017	PTSD, CP	Norwegian	32% of CP patients had PTSD; exposure to intentional traumatic events & PTSD related to more severe pain; PTSD moderated relationship between trauma exposure & pain	Follow-up assessment	Limited sample size
Häuser et al., 2015	FMS, PTSD	German & US-American	Abuse & trauma are potential risk factors for developing FMS across different cultures; High prevalence of potential mental disorders in FMS-patients	Transcultural study	No standard psychiatric interview was conducted; no control group; no comparison with culturally more distinct samples from other / non-western countries

<b>Source</b>	<b>Condition</b>		<b>Findings</b>	<b>Merits</b>	<b>Limitations</b>
Karsikaya et al., 2013	PTSD, Migraine, Alexithymia	Turkish	PTSD is a common factor in migraine patients; Pain severity is high in patients with PTSD & migraine; High prevalence of alexithymia in migraine patients	Comparison group	No other psychiatric disorders than PTSD were assessed
Friedman et al., 2017	Migraine, PTSD	Peruvian	PTSD is increased in pregnant women with migraine (independent of antepartum depression)	Large sample size	Only low-income women were assessed; no standardized diagnostic evaluations were applied
Balaban et al., 2012	PTSD, Migraine, Alexithymia	Turkish	PTSD & alexithymia are common among medical students with migraine; PTSD symptoms correlate with pain-related disability	Standardized evaluation by a neurologist & psychiatrist	Results may not be generalized to general population
Roper et al., 2017	PTH*, TBI**, PTSD	British English	Patients with chronic PTH have greater headache disability if they also have PTSD; In patients with chronic PTH & PTSD, headache disability might be improved if PTSD is actively managed alongside headache management	Standardized assessment	History of migraine not assessed; Data collection at a single time point

<u>Source</u>	<u>Condition</u>		<u>Findings</u>	<u>Merits</u>	<u>Limitations</u>
Ioro et al., 2014	IBS, PTSD	African American (AA)	High prevalence of emotional and/or physical trauma in AA with IBS; AA with IBS were twice as likely to suffer from PTSD; PTSD were associated with drug & alcohol misuse; Negative correlation with QOL***	Novel study population	Low-income population; self-reported questionnaires; no assessment of impact of study design effect (stratified sampling)
Åkerblom et al., 2017	PTSD, CP	Swedish	Nearly 1/3 of patients with CP had PTSD. Poorer clinical presentations in patients with co-morbid CP & PTSD, as in comparison groups; PTSD in CP patients had greater treatment need	Relatively large sample size	Relatively homogeneous clinical sample (high educated women)
Morasco et al., 2013	PTSD, CP, Depression, Coping	U.S. American military veterans	Patients with CP & PTSD had more severe pain & poorer pain related functioning, compared to CP patients; Illness-focused pain coping styles mediated effect of PTSD on pain interference & pain severity in co-morbid PTSD & CP; Depressive symptoms mediated effect of PTSD on pain interference	Evaluation of total and individual mediating latent effects	Specific sample of military veterans; predominantly male; no evaluation of substance use as coping strategy
Teodorescu et al., 2015	CP, PTSD	Refugees from Africa, Middle East, Eastern Europe & other, resettled in Norway	High rates of co-morbid PTSD & CP	Clinical structured interview; diversity of studied population; validated co-morbid PTSD & CP at same point in time	Small sample size; no control group; assessment of CP by DESNOS criteria; exclusion of outpatients with lack of proficiency in Norwegian language

\* Posttraumatic headache  
 \*\* Traumatic brain injury  
 \*\*\* Quality of Life

## CHAPTER V: DISCUSSION

### Summary and discussion of the findings

Comorbid psychiatric disorders in people suffering from CP are highly prevalent. Among them, the predominance of PTSD in patients with CP and the symptom overlap is striking, independent of the origin or kind of pain. PTSD is associated with more severe pain in CP patients, with intentional trauma being strongly related to pain severity. PTSD correlates positively with pain-related disability and impairment in (pain related) functioning. Trauma exposure, independent of the type of trauma, relates to CP in the same way as to mental disorders. In sum, it seems that PTSD not only mediates the relationship between trauma exposure and CP, but also moderates pain interference and pain severity. Individual coping strategies play an important role regarding pain interference. Asking for assistance, guarding, and resting represent an illness-focused coping style and contribute to poorer pain related functioning. Depressive symptoms are likely to mediate the relationship between PTSD and pain interference, impacting on the illness-focused coping style. Besides that CP patients with PTSD display a greater need for treatment, their condition correlates negatively with their overall quality of life. As expected, prevalence of comorbid CP and PTSD in the reviewed studies was found to be higher in women than in men. These findings are in line with the mainstream research on gender differences in CP prevalence (Unruh 1996; Tsang et al., 2008; Schubert & Punamäki 2010; Celentano, Lenet, & Stewart, 1990). In contrast, a study on tortured refugees found no significant gender differences (Williams, Peña, & Rice, 2010), which is opposite to Teodorescu et al. (2015) who found the above-mentioned skewed distribution in a sample of refugees.

### Integration of the findings

Even though psychological models may give (partial) explanation and new impulses, they do not provide a satisfactory comprehension on these conditions. After reading and reviewing numerous research articles, the whole picture still remained fragmented.

In a need to comprehend the subject from a more holistic point of view, I made the attempt to integrate the findings in a broader (neurobiological) context: Scaer (2001) stated that the symptoms of CP are more an experience than an injury, after observing visual complaints, vertigo and dizziness, bowel complaints and an exaggerated startle response in CP patients who have had a car accident. None of these symptoms were compatible with the mechanism of trauma associated with the accident. Van der Kolk (1994) found that a destabilization of the brain and body (especially the autonomic nervous system) occurs by physiological disruption and called it “dissociation”:

“When people are traumatized, they are said to experience “speechless terror”: the emotional impact of the event may interfere with the capacity to capture the experience in words or symbols.”

Piaget (1962) stated that under traumatic stress, failure of the semantic memory leads to the organization of the memory on a somatosensory level:

“It is precisely because there is no immediate accommodation that there is complete dissociation of the inner activity from the external world. As the external world is solely represented by images, it is assimilated without resistance (i.e., unattached to other memories) to the unconscious ego.”

Scaer (2001) brought up that all the symptoms and sensations could be explained by destabilization of the autonomic nervous system and the procedural memory. Van der Kolk (1994) highlighted the association between trauma and the brain’s memory mechanisms.

He outlined that especially the unconscious procedural memory is a critical feature that stores information during a traumatic event. A related approach comes from animal studies. For decades, Peter A. Levine has explored how animals deal with life threats (Levine, 1997). He argues that trauma may begin as acute stress from a perceived life-threat or may be the result of cumulative stress. Levine (1997) illustrates that when neither fight nor flight will ensure escape, animals may undergo immobility, a freezing response due to the threat. Interestingly, animals come out of the freeze response with trembling and shaking which represents the continuation of the behavior displayed before the freezing (Levine, 1997). He states further that this shaking is the “completion of the escape” and that completing the escape allows the procedural memory of the trauma to vanish (Levine, 1997). Applying Levine’s arguments to Scaer’s CP patients with comorbid PTSD, their symptoms would be the manifestation of their coping strategy (i.e. helplessness) during the traumatic event, which resulted in freezing (Bobrow, The Pain Project). That means that the “completion of the escape” from the traumatic event “got stuck” in the procedural memory, which is the memory system for emotional and conditioned responses. In sum, this would mean that the completion of escape eliminates the memory of the incident. In contrast, if the organism does not live through the whole experience, finalizing the chain of all physical and emotional reactions involved, the trauma remains in unconscious memory forcing the individual to re-experience the upsetting symptoms over and over again (Bobrow, The Pain Project).

## CHAPTER VI: LIMITATIONS

This review has certain limitations. To begin with, regarding the exclusion criteria “antipsychotics, current intake”, no reviewed study reported medication intake in detail. Therefore, no statement could be made about this issue. Another shortcoming of this systematic review is that it did not involve an independent reviewer/ rater besides the author. That means that there is no measure of inter-rater agreement regarding study selection, which would have accounted for potential bias. A third issue is the restricted time frame wherein studies have been searched for this review. Limiting the dates from 2012 until 2017 might have resulted in a loss of valuable studies that would have been worth to include for review.



## CHAPTER VII: CONCLUSION AND PERSPECTIVE

Independent of gender, cultural or ethnical background, and socioeconomic status, patients seeking help for CP should by norm be screened for comorbid PTSD. The notable prevalence of alexithymia and PTSD in individuals suffering from CP should be further investigated. It remains to be seen if it is a stable personal trait or rather a state, similar to a symptom that appears after psychological distress. Furthermore, it is important to explore more deeply the individual facets and emotional dimensions of PTSD such as anger, impulsivity, and aggression and the autonomic sensitivity and reactivity of the individuals in question. Unfortunately, the DSM-V does not take the above-mentioned emotional dimensions into account. Further research should be looking for emotional traits as biomarkers for a heightened risk to develop PTSD. Investigating the relationship between the individual's (usual) reaction patterns (fight, flight or freeze) to stressors or traumatic events, and the long-term outcome of his physical and mental well-being would provide additional insight into the underlying mechanisms of CP and PTSD.

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## APPENDIX

## The PRISMA statement 2009 checklist

Section/Topic	#	Checklist Item	Reported on Page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

## PRISMA 2009 Flow Diagram

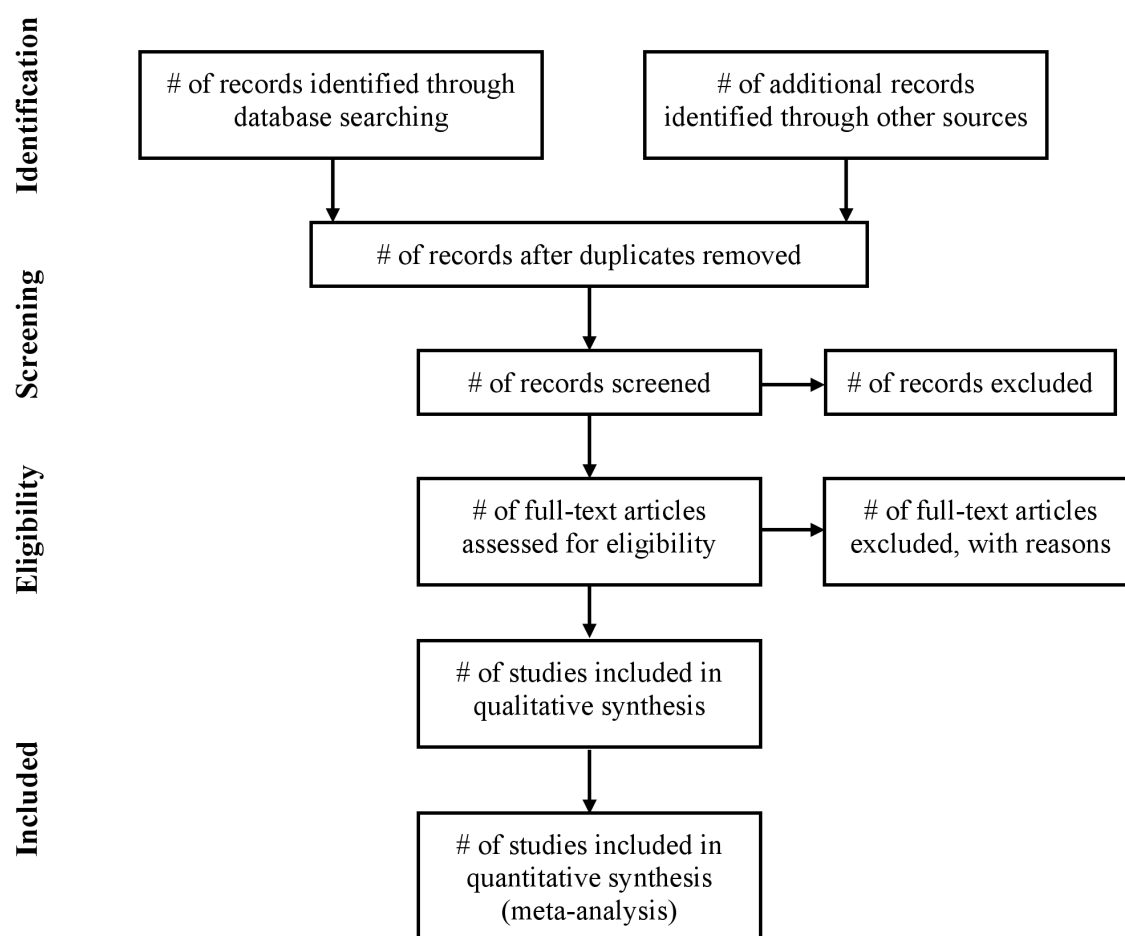


Table A. STROBE and CONSORT: Quality review criteria

STROBE Criteria for Observational Studies*	CONSORT Criteria for Clinical Trials*
<b>Intervention:</b> 1. Is the intervention clearly described? <b>Selection of participants:</b> 2. Is the target population defined? 3. Is there a comparison group (e.g. baseline, control)? 4. Are the inclusion and exclusion criteria defined? <b>Statistical methods:</b> 5. Is the sample size / method justified with statistical basis? 6. Is there a statistical test (p-value or confidence interval)? 7. Is there adjustment for confounding? <b>Limitations:</b> 8. Are study limitations explained (e.g. biases)?	<b>Eligibility</b> 1. Did study state # not meeting inclusion criteria? 2. Did study state # declined to participate? <b>Once Randomised:</b> <b>Allocation:</b> 3. Did study state # receiving intervention? 4. Did study state # not receiving intervention? <b>Follow-Up:</b> 5. Did study state # lost to follow-up? 6. Did study provide reasons for loss to follow-up? <b>Analysis:</b> 7. Did study state reasons participants were excluded from analysis? 8. Are limitations of the study explained (e.g. biases)

Table B. Quality assessment for this systematic review corresponding to the above listed STROBE and CONSORT criteria.

Source	STROBE criteria (observational studies)							
	1	2	3	4	5	6	7	8
Siqveland et al., 2017	+	+	+	+	+	+	-	+
Häuser et al., 2015	+	+	+	+	+	+	+	+
Karsikaya et al., 2013	+	+	+	+	+	+	-	+
Friedman et al., 2017	+	+	-	+	+	+	+	+
Balaban et al., 2012	+	+	+	+	+	+	+	+
Roper et al., 2017	+	+	-	+	+	+	+	+
Iorio et al., 2014	+	+	-	+	+	+	+	+
Åkerblom et al., 2017	+	+	-	+	+	+	+	+
Morasco et al., 2013	+	+	+	+	+	+	+	+
Teodorescu et al., 2015	+	+	-	+	+	+	-	+

Table C. Rating categories by STROBE and CONSORT

Level of Quality	Rating of Evidence per STROBE / CONSORT
HIGH	7-8 criteria met = high quality evidence
MODERATE	4-6 criteria met = moderate quality evidence
LOW	1-3 criteria met = low quality evidence

The study designs of the reviewed articles were determined by addressing the following issues:

**1. What was the aim of the study?\***

To simply describe the population? ⇨ descriptive

To quantify the relationship between factors? ⇨ analytic

**2. If analytic, was the intervention randomly allocated?**

Yes? ⇨ RCT (randomised controlled trials)

No? ⇨ Observational study

For observational studies the main types depend on the timing of the outcome measurement.

**3. When were the outcomes determined?**

Some time after exposure / intervention? ⇨ cohort-study (prospective study)

At the same time as exposure / intervention? ⇨ cross-sectional study / survey

Before exposure was determined? ⇨ case control study (retrospective based on recall of exposure)

\*Centre for Evidence-Based Medicine, 2018 doi:<http://www.cebm.net/blog/2014/04/03/study-designs/>

Table 2. Abbreviations “diagnostic criteria” (p. 15 f.)

<sup>1</sup> Life Events Checklist

<sup>2</sup> Mini International Neuropsychiatric Interview 5.0.0 Norwegian adaptation

<sup>3</sup> Visual Analogue Scale

<sup>4</sup> Diagnostic and Statistical Manual 4<sup>th</sup> edition

<sup>5</sup> Body Diagram

<sup>6</sup> Polysymptomatic Distress Scale

<sup>7</sup> Patient Health Questionnaire - 4 items

<sup>8</sup> Pain Disability Index

<sup>9</sup> Childhood Trauma Questionnaire

<sup>10</sup> Munich Composite International Diagnostic Interview

<sup>11</sup> Post-traumatic Diagnostic Scale

<sup>12</sup> Structured Clinical Interview for DSM-IV Axis I

<sup>13</sup> Clinical Administered Post-Traumatic Stress Disorder Scale

<sup>14</sup> Toronto Alexithymia Scale

<sup>15</sup> International Classification of Headache Disorders III-beta criteria

<sup>16</sup> PTSD Checklist-Civilian Version

<sup>17</sup> Patient Health Questionnaire-9

<sup>18</sup> International Headache Society for Migraine criteria

<sup>19</sup> Migraine Disability Assessment Scale – Turkish Version

<sup>20</sup> Identification of Migraine

- 21 Traumatic Brain Injury  
 22 Headache Impact Test Version 6  
 23 Irritable Bowel Syndrome  
 24 Hospital Anxiety and Depression Scale  
 25 36-Item Study Short Form Health Survey,  
 26 Multidimensional Pain Inventory Version 2  
 27 Numerical Rating Scale  
 28 Tampa Scale of Kinesiophobia  
 29 CP Coping Inventory  
 30 Multidimensional Pain Inventory  
 31 Beck Depression Inventory Second Edition  
 32 TimeLine Follow-Back  
 33 International Classification of Diseases 9<sup>th</sup> Revision Clinical Modification  
 34 Structured Interview for Disorders of Extreme Stress  
 35 International Neuropsychiatric Interview 5.0.0 (M.I.N.I.)  
 36 Impact of Event Scale - Revised  
 37 Hopkins Symptom Checklist

List of pre-selected, but from review excluded studies

Number	Article	Reason for exclusion
1	Atwoli, L., Platt, J. M., Basu, A., Williams, D. R., Stein, D. J., & Koenen, K. C. (2016). Associations between lifetime potentially traumatic events and chronic physical conditions in the South African Stress and Health Survey: a cross-sectional study. <i>BMC Psychiatry</i> , 16, 214. <a href="http://doi.org/10.1186/s12888-016-0929-z">http://doi.org/10.1186/s12888-016-0929-z</a>	PTSD diagnosis missing
2	McGeary, C. A., McGeary, D. D., Moreno, J., & Gatchel, R. J. (2016). Military Chronic Musculoskeletal Pain and Psychiatric Comorbidity: Is Better Pain Management the Answer? <i>Healthcare</i> , 4(3), 38. <a href="http://doi.org/10.3390/healthcare4030038">http://doi.org/10.3390/healthcare4030038</a>	Evaluation of the effect of comorbid psychiatric symptoms on post-treatment outcome
3	Sonne, C., Carlsson, J., Bech, P., Vindbjerg, E., Mortensen, E. L., & Elklit, A. (2016). Psychosocial predictors of treatment outcome for trauma-affected refugees. <i>European Journal of Psychotraumatology</i> , 7, 10.3402/ejpt.v7.30907. <a href="http://doi.org/10.3402/ejpt.v7.30907">http://doi.org/10.3402/ejpt.v7.30907</a>	Identifying predictors of treatment outcome
4	Kanuri, N., Cassell, B., Bruce, S. E., White, K. S., Gott, B. M., Gyawali, C. P., & Sayuk, G. S. (2016). The Impact of Abuse and Mood on Bowel Symptoms and Health-Related Quality of Life in Irritable Bowel Syndrome (IBS). <i>Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society</i> , 28(10), 1508–1517. <a href="http://doi.org/10.1111/nmo.12848">http://doi.org/10.1111/nmo.12848</a>	PTSD diagnosis missing
5	Sciolli-Salter, E. R., Johnides, B. D., Mitchell, K. S., Smith, B. N., Resick, P. A., & Rasmussen, A. M. (2016). Depression and Dissociation as Predictors of Physical Health Symptoms Among Female Rape Survivors with PTSD. <i>Psychological Trauma: Theory, Research, Practice and Policy</i> , 8(5), 585–591. <a href="http://doi.org/10.1037/tra0000135">http://doi.org/10.1037/tra0000135</a>	PTSD diagnosis missing

6	Gandjalikhan-Nassab, S.-A.-H., Samieirad, S., Vakil-Zadeh, M., Habib-Aghahi, R., & Alsadat-Hashemipour, M. (2016). Depression and anxiety disorders in a sample of facial trauma: A study from Iran. <i>Medicina Oral, Patología Oral Y Cirugía Bucal</i> , 21(4), e477–e482. <a href="http://doi.org/10.4317/medoral.21068">http://doi.org/10.4317/medoral.21068</a>	PTSD & CP diagnosis missing
7	Archer, K. R., Heins, S. E., Abraham, C. M., Obremskey, W. T., Wegener, S. T., & Castillo, R. C. (2016). Clinical significance of pain at hospital discharge following traumatic orthopaedic injury: general health, depression, and PTSD outcomes at 1 year. <i>The Clinical Journal of Pain</i> , 32(3), 196–202. <a href="http://doi.org/10.1097/AJP.0000000000000246">http://doi.org/10.1097/AJP.0000000000000246</a>	CP diagnosis missing
8	Koffel, E., Krebs, E. E., Arbisi, P. A., Erbes, C. R., & Polusny, M. A. (2016). The Unhappy Triad: Pain, Sleep Complaints, and Internalizing Symptoms. <i>Clinical Psychological Science: A Journal of the Association for Psychological Science</i> , 4(1), 96–106. <a href="http://doi.org/10.1177/2167702615579342">http://doi.org/10.1177/2167702615579342</a>	CP diagnosis missing
9	Sherman, A. L., Morris, M. C., Bruehl, S., Westbrook, T. D., & Walker, L. S. (2015). Heightened Temporal Summation of Pain in Patients with Functional Gastrointestinal Disorders and History of Trauma. <i>Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine</i> , 49(6), 785–792. <a href="http://doi.org/10.1007/s12160-015-9712-5">http://doi.org/10.1007/s12160-015-9712-5</a>	Studied sample under the age of 18 years
10	McBeth, J., Tomenson, B., Chew-Graham, C. A., Macfarlane, G. J., Jackson, J., Littlewood, A., & Creed, F. H. (2015). Common and unique associated factors for medically unexplained chronic widespread pain and chronic fatigue. <i>Journal of Psychosomatic Research</i> , 79(6), 484–491. <a href="http://doi.org/10.1016/j.jpsychores.2015.10.004">http://doi.org/10.1016/j.jpsychores.2015.10.004</a>	PTSD diagnosis missing
11	Egloff, N., Hirschi, A., & von Känel, R. (2013). Traumatization and CP: a further model of interaction. <i>Journal of Pain Research</i> , 6, 765–770. <a href="http://doi.org/10.2147/JPR.S52264">http://doi.org/10.2147/JPR.S52264</a>	Synopsis of mechanisms and model
12	Powers, A., Fani, N., Pallos, A., Stevens, J., Ressler, K. J., & Bradley, B. (2014). Childhood abuse and the experience of pain in adulthood: The mediating effects of PTSD and emotion dysregulation on pain levels and pain-related functional impairment. <i>Psychosomatics</i> , 55(5), 491–499. <a href="http://doi.org/10.1016/j.psym.2013.10.004">http://doi.org/10.1016/j.psym.2013.10.004</a>	Inclusion criteria for CP was pain duration of 4 weeks
13	Usui, C., Hatta, K., Aratani, S., Yagishita, N., Nishioka, K., Okamura, S., ... Nishioka, K. (2013). Vulnerability to traumatic stress in fibromyalgia patients: 19 month follow-up after the great East Japan disaster. <i>Arthritis Research &amp; Therapy</i> , 15(5), R130. <a href="http://doi.org/10.1186/ar4310">http://doi.org/10.1186/ar4310</a>	PTSD diagnosis missing
14	Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2012). Physical Health Conditions Associated with PTSD in U.S. Older Adults: Results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. <i>Journal of the American Geriatrics Society</i> , 60(2), 296–303. <a href="http://doi.org/10.1111/j.1532-5415.2011.03788.x">http://doi.org/10.1111/j.1532-5415.2011.03788.x</a>	PTSD diagnosis missing
15	Eriksen, A. M. A., Schei, B., Hansen, K. L., Sørli, T., Fleten, N., & Javo, C. (2016). Childhood violence and adult CP among indigenous Sami and non-Sami populations in Norway: a SAMINOR 2 questionnaire study. <i>International Journal of Circumpolar Health</i> , 75, 10.3402/ijch.v75.32798. <a href="http://doi.org/10.3402/ijch.v75.32798">http://doi.org/10.3402/ijch.v75.32798</a>	PTSD diagnosis missing

Palma de Mallorca

**Statutory declaration**

I declare that I have authored this thesis independently, that I have not used other than the declared sources / resources, and that I have explicitly marked all material which has been quoted earlier either literally or by content from the used sources.

25<sup>th</sup> of January 2018

Christine Winterholler