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Cohort Studies in the Understanding of Chronic Musculoskeletal Pain

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Abstract

Chronic pain is an important clinical and social problem worldwide, affecting one in every five people. It generates a large economic burden on the health system and million dollar losses in the socio-labour field, and also directly impacts the health and quality of life of people by generating different levels of disability. Nowadays, it has been shown that this clinical manifestation is influenced by biological, psychological and social components, creating a complex scenario when proposing an effective therapeutic intervention. In consideration of this reality, we present a review of the available scientific evidence regarding the contributions that cohort studies provide for understanding chronic musculoskeletal pain, with the aim of identifying risk factors, prognostic factors and rehabilitation.

Keywords: chronic pain, cohort studies, risk factors, prognosis, physical therapy, rehabilitation

1. Introduction

Chronic pain is an important clinical, social and economic problem worldwide [1]. It is a common problem that entails a series of consequences affecting the quality of life of those patients afflicted with chronic pain, along with the difficulty placed on the health system due to the various benefits provided, producing permanent economic conflicts [2].

This reality leads to the constant pilgrimage of patients through various medical specialties, physical medicine and rehabilitation services, excessive and varied consumption of drugs that together have highly unsatisfactory results, thus producing a hopeless scenario for people with chronic musculoskeletal pain [3].

Therefore, the governments of each country are concerned about finding means that provide a solution for this situation, searching and promoting different strategies for the health system [4].

This demand for assistance has proved a great challenge for the worldwide scientific community, where they must focus their efforts on finding and providing evidence for a better understanding of the nature of chronic pain and its intervening mechanisms; seeking to contribute to the development of effective health interventions, both preventive and curative.

Pain is a complex clinical manifestation, difficult to describe fully, especially when it becomes persistent and disabling. Therefore, defining the experience of each individual and reaching a full consensus on the matter is not easy. The understanding of pain has been a subject of extensive discussion, especially over the last two decades where exponential advances have been made.

The International Association for the Study of Pain (IASP) defines it as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [5].

The World Health Organization classifies the pain as acute, chronic malignant and chronic non-malignant, incorporating chronic musculoskeletal pain in the latter.

Chronic musculoskeletal pain is conceptualized in diverse ways; either as pain that lasts for more than 3 months or pain that exceeds the time of tissue recovery. It is also known as pain that lasts for more than 6 months [5].

1.1. Epidemiology of chronic pain

The prevalence of chronic pain is on average 20% worldwide [6], but the numbers are variable depending on different factors such as, the methodology used in each study, the region or country analyzed and the age range; it fluctuates between 2 and 50% [2]. The prevalence of chronic pain in adults is in the range 12–42% worldwide [7].

In Europe, non-oncological chronic pain in 2011 fluctuated between 10 and 30%. In 2013, an estimated 20% of adults suffered from chronic pain [2].

In the USA, the reported frequency of chronic pain in women is 34.3 and 26.7% in men, increasing with age, and with lumbar pain being the most frequent cause (8.1%, followed by osteoarthritis 3.9%). During the year 2010, the National Health Interview Survey reported that 39.4 million American adults suffered from persistent pain of which 67.2% manifested constant pain and 50.5% reported unbearable pain [7, 8].

In 2001, the Australian population presented a prevalence of 17.1% in men and 20% in women, increasing to 27% in women between 65 and 69 years, with a peak of 31% in the age range of 80–84 years [9].

A study in 2005 reported that in Spain, the prevalence of chronic pain ranged between 10.1 and 55.2%, with a higher incidence in women [10]. On the other hand, in 2002, a study estimated a

prevalence of 23.4%, where 23% were rheumatological diseases (7 million people) and 50% comprised work disabilities [11, 12].

Regarding chronic pain in the elderly population, in Sweden in 2016, the prevalence was 38.5%, being more common in women and in the age range 85–94 years, with an incidence of 5.4% per year [13]. In 2013, in the United States, the prevalence in older adults ranged between 27 and 86%, and between 13.3 and 20% patients developed pain after 3 to 6 years.

In children and adolescents, the prevalence of back pain for longer than 3 months ranges from 18 to 24% [1, 7, 14].

1.2. The economic impact of chronic pain

Considering the high healthcare demand generated by chronic musculoskeletal pain, added to the functional limitations and disability that this entails, chronic pain involves a high economic cost and diverse social consequences.

In Australia, the impact of lumbar spine disorders on the labour force generates a loss of AU \$ 4.8 billion per year. Estimating that people with chronic moderate–severe pain lose an average of 8 work days every 6 months, the government spends millions in additional payments for welfare and large losses in tax revenues, adding annually AU \$ 2.9 billion in losses of internal product gross (GDP) [15].

It is estimated that older Australians who do not work due to poor health, reduce the GDP by 14.7 billion per year, with lumbar pain and arthritis responsible for half of this burden [16].

The total indirect and direct costs resulting from adolescents with chronic pain in the United Kingdom is approximately £8.000 per year [17].

In Europe, chronic pain produces a total estimated cost of 1.5 to 3.0 of the GDP [18].

In Belgium, the cost for the health system only for back pain ranges between € 83.8 and € 164.7 trillion per year, in the UK £1 trillion, and Germany €5.11 trillion [1, 6].

In 2010 in the USA, the total costs resulting from chronic pain varied between \$560 and \$635 billion, exceeding the annual costs produced by heart disease, cancer and diabetes [7].

Consequently, it is clear that we are facing a large clinical and socio-economic problem; the pandemic nature of chronic pain has been difficult to control by health services throughout the world.

Despite its great impact, therapeutic approaches and rehabilitation for people with chronic musculoskeletal pain is still a pending issue and remains an important challenge to the scientific field. Although scientific advances have reoriented therapeutic approaches, there is still a great need to strengthen knowledge and provide greater support to the clinical field.

There are various interventions and factors that act on pain and that deserve to be studied through analytical and observational designs to deepen our knowledge in this field.

Consequently, this chapter proposes to review the available scientific evidence from cohort studies, emphasizing their importance and contribution to understanding chronic musculoskeletal pain, the identification of risk factors, associated prognostic factors, visualizing the development of follow-ups after rehabilitation interventions, assessing the clinical impact of the delivered evidence, and also trying to identify the components that can contribute to daily clinical practice.

Observational studies can provide more information than clinical studies in diverse components due to the multifactorial and multidimensional nature of pain.

2. Cohort studies of chronic musculoskeletal pain

Cohort studies allow us to identify the behaviour of different factors that can influence chronic musculoskeletal pain over the course of time, such as risk factors, protective factors and prognostic factors, as well as observe the short and long term results of a specific therapeutic intervention.

2.1. Risk, protector and prognostic factors in chronic pain

In this review, it can be observed that the research found mainly focus on the study of pain in high prevalence musculoskeletal disorders, such as generalized musculoskeletal pain, chronic lower back pain syndrome (LBPS), and whiplash (**Table 1**). The risk factors observed were stress, anxiety, fear of movement, fear-avoidance behaviors, catastrophic beliefs of pain, pain intensity, depressive symptoms, psychological distress, somatisation, perceived physical exertion, traumas, critical life events, co-morbidities, smoking and obesity.

As protective and prognostic factors, we find self-efficacy, active pain coping, resilience, self-perception of health, social support at work, quality of sleep, stress and anxiety control, level of disability related to pain, acceptance of pain, body awareness, behaviour, quality of life related to health, recovery expectations, classification by subgroups of risk, influence of a healthy lifestyle, self-perception of prognosis and high uric acid plasma concentrations.

2.1.1. Generalized chronic pain (GCP)

GCP is a common symptom of musculoskeletal pain, especially in older adults. This condition often has an important impact on functional capacity, generating different disability levels.

Since the elder population is prone to developing fragility due to different factors, a longitudinal study performed over an average of 4.3 years of a cohort of 2736 European men recruited from cities in eight countries (Florence (Italy), Leuven (Belgium), Lodz (Poland), Malmo (Sweden), Manchester (United Kingdom), Santiago de Compostela (Spain), Szeged (Hungary) and Tartu (Estonia)), showed that people with GCP were significantly more likely to develop or increase fragility, independent of previously identified risk factors such as smoking or alcohol consumption. Therefore, a comprehensive evaluation of elderly people

Reference	Sample	Follow-up time	Factors related to pain	Measurement	Instrument	Outcomes
Fredrika et al., 2016	2.736	4.3 years	Chronic pain and frailty	Frailty	Frailty index (FI)	Among men who were non-frail at baseline, those with chronic widespread pain were significantly more likely to develop frailty. After adjustment for age and centre, compared with those with no pain, those with Chronic widespread pain at baseline had a 70% higher frailty index at follow-up
				Depression	Beck's Depression Inventory-II (BDI-II)	
				Quality of life	36-Item Medical Outcomes Study Survey (SF-36)	
				Physical activity	Physical Activity Scale for the Elderly (PASE)	
				Physical performance	Physical Performance Test (PPT)	
Melloh et al. [24]	315	6 months	Pain prognostic occupational factors	Location of pain	Body pain drawing	Social support at work should be considered as a resource preventing the development of persistent LBP (an overall predictive value of 78%). Somatization should be considered as a risk factor for the development of persistent LBP.
					Model from Pfau et al.	
Andersen et al. [20]	4.977	3 years	Perceived physical exertion during healthcare work	Perceived exertion	Borg's rate perceived exertion scale (RPE)	Female healthcare workers with light perceived physical exertion during healthcare work have a better prognosis for recovery from long-term pain in the low back and neck/shoulders
				Musculoskeletal symptoms	Standardized Nordic Questionnaire	
Bohman et al. [25]	8.994	4 years	Influence of the behavior of a healthy lifestyle in the prognosis of the lower back pain	Musculoskeletal symptoms	Standardized Nordic Questionnaire	The risk was reduced by 35% for women with one healthy lifestyle factor and 52% for women with all four healthy lifestyle factors
				Healthy lifestyle behaviour	Self-report questionnaire on healthy lifestyle behaviour	

Reference	Sample	Follow-up time	Factors related to pain	Measurement	Instrument	Outcomes
Williamson et al. [26]	599	12 months	Risk factors for chronic disability in patients with acute whiplash associated disorders seeking.	Neck disability	Neck Disability Index (NDI)	30% of participants (n = 136/459) who returned their 12 month questionnaire had developed chronic disability.
				Pain intensity	Modified Von-Korff Pain Scale	
				Whiplash grades	The Quebec Taskforce WAD grading system	
				Neck of movement		Baseline disability had the strongest association with chronic disability, also psychological and behavioral factors were important.
				Coping	Neck range of movement (ROM)	
				Pain catastrophizing	Coping strategies questionnaire (CSQ)	
				Fear Avoidance Beliefs		The total number of risk factors present should be considered when evaluating the potential for poor outcome
				Coping	The Pain Catastrophizing Scale (PCS)	
					Fear Avoidance Beliefs Questionnaire (FABQ)	
					Pain coping questionnaire (PCQ)	
Andersson et al. [21]	107	12 months	Increase in serum uric in chronic pain		Passive coping	A relative increase in serum uric in combination with report of a high number of pain locations turned out to be a risk factor of increased pain extension
				General Health	General Health Questionnaire (GHQ)-12	
				Social support	Multidimensional scale of perceived social support	
				Number of pain locations	The sum of reported areas with current pain location	
				Pain intensity	Visual analogue scale (VAS)	
				Pain duration	Question on duration of current pain	Corticosteroids diminished the risk of developing an increased number of pain locations
				Body mass index	Calculated from initial measurements of height and weight.	

Reference	Sample	Follow-up time	Factors related to pain	Measurement	Instrument	Outcomes
				Alcohol consumption	An index based on frequency of intake for strong beer, red and white wine and spirits	
				Report of stress	Multidimensional Pain Inventory (MPI)	
				Sleeping difficulties	Multidimensional Pain Inventory (MPI)	
				Depression	Hospital Anxiety and Depression Scale" (HADS)	
				Use of steroid	Answer to a question on the use of steroids (oral, intramuscular or intraarticular) last month	

Table 1. Risk factors in chronic pain.

with generalized pain is important to visualize the impact of musculoskeletal pain on functionality and general health wellbeing [19].

In the adult population, a prospective study with a cohort of 4977 Danish people working in the health industry sought to determine how different levels of perception of physical effort during work influence the prognosis of long-term recovery of those with pain in different regions of the body (lumbar area, neck/shoulder and knees). They concluded that a physical effort perceived as light was associated with a good long-term prognosis for pain in the lower back, but not for knee pain. A perception of moderate physical effort is associated with a poor long-term prognosis for all the regions with reported pain [20].

Another study in adult women about GCP and the increase in pain locations shows a significant correlation with the increase in uric acid plasma concentrations after a one-year follow-up, recognizing this combination as a risk factor for the expansion of inflammatory and non-inflammatory pain [21].

2.1.2. Chronic low back pain

Physical, psychological and behavioral components of chronic LBPS have a direct implication on the transition from acute to chronic pain. The risk factors for this transition include anxiety,

depression, traumas and critical life events; meanwhile, the protective factors include resilience, coping strategies, stress management and self-efficacy.

Another study determined that depression, psychological distress, passive coping strategies and high levels of fear related to pain are predictors of a poor evolution in patients suffering from chronic LBPS [22]. They also added the knowledge of the possibility of developing chronicity at the onset of pain as another risk factor.

Self-perception of general health, considering both physical and psychosocial dimensions, plus the expectations of patient recovery, presents a strong relation for a positive evolution [23].

Additionally, assessment of the chronicity of occupational back pain discovered two predictors related to work with a predictive value of 78%. The report observed social support as a protective factor and somatisation as a risk factor for development of persistent pain. Consequently, cognitive and psychological components play a vital role in the development or control of chronic low back pain [24].

When considering the influence of a healthy lifestyle as a prognostic factor for lower back pain, a Swedish study followed a cohort of 3938 men and 5056 women over 4 years. They were classified into five levels according to the number of healthy lifestyle factors they presented (0 to 4), declaring healthy factors as: non-smoking, no alcohol risk consumption, a recommended level of recreational physical activity and recommended weekly consumption of fruits and vegetables. The study established cut-off points (healthy / unhealthy) according to the recommendations for a healthy lifestyle established by the World Health Organization (WHO). There was a decrease in the risk of developing persistent lower back pain in women who only presented occasional lower back pain; decreasing the risk by a larger proportion as more healthy factors were present. Therefore, a healthy lifestyle is an effective indication of an improved prognosis [25].

2.1.3. Whiplash pain

People with acute disorders associated with whiplash are exposed to a complex clinical outcome, hindering favorable evolution due to the psychological impact generated by the traumatic circumstances experienced due to the injury. In this disorder, there are a high number of risk factors, such as psychological distress, passive coping, high initial disability, intense pain and long recovery time. A longitudinal study performed in the United Kingdom identified and assessed the impact of risk factors of developing chronic disability in acute whiplash disorders. The study consisted of a cohort of 430 subjects with a history of whiplash, initially assessing risk factors on average 32 days after injury, with a follow-up 12 months later. They found that the presence of a risk factor increased the risk of developing a chronic disability by 3.5 times and the presence of four or five risk factors increased this risk 16 times. Therefore, it is evident that the disability is directly influenced by psychological factors, behavioral factors and the presence of initial disability [26].

2.2. Therapeutic approaches for chronic musculoskeletal pain

Cohort studies have also contributed to the development of convincing evidence useful for developing therapeutic approaches for chronic pain, indisputably supporting clinical procedures and the establishment of public health policies.

The elaboration of an effective intervention plan for the rehabilitation of chronic pain patients is a constant challenge. It is for this reason that current therapeutic strategies and procedures try to cover the different components involved in the development of this clinical situation. Based on this need, the evidence from observational studies shows different intervention measures, such as polymodal or interdisciplinary programmes, studies about the acceptance of pain, pain education programmes, the involvement of attention/distraction and self-care plans on pain, and auto-therapeutic indications that focus on self-efficacy and recovery expectations or patient-centred approaches (**Table 2**).

A therapeutic programme based on pain education showed significant improvements regarding pain intensity, disability, catastrophism, depression, anxiety and health, with few positive results on anguish and cognition [27]. Acceptance of pain, considered as the willingness to participate in various activities in the community despite the pain, has been associated as a positive mechanism regarding the intensity of the perceived pain, improvements in the

Reference	Sample	Follow-up time	Intervention	Measurement	Instrument	Outcomes
Mehlsen et al. [22]	87	5 months	The Chronic Pain Self-Management Programme is a lay-led patient education	Pain	Visual analog scale (VAS)	Participants showed significant improvements in pain, disability, catastrophism, depression, anxiety and health worry, and the changes remained stable during the follow-up period.
				Pain intensity	McGill Pain Questionnaire	
				Physical disability	Modified Roland-Morris Disability Questionnaire	
				Pain Catastrophizing	Pain Catastrophizing Scale	A consistent pattern of stable improvements in pain, cognition of pain and distress was observed, but the scope of the changes was modest.
				Pain-related self-efficacy	Arthritis Self efficacy Scale	
Pieber et al. [29]	96	18 months	Multidisciplinary rehabilitation program.	Depression, anxiety, physical symptoms, illness worry	The Common Mental Disorders Questionnaire	Persistent improvements in muscle strength, pain, function and quality of life in patients with chronic low back pain.
				Pain	Visual analog scale (VAS).	
				Physical disability	Roland-Morris disability Questionnaire (RM)	
				Mobility	Range of motion (ROM)	
				Muscle strength	Muscle strength	
				Quality of life	Short Form Health Survey (SF-36)	

Reference	Sample	Follow-up time	Intervention	Measurement	Instrument	Outcomes
Verkerk et al. [31]	1.760	5 and 12 months	Multidisciplinary therapy	Pain	Visual analog scale (VAS)	30% Improvement Between Baseline and 5- and 12-month follow-ups. The prognostic factors were: being married or living with one adult, having no comorbidity, younger age, a higher education level, higher disability score at baseline, no previous rehabilitation, reporting low pain intensity at baseline, and a higher score on the SF-36 and PCS.
				Fatigue	Fegree of present fatigue	
				Kinesiophobia	Tampa Scale for Kinesiophobia (TSK) score	
				Quality of life	Short Form Health Survey (SF-36) Physical Component Summary (PCS) Mental Component Summary (MCS)]	
Koele et al. [32]	165	21 months	15-week multidisciplinary rehabilitation program	Pain	Numerical rating scale (NRS pain)	Improvements in pain, activities and participation over time.
				Disability	Pain Disability Index (PDI) The Multidimensional Pain Inventory (MPI)	
				Pain catastrophizing	Pain Catastrophizing Scale (PCS)	
				Fatigue	Numerical rating scale (NRS fatigue)	
				Overall quality of life	Short Form Health Survey (SF-36)	
Pietilä Holmner et al. [33]	93	8 years	Interdisciplinary team assessment and a 4-week rehabilitation program	Pain	Visual analog scale (VAS) The Multidimensional Pain Inventory (MPI)	There were significant differences seen in pain severity, interference of daily living, life control, negative mood, support, as well as anxiety and depression.
				Anxiety, depression	Hospital Anxiety and Depression Scale	

Reference	Sample	Follow-up time	Intervention	Measurement	Instrument	Outcomes
Gerdle et al. [30]	227	12 months	Multimodal rehabilitation programs (MMRP)	Characteristics of pain	Numeric rating scale	There were strong improvements in pain intensity and emotional aspect. The significant predictors were weak.
					Multidimensional Pain Inventory (MPI)	
					Hospital Anxiety and Depression Scale (HADS)	
					The Chronic Pain Acceptance Questionnaire (CPAQ)	
					The Tampa Scale for Kinesiophobia Life Satisfaction Questionnaire (LISAT-11)	
Gardner et al. [34]	20 392	2 months	Test the preliminar effectiveness of a patient-led goal-setting intervention	Disability	The European Quality of Life instrument (EQ-5D)	Disability, pain intensity, physical quality of life, mental quality of life, total quality of life, self-efficacy and fear avoidance measures improved significantly between baseline and 2 months. Non-significant changes occurred in depression, anxiety and stress ($P = 0.78$).
					The Quebec Back Pain Disability Scale (QBPDS)	
				Pain intensity	Numerical rating scale (NRS pain)	
				Quality of life	Short Form Health Survey (SF-36)	
				Negative emotional states of depression, anxiety and stress	The Depression Anxiety Stress Scale (DASS)	
				Self-efficacy	Pain Self-Efficacy Questionnaire (PSEQ)	
				Fear of movement/ (re) injury	Tampa Scale for Kinesiophobia (TSK)	

Reference	Sample	Follow-up time	Intervention	Measurement	Instrument	Outcomes
Jensen et al. [28]		3.5 years	Pain acceptance	Pain acceptance Average pain intensity Pain interference Depressive symptoms Physical function Sleep disturbance	Chronic Pain Acceptance Questionnaire (CPAQ) Numerical rating scale (NRS pain) Patient-Reported Outcomes Measurement Information System (PROMIS)	In every case, higher initial levels of pain acceptance were associated with better outcomes over time; ie, more improvement in depressive symptoms and sleep disturbance, and less increase in pain intensity and pain interference. Positive and significant association between change in pain and change in depression among those with relatively low activity engagement acceptance

Table 2. Therapeutic approaches for chronic musculoskeletal pain.

interference of pain in activities, in physical function, depressive symptoms and quality of sleep, which manage to endure over time [28].

When the intervention of chronic lower back pain is based on multidisciplinary rehabilitation including sensorimotor training, aerobic resistance, education and stress management, significant improvements were observed on lumbar extensor strength, range of motion, pain intensity and quality of life. These improvements persisted long term, over 18 months after the intervention had ceased [29].

A 12-month monitoring of a multimodal chronic pain rehabilitation programme reported significant improvements regarding pain, psychological symptoms, social participation, health and quality of life, although this type of approach requires more research support [30].

The observation of a 2-month multidisciplinary approach (16 sessions) in 1760 patients with lower back pain showed a greater than 30% reduction in disability after a follow-up of 5 and 12 months after the intervention, recognizing influential prognostic factors among the controlled patients, such as improved self-perception of health, a lower degree of initial disability, no co-morbidities and a positive prognosis relation at a younger age [31].

Predictors of the improved results of multidisciplinary therapy as regards to generalized pain are associated with greater self-efficacy, lower anxiety, higher educational levels, less beliefs about the consequences and the male sex. Therefore, this information indicates that we should guide treatment towards these specific characteristics and/or facilitate the selection of patients that will have a better response to this type of treatment based on this information [32].

An interdisciplinary evaluation performed over 8 years after a 4 week rehabilitation programme in 93 women with chronic musculoskeletal pain, showed a significant short-term and long-term improvement in pain, control of anxiety and depression [33].

Additionally, a novel pilot study based on a therapeutic approach with the establishment of objectives led by the patients themselves and supervised by a physiotherapist specialized in chronic lower back pain, showed significant improvements on quality of life, pain intensity, self-efficacy, fear-avoidance and level of disability, after 2 months of intervention and after a 2 month follow-up. This supports the importance of therapeutic goals being based on the patient when planning an intervention plan [34]. Another study reported that including the distraction of pain in the therapeutic process benefited patients with chronic pain, especially those who show greater catastrophism. Therefore, the increase in pain intensity could be due to a higher level of attention to pain (hypervigilance) [35] (**Figure 1**).

In conclusion, this review about the evidence from existing cohort studies related to chronic musculoskeletal pain oriented on the understanding of risk factors, prognostic factors, protective factors and therapeutic approaches, allows us to extract important information for recognizing different clinical and psychosocial components involved in this condition that generally affect patients. This helps us to understand the characteristics of their behaviour and the pertinent therapeutic projections; facilitating the development of good clinical practices.

Although it is true that observational research regarding chronic musculoskeletal pain remains insufficient, there is still some important information that potentiates our understanding and redirects the rehabilitation of chronic pain; emphasizing the contribution of existing and related controlled clinical trials, proposing a rehabilitation programme based on biopsychosocial care, trying to cover all the involved factors and dimensions, and giving way to polymodal and interdisciplinary intervention.

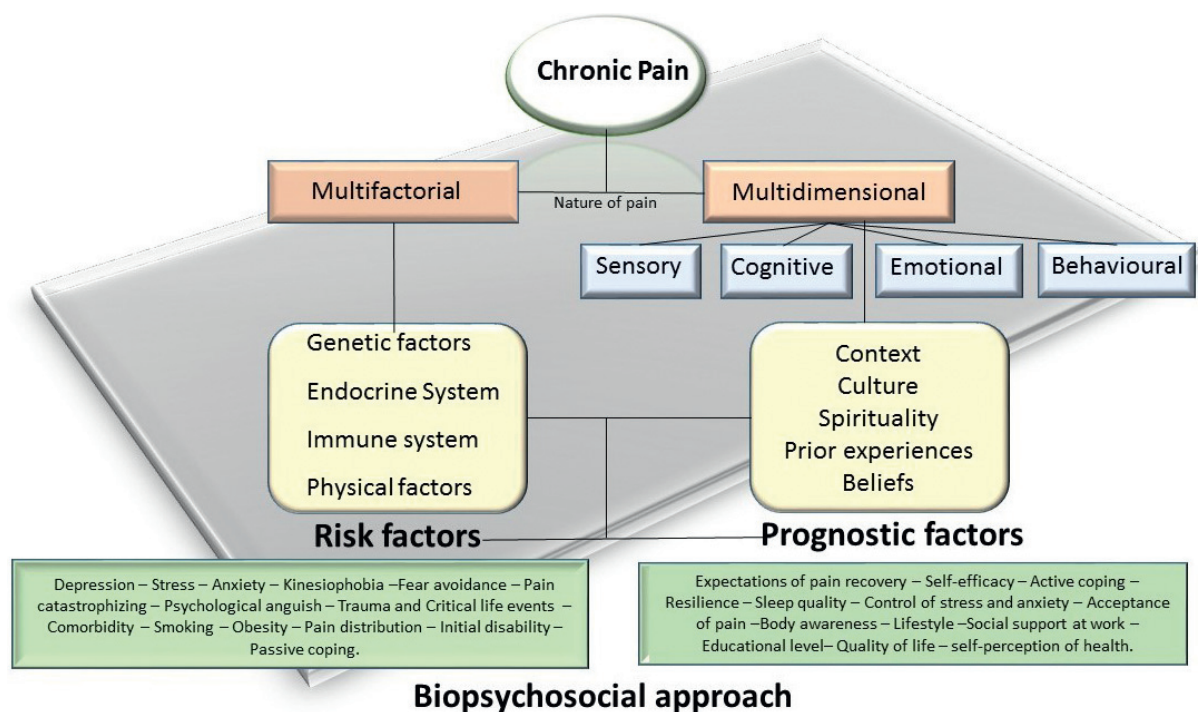


Figure 1. Conceptual model of chronic pain.

The contribution of cohort studies to the understanding of chronic musculoskeletal pain, is supported under the methodological rigor of objectively establishing the definition of results of the observed variables, and favors the control of biases by using different instruments to obtain measurements that allow a conclusive description of an outcome. In the case of the assessment of pain intensity, the studies reviewed used the visual analogue scale (VAS), the McGill pain questionnaire, scale for the numerical assessment of pain, and the pain inventory. Regarding exposure variables for psychosocial factors such as pain catastrophizing, self-perception of health, stress, anxiety, perception of disability, etc., the studies applied the catastrophizing scale of pain, Tampa scale of kinesiophobia, arthritis self-efficacy scale, the common mental disorders questionnaire, the quality of life survey (SF-36), the pain disability index, and the Roland–Morris disability questionnaire, among others.

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