Early Prognostic Factors in Complex Regional Pain Syndrome: A Biopsychosocial Investigation Towards Stratified and Personalized Management

Subtitle: Early prognostic factors in CRPS

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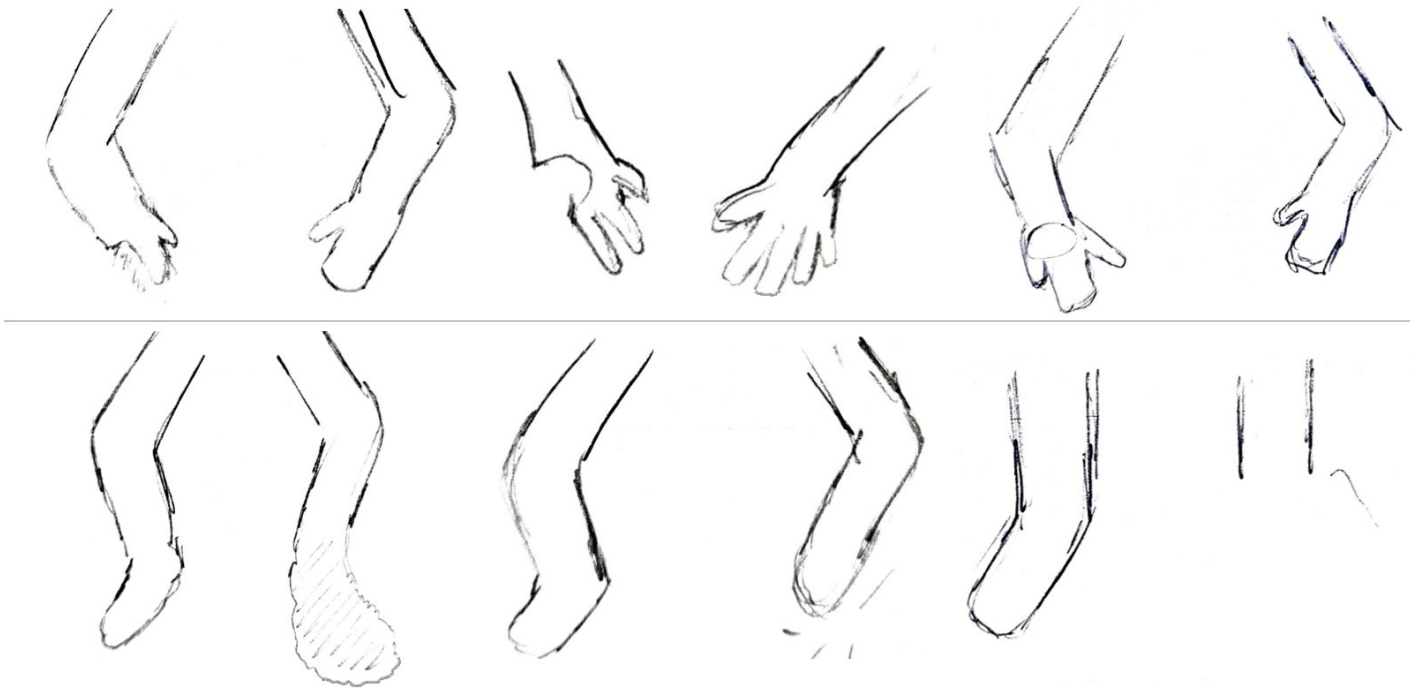

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Résumé : Cette thèse examine les facteurs pronostiques précoces du syndrome douloureux régional complexe (SDRC), une affection douloureuse rare mais invalidante caractérisée par une hétérogénéité clinique et une évolution incertaine. À travers une revue systématique, une cohorte prospective (n = 113, apparition depuis moins de 6 mois) et un suivi d'un an, elle a examiné les déterminants biologiques et psychosociaux du pronostic. Une analyse de classes latentes a permis d'identifier quatre profils précoces (BE-CRPS). Les facteurs psychosociaux (tels que la sévérité psychosociale) apparaissent comme les prédicteurs majeurs de l'évolution, bien que l'allodynie montre une valeur prédictive. Ces résultats démontrent que le pronostic du SDRC est largement influencé par des facteurs biopsychosociaux dont certains sont potentiellement modifiables, soutiennent la faisabilité d'une prise en charge stratifiée fondée sur les profils précoces identifiés et soulignent la nécessité de disposer d'outils pronostiques validés pour prévenir la chronicisation et améliorer la prise de décision clinique individualisée.

Summary: This thesis investigates early prognostic factors in Complex Regional Pain Syndrome (CRPS), a rare yet disabling condition marked by heterogeneity and unpredictable outcomes. Through a systematic review, a prospective cohort (n=113, <6 months onset), and a 1-year follow-up, it examined biological and psychosocial determinants of prognosis. Latent class analysis identified four biopsychosocial early profiles (*BE-CRPS*). Psychosocial factors (such as psychosocial severity) emerge as the strongest predictors of evolution, though allodynia retained predictive value. These findings demonstrate that prognosis in CRPS is largely shaped by biopsychosocial factors, support the feasibility of stratified management grounded in identified early profiles, and emphasize the need for validated prognostic tools to prevent chronification and guide personalized interventions.

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I. Table of Contents

II. Abbreviations List

BE-CRPS profiles: Biopsychosocial Early CRPS profiles

BMI: body mass index

BPI-SF: brief pain inventory – short form

BRD: body representation disturbance

CDT: cold detection threshold

CI: confidence interval

CPM: cold pain modulation

CPT: cold pain threshold

CRPS: complex regional pain syndrome

CSQ: coping strategies questionnaire

CSS: CRPS severity score

DFNS: German Research Network on Neuropathic Pain

DRF: distal radius fracture

DMA: dynamic mechanical allodynia

EQ: EuroQol

EQ-5D-5L: EuroQol – 5 dimensions – 5 levels

HADS: hospital anxiety depression scale

HLA: Human Leukocyte Antigen

HPT: heat pain threshold

ICF: International Classification of Functioning, Disability and Health

LBP: low back pain

LCA: latent class analysis

LEFS: lower extremity functional scale

LMM: linear mixed model

MDT: mechanical detection threshold

MeSH: Medical Subject Headings

MPS: mechanical pain sensitivity

MPT: mechanical pain threshold

MRC: Medical Research Council

MRI: Magnetic resonance imaging

NSAIDs: non-steroidal anti-inflammatory drugs

N = …: number of studies

n = …: number of participants

ÖMPSQ-SF: Örebro musculoskeletal pain questionnaire – short form

OR: odds ratio

Patient Reported Outcomes Measurement Information System 29-item Health Profile: PROMIS-29 profile

PAG-RVM: periaqueductal gray - rostral ventromedial medulla

PHS: paradoxical heat sensation

PSQ: pain sensitization questionnaire

PSS: point of subjective simultaneity

PPT: pressure pain threshold

QST: quantitative sensory testing

QoL: Quality of life

QUIPS tool: Quality In Prognostic Studies tool

r-B-CRPS-BPDS: revised-Bath-complex regional pain syndrome-body perception disturbance scale

RoM: range of motion

RtW: return to work

STarT: Subgroups for Targeted Treatment

SBT: STarT Back screening Tool

SD: standard deviation

SSQ6: social support questionnaire-short form

S1: primary somatosensory cortex

TOJ: temporal order judgement task

TSK-11: Tampa scale for kinesiophobia-11

TSL: thermal sensory limen

VAS: visual analogue scale

VDT: vibration detection threshold

VIF: variance inflation factor

WDT: warm detection threshold

III. Introduction of the Thesis

The introduction opens with a general overview that summarizes the objectives of this thesis and its principal findings. It then presents several illustrative clinical cases drawn from a prospective study (*Chapter 2* and *3*), highlighting the heterogeneity of Complex Regional Pain Syndrome (CRPS) presentations. Next, key concepts related to pain mechanisms, prognostic factors, and the rationale for stratifying patients according to their individual prognosis are discussed. Finally, the introduction provides an overview of CRPS itself and examines the main methodological and conceptual challenges that have historically limited research in this field.

The cover figure corresponds to the mental representations of the affected and contralateral limbs of the first two described cases (Patients 1 and 2), at study inclusion (left), six months (middle), and twelve months (right) after symptom onset.

1. General Introduction

CRPS is a rare but highly disabling pain disorder that usually develops after limb trauma or surgery. It is defined by disproportionate pain in combination with sensory, vasomotor, sudomotor, motor, and trophic disturbances. The condition displays marked clinical heterogeneity: while some patients experience spontaneous recovery within months, others evolve toward chronic pain and long-term disability. This unpredictability complicates diagnosis, prognosis, and therapeutic decision-making. Early identification of patients at risk of poor outcomes is therefore essential, as timely interventions may reduce the risk of chronification and its associated individual and societal burden.

Despite its clinical importance, current knowledge on prognostic factors in CRPS remains limited. Previous studies have been constrained by small cohorts,

heterogeneous diagnostic criteria, variable follow-up durations, and inconsistent reporting. Consequently, clinicians lack robust tools to anticipate disease trajectories in the early phase, hindering the implementation of stratified management strategies.

This thesis was conceived to address these gaps by examining biological and psychological prognostic factors in early CRPS through three complementary approaches.

First, a systematic review of the literature synthesized available evidence on predictors of CRPS evolution. It identified six factors consistently associated with poorer outcomes with moderate evidence: higher pain intensity, self-rated disability, anxiety, pain-related fear of movement, female sex, and a high-energy triggering event. At the same time, the review exposed significant methodological limitations in the field.

Second, a latent class analysis (LCA) was performed on a prospective cohort of early CRPS patients (n = 113, symptom onset < 6 months). This analysis investigated whether subgroups of patients with distinct biopsychosocial profiles could be identified. It revealed four clinically meaningful CRPS profiles characterized by different levels of pain, disability, and psychological burden, and further demonstrated that previously proposed classifications did not achieve to fully account for the heterogeneity observed in early CRPS.

Third, these patients were followed over 1 year, with clinical, psychological, and biological assessments conducted at four time points. This longitudinal study confirmed that higher baseline pain, functional impairment, and psychological variables (e.g., coping strategies, psychosocial severity, and anxiety) were associated with poorer outcomes over 1 year. By contrast, demographic variables and routine biological markers had limited prognostic value. Importantly, the

early biopsychosocial profiles identified through LCA were linked to divergent clinical trajectories, supporting the concept of clinically relevant subgroups.

Taken together, the findings of this thesis provide a more comprehensive understanding of early prognostic factors in CRPS. By combining systematic evidence synthesis with prospective cohort data and data-driven phenotyping, this work highlights key predictors of poor outcomes and demonstrates that CRPS is not a homogeneous condition but encompasses distinct clinical subgroups. These results strengthen the rationale for developing stratified and personalized treatment strategies aimed at preventing chronification and improving long-term patient outcomes.

2. Clinical cases

Before presenting the scientific investigations underpinning this thesis, it is worth first considering the lived experiences of patients facing the condition explored throughout this manuscript. The following clinical cases, drawn from participants in the studies described below, illustrate markedly different clinical situations — varying in pain intensity, delays in obtaining a diagnosis, uncertainty regarding prognosis, and confusion about symptom management.

Despite these differences, which reflect the striking heterogeneity in initial presentation, triggering events, and early disease course, all met the criteria for early CRPS. Together, these examples underscore the core challenge addressed in this work: the urgent need to identify early prognostic factors that can inform timely, stratified, and personalized interventions, thereby preventing the transition from early to persistent CRPS.

As aforementioned, the cover image illustrates the mental representations – drawn by the author of this thesis – of the affected and contralateral limbs in the first two cases presented below (at study inclusion [left], after 6 months [middle], and after 12 months [right]). Unfortunately, both cases progressed to chronification and continued to present with persistent CRPS at 1 year.

2.1. PATIENT 1 – Mr. M

Mr. M is a 43-year-old man who sustained a domestic accident resulting in the amputation of two fingers on his right hand. Following multiple surgeries, he gradually developed widespread pain throughout the hand, accompanied by a sensation of cold, accelerated hair growth, loss of mobility, and intense hyperalgesia. He is currently unable to RtW and suffers from significant psychological consequences related to the trauma of the accident. Given the clinical presentation, his surgeon requested a bone scintigraphy, which supported

the diagnosis of a CRPS. He is confused and distressed, struggling to understand what is happening to him, and asking “will I continue to suffer such pain?”.

2.2. PATIENT 2 – Mrs. M

Mrs. M is a 37-year-old woman who consulted a rehabilitation centre for lower limb pain (left extremity). She describes a burning, constant pain in her entire foot and ankle, which began few months ago after a minor soft tissue injury. At work, her left ankle was slightly crushed between a wall and a pallet jack. She did not report pain immediately but began experiencing painful sensations two days later. X-rays were reassuring, but she gradually became unable to bear weight on her foot and had to rely on crutches or a wheelchair for mobility.

Since the diagnostic tests showed no lesions, she faced pressure from both her employer and her insurance provider to return to work, which she describes as impossible. In addition to her functional impairment and constant pain, she exhibits diffuse contact allodynia across the entire foot, making activities like showering painful. Lastly, upon systematic anamnesis, she reports that her affected foot is more swollen, generally colder than the other side, and frequently changes colour, ranging from red to purplish hues.

2.3. PATIENT 3 – Mrs. O

Mrs. O is a 53-year-old right-handed woman who has been experiencing diffuse pain throughout her right hand for the past 4 weeks. She initially underwent bilateral carpal tunnel release surgery on the same day, performed by the same surgeon with the same anaesthetist. Although her initial complaint (numbness in part of the hand) resolved in both hands, she began to notice colour changes, sweating disturbances, and the onset of unilateral stiffness, which only affected the right hand, one week after surgery. During her postoperative consultation, her surgeon explained that the surgery had gone well and that she should no longer be experiencing pain.

2.4.PATIENT 4 – Mr. P

Finally, Mr. P is a 47-year-old former professional athlete. During a tennis match, he felt a sharp pain in the arch of his right foot. After various examinations, a small lesion in the plantar fascia was identified as the cause of localized, electively triggered pain. In the following weeks, he began to experience temperature changes, and most notably, marked colour changes after showering (**Figure 1.1**). He also describes diffuse pain throughout the foot, though not significantly disabling.

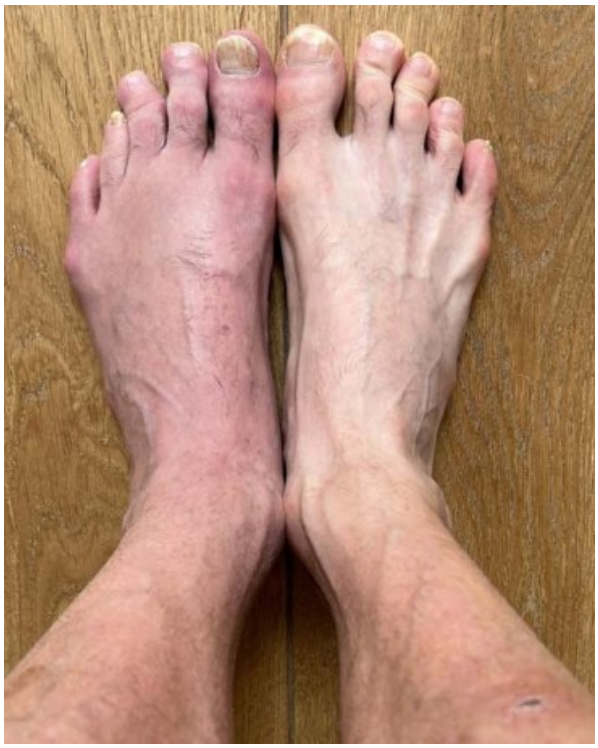

Figure 1.1. Early CRPS of the left foot (patient 4).

3. Pain

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [210,260]. This concept is currently dichotomized in the International Classification of Diseases 11th Revision (ICD-11) depending on pain duration: acute (< 3 months) or chronic (persistent or recurrent pain lasting longer than 3 months) [261].

Other classifications exist, depending on the aetiology (e.g., postoperative), body site (e.g., back pain, knee pain but also widespread pain), or mechanisms (nociceptive, neuropathic, or nociplastic[1]) for instance [210,260]. These terms help clinicians and researchers to categorize patients into more specific subgroups, enabling more personalized management (diagnosis, prognosis, treatment, etc.).

The current consensus in pain pathophysiology is the *biopsychosocial model*, which posits that pain is a "personal experience that is influenced to varying degrees by biological, psychological and social factors" [260]. This model underscores the need for multimodal interventions — encompassing biological, psychological, and social dimensions — particularly for the management of chronic pain [52].

[1] *nociceptive* (normal activation of nociceptors), *neuropathic* (direct consequence of a lesion or disease of the somatosensory nervous system), and *nociplastic* ("pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain") [256]. It should be noted than the term "*mixed pain*" has been recently proposed to represent condition where several types of pain simultaneously occur [83].

3.1. CHRONIC PAIN

In ICD-11 [261], chronic pain is categorized into two major groups: *chronic primary pain*[2] and *chronic secondary pain* (including cancer pain, posttraumatic and postsurgical pain, neuropathic pain, headache and orofacial pain, visceral pain, and musculoskeletal pain). Chronic pain represents a major global public health challenge, affecting approximately 20% of the population worldwide and contributing significantly to the reduction in quality of life (QoL) [260,261].

While chronic pain is formally defined by its duration, this definition oversimplifies a very complex phenomenon. There is increasing recognition that chronic pain is not merely a prolonged form of acute pain or a secondary symptom, but rather a distinct disease entity in its own right [260]. Indeed, it implies distinct pathophysiological mechanisms that differentiate chronic from acute pain [143]. These mechanisms explain why chronic pain tends to have a poorer prognosis and cannot be effectively managed by simply increasing the intensity of the therapeutic strategies used for acute pain [52].

Despite broad consensus on the multifactorial nature of chronic pain, a disconnect remains in the scientific literature. Recent narrative reviews published in high-quality journals [90,143,203,241] detail a wide range of abnormal biological processes involved in chronic pain — ranging from molecular to neural network levels — yet they rarely establish direct causal relationships with

[2] *Chronic primary pain*: "pain in one or more anatomical regions that (1) persists or recurs for longer than 3 months, (2) is associated with significant emotional distress (e.g., anxiety, anger, frustration, or depressed mood) and/or significant functional disability (interference in activities of daily life and participation in social roles), (3) and the symptoms are not better accounted for by another diagnosis" [188].

psychosocial variables, even though the evidence of predictors associated with pain chronification[3] in clinical studies are mostly based on these variables.

3.1.1. Specific mechanisms inducing chronification

In the following section, we will focus exclusively on the mechanisms implicated in the transition from acute to chronic pain. Specifically, we aim to identify studies that have examined the role of early factors in the development of chronic forms. Unfortunately, only a limited number of studies have directly investigated these mechanisms. Most of the available evidence is derived from animal and human post-surgical models [90,241,250,259] and, to a lesser extent, from studies on low back pain (LBP; see below).

However, most studies do not integrate the observed biological alterations with the well-established psychological and social factors known to influence prognosis. This has resulted in a fragmented understanding of pain chronification, despite the likelihood that it is the interaction and combination of these factors that drive the transition from acute to chronic pain [241].

Among the biological processes implicated in post-surgical pain chronification are a *dampened inflammatory response*, which paradoxically may impair pain resolution and increase the risk of chronification [199][4], modifications into the

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[3] Defined as "*the process of transient pain progressing into persistent pain; pain processing changes as a result of an imbalance between pain* amplification and pain* inhibition; genetic, environmental and biopsychosocial factors determine the risk, the degree, and time-course of chronification*" [180]. In line with the International Classification of Functioning, Disability and Health (ICF) framework [141], we adopted the broader term "chronification" to describe the process by which a transient condition evolves into a persistent one impacting body function, activities, or participation. Nota bene*: in this definition, the term "pain" might be less appropriate than "nociception" - however a discussion of this topic is outside the scope of the current work.

[4] In a murine model of nociceptive pain, inhibition of the inflammatory response using dexamethasone resulted in a reduction of immediate paw allodynia but paradoxically prolonged the duration of pain compared to the control group. This prolongation was not observed in models of neuropathic pain and was replicated with diclofenac, but

dorsal horn of spinal cord [143][5], dysregulation in *descending modulatory pathways*, such as the periaqueductal gray - rostral ventromedial medulla (PAG-RVM) circuit [90][6], *synaptic dendritic spine modifications* in cortical neurones [143][7], …(see [90,143] for a complete review on the topic).

Emerging human studies provide further insights on the mechanisms implicated in other painful conditions, particularly in LBP. After identifying protective roles of inflammatory processes in mice (see [4]), Parisien et *al*. analysed a large UK cohort and found that the use of non-steroidal anti-inflammatory drugs (NSAIDs) during acute LBP was associated with a higher risk of persistent pain 2 to 6 years later, even after controlling for potential confounders [199]. Notably, this effect was specific to NSAIDs and was not observed with paracetamol. Furthermore, a higher proportion of circulating neutrophils during the acute phase

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not with gabapentin, morphine, or topical lidocaine. One proposed mechanism involves the suppression of the physiological inflammatory response, particularly the role of neutrophils. Supporting this hypothesis, neutrophil-depleted mice demonstrated a similar pattern of prolonged pain, suggesting that early neutrophil-mediated inflammation may play a protective role in limiting the persistence of nociceptive pain.

[5] Notably, spinal presynaptic and postsynaptic changes (N-methyl-D-aspartate receptors [NMDARs] [126], RAC1 and KAL7 expression [both implicated in dendritic spines formation and maintenance]), C1q-driven signals, …), resulting in a modification of dendritic spines density [143].

[6] Physiologically, PAG-RVM pathway inhibits spinal responses to noxious stimuli, whereas stimulation of the RVM can both inhibit and facilitate nociceptive signals [90]. The involvement of the PAG–RVM pathway in the development of chronic pain is supported by animal models: lesions at the spinal entry point of descending fibres from the PAG–RVM prevent the development of neuropathic pain. Furthermore, in mouse models, stress has been shown to modify GABAergic activity in specific RVM neurons, thereby modulating pain thresholds. Acute stress induces antinociception, but prolonged stress exposure leads to mechanical hypersensitivity [82]. These findings suggest that the RVM circuit exhibits differential responses to short- versus long-term stress, potentially contributing to the increased risk of chronic post-surgical pain in individuals with preexisting stress.

[7] Increased turnover of superficial dendritic spines in primary somatosensory cortex (S1) after neuropathic pain, dendritic spine remodelling in medial prefrontal cortex in neuropathic mice models, …

was associated with a lower risk of chronification, suggesting that an *active inflammatory response* may serve a protective function during the acute stage (see [199] for complete explanations).

Supraspinal mechanisms also play a pivotal role. In acute LBP, the structural characteristics of the *corticolimbic circuitry* — a brain network implicated in emotion and reward processing — were predictive of chronic pain development 3 years later (n = 39) [263].

In a study of individuals with subacute back pain (n = 32), those who developed persistent pain exhibited a marked decrease in *hippocampal connectivity with the medial prefrontal cortex* [187]. According to these authors, the findings support the hypothesis that associative brain circuits may play a critical role in the chronification of pain.

In contrast to findings in surgical contexts, pain sensitivity measures (assessed by heat pain threshold [HPT], pressure pain threshold [PPT], and cold pain modulation [CPM]) did not predict pain chronification in acute LBP in a recent prospective study (n = 118) [44]. In the same cohort, however, a subgroup characterized by high psychological distress — corresponding to elevated levels of depression, anxiety, stress, rumination, and helplessness — was associated with significantly greater disability at 6-month follow-up compared to the other subgroups.

This finding is consistent with a robust body of literature highlighting the role of *psychosocial factors* in the transition to chronic pain. Factors such as anxiety, depression, pain catastrophizing, pain-related fear of movement, and poor social support have been repeatedly linked to chronification of acute pain conditions (see [241] for references).

The underlying mechanisms are supported by well-established theoretical models. For instance, the *fear-avoidance model* posits that catastrophic thinking in

response to pain can lead to pain-related fear of movement, behavioural avoidance, and a cycle of increased disability and pain [275].

An additional mechanism recently proposed is *pain interpretation bias* (defined as "excessive interpretation of ambiguous pain information as threatening"), which has recently been correlated with pain interference (but not pain severity) in both acute and chronic pain patient samples [259]. Notably, the same study found that pain-related interpretation bias predicted pain anxiety at the acute stage, which, in turn, was a strong predictor of both pain severity and interference at 3-month follow-up. Interestingly, in adjusted models, acute pain avoidance was not a significant predictor of pain outcomes.

In contrast to the models and mechanisms of pain chronification discussed above, a critical discrepancy is noted by Butler: the majority of chronic pain patients do not report a clear triggering event [40] — with only 1% of chronic pain situations linked to surgery and 21.8% reporting an acute onset, with or without an identifiable initiating factor [29]. Butler also emphasizes that most animal studies investigating the transition from acute to chronic pain are based on short observational windows, typically 7 to 14 days post-injury, which may not capture the full complexity of the chronification process. He ultimately suggests that "acute and chronic pain may be only points on a longer continuum that is a part of the plastic processes of the central nervous system throughout life and also with a genetic predisposition."

While pain chronification models based on an acute painful event may apply more directly to chronic post-surgical pain and, to a lesser extent, to the development of CRPS or chronic LBP cases, it is essential to acknowledge that most current evidence on chronification is derived from models that may not represent the majority of individuals living with chronic pain.

In summary, research has identified several biological mechanisms — including dysregulated inflammation, alterations in neural circuitry, and changes in brain connectivity — that contribute to the transition from acute to chronic pain, particularly in post-surgical contexts and, to a lesser extent, in LBP models. While psychosocial variables such as depression, anxiety, and pain catastrophizing have consistently emerged as strong predictors of pain chronification in clinical studies, biological research has rarely established clear mechanistic links with these psychosocial factors. This disconnect has contributed to a fragmented understanding of chronic pain pathophysiology.

As the biopsychosocial model has become the dominant conceptual framework — recognizing that psychological and social dimensions are integral to pain experience — there is an urgent need to better understand how neurobiological processes interact with cognitive-emotional states and social environments.

4. (Early) Prognostic Factors in Pain

4.1. WHAT IS A PROGNOSTIC FACTOR?

Prognosis, in healthcare, is defined as "the forecast of future outcomes in people with a particular health condition" [219]. Therefore, a *prognostic factor* is a measure "associated with subsequent clinical outcome in people with a particular disease or health" [217]. It aims to distinguish groups of people with a different average prognosis, and thus different outcomes.

It can therefore be used to (1) define the disease/condition at diagnosis, (2) inform clinical and therapeutic decision, (3) enhance the design and analysis of intervention trials, and (4) help identify targets for new interventions aiming to modify the course of the disease [217].

In many diseases, the prognostic research focused on *biomarkers*, including a vast range of biological (e.g., genomic), pathological, imaging, clinical, and physiological variables [217]. Nevertheless, in chronic pain field, the most relevant identified predicting variables appeared to be psychosocial variables, such as catastrophizing, coping strategies, anxiety and depressive disorders, pain related fear of movement, life stressors… [52,231,251,281]. These factors are commonly called "*yellow flags*" [236]. For instance, in LBP, rehabilitation interventions incorporating psychological components are more effective than traditional ones that lack these elements [123].

A recent large prospective and multicentric study perfectly illustrates the importance of psychosocial factors [249]. The authors investigated the variables predicting the transition from acute LBP (inclusion, n = 9547) to chronic LBP (6 months, n = 5233 which 32% still presented significant impairment). Independent factors included *baseline disability* (severe and very severe disability: OR, 1.82; 95% CI, 1.48-2.24 and OR, 2.08; 95% CI, 1.60-2.68 respectively), *health insurance* (OR depending on the insurance), *BMI* (obesity: OR, 1.52; 95% CI,

1.28-1.80), *smoking* (OR, 1.56; 95% CI, 1.29-1.89), *anxiety or depressive diagnosis* (OR, 1.66; 95%CI, 1.28-2.15), and *Subgroups for Targeted Treatment Back tool [STarT Back Screening tool, SBT]* (high-risk subgroup vs. low-risk: OR, 2.45; 95% CI, 2.00-2.98).

This latter variable (the SBT) corresponds to one of the questionnaires (briefly described below), based on *yellow flags*, designed to assess the risk of chronification in acute LBP patients.

4.1.1. STarT Back Screening Tool

The SBT is composed of 9 items (dichotomic reply, [yes/no]), enabling clinicians to quickly assess modifiable psychosocial factors in acute LBP [122]. The score is then used to select one of three treatment regimens: low-risk patients are reassured and encouraged to stay active, physiotherapy is added for medium-risk individuals, and high-risk patients are invited to follow a more complex programme including management of psychosocial factors such as fear avoidance (see below "Successes of stratified care" for further explanations regarding the studies that underpinned its creation).

Other questionnaires have been developed to assess prognostic factors in musculoskeletal (MSK) pain, notably the *Örebro Musculoskeletal Pain Screening Questionnaire* (ÖMPSQ).

4.1.2. Örebro Musculoskeletal Pain Screening Questionnaire

The ÖMPSQ was specifically designed to capture the multiple dimensions involved in the transition from acute to chronic and disabling MSK conditions. After reviewing the literature and identifying key items from validated questionnaires, the authors proposed a tool initially composed of 25 items [153], later adapted into a shorter version [154] (10 questions), which evaluates

symptom severity, functional limitations, work-related issues, and psychological factors associated with pain prognosis and work disability.

Like SBT, the ÖMPSQ classifies patients into risk subgroups for chronification. While this questionnaire is more time-consuming to complete than SBT and does not provide treatment stratification, it is more multifaceted, offering better insight on individual prognostic factors. Notably, it has demonstrated stronger predictive value for work-related outcomes, is more closely associated with lifestyle factors, and is not limited to LBP, thereby supporting its applicability across a wider range of MSK conditions [131,150,239].

Later in this thesis, we will discuss these two questionnaires in more detail — the SBT as an important example of a stratified approach in another condition (i.e., LBP), and the ÖMPSQ as a potentially valuable prognostic tool in CRPS.

4.2. WHY "EARLY" PROGNOSTIC FACTORS?

As it has been established that chronic pain is frequent, difficult to manage [52] and present a higher impact on QoL and poorer prognosis than acute pain [53], clinicians want to prevent the risk of developing a chronic painful and disabling condition (secondary prevention) [175].

To achieve this, it is necessary to identify, at an early stage, which patients are at risk of poorer outcomes, and therefore which *early* modifiable prognostic factors (i.e., predictors gathered during the early stage of the condition) are associated with the development of chronic conditions.

This goal has led to different therapeutic strategies, including in MSK conditions stratified and personalized management, reviewed in the next chapter.

5. Stratified Approach: Definition, Successes and Failures

In the following section, we present the concept of stratified approach, its origins, the evidence supporting its success as a care model, as well as studies that failed to demonstrate significant improvements with this type of management in MSK conditions.

5.1. DEFINITIONS

In the clinical setting, the early identification of prognostic factors is necessary — but not sufficient — to improve patient outcomes. For predictors to be clinically meaningful, they must (1) be easily measurable in routine care, and (2) influence clinical decision-making. Regarding the latter point, it means that they might be modifiable, although it could be argued that it might also be useful to inform the clinician and patient without necessarily changing the course of treatment [219].

Given the constraints on healthcare resources, therapeutic strategies should be risk-adapted, prioritizing individuals at higher risk of chronification who present with modifiable risk factors, rather than allocating identical care to all patients with the same diagnosis regardless their actual needs.

A *classical* therapeutic approach is condition-driven, applying all evidence-based treatments uniformly depending on the pathology. In contrast, a *stepped-care* model advocates for graduated treatment intensity, tailoring interventions to the severity, progression, and treatment response. This model is commonly applied in conditions like hypertension, where clinicians may start with a single antihypertensive agent and escalate therapy based on patient's response. In the context of pain management, a *stepped-care* approach involves the progressive intensification of both pharmacological and non-pharmacological interventions, including adjustments in dosage, frequency, and therapeutic complexity, in

accordance with the patient's symptom severity, functional impairment, and treatment responsiveness.

Von Korff was one of the pioneers of *stepped-care* in back pain [276], proposing in 2001 a model consisting of three sequential treatment levels. Rather than constituting a specific intervention, the *stepped-care model* was introduced as “a way to sequence interventions so that the intensity, complexity and costs of care, guided by each patient’s observed outcome”, with the overarching goal of delivering appropriate and cost-effective treatment tailored to individual needs.

The first step involved simple physician advice (e.g., “stay active” and “continue ordinary activities as normally as possible”), primarily aimed at addressing specific patient concerns. Step 2 was intended for patients still experiencing activity limitations at 6 to 8 weeks and included more structured interventions focused on increasing physical activity and supporting the resumption of normal daily roles. If this approach did not allow significant improvement, the final step provided a graded exercise program and addressed comorbid psychological conditions, targeting individuals with substantial disability in work or family life.

This approach was later reinterpreted by Hill et *al*., proposing a *stratified-care model* based on patient prognosis [119,122]. In contrast to the classical stepped-care approach, stratified-care allows clinicians to propose more intensive treatments upfront for patients identified as high risk, without requiring prior failure of lower-intensity steps.

Finally, a *personalized-care model* — which may be combined with stepped or stratified strategies — adapts the timing, intensity, and type of intervention to the patient’s unique clinical profile (e.g., for hypertension using beta-blockers in cases of comorbid heart failure, or ACE inhibitors in patients with concomitant diabetes with albuminuria).

In the pharmacological management of chronic pain, this personalized approach has been the focus of ongoing research efforts aiming to identify patient subgroups that are more likely to respond to specific medications ("*mechanism-based treatment*"), thereby reducing the reliance on trial-and-error prescribing.

5.2. SUCCESSES OF STRATIFIED CARE

In 2011, Hill et *al*. demonstrated that a stratified-care approach for LBP patients — using the SBT — was both cost-effective and associated with improved disability outcomes at 12 months, compared to non-stratified best current practice, in a randomized primary care cohort in the UK (n = 1,573) [122]. These findings were later replicated in a two-phase prospective study conducted in primary care settings, which also reported better outcomes in the SBT-guided group (n = 554) compared to those receiving usual care (n = 368) [81].

Following these promising results, the SBT was translated into multiple languages and incorporated into several national clinical guidelines, including those of the UK, Germany, Belgium, and Australia. Today, it is used in clinical practice across approximately 50 countries and has significantly influenced LBP management globally — particularly in Western healthcare systems (see [54] for references).

5.3. FAILURES OF STRATIFIED APPROACH

Using SBT, several large longitudinal studies have attempted to replicate the findings of Hill and colleagues in other clinical settings (N = 6, see [54] for references). With the exception of one study that included a questionable control group [46,288], none of these trials demonstrated significant benefits of the stratified approach (using SBT) over usual care in reducing disability or healthcare costs of acute LBP patients.

In their review, Croft et *al*. [54] analysed and compared these studies, identifying several possible explanations for the lack of consistent positive outcomes: (1) limited adherence and fidelity in applying the SBT and matched interventions, (2)

less rigorous training of healthcare providers, (3) systemic differences in healthcare delivery, (4) control groups not accurately reflecting real-world "usual care," (5) low proportions of high-risk patients (for whom the largest benefits are expected), and (6) variation in study designs, including differences in outcome measures, follow-up durations, and statistical methods.

In 2021, the Keele research team — the group that developed the original SBT — introduced the Keele STarT MSK Tool to extend stratified-care to a broader population. This new tool targeted patients in primary care presenting with one or more of the five most common MSK pain sites (back, neck, knee, shoulder, or multisite pain) [70,121].

Although the tool demonstrated predictive validity, Hill and colleagues [120] were unable to replicate the earlier positive outcomes observed in their 2011 study. In a large cohort (n = 1,211), there were no significant differences in pain, disability, or cost-effectiveness between the risk-stratified intervention group and those receiving usual care. Similar null findings emerged from stratification studies focused on conditions such as sciatica and whiplash injury [139,212], further challenging the generalizability of the original 2011 results.

Nevertheless, as George pointed out in a 2023 commentary [86], the absence of observed benefits may partly reflect improvements in the quality of "usual care" in more recent trials. Echoing Croft et *al*.'s conclusions, other contributing factors may include: "(1) the limited use of the screening tool, (2) lower than anticipated primary care referrals, and (3) poor uptake of the training and unknown delivery of psychologically informed physical therapy".

6. Complex Regional Pain Syndrome (CRPS)

To avoid redundancy, this section is deliberately brief, as the different *chapters* (*1* to *3*) cover many aspects of this condition. The following paragraphs summarize the current concepts and characteristics of CRPS, the specific difficulties encountered in CRPS research, and the hypotheses and aims subtending the present thesis.

For French or Dutch speakers looking for a quick overview current knowledge about CRPS, we published a free-access Editorial ([8], references in annexes).

6.1. CURRENT KEY CONCEPTS AND INTRIGUING CHARACTERISTICS

6.1.1. Definition

In the absence of other definition, we can consider that CRPS is currently defined by the *Budapest criteria*[9]: a syndrome characterized by continuing regional pain (but not in a specific nerve territory or dermatome), disproportionate (in time or degree) to the possible inciting event [104,109], associated with symptoms and signs of different categories: neurological (hyperesthesia, hyperalgesia and allodynia), vasomotor (change in colour and temperature of the affected limb), sudomotor (oedema and sweating disorders), motor (weakness, restricted range of motion [RoM]), and/or trophic (changes in skin, nail and hair growth). Furthermore, the absence of "other diagnosis that can better explain the signs and symptoms" is required [92].

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[8] French-version: http://hdl.handle.net/2078.1/301107
Dutch-version: http://hdl.handle.net/2078.1/301108

[9] See below for further explanations regarding those criteria.

Some neurocognitive symptoms, such as altered body representation of the affected limb, are commonly associated with CRPS[10]. However, as detailed in section *6.1.3.4. Central nervous system changes*, their expression varies markedly across patients, with some exhibiting no neurocognitive features at all. Consequently, these symptoms are not included in the diagnostic criteria.

CRPS has recently been classified as a *chronic primary pain*, in which pain is mostly driven by nociplastic mechanisms [188]. It should be noted that a "*mixed pain concept*" is currently debated (e.g., see 2025 EFIC Congress 2025 scientific program[11] and [83]). Despite no clear consensus, CRPS could potentially been classified in this particular category [168].

Finally, two subtypes have been historically described: type I, in the absence of identified peripheral neurological lesions (e.g., after an ankle sprain), and type II, in the presence of a confirmed neurological lesion (e.g., peripheral nerve injury) [92]. However, no consistent differences in clinical presentation, prognosis, or treatment response have been demonstrated between these two historical subtypes, calling their clinical relevance into question [92].

6.1.2. Clinical Presentation

CRPS may present as a very 'florid' case, where the patient presents a red, hot, swollen and permanently painful hand or foot, which he/she is totally unable to move. Patients can also present by an equally painful limb showing at first sight

[10] In 2007, Lewis et *al*. explored the concept of "body perception disturbance" in CRPS by a qualitative analysis [148]. They found several key themes reported by patients but also noted that none of these elements was described by all participants (n = 27, mean symptoms duration: 6 years), underlying the variability of experiences among CRPS patients. Interestingly, severe conditions were associated with an increased number of reported difficulties.

[11] https://efic2025.abstractserver.com/program/#/details/sessions/80

only a slight oedema and restricted RoM, associated with a strong and diffuse contact allodynia making activities of daily living impossible.

In the vast majority of cases, CRPS affects one extremity of a limb that has undergone physical trauma (whose severity may range from benign, such as a small sprain or contusion, to severe, such as surgery or fracture) [181,194,230]. Its location often does not strictly correspond to the site of the initial trauma. For example, CRPS of the whole hand may be observed after a fracture of the humerus, without any features on the arm. One can also observe CRPS localised to restricted areas, such as a finger.

All those clinical presentations notably reflect diverse pathophysiological mechanisms, present with different intensity from patient to patient, underlying probable different phenotypes.

6.1.3. Pathophysiology

The pathophysiology of CRPS remains incompletely understood but is generally considered to involve an aberrant systemic and local response to physical trauma. This dysregulated response includes a combination of inflammatory and immune mechanisms, autonomic dysfunction, peripheral and central nervous system changes (including maladaptive neuroplasticity), and potential genetic predispositions [26,77]. **Table 1.1** provides a synthesis of the current understanding and key recent findings regarding the multifactorial pathophysiology of CRPS.

Categories	*Observed modifications*	**"*Early*" CRPS (< 1 year)**	**"*Persistent*" CRPS (> 1 year)**
Inflammatory components	Proinflammatory cytokines (TNF-α and soluble TNF receptors 1 and 2, IL-6, IL-8…)	↑	(↑) or =
	Anti-inflammatory cytokines	↓	(↓) or =
	Keratinocyte proliferation	↑	↓
	Mast cells proliferation (also responsible for vasomotor dysfunction by releasing tryptase, histamine, cytokines, proteases, …)	↑	↓
	Langerhans cells	?	↓
	Bradykinin & substance P	↑	↑
	Calcitonin gene-related peptide (CGRP)	= or (↑)	= or (↑)
	CD4+ and CD8+ lymphocytes number	?	↑
Autoimmune components	IgG activating β2 adrenergic or M2 muscarinic receptors	Demonstrated	?
	IgG activating α-1a receptors	?	Demonstrated
	IgG inducing microglia and astrocyte activation in nociceptive pathway (ipsilateral spinal cord dorsal horn, the periaqueductal gray, and the contralateral somatosensory cortex).	?	Demonstrated
	Passive transfer- trauma mouse model using IgG from CRPS patients	?	Demonstrated
Bone metabolism	Alkaline phosphatases	↑	?
	Uptake scintigraphic ratio (localized bone turnover)	↑	(↑) or =
	Osteoprotegerin	Conflicting[a]	?
	Other serum bone makers	=	?
Autonomic components	α1-adrenoceptors expression	↑↑	↑
	Deep breathing test	Abnormal in some (<15%)	
	Sympathetic skin response	Abnormal in some (<15%)	
	Orthostatic test	=	
CNS modifications	Mechanical and thermal hyperalgesia in pain-free body regions, suggesting central sensitisation[b]	↑	↑↑
	Auditory (ipsilateral hyperacusis), olfactory and visual disturbances[c]	?	Found
	Brain modifications (structure and function)[1]	Found	Found
	Neuropsychological changes	↑	↑
Genetic predisposition	Abnormal frequence of HLA alleles and four SNPs	(Demonstrated)	Demonstrated
	Epigenetic mechanisms (abnormal methylation of some genes)	Demonstrated	
Gut microbiome composition	Alterations of bacterial taxa responsible for the metabolism of short-chain fatty acids	?	Demonstrated

Table 1.1. Systems involved in CRPS physiopathology and their respective identified modifications. *Abbreviations: ↑, increased vs. healthy subjects and/or contralateral limb; ↓, vs. healthy subjects and/or contralateral limb; =, no significant change; ?, data unavailable; (), slight changes or very limited evidence; CRPS, complex regional pain syndrome; CNS, central nervous system; IL, interleukin; HLA, human Leukocyte Antigen; SNP, single nucleotide polymorphisms.*

The decision to apply a 1-year cut-off between early and persistent CRPS in this synthesis reflects the heterogeneity of definitions used across studies included in Table 1.1, which numerous of them using this cut-off. However, as discussed in Chapters 2 and 3, accumulating

evidence suggests that a 6-month threshold may represent a more clinically relevant distinction, particularly in relation to prognosis.

It is important to note that psychosocial factors are not represented in Table 1.1, despite their established importance in CRPS condition [77]. *This omission reflects the current lack of mechanistic studies linking psychosocial variables to specific pathophysiological pathways in CRPS onset.*

[a], *Similar to healthy subjects in the most recent and larger study* [111]*, increases in an older and smaller study* [142].

[b], *Could also be explained by peripheral/systemic sensitisation, without involvement of central nervous system.*

[c], *Discomfort provoked by normally innocuous visual stimuli* [255].

6.1.3.1. Autoimmunity and Inflammatory Response

As reported by Ferraro et *al*., an "aberrant immune-mediated inflammatory response could be a key pathophysiological mechanism of CRPS" [77]. Indeed, CRPS has been associated with increased proinflammatory cytokines and decreased anti-inflammatory cytokines levels, as well as keratinocyte proliferation, mast cell activation (also responsible for vasomotor dysfunction by releasing tryptase, histamine, cytokines, proteases, …), bradykinin & substance P augmentation[12], … [27,77,201]. It should be noted that a considerable overlap exists between individuals' levels of these biological parameters, for instance some CRPS patients show normal levels of TNF- α.

Furthermore, some evidence suggests the involvement of autoimmune mechanisms, potentially triggered by the initial traumatic event. A series of experiments support this last point. First, if immunoglobulin G (IgG) serum from persistent CRPS patients is daily administered injected intraperitoneally into

[12] Another argument in favour of an impaired metabolism of bradykinin and substance P is the potential association between angiotensin converting enzyme (ACE, involved in the regulations of these two neuropeptides) inhibitors and a higher risk of developing CRPS [182] .

mice, nothing happens [94][13]. However, if one reproduce the same methodology but combine it with the induction of a lesion in the hind paw, a 'CRPS-like' disease develops (i.e., mechanical hyperalgesia [remaining stable] and paw oedema [resolving over time]) [114,252]. The changes were only localised to the injured paw and were strongly differentiated from the effect of saline injections or injection of healthy volunteers IgG. This reinforces the importance of trauma, which probably induces the expression of receptors on neurons targeted by autoantibodies in the initiation of CRPS, producing neuroinflammation.

Another study, using the same methodology to induce CRPS in mice, identified differential expression of 125 genes in the unilateral L3–L5 dorsal root ganglia following CRPS induction [207]. These genes were primarily involved in inflammatory and immune responses, including cytokines, chemokines, and neuropeptides. Pathway analysis highlighted the involvement of TNF-α and Janus kinase (JAK-STAT) signalling. Notably, the use of TNF-α and JAK-STAT inhibitors (etanercept and tofacitinib, respectively) attenuated mechanical hyperalgesia and reduced activation of astrocytes and microglia in the central nervous system induced by CRPS-IgG. These findings establish a link between autoimmunity and central neuroinflammation.

6.1.3.2. Bone Metabolism

Based on scintigraphic findings and the potential efficacy of bisphosphonates, bone metabolism has long been considered a possible contributor to CRPS pathophysiology. A recent prospective cross-sectional study conducted in Germany (n = 114; CRPS duration < 1 year) aimed to explore this hypothesis [111]. Harnik et *al*. investigated various bone turnover markers, including alkaline

[13] Conversely, if the same injection is made with serum from fibromyalgia patients, hyperalgesia (to mechanical stimulation and cold) is observed by sensitisation of peripheral nociceptive afferents, as well as a reduction in locomotor activity, paw grip strength, and epidermal innervation (nerve density) [93].

phosphatase, 25-OH vitamin D, osteoprotegerin, and procollagen type I N-terminal propeptide, and found no significant differences compared to healthy controls. The sole exception was an elevation of alkaline phosphatase in patients with warm CRPS (defined using skin temperature difference), which was significantly higher than in both healthy controls and cold CRPS participants. However, this increase did not correlate with bone scintigraphy findings or with other bone markers, leading the authors to suggest that it may reflect broader pathophysiological processes. Indeed, alkaline phosphatase has been implicated in (anti-)inflammatory pathways via its ectonucleotidase activity, converting proinflammatory ATP into the anti-inflammatory nucleotide adenosine.

With respect to bone scintigraphy, 95% of the participants of the same study showed increased radiotracer uptake [111]. The uptake ratio between affected and contralateral limb was independent of CRPS subtype (warm vs. cold), duration of immobilization, or PPT (measured at the thenar muscles). These results suggest that most of patients suffering from "early" CRPS (defined in the study as < 1 year duration) present altered bone metabolism, without consistent association with clinical presentation.

Such metabolic changes may be driven by neurogenic inflammation, potentially involving the release of substance P and CGRP, which stimulate receptor activator of nuclear factor kappa-B ligand (commonly labelled RANK-L), a key factor in osteoclastogenesis and bone resorption. TNF-α may also contribute by promoting osteoclast formation. Additionally, in vitro studies have shown that activation of β2-adrenergic receptors can induce osteoclastogenesis, suggesting another possible mechanism of bone involvement in CRPS (see [111] for references).

6.1.3.3. Vasomotor Dysfunction

Based on clinical features such as abnormal sweating, skin colour changes, and temperature asymmetry, CRPS was initially conceptualized as a disorder of the autonomic nervous system, potentially relieved by sympathetic blockade.

However, randomized controlled trials have demonstrated limited efficacy of sympathetic blocks [191], and the so-called “autonomic symptomatology” can often be attributed to other mechanisms — for example, oedema resulting from inflammation, or temperature changes caused by central and peripheral sensitization.

Nevertheless, the autonomic nervous system likely plays a role in the pathophysiology of certain CRPS subtypes. For instance, increased adrenergic receptors density has been observed in some patients and may contribute to pain and hyperalgesia [67]. Notably, these findings were not associated with skin temperature changes.

Furthermore, a retrospective study conducted in South Korea involving 199 patients with CRPS who presented to a pain clinic found that 26% exhibited signs of systemic dysautonomia, as assessed through deep breathing tests or sympathetic skin response. These dysautonomic features, however, did not predict response to sympathetic nerve blocks [146].

6.1.3.4. Central Nervous System Changes

Some findings suggest central nervous system involvement, such as mechanical and thermal hyperalgesia in pain-free body regions observed in cross-sectional studies [58,59,66]. Increased temporal summation of pain, considered a marker of spinal sensitization, has also been reported [58][14]. This observation was significant in comparison to contralateral arm but healthy subjects.

[14] It should be noted that a recent systematic review and meta-analysis [245], published prior to that study ([58]), found no significant temporal summation of pain increase on either the affected or contralateral side. Similarly, our study (*Chapters 2* and *3*) did not find higher temporal summation of pain scores compared to normative values. This discrepancy may stem from the longer temporal summation of pain assessment method used in [58], potentially more sensitive than the German protocol [224].

In cases of persistent CRPS (but also in fibromyalgia), reduced tolerance to auditory, visual, and olfactory stimuli (considered signs of central sensory processing dysfunction) has been observed compared to pain-free controls [65,255], which also suggests an influence on the central nervous system. In Drummond's study, some of these findings were more pronounced on the affected side than on the contralateral side [65].

Brain imaging studies have also revealed structural and functional alterations in CRPS. A 2013 systematic review summarized one of the earliest and most consistent findings: the cortical representation of the affected hand in the contralateral primary somatosensory cortex (S1) is abnormally reduced compared to that of the unaffected hand [61]. In early CRPS, this reorganization appears to be primarily driven by the level of mechanical hyperalgesia according to the authors [165], whereas it seems to reverse in patients who experience significant pain reduction over the following 12 months [164]. More specifically, changes in neuropathic pain intensity between baseline and 12 months were found to predict the degree of cortical reorganization [164]. It should be noted that similar abnormalities have been observed in other chronic limb pain conditions [136,269].

However, a more recent study by Mancini et *al*. challenged these observations [166]. The authors reported that the S1 representation of the affected hand in patients with persistent CRPS was largely comparable to that of the unaffected hand and of healthy controls. These results question the idea that S1 reorganization drives pain or disability, and they also call into doubt the rationale behind treatments such as mirror therapy that aim to “restore” somatotopic representations. The discrepancy with earlier findings may be explained by advances in modern functional MRI techniques, which now provide more reliable and less biased measurements of cortical hand somatotopy (see discussion in [166] for further information).

Other studies further support the view that CRPS-related alterations may not primarily involve S1. Di Pietro et *al*. found no structural differences in S1 between patients with persistent CRPS and healthy controls [60]. Instead, they observed abnormal resting rhythms in the contralateral thalamus and increased thalamus–S1 connectivity, which correlated with pain intensity and tactile acuity. These findings point to disrupted thalamocortical loop dynamics that may sustain the constant perception of pain in CRPS.

Similarly, abnormal resting rhythms have been identified in the contralateral putamen [145], particularly in regions representing the upper limb (in upper limb CRPS patients), along with increased connectivity between these putaminal areas and cortical regions [7,145]. These observations, highlighting alterations in basal ganglia function (similarly to Parkinson's disease), could play a role in motor disturbances, commonly observed in CRPS. We did not find any study investigating similar abnormalities in other pain conditions.

Finally, involvement of the parietal cortex has also been suggested. Evidence includes abnormal performance on neurocognitive tests and functional as well as structural parietal changes (see [102], page 18 for references). These alterations may (partly) underlie CRPS-related neuropsychological symptoms[15] such as

[15] This term is preferred to the old "neglect-like symptoms" label. Indeed, the latter does not fully capture the neuropsychological changes found in CRPS [102,148].

distorted body representation[16] and both lateralized[17] spatial and non-lateralized[18] cognitive deficits (see [102] for a review). However, these findings vary between individuals[19], and some are not specific to CRPS [102].

6.1.3.5. Genetic Predisposition

In 2009, Rooij et *al*. suggested a heritable component in CRPS [227]. Among 31 patients with at least one affected relative, earlier disease onset, involvement of multiple extremities, and more frequent dystonia were observed compared to sporadic cases.

The same group further supported a genetic predisposition by analysing Human Leukocyte Antigen (HLA) alleles in two CRPS cohorts (with or without dystonia; n = 150 and 131) and in a large cohort of healthy controls (n = 5,604) [228][20].

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[16] It includes distorted perceptions of the affected limb's size, shape, or weight, feelings of disownership, or even aversion toward the limb [102].

[17] Deficits in lateralized spatial cognition include motor neglect of the affected limb, with reduced initiation and execution of movements, and spatial attention biases away from the affected side in experimental tasks such as temporal order judgements (TOJ). In addition, subjective body midline perception is frequently shifted, typically toward the affected side, though findings are inconsistent, with some studies showing opposite or no directional biases [102].

[18] Non-lateralized cognitive impairments include somatosensory recognition problems such as finger agnosia, astereognosis, and dysgraphesthesia; motor and visuoconstructive difficulties including apraxia; as well as language and calculation deficits, such as dyscalculia and dysgraphia. Broader cognitive impairments have also been observed in domains of working memory, verbal fluency, and episodic memory [102].

[19] For instance, some will present a significant bias towards the affected limb, others will present the contrary, while others will report an absence of any spatial bias [78,79,157].

[20] Particularly, they identified an association with HLA-DQ8 in CRPS patients, an allele strongly linked to celiac disease.

More recently, genetic susceptibility was reinforced by the identification of four non-synonymous single nucleotide polymorphisms (SNPs)[21] in two persistent CRPS cohorts (n = 34 and 50) compared to a chronic pain control group (n = 39; fibromyalgia or LBP) and two population databases [238]. These SNPs, all involved in monocyte/macrophage lineage function, showed significantly altered rare allele frequencies in CRPS patients. While age was not associated with these findings, males appeared more frequently affected than females (at least one SNP in 8/14 males vs. 17/70 females). The clinical implications of these genetic variants for disease presentation, prognosis, or treatment remain to be clarified.

Epigenetic mechanisms are probably involved, as demonstrated by the abnormal methylation of some genes in CRPS induced by amputation in military trauma context (n = 9) in comparison to subjects presenting only non-CRPS neuropathic pain (n = 38). These findings were validated in an independent DNA biobank database [32].

6.1.3.6. Gut Microbiome Alterations

A very recent study has highlighted notable differences in the gut microbiome between individuals with CRPS and pain-free controls [95]. These alterations affected bacterial taxa responsible for the metabolism of short-chain fatty acids, which are potentially influencing several biological mechanisms: differentiation of T helper 17 (Th17) and regulatory T (Treg) cells, modulation of neurotransmitter and neuropeptide levels within the central nervous system, and microglia activation.

[21] rs41289586 in ANO10, rs28360457 in P2RX7, rs1126930 in PRKAG1 and rs80308281 in SLC12A9.

Interestingly, the microbiome abnormalities observed in CRPS patients resemble those reported in fibromyalgia, another predominantly nociplastic pain syndrome in which the gut microbiota is suspected to play a significant role [42].

Importantly, the study reported no significant differences in dietary intake between CRPS patients and controls, suggesting that the observed microbiome alterations are not primarily driven by diet.

6.1.4. Onset and Risk Factors for CRPS Onset

The timing of onset of CRPS is surprising. The condition generally appears a few weeks after an initial physical trauma. In rare instances (around 5% of cases), no triggering event is found [91]. Several risk factors for the onset of CRPS have been identified, such as a more intense traumatic event, high pain intensity after the initial trauma or before/after surgery and the immobilisation of the injured limb [20,34,77,208].

Regarding the immobilisation as a risk factor, it is mostly estimated through the duration of cast, considered an objective indicator of the time during which the limb was mechanically constrained. However, the concept of immobilization is likely broader: it is not limited to external devices but also includes the reduced voluntary or unconscious use of the limb. Pain, fear of movement, or avoidance behaviours driven by anxiety may contribute to a "functional disuse" that can, in some cases, be more restrictive than the duration of casting. This broader conceptualization may help explain why some patients develop CRPS after trauma while others, exposed to similar clinical circumstances, do not. In clinical practice, the underuse is difficult to quantify. One methodological avenue would be the use of actimeters or wearable motion sensors, which could objectively track activity levels and compare them with normative values. Such an approach would provide a quantitative and dynamic measure of immobilization, but would require substantial resources in terms of cost, logistics, and patient compliance.

Concerning psychological factors, a multicentric prospective study questioned their supposed involvement: no association was observed between the investigated psychological factors and the onset of CRPS (n = 596 patients, 7% developed a CRPS) [20].

It is probable that the interaction of biological, psychological and social factors triggers CRPS, but the reason why some patients develop CRPS and others do not is still largely unknown [77]. In our cohort (see *Chapters 2* and *3*), several participants had a medical history of fractures or other physical trauma and were unable to explain why 'this time' was different. This is illustrated by the third clinical case developed in the beginning of this introduction, where a woman developed CRPS of one hand only after bilateral carpal tunnel surgery.

6.1.5. Therapeutic management

Management of CRPS still varies widely from one practitioner to another. Older treatment modalities, based on very limited evidence or even proven ineffective, are still offered to patients (e.g., targeting the sympathetic system [sympathetic blocks and neurolytic sympathetic procedures, clonidine, contrast baths], or the oxidative stress [acetylcysteine]).

The optimal currently recommended treatment includes educational therapy, antalgics (paracetamol and NSAIDS), physiotherapy, and in refractory cases, atypical analgesics (e.g., gabapentin, topical anaesthetics), intensive rehabilitation (including more specific techniques such as mirror therapy and sensorimotor modalities), and psychological therapy [77,109].

Several other therapies, focusing on immunity (interferons, TNF-alpha blockers, etc.), bone metabolism (bisphosphonates), or inflammatory responses (glucocorticoids) have been proposed, with varying levels of effectiveness [109].

6.1.6. Prognosis and potential predictors

As detailed in *Chapters 1* and *3*, most patients do not fully recover from CRPS, with some developing a chronic, painful, and disabling condition. The mechanisms underlying these divergent trajectories remain unclear, and evidence on early prognostic factors is scarce (see *Chapter 1* for a systematic review of the topic).

In the absence of scientific evidence, a 2011 Delphi survey assessed experts' opinions on the prognosis of CRPS [38]. Twenty-eight experts associated 49 items with increased risk of poorer outcomes. The most important factors cited by the experts were *sensory changes* (e.g., allodynia, hyper-hypoesthesia/algesia, but also pain intensity), *motor changes* (weakness), *trophic changes* (i.e., joint contractures, skin lesion and faster nail growth), *autonomic changes* (e.g., vasomotor and sudomotor changes), *initiating event* (fracture and spontaneous onset), and symptom *duration* (symptoms between 6 and 12 months). Two social factors were reported: the *lack of social network* and a *medicolegal context* (someone/something caused the problem or a conflict with the employer). Other social factors were considered less important, while psychological factors were surprisingly not mentioned at all.

More recent research identified the importance of psychological factors in the development of chronic CRPS, as in LBP [16,158]. These factors could help understand the otherwise unexplained variability in the observed clinical trajectories of patients with CRPS.

6.2. ISSUES ENCOUNTERED IN CRPS RESEARCH

In comparison with other painful conditions (e.g., LBP, fibromyalgia, or neuropathic pain), CRPS is still poorly understood and related evidence is scarce, despite the fact that this condition was already described in the 19th century

("*causalgia*") [277]. As an illustration, using their related MeSH[22] terms in Pubmed, we identified over 28,500 articles related to LBP, 21,400 to neuropathic pain, 9,900 in fibromyalgia, but only 4,262 related to CRPS[23].

In the following section, we try to summarize the numerous obstacles to study this disorder, which are (1) the outdated denominations and diagnostic criteria, (2) the lack of consensus on how to define CRPS duration, and (3) the challenges of recruiting a meaningful sample of CRPS patients.

6.2.1. Name and Diagnostic Criteria

Many names have been used to label CRPS, some authors reporting more than 80 names in the Anglo-Saxon literature, 50 in German, 30 in French, and 15 in Dutch [85]**.** As mentioned by Geertzen and Dijkstra in 2000, these names were related either to a supposed pathogenesis, clinical presentations, radiographic characteristics or triggering event [85].

Some of these terms may today seem quite silly, but the lack of consistency is still a major source of confusion for researchers and clinicians, as they (1) have biased the dominant hypotheses about pathophysiology and therefore the proposed therapeutic management of the disorder, (2) have been associated with many different diagnostic criteria (or even, in some studies, with an absence of reported criteria), making it very difficult to create meaningful cohorts. As a result, it is risky to interpret results from different (old) studies.

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[22] Medical Subject Headings (MeSH) is the reference thesaurus used in PubMed to index scientific articles and to facilitate structured and standardized literature searches.

[23] From 1990 to June 2025, the time frame was chosen to enable comparisons across conditions and because the current conceptualization of CRPS was established during this period.

To solve this issue, a first consensus was reached in 1994 to name the condition: *complex regional pain syndrome* [173]. A standardized set of criteria for CRPS diagnosis (labelled "*IASP 1994 criteria*") was also proposed. Unfortunately, those criteria were poorly validated, raising concerns regarding their sensitivity and specificity [106]. To address this problem, a consensus meeting held in Budapest released a new set of criteria in 2003: the "*Budapest criteria*" [105]. These criteria, validated in 2010 [104] and slightly adapted in 2019 [92], are still the internationally recognized criteria to diagnose CRPS.[24]

The CRPS consensus term and the Budapest criteria are widely used in recent research on patients with CRPS, but their systematic use in the day-to-day clinical setting still needs to be improved[25]. In contrast to the recommendations based on clinical assessment only (signs and symptoms), technical investigations are still sometimes preferentially used, such as scintigraphy.

The interpretation of bone scan mainly relies on subjective visual comparison of tracer uptake between limbs (primarily during the third phase) and occasionally supported by quantitative side-to-side analyses (see **Fig 1.2** below). A systematic review and meta-analysis assessed the bone scan characteristics taking into account the sensitivity and specificity of the clinical Budapest criteria [280]. They found a poor sensitivity (0.55) and a great specificity (0.94) to diagnose CRPS. Given its limited diagnostic value, high false-negative rate, and potential to delay

[24] To date, two other consensus-based terms were proposed in 2019: *CRPS with remission of some features* (i.e., "previously documented as having fully met CRPS criteria […] but who currently display CRPS features insufficient to fully meet the diagnostic criteria") and *CRPS Not Otherwise Specified* (NOS, patients presenting some CRPS features but have never been documented as meeting all the IASP criteria) [92].

[25] This observation is based on personal experience in Belgian clinical settings, as to our knowledge no related studies have unfortunately ever been published.

treatment, routine use of bone scan is not recommended [91,92,213], while its prognostic value remains unknown.

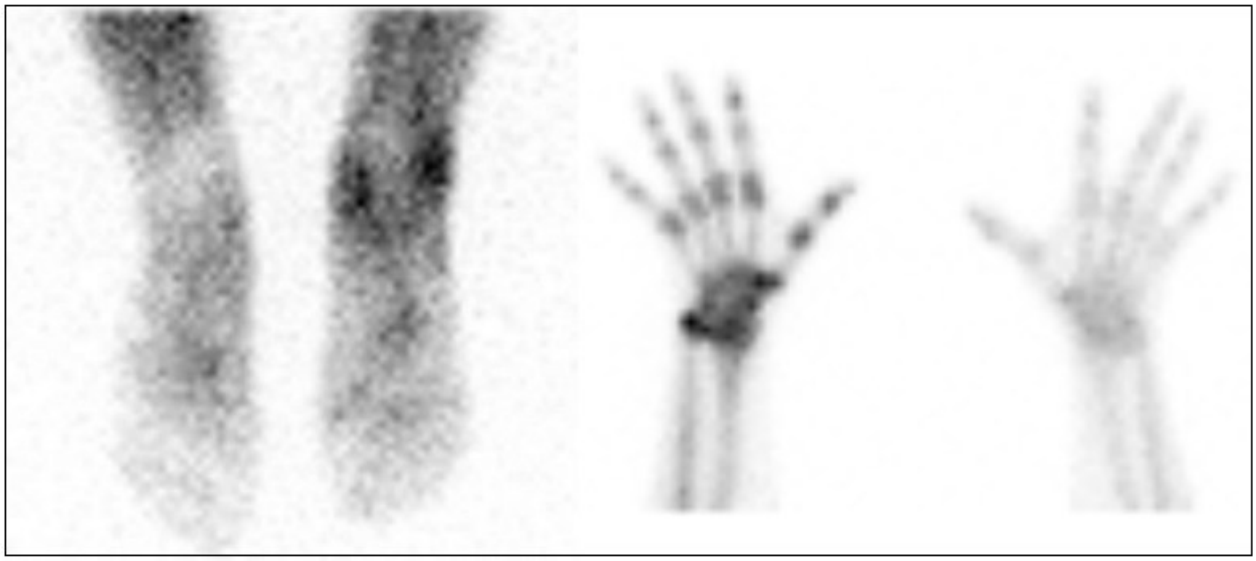

Figure 1.2. ***Examples of bone scan pictures of right foot and left hand CRPS (3rd phase).*** *Pictures from participants of Chapters 2 and 3.*

6.2.2. Duration of the Condition

Beyond the question of diagnostic criteria, the definition of condition duration remains a matter of debate — particularly regarding (1) how to determine the onset of CRPS, (2) which cut-off used to determine early vs. persistent CRPS, and (3) whether a minimum time interval should be required before establishing the diagnosis.

First, the time-point considered as indicating the onset of the condition ("starting point") varies from one study to another: date of the triggering physical event, of the onset of symptoms (i.e. retrospectively reported by the patient), or of the diagnosis made by the practitioner. These methodological differences have led to considerable variability between studies, once again making comparisons and aggregation of cohorts hazardous.

To illustrate this point, in our longitudinal cohort (*Chapter 2* and *3*) we observed on average 44 ± 28 days between the triggering event and the onset of the

condition. However, some participants were diagnosed several months later. This delay between the onset of the disease and diagnosis is frequently reported in clinical practice, as shown by a Swedish study which reported an average delay of 4 years between the onset of symptoms and diagnosis (standard deviation: 1.42; range: 6 months to 10 years; n = 55) [159]. Although this may seem longer than what we have observed clinically, it is a perfect illustration of the problem.

Second, it is assumed that after 12-18 months from onset CRPS becomes more difficult to manage and the condition is therefore defined as *persistent* CRPS [92]. Before reaching this stage, the condition is described as *early* CRPS, although this term encompasses a broad and poorly defined time window.

These designations have been proposed to avoid confusion with the commonly used terms *acute* and *chronic*, which have specific meanings in the broader field of pain research. The pathophysiological changes typically associated with chronic pain make it problematic to equate a patient experiencing continuous CRPS for 11 months with another individual reporting symptoms for only three months.

Third, the absence of clarification regarding a required minimum delay between the inciting event and the diagnosis is problematic. CRPS is classified as a *chronic* primary pain, and some experts have recommended a minimum delay of three months following the inciting event before a diagnosis could be made[26]. However, no minimum duration between the triggering event and the diagnosis of CRPS is required in the Budapest criteria or has been proposed internationally [91,92], while an early management (and therefore, an early identification) is

[26] Statement based on several oral recommendations heard in congress / comments from reviewers, no related paper.

highly recommended [91]. We discussed this point with more details in *Chapter 3*, where we present some recent findings on this subject.

6.2.3. Recruiting meaningful CRPS cohorts

In addition to the above-mentioned problems that contribute to heterogeneity within and between cohorts of CRPS patients, another major challenge facing CRPS research is the recruitment of meaningful samples. The number of patients recruited in most CRPS studies is often very small for several reasons: (1) the relatively low incidence of the condition, (2) the spontaneous 'recovery' observed in some patients who no longer meet the Budapest criteria a few months after onset, (3) the absence of a simple gold standard for diagnosis, and (4) the heterogeneous clinical presentation of CRPS.

First, the incidence of CRPS in the general population is classically estimated between 5 and 26/100,000 person-years [181,230], while its prevalence is unknown. It is therefore commonly considered as a rare disease. However, recent longitudinal have shown an incidence of around 5% following physical trauma [1,20,34], highlighting likely under-diagnosis.

Second, it has been suggested that most CRPS patients recover spontaneously within a few months [291]. However, the results of recent prospective studies are more pejorative, showing that few patients are experiencing fully resolving symptoms, and most patients suffering from sequelae [18,128] (see *Chapter 1* and *3* for a detailed discussion). Approximately 50% of early CRPS patients will not meet the diagnostic criteria at 4.5 months after the onset of the condition (see *Chapter 3*). As a result, these individuals are excluded from prospective cohorts when the first assessment occurs too late, despite persisting disability. This issue substantially reduces sample size and probably biases research towards more severe cases.

Third, the absence of a "simple" gold-standard diagnostic tool — such as a blood test, imaging biomarker, or other objective medical procedure — significantly complicates diagnosis and recruitment. Identifying eligible patients relies heavily on clinicians' expertise in recognizing the full spectrum of CRPS presentations. This dependence introduces several challenges: recruitment can be slow due to misdiagnosis or undetected cases; inclusion criteria may vary across centres, complicating multicentre studies; and data aggregation from national registries is limited, as CRPS coding is often inconsistent.

Nevertheless, the exclusive reliance on clinical diagnostic criteria is not unique to CRPS. Other conditions, such as migraine, fibromyalgia or adhesive capsulitis of the shoulder, are also diagnosed solely on clinical grounds. Moreover, even when biological or imaging markers are available, they are rarely perfect indicators of disease: for example, the presence of bacteria in urine without symptoms does not define a urinary tract infection, and structural tendon lesions on shoulder imaging are frequently asymptomatic. These parallels emphasize that the absence of a definitive biomarker does not diminish the validity of clinical diagnosis but rather highlights the need for rigorous application of standardized criteria and careful clinical evaluation in both practice and research.

The final reason is that CRPS presentations (i.e., signs and symptoms) can be highly variable from one patient to another, making different underlying processes highly likely, but also within the same patient from day to day or even from one hour to another (see *Chapter 2 discussion section* for further details). This variability increases heterogeneity within cohorts and, consequently, the number of participants required for robust statistical analyses.

Given the aforementioned limitations, larger, well-defined cohorts (both in terms of symptom duration and clinical presentation) are essential to improve the overall quality of evidence in CRPS research.

7. Summary, Hypotheses, and Aims

In summary, clinicians and researchers are confronted with the marked heterogeneity of CRPS, both in its clinical presentation and its trajectory. To date, it remains impossible to reliably determine which patients will recover and which are at risk of developing persistent CRPS. Historically, research has predominantly focused on biological mechanisms; however, growing evidence indicates that psychosocial factors also play a critical prognostic role — similar to what has been consistently demonstrated in LBP, another condition classified as chronic primary pain. In this context, stratified approaches based on psychosocial risk profiles have shown promise in reducing the risk of chronification [122].

We hypothesize that the combined identification of biological and psychosocial prognostic factors at an early stage could enable the development of stratified care approaches for CRPS. Such an approach would assist clinicians in tailoring therapeutic strategies to each patient's initial clinical presentation, with the overarching aim of preventing progression from early to persistent CRPS. Furthermore, the systematic identification of early prognostic markers may enhance our understanding of the underlying pathophysiological mechanisms, potentially opening avenues for novel therapeutic targets.

Beyond its clinical implications, the identification of reliable prognostic factors also has methodological relevance. Incorporating these factors into the design and analysis of clinical trials could help account for confounding influences, improve patient stratification, and clarify the intrinsic efficacy of therapeutic interventions. This may partly explain why many CRPS trials to date have failed to demonstrate significant effects, as heterogeneous patient populations likely diluted treatment responses.

This thesis was designed to address these issues through three complementary approaches. First, *Chapter 1* presents a systematic review of the literature on early prognostic factors in CRPS. Its objectives were (1) to synthesize the available evidence, (2) to evaluate the methodological quality of existing studies, and (3) to identify candidate predictors consistently associated with outcomes. Six factors emerged with moderate evidence. Beyond summarizing current knowledge, this chapter highlights key methodological shortcomings that the subsequent studies tried to address and delineates the variables that need to be assessed in further chapters.

Second, *Chapter 2* describes in detail a prospective cohort of early CRPS patients (n = 113), all meeting the Budapest criteria. To overcome the aforementioned limitations of small and heterogeneous samples, the most recent CRPS diagnostic consensus was applied [92], all participants were assessed by a single investigator, and a broad set of variables covering the biological, psychological, and social domains was systematically collected. Clinical data included CRPS history and presentation (notably, pain intensity, sensory disturbances, motor impairment, self-rated disability, but also triggering event and personal medical history); psychological assessments covering anxiety, depression, coping strategies, and pain-related fear of movement; social and contextual variables encompassing work status, lifestyle factors, and perceived social support; and an exploration of the somatosensory system using a quantitative approach. The aims of this chapter were twofold: (1) to comprehensively characterize the early CRPS population and (2) to explore whether distinct biopsychosocial profiles could account for the observed heterogeneity. This data-driven approach sought to test whether CRPS is better understood as a collection of subgroups rather than a uniform entity.

Third, *Chapter 3* presents longitudinal analyses of the cohort assessed in *Chapter 2*. Participants were followed over 1 year, with data collected at four standardized time points (baseline, 4.5, 6, and 12 months). The outcomes included pain,

disability, QoL, and global recovery status, providing a multidimensional picture of condition evolution. Baseline biopsychosocial factors were tested for their ability to predict outcomes over 1 year. Finally, the early biopsychosocial profiles identified in *Chapter 2* were linked to longitudinal outcomes to assess whether distinct patient subgroups followed divergent clinical trajectories. The aims of this chapter were therefore (1) to examine the clinical evolution of a well-characterized early CRPS cohort, (2) to identify baseline predictors of poor outcomes at 1 year, and (3) to determine whether CRPS subgroups can meaningfully predict differences in clinical course.

Finally, the *General Discussion* integrates the findings of these three chapters, situates them within the broader literature, and considers their implications for research and clinical practice. Particular emphasis is placed on the potential for stratified and personalized management strategies, and on methodological recommendations for future CRPS trials.

IV. CHAPTER 1. Biological and Psychological Early Prognostic Factors in Complex Regional Pain Syndrome: a Systematic Review

Reference: Louis MH, Meyer C, Legrain V, Berquin A. *Biological and psychological early prognostic factors in complex regional pain syndrome: A systematic review*. Eur J Pain (**editor choice**). 2023 Mar;27(3):338-352. doi: 10.1002/ejp.2068. Epub 2022 Dec 25. PMID: 36516373.

Presented *in Congrès national de la SFETD (commented poster, 11/22), EFIC Congress (poster, 09/23), CRPS SIG: early career research showcase (oral presentation, 05/24).*

1. Abstract

Background and Objective: Several risk factors for the onset of CRPS have been found, but evidence for prognostic factors associated with progression of this condition remains sparse. However, detection and management of these factors are necessary to design secondary prevention strategies. The objective of this systematic review was to identify prognostic factors in adult individuals with early CRPS.

Database and Data Treatment: PubMed, Embase, PsycINFO, Cochrane Library, and Scopus, published between Jan 1990 and Nov 2021. Two independent investigators selected cross-sectional and longitudinal studies looking at early (<12 weeks from onset) prognostic factors for pain, CRPS severity score, disability, return to work, or Quality of life. The Quality In Prognostic Studies (QUIPS) tool was used to assess the risk of bias. A qualitative meta-synthesis was performed.

Results: Out of 4,652 different articles, six studies met inclusion criteria. We identified 21 early factors associated with poorer prognosis in type I CRPS. We found moderate evidence to support six of them: higher pain intensity, self-rated

disability, anxiety, pain-related fear of movement, being a female, and high-energy triggering event. Only two studies had an overall low risk of bias.

Conclusions: This study showed an important lack of information on early prognostic factors in CRPS. Only one article investigated the link with psychological characteristics. There is a crucial need of larger studies, with well-defined population using validated measures.

2. Introduction

CRPS most often occurs following surgery or trauma of an extremity [181,194,230]. This condition is characterized by pain as well as sensory, vasomotor, sudomotor, trophic, and motor disturbances. Its diagnosis is clinical, based on the 'Budapest criteria' [104,92]. Although the distinction seems tenuous and relative [89,92], this syndrome is classically subdivided into two subtypes: type I in the absence of identified neurological lesions, and type II in the case of proven neurological lesions. A third subtype, "*CRPS with Remission of Some Features,*" has recently been introduced [92]. Finally, CRPS Not Otherwise Specified (NOS) refers to individuals who have some CRPS features but have never been documented as meeting all the IASP criteria [92].

The CRPS pathophysiology has not been fully elucidated, but it is multifactorial, and involves both peripheral (e.g., neurogenic inflammation) and central (e.g., maladaptive plasticity) mechanisms [10,26,102]. Epidemiological data are divergent if not contradictory [194,181,230,20,135,291]: several sets of diagnostic criteria have been used, resulting in heterogeneous populations and variable results in the literature [92,24,271,172,33,174,104]. Some subjects recover spontaneously, whereas others develop a chronic disabling condition [230,14,57,37,18], leading to an important additional cost for society [234]. Recent longitudinal studies suggest that the vast majority of individuals do not reach complete remission, and 14 to 27% of participants still meet Budapest

criteria at 12 months [14,20,37]. Several risk factors for the onset of the condition have been highlighted [208], but evidence for prognostic factors associated with established CRPS progression remains sparse [279]. This makes it difficult to develop interventions aiming at secondary prevention (i.e., reducing the impact of disease or injury, in this case preventing chronification of acute or subacute pain [175]) whereas it has been showed that a therapeutic stratified approach, allowed by the early assessment of the risk of chronification, seems effective in reducing long-term disability in patients with MSK pain [175].

To our knowledge, only one systematic review has been published on the prognostic factors in CRPS [279]. Based on the literature published between 1990 and 2011, the authors identified that *sensory disturbance* and *cold skin temperature* in type I CRPS could predict a poor outcome. For the remaining 26 factors examined, results were inconsistent or conflicting. The authors concluded that evidence about prognostic factors for type I CRPS was scarce and recommended further high-quality aetiology and clinical research.

Surprisingly, psychosocial factors were not identified, even though there is ample evidence that they play a crucial role in the chronification of MSK pain [152,189].

In contrast, some authors tried to identify the prognostic value of psychological factors in CRPS in the last decade. In a longitudinal study, anxiety and pain-related fear of movement were associated with poorer outcome at 1-year follow-up [16].

The aim of this systematic review is to identify and summarize the prognostic factors influencing the progression of early type I or type II CRPS. We defined these factors as any set of clinical and non-clinical parameters (e.g., psychological, physical, demographic, etc) with an impact on the outcomes that, according to *the International Classification of Functioning, Disability, and*

Health (ICF), refer to one of the three following components: Body structures and functions (*pain*, *CSS*), Activities (*disability*) or Participation (*RtW* and *QoL*).

3. Literature Search Methods

This systematic review followed the PRISMA guidelines [197]. The study protocol was registered on December 2, 2021, in the international prospective register of systematic reviews (PROSPERO, Ref. CRD42021288676).

3.1. DATA SOURCES

Studies corresponding to inclusion and exclusion criteria were identified by searching the following databases between Jan 1st, 1990 and Nov 2nd[27], 2021: PubMed, Embase, PsycINFO, Cochrane Library, and Scopus. We also screened the bibliographies of all included papers or relevant reviews and evaluated any conference posters or abstracts on this topic. The detailed search strategy can be found in the Appendix 1 ("Research equations"). It was based on recommended search terms for systematic reviews on prognostic factors [5]. Because the current definition of CRPS was introduced in the '90s [172], we restricted our search to 1990 and beyond.

3.2. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria were: (1) longitudinal (prospective or retrospective) or cross-sectional studies, (2) English or French language, (3) peer-reviewed journals, (4)

[27] The choice of using 1990 as a cut-off was based on several reasons. First, as summarized in the Introduction of the thesis, the concept of CRPS was defined in 1994 and it is highly complex to interpret results of studies previous this moment. Second, it was also proposed by the previous study on the topic [279]. We considered that choosing this cut-off help us to find more meaningful cohorts without excluding relevant studies. was based on several considerations. First, as outlined in the Introduction, the formal concept and definition of CRPS were established in 1994, rendering the interpretation of earlier studies complex and potentially inconsistent. Second, this threshold had already been adopted in a previous systematic review on the topic [313], ensuring methodological consistency. Finally, selecting 1990 as the starting point was expected to optimize the balance between inclusivity and relevance by capturing cohorts with meaningful diagnostic value while limiting the inclusion of less relevant studies.

human subjects only, (5) identification of at least one factor having a statistically significant ($p < 0.05$) impact on pain, CSS, disability, return to work or QoL, and (6) adult population (≥18 years) with an early type I or II CRPS (<12 weeks from the diagnosis of the condition, at the time of study inclusion); or cross-sectional data looking at prognostic factors.

There is currently no consensus on what constitutes early or persistent CRPS [92]. As our ultimate goal was to identify prognostic factors that can be used for early management of at-risk subjects, in the context of this study, we decided to define "*early CRPS*" as <12 weeks from the onset of the condition.

Exclusion criteria were: (1) studies not published in full article format or from which data could not be extracted, (2) studies looking at the effect of a specific therapy, (3) studies that did not specify their diagnostic criteria[28], (4) studies looking at risk factors for the onset of the condition, (5) paediatric population (<18 years) or post-stroke CRPS (also known as "shoulder-hand syndrome").

Because we only included peer-reviewed articles in full-text format, we excluded posters or grey literature.

All the identified records were screened by two independent reviewers (MHL and CM), based on title and abstract. The full text of the records meeting inclusion and exclusion criteria were then evaluated. Both steps were blind from one reviewer to the other. Disagreements after steps 1 and 2 were solved either by consensus or, if needed, by the decision of a third person (AB). The software system for recording decisions was Rayyan [195].

[28] We deliberately chose **not** to restrict inclusion to specific diagnostic criteria (e.g., the Budapest criteria), as this would have unduly narrowed the scope of our review. Instead, studies were excluded only if no diagnostic criteria were reported, which allowed us to account for and interpret the results in light of the diagnostic framework applied.

3.3. DATA EXTRACTION

At the end of the selection phase, the main reviewer (MHL) extracted the data and pooled preliminary results in an Excel database. In case of missing or contradictory data, study investigators were contacted for clarification. Tables were used to summarize results and qualitative analysis.

3.4. RISK OF BIAS ASSESSMENT

As recommended by The Cochrane Prognosis Methods Group [218] and Prospero, the risk of biais was assessed using the Quality In Prognostic Studies (QUIPS) tool [113]. This tool analyses six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting. Each domain is assessed as "*yes*", "*partial*", "*no*", or "*unsure*", leading to a final judgment. An overall subjective appreciation of the domain is then given (*high*, *moderate,* or *low*). Two independent reviewers (MHL and CM) were involved in this step and any disagreement was solved by consensus or, if needed, by a third reviewer's decision (AB).

3.5. CERTAINTY OF EVIDENCE ASSESSEMENT

A qualitative meta-synthesis was conducted following the method recommended by Hayden [112] and used in several systematic reviews since then [167,274]. Prognostic factors were qualified as having "limited evidence" if found in only one study, "moderate evidence" if found in one low risk study or more than one high risk of bias study with >75% positive association with outcome, and "strong evidence" if found in more than one low risk of bias study with positive association. "Conflicting evidence" is given if evidence is inconsistent with <75% studies showing the same direction of effect and "No evidence" is given if no association between variables is found.

4. Results

4.1. STUDY SELECTION

Our search strategy identified 4,652 different articles, of which six (four prospective studies and two cross-sectional studies) were included in the final analysis (**Fig. 2.1**) [15,16,56,69,144,222]. No additional relevant articles were found in the bibliographies of reviews and the included articles.

Most of the rejected studies, especially the cross-sectional studies, did not identify or did not look at prognostic factors (N = 31). Several cohorts did not meet our inclusion/exclusion criteria (N = 27) including either a sample of paediatric participants, post-stroke CRPS or subacute/persistent CRPS.

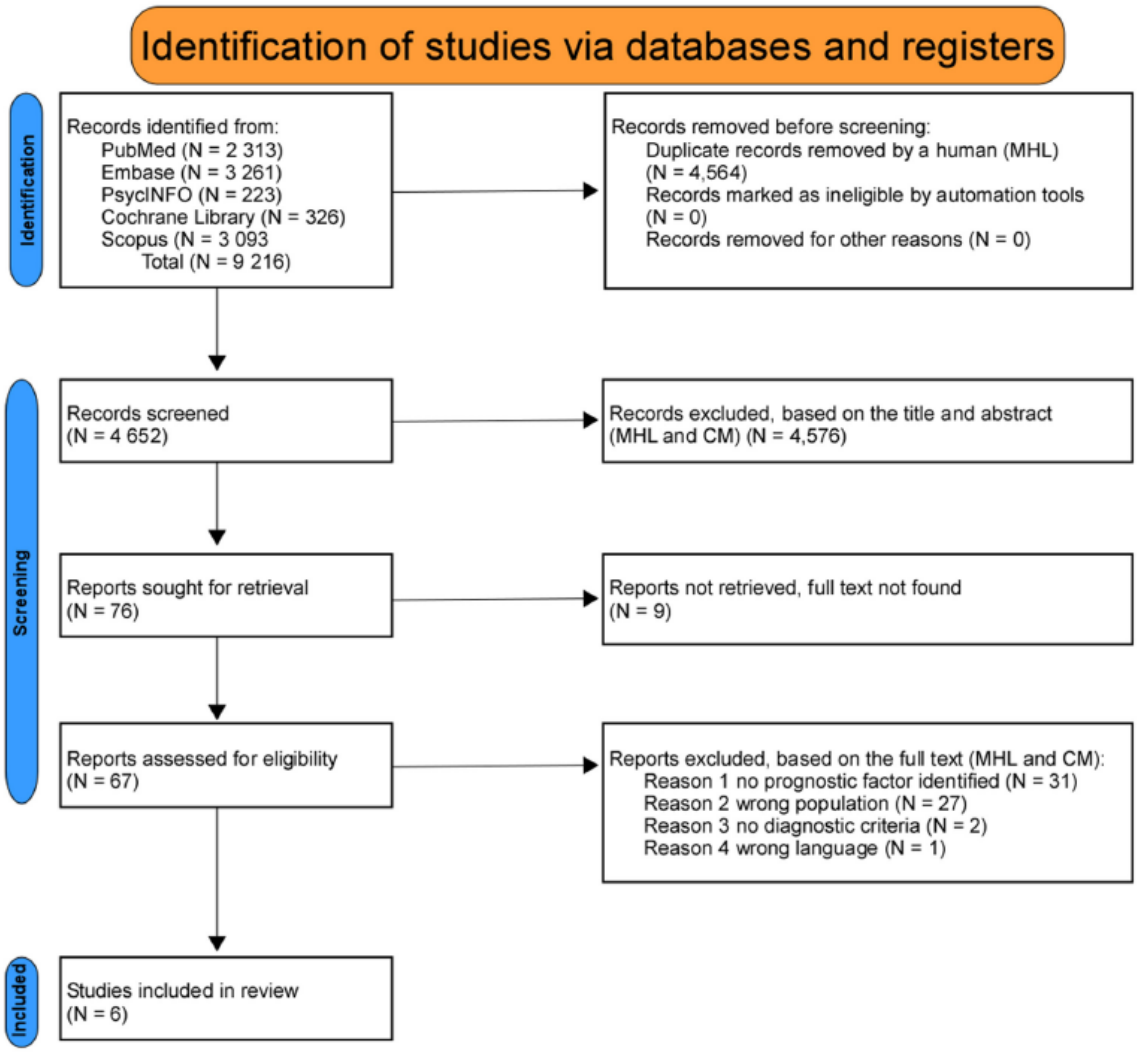

Figure 2.1. ***Prisma flowchart.***

4.2.STUDY CHARACTERISTICS

The characteristics of the included studies are described in **Table 2.1**. The total number of participants in this review is 213 and the sample sizes ranged from 16 to 66. Two articles related to the same cohort [15,16]. Mean age of the participants ranged from 34 to 58 years. All the studies included type I CRPS subjects only. Most participants (85.9%) had upper extremity CRPS, with 2 articles having only included distal radius fractures (DRF) (n = 84). Diagnosis was based on one of the following criteria: Veldman [271] (N = 2), 1994 IASP [172] (N = 2), Budapest research [104] (N = 1) or on non-validated clinical criteria [144] (N = 1)[29].

It should be noted that 89% of Bean's cohort [15,16] met the clinical Budapest criteria. In the prospective studies, the mean CRPS duration at follow-up was 12 (N = 3) or 18 months (N = 1). The outcomes were related to professional status (N = 3), CRPS status (N = 3), disability (N = 2) or pain (N = 1).

Author, year	Study design	Sample size (f:m)	Sample attrition (%)	Mean age (years)	Subtype CRPS (I/II)	Triggering event (trauma/'spontaneous')	Localization (UE/LE/other)	Diagnostic criteria used	Mean CRPS duration at baseline	Follow-up duration
Laulan et al. (1997)	Prospective	26 (18:8)	Not reported	58.23	26/0	26/0 Only DRF	26/0	Clinical algodystrophy score	<3 months	12 months
Dauty et al. (2000)	Prospective	16 (1:15)	0 (0%)	34 [22–59]	16/0	16/0	10/5/1	1993 Veldman	35 ± 10.2 days [7–50], *from the triggering event*	18 months
Roh et al. (2019)	Prospective	58 (41:17)	0 (0%)?	56.1 ± 16.9	58/0	58/0 Only DRF	58/0	Budapest research criteria	?	12 months
Bean et al. 2015)	Prospective	66 (48:18)	3 (4.55%)	47.06 ± 14.03	66/0	60/6	60/6	1994 IASP	61.23 ± 22.58 days	12 months
Bean et al. (2016)	Cross-sectional	66 (48:18), 49 for data related to keep working	Not applicable	47.06	66/0	60/6	60/6	1994 IASP	61.23 ± 22.58 days	Not applicable
Dumas et al. (2011)	Cross-sectional	47 (30:17) *but 33:22 in manuscript*	Not applicable	48 [24–64]	47/0	Not reported	29/18	1993 Veldman	Not reported	Not applicable

Table 2.1. ***Study characteristics****. Abbreviations: DRF, distal radius fractures; LE, lower limb; UE, upper limb.*

[29] Given these particular diagnostic criteria, the results of this study should be interpret with caution.

4.3. QUALITY ASSESSMENT

The risk of bias of each included study was assessed with the QUIPS tool (**Table 2.2**). Only 2 studies [15,16] had an overall low risk of bias, whereas the others suffered from numerous biases. Justifications for these assessments are available in Appendix 2 ("Justification for RoB").

Regarding the participation domain, only one study was assessed as low risk of bias [16]. Questionable or unclear inclusion criteria [69,144,222] or a lack of information on sample characteristics [15,56,69,144,222] accounted for this result. Sample sizes were particularly small in 2 studies [56,144].

The evaluation of study attrition was not relevant in cross-sectional studies (reported as '*Not Applicable*'). According to our assessment, three studies had a high risk of bias: either they did not report study attrition [56,144], or their inclusion criteria precluded any loss during the study (i.e., participants had to "*complete the 12-month follow-up*" to be included) [222].

All studies except one [69] used similar methods and settings to measure prognostic factors and outcomes for all participants. Both prognostic factor and outcome measures were not always clearly defined or assessed with validated instruments. Moreover, some studies could have been less dichotomous in their outcome criteria (e.g., Roh et *al*. used '*meeting research Budapest criteria at 12 months (yes/no)'* instead of CSS, a continuous and well-studied parameter [107,108]). Confounding factors were only investigated in one cohort [15,16].

Apart from two studies [15,16], no other study performed multivariable analyses, and only one [69] justified this choice (*lack of power*). Results corresponded therefore to descriptive analyses in small samples and must be read with caution. Data on the effect size of prognostic factors were mostly lacking and could not be extracted.

Author, year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Roh et al. (2019)	High	High	Moderate	Moderate	High	High
Dauty et al. (2000)	High	High	Low	Moderate	High	High
Laulan et al. (1997)	High	High	Moderate	Moderate	High	High
Bean et al., 2015	Low	Low	Low	Low	Low	Low
Bean et al.	Moderate	NA	Low	Low	Low	Low
Dumas et al. (2011)	Moderate	NA	High	High	High	High

Table 2.2. ***Risk of bias assessment using QUIPS tool****. Abbreviation: NA, not applicable.*

4.4.STUDY RESULTS

The results from individual studies are presented in **Table 2.3.** Due to the heterogeneity of the investigated prognostic factors, outcomes, and the lack of data on effect sizes, we did not perform any quantitative analysis.

Author, years	Study design	Positive prognostic factors	Negative prognostic factors	Outcomes
Laulan et al. (1997)	Prospective	/	- UA: Clinical score for algodystrophy >7 at 6 weeks	Clinical score for algodystrophy at 12 months
Dauty et al. (2001)	Prospective	/	- UA: severe trauma (polytrauma or multiple fractures of the same limb), distal joint location (wrist, hand, ankle foot) and work injury	Return to work at 18 months, and time to return to work
Roh et al. (2019)	Prospective	/	- UA: higher PSQ score at 3 months after injury, lower PPTs at 3 months after injury and high-energy injury	(still meeting) Budapest research criteria at 12 months
Bean et al. (2015)	Prospective	(1) On CSS: - MA: sex (male, $\beta = 1.18$), and time ($\beta = -2.74$)	(1) On CSS: - UA: disability, depression, anxiety, stress, body perception disturbance, perceived ownership of the affected limb - MA: pain intensity ($\beta = 0.31$) and disability ($\beta = 0.06$) at baseline (2) On pain intensity: - UA: allodynia, disability, depression, anxiety, stress, catastrophizing, pain-related fear, body perception disturbance, perceived ownership of	CRPS severity score, pain intensity and self-reported disability over the following 12 months

			the affected limb - MA: disability ($\beta = 0.04$) and anxiety ($\beta = 0.14$) at baseline (3) On disability: - UA: depression, anxiety, stress, catastrophizing, pain-related fear, body perception disturbance and perceived ownership of the affected limb - MA: pain intensity ($\beta = 2.50$) and pain-related fear ($\beta = 0.52$) at baseline	
Bean et al. (2016)	Cross-sectional	/	(1) On keep working (predict sick leave): - UA: depression, disability, work physical demands, injury severity - MA: self-reported disability (OR: 1.13 [1.01–1.27]), work physical demands (OR: 3.00 [1.30–6.95]) and injury severity (OR: 2.23 [1.01–4.91]) (2) On disability: - UA: CRPS severity score, pain intensity, pain catastrophizing, pain-related fear, depression, anxiety, stress, sweating symptom, allodynia symptom, restricted ankle/wrist flexion and extension, motor sign - MA: pain intensity ($\beta = 0.477$), restricted ankle/wrist extension ($\beta = -0.280$) and depression ($\beta = 0.333$)	Keep working at ±2 months and disability at ±2 months
Dumas et al. (2011)	Cross-sectional	-UA: Upper limb involvement	-UA: Lower limb involvement	Return to work, and time from triggering event to return to work

Table 2.3. ***Studies results***. *Abbreviations: β, regression coefficient; CSS, CRPS severity score; MA, multivariable analysis; UA, univariable analysis; PSQ, pain sensitivity questionnaire; PPT, pressure pain threshold; OR, odds ratio.*

We reported prognostic factors below according to the outcomes and the number of studies that investigated these outcomes.

4.4.1. Measures Related to Return to Work (N = 3, n = 112, Participation in CIF classification)

Two studies (one prospective [56], one cross-sectional [69]) assessed return to work, while another cross-sectional study [15] assessed factors predicting which participants were still working approximately 2 months after the onset of the condition.

The prospective study, by Dauty et *al*., had the smallest sample size (n = 16). All participants were hospitalized after trauma. *Severe trauma* (polytrauma or multifracture of the same limb), *distal fracture localization* and *work injury* were associated with a longer mean time to return to work.

In their cross-sectional study looking at return to work, Dumas et *al*. identified that *upper limb involvement* was correlated with a higher probability of return to work than lower limb involvement. Younger age, sedentary job, higher level of education, and early introduction of analgesic treatment associated with physiotherapy were also suggested to be associated with return to work, but these associations were described as non-significant in the table. Unfortunately, we were not able to get in touch with the authors for clarification, and consequently they were not incorporated into **Table 2.3**.

Finally, a recent cross-sectional study [15] investigated participants who were working or studying before the onset of their CRPS (n = 49, 74% of the study sample). Only 21 participants were still working or studying two months later. The authors showed that the following variables were associated with a smaller probability to keep working at 2 months in univariable analysis: *higher depressive score*, *self-reported disability*, *heavier work*, *more severe injury*. In multivariable analysis, three variables still predicted sick leave: *severity of the injury*, *physically demanding jobs,* and *self-reported disability*. Contrary to the previous study [69], the *involved limb* (upper or lower) had no impact on work status.

4.4.2. Measures Related to CRPS Status (N = 3, n = 150, Body structure and Function in ICF classification)

All three studies assessing CRPS status were prospective, with a 12-month follow-up. The outcomes evaluated were different: non-validated clinical algodystrophy score [144], still meeting Budapest research criteria [222], or CSS [16]. The prognostic factors investigated were also different.

Two studies exclusively included post-DRF individuals [144,222]. Laulan et *al*. followed 126 individuals. Among them, 26 developed a CRPS. In this subgroup, a *clinical score for algodystrophy>7 at 6 weeks* was associated with the same score at 12 months. After contacting the authors, *displaced fracture of*

ulnar styloid and *distal radioulnar joint pain* parameters were found not to be prognostic factors in this CRPS subgroup (n = 26). Therefore, we did not include them in our results.

Roh et *al*. identified that *higher Pain Sensitivity Questionnaire (PSQ) score*, *lower PPT*, and *high-energy injury* at 3 months after DRF were associated with still meeting Budapest research criteria after 12 months. Almost half of the cohort (48%) still met Budapest research criteria at 12 months (n = 58).

Bean et *al*. focused on psychological factors [16]. The following variables at the first assessment (± 61 days) were correlated with a higher CSS over the following 12 months: *disability*, *depression*, *anxiety*, *stress*, *body perception disturbance*, and *lower perceived ownership of the affected limb*. In multivariable analysis, two factors still significantly impacted this outcome: *pain intensity* and *self-reported disability score*. Conversely, *being a male* improved the outcome, and the CSS also decreased by an average of 2.74 points in the whole cohort at each follow-up visit.

4.4.3. Measures related to Disability (N = 2, n = 66, Activities in ICF classification)

Only the single cohort of Bean et *al*. investigated this outcome in two articles: a cross-sectional analysis at inclusion (± 2 months [15]) and a mixed-effects model for repeated measures after the 12-month follow-up [16].

At inclusion, the following parameters were associated with greater disability scores: CSS, pain intensity, pain catastrophizing, pain-related fear, depression, anxiety, stress, sweating symptom, allodynia symptom, ankle/wrist flexion and extension, motor sign. In multivariable analysis, the independent predictors of disability were: pain intensity, lower ankle/wrist extension, and higher depressive score.

In the longitudinal study, several baseline variables were associated with greater disability over the following 12 months: *depression*, *anxiety*, *stress*, *catastrophizing*, *pain-related fear*, *body perception disturbance,* and *perceived ownership of the affected limb*. Once adjusted, two factors had a significant effect on self-reported disability: *pain intensity* and *pain-related fear,* whereas disability scores were reduced by a mean of 11.29 points at each follow-up.

4.4.4. Measures related to Pain (N = 1, n = 66, Body structure and Function in ICF classification)

Similarly, the aforementioned prospective study [16] also assessed early predictive factors for pain intensity over the following 12 months. Parameters at baseline that were associated with greater pain scores were: *allodynia*, *disability*, *depression*, *anxiety*, *stress*, *catastrophizing*, *pain-related fear*, *body perception disturbance* and *perceived ownership of the affected limb*. In multivariable analysis, two parameters still impacted the outcome over the following 12 months: *self-reported disability* and *anxiety scores*. At each follow-up visit, pain scores were reduced by a mean of 1.22 points.

4.5. CERTAINTY OF EVIDENCE ASSESSEMENT (QUALITATIVE META-ANALYSIS)

The certainty of evidence for each factor is summarized in **Table 2.4**. We chose to consider symptoms/signs as "Modifiable factors".

Because it was a cross-sectional study, we graded the variables that were only found in Bean et *al*., (2016b) as "Limited Evidence" (instead of "Moderate Evidence"). Similarly, the crude variables that were only described in the papers of Bean et *al*. (2015, 2016b) were considered as "Limited Evidence" because these results are related to a single cohort.

	Level of evidence	Positive prognostic factors	Negative prognostic factors
Non-modifiable early prognostic factors	Moderate evidence	Demographic factor: • *Being a male*[a]	Demographic factor: • *Being a female*[a] Event-related factor: • *High-energy trauma*[b]
	Limited evidence	Localization: • *Upper limb*[b]	Localization: • *Distal joint*[b] • *Lower limb*[b] Work-related variables: • *Work injury*[b] • *High occupational physical demands*[a] Self-reported factors: • *Higher PSQ score*[b]
	No evidence	Demographic factors: • *Age* • *Limb dominance*	
Modifiable early prognostic factors	Moderate evidence		Self-reported factors: • *Higher disability*[a] • *Higher pain intensity*[a] • *Higher anxiety*[a] • *Higher pain-related fear*[a]
	Limited evidence		Symptoms/signs: • *Lower PPT*[b] • *Clinical score for algodystrophy>7 at 6 weeks*[b] • *Restricted ankle/wrist extension*[a] • *Allodynia symptom*[b] • *Sweating symptom*[b] • *Motor sign*[b] Self-reported factors: • *Higher depression score*[a] • *Higher body perception disturbance*[b] • *Lower perceived ownership of the limb*[b] • *Higher catastrophizing score*[b]
	No evidence	Demographic factors: • *BMI* • *Smoking habits* • *Treatments*	

Table 2.4. ***Quality of evidence assessment****. Abbreviations: BMI, body mass index; PSQ, pain sensitivity questionnaire; PPT, pressure pain threshold;* [a]*, Significant in multivariable analysis;* [b]*, Significant only in univariable analysis.*

We found moderate evidence for several early prognostic factors, associated with poorer outcomes: *being a female, higher self-rated disability*, *pain intensity, anxiety*, *pain-related fear*, and *high-energy trauma.* It should be noted that the last factor was considered significant in two high risk of bias longitudinal studies and in one low risk of bias cross-sectional study but was not significant in the low Ro risk of bias B longitudinal study.

We found limited evidence of effect for *distal joint localization, lower limb involvement* (reported in one high risk of bias cross-sectional study, not significant in others)*, work injury* (significant in one high risk of bias study, not significant in low risk of bias studies)*, more physically demanding works, lower PPT, higher PSQ score*, *sweating symptom*, *restricted ankle/wrist extension, allodynia symptom*, *motor sign*, *higher depression score*, *higher body perception disturbance*, *lower perceived ownership of the limb*, *higher catastrophizing score*.

No evidence was found supporting an influence of *age*, *BMI, smoking habits*, *treatments,* or *limb dominance* on prognosis.

It should be noted that the level of evidence within the "Limited Evidence" category is variable. For instance, most of the factors were derived from univariable analyses or were identified in poor quality studies. The prognostic value of these factors should be interpreted with caution.

5. Discussion

5.1. SUMMARY OF RESULTS

This systematic review aimed to identify and summarize the current state of knowledge of early prognostic factors that determine the CRPS trajectory. We identified six longitudinal or cross-sectional studies investigating prognostic factors in adult individuals with early CRPS. Two articles [15,16] studying the same cohort could be considered as having an overall low risk of bias, whereas the others [56,69,144,222] suffered from moderate to high risk of bias in most domains. All studied cohorts were small (n = 16 to 66). In terms of demographic characteristics, the samples were similar overall. Conversely, the studied prognostic factors and outcomes varied widely.

We found moderate evidence to support six early factors leading to poorer prognosis. The *severity of the triggering event* was identified in three studies. *Being a female*, *higher pain intensity, self-reported disability* and psychological factors such as *higher pain-related fear* and *anxiety* were described in two articles from a single cohort. Regarding the factors with limited evidence of effect, we identified 15 factors but only some early sensory characteristics (e.g. *lower PPT*) seemed reliable enough to be considered. The poor quality of the evidence and the multiplicity of other reported prognostic factors did not allow further conclusions.

5.2. INTERPRETATION

5.2.1. Non-modifiable Factors

In the literature, *the severity of the triggering event* (e.g., dislocation, intra-articular fracture or high energy trauma) was also associated with the onset of CRPS [20,208,223]. Although it is not a modifiable factor, the presence of high-energy trauma should prompt more careful follow-up by the clinician.

In our review, we found that *being a female* had a significant impact on having a higher CSS at one year [16]. However, it was not significant for other outcomes (disability, pain) nor in other studies. In the literature, the influence of *gender* on prognosis is contradictory [75,272,279].

5.2.2. Modifiable Factors

Higher pain intensity seemed to be associated with poorer outcomes [16,35,268], except for one study [146]. Higher early pain intensity has also been reported as a risk factor for the onset of the condition [62,74,183,208,232]. In a recent longitudinal study with total knee arthroplasty patients (n = 110) [34], *greater preoperative pain intensity* was predictive of higher CSS at 6-week and 6-month follow-up. It also predicted dichotomous CRPS diagnosis at 6-month follow-up.

Concerning *early sensory symptoms*, *lower PPT* and *allodynia* appear to be associated with poorer outcomes in the literature [35,62,72,125,176,230,267]. Similarly, one longitudinal study correlated *widespread preoperative pain* and *higher temporal summation of pain* to CSS at 6-month post-total knee arthroplasty [34].

Some *psychological factors* (‘*yellow flags*’) are related to long-term disability in MSK pain [152,189]. Several tools, such as STarT back tool and the Örebro Musculoskeletal Pain Questionnaire, facilitate their identification during consultation. Initially validated in neck and LBP, some of these tools have now been also validated for MSK pain [70,140,270].

None of these have been tested with CRPS subjects, although it can be hypothesized that psychological prognostic factors of CRPS are similar to those of other chronic pain syndromes [17,140,200]. In support of this statement, some studies have suggested a link between psychological factors and CRPS outcomes. For example, *depressive scores* were associated to pain intensity [137,200]. *Pain*

catastrophizing score was correlated with disability, pain at rest, and pain with movement [75]. In contrast, in a two-round Delphi-survey [38], 39 experts associated a worse prognosis in CRPS with some clinical manifestations (*pain intensity>5 on visual analog scale [VAS]*, *allodynia*, *hypoesthesia*, *joint contracture*, …). *Psychological factors* were considered less important.

5.2.3. Other Potential Prognostic Factors

A previous systematic review [279] on the topic analysed longitudinal studies published between 1990 and 2011 that assessed prognostic factors in type I CRPS, regardless of condition duration. *Cold skin temperature* and *sensory disturbance* were reported as negative prognostic factors. Only two of their 12 articles met our inclusion criteria [56,144]. Specifically, we included cross-sectional studies and restricted our search to early prognostic factors.

Some studies that did not meet our criteria could give useful complementary information for the clinician. One longitudinal study followed 152 CRPS participants with different durations [35]. They identified three baseline clinical predictors associated with patients no longer meeting Budapest criteria at 3-month follow-up: *lower baseline pain intensity*, *warmer skin on the affected side*, and *absence of allodynia*. *Shorter condition duration* at inclusion was also a positive prognostic factor. *Fracture*, *absence of sensory symptoms*, and *presence of objective swelling* were reported as positive predictive factors [230]. Another study associated *upper extremity involvement*, *initiating events other than fracture* and *cold CRPS* with poorer outcomes (based on self-reported recovery and work status) [57]. Vaneker et *al*. identified that *cold skin temperature* at an early stage was associated with higher clinical pain intensity about 8 years after the diagnosis, while *higher pain intensity* measured by VAS predicted higher Impairment Level SumScore at one and eight years [267,268]. Unpublished data from Bean's cohort [14] suggested that baseline *self-reported disability* also predicted CRPS

individuals' work status at 12 months (personal communication). In contrast to the previous results, Lee HJ et *al*. performed multivariable analysis and identified that *higher pain intensity at baseline* (moderate to severe) was associated with better pain reduction at follow-up [146]. Regarding cognitive biases in CRPS, a study reported that having more *cognitive symptoms* was associated with higher pain intensity at 6-month follow-up in long-standing CRPS individuals [283]. However, this result was not significant in early CRPS and was only true for self-reported cognitive symptoms, but not when directly measured by neuropsychological tests. *Higher revised-Bath-CRPS-Body Perception Disturbance Scale score* was positively associated with pain intensity and pain-related fear of movement in participants with persistent CRPS [253]. In a small sample (n = 17) with long-standing CRPS, the same authors also observed a very strong positive relationship between the *body perception disturbance score* and the upper limb function (assessed by Quick DASH).

5.3. IMPLICATIONS

Of the identified factors, several are considered modifiable and are therefore more relevant to the clinician. We could hypothesize that minimizing *disability*, *pain intensity*, *pain-related fear of movement*, and *anxiety* at an early stage could reduce the risk of chronification. This approach, that focuses on factors associated with poorer prognosis, has been successful in MSK pain [122,175]. However, to our knowledge, there is no similar study in the area of CRPS.

Given our results and after a thorough reading of the literature, certain early sensory characteristics (i.e., *lower PPT* and *allodynia*) seemed to be associated with poorer outcomes. These variables could be important markers of poorer prognosis in this condition.

5.4. STUDY LIMITATIONS

Our systematic review suffers from limitations related to both the evidence included and the review process.

Concerning the evidence, some issues need to be discussed. First, the reliability of certain reported prognostic factors is uncertain. Apart from the cohort of Bean et *al*., the included studies suffered from several biases, and their quality was globally poor. As recently stated., the small number of participants in several studies significantly decreases the confidence in their results [179]. Furthermore, the results from cross-sectional studies [15,69] should be read with caution. Second, our findings are almost exclusively related to upper limb CRPS (86% of the participants), and none of the studies included type II CRPS although the Valencia consensus emphasized the very low clinical relevance of subgrouping CRPS [92]. Third, the severity of the triggering event was assessed using different criteria. A more accurate categorization could be used in the future to assess this hypothesis [244].

Regarding the study protocol, various limitations must also be reported. The first is our restriction to early CRPS (defined as <12 weeks). While the Valencia consensus tentatively defined the transition to a more prolonged and difficult to manage condition at 12-18 months after onset [92], some studies pointed out that CRPS individuals either spontaneously recover in 3 - 6 months or become long-standing [14,37]. We considered that a shorter timeframe allowed us to select a more defined population and thus to identify more reliable but fewer prognostic factors. Moreover, our main goal was to identify prognostic factors that can be used for early management of at-risk individuals.

The second limitation is potential selection bias. We did not include any article that could not establish a link between a factor and an outcome. This issue stems from our absence of restriction on the type of prognostic factors. To the best of

our knowledge, three articles could have been considered. The average temperature differences between the affected and contralateral limb were similar among four CRPS duration groups (0-3 months to>12 months) [45]. As mentioned above, *self-reported cognitive symptoms* had a non-significant impact on pain intensity at 6-month follow-up in early CRPS, in contrast with long-standing participants [283]. No correlation was found between *osteoprotegerin* concentration and CRPS symptoms or duration (<12 vs. ≥12 weeks) [142]. The third issue is condition duration, which depends of the chosen starting point (from the triggering event [56] vs. CRPS symptoms vs. CRPS diagnosis). The last limitation is the data extraction process. Only one reviewer extracted the data, which could be a source of error or bias. Nevertheless, the small number of included studies limits this risk of bias. Furthermore, we were unable to extract effect size for most prognostic factors.

It should also be noted that the literature on early prognostic factors in adults CRPS individuals remains limited. Most longitudinal studies have not assessed predictors [17,20,24,37,204], have used suboptimal diagnostic criteria [24,56,69,144,221,265,271,291], or have studied mixed populations (i.e., including paediatric participants, post-stroke CRPS or persistent CRPS) [35,214,221,235,265,271,291].

5.5.CONCLUSIONS

We found moderate evidence to support six early factors associated with poorer prognosis in type I CRPS. Higher *pain intensity*, *self-rated disability*, *anxiety*, *pain-related fear*, *being a female*, and *high-energy trauma* negatively affected return to work (N = 3), CRPS status (N = 3), disability (N = 2) or pain (N = 1).

The literature is sparse on early prognostic factors in CRPS. There is a crucial need for larger cohorts, with well-defined populations using validated measures.

Regarding clinical implications, *psychological factors* are the most promising variables. They could be assessed at an early stage and, if necessary, appropriate treatment could be provided to potentially modify the course of the condition.

V. CHAPTER 2. Early CRPS is a Heterogeneous Condition: Results from a Latent Class Analysis

Reference: Louis MH, Legrain V, Aron V, Filbrich L, Henrard S, Barbier O, Libouton X, Mouraux D, Lambert J, Berquin A. *Early CRPS Is a Heterogeneous Condition: Results From a Latent Class Analysis*. Eur J Pain. 2025 Feb;29(2):e4785. doi: 10.1002/ejp.4785. PMID: 39825738.

Presented *in EFIC Congress (poster, 09/2023), CRPS SIG: early career research showcase (oral presentation, 05/24), IASP Congress (oral presentation [CRPS SIG meeting award] and poster, 08/24).*

Article of the week (IASP selection).

1. Abstract

Background: Complex regional pain syndrome (CRPS) is a debilitating condition characterized by sensory, vasomotor, sudomotor, and trophic/motor disturbances of a limb. Its pathophysiology is poorly understood. This study presents data from patients suffering from (very) early CRPS, to better understand the mechanisms of this condition and the existence of putative subgroups of patients.

Methods: 113 early CRPS patients were recruited and completed online questionnaires, 89 of which were physically assessed. Collected data were demographic variables, work-related factors, CRPS history and clinical features, body perception disturbances, quantitative sensory testing (QST), and a visuospatial attentional task.

Results: QST revealed thermal and mechanical stimuli detection deficits and increased pain sensitivity to thermal stimuli and blunt pressure. Visuospatial

biases were observed in two subgroups of patients. Participants reported body perception disturbances similar to those of persistent CRPS. A latent class analysis (LCA), based on five clinical parameters and 85 participants, identified four profiles. The first two, *Mild* and *Moderate* profiles, were typically triggered by severe trauma and differed in outcomes, more pejorative for the second subgroup. The two other subgroups (labelled *Body representation disturbance [BRD] and Pressure allodynia CRPS*) occurred after mild trauma but demonstrated the poorest outcomes. *BRD CRPS* showed severe body perception disturbances, *Pressure allodynia CRPS* presented the highest sensitivity to pressure and psychosocial risk of chronification.

Conclusions: these results highlight the heterogeneity within early CRPS patients and indicate a potential role of central/systemic mechanisms in severe conditions. Future research should focus on refining classification systems and their underlying mechanisms.

2. Introduction

Complex regional pain syndrome (CRPS) is a painful condition, typically affecting one limb and characterized by sensory, vasomotor, sudomotor, and trophic/motor disturbances [92,104]. Diagnosis is clinical and follows the internationally recognized Budapest criteria [104]. The incidence of CRPS has been retrospectively estimated between 5.5 to 26.2 cases per 100,000 persons [181,230]; although recent prospective studies and meta-analyses suggest a risk as high as 10% following surgery or trauma of a body extremity [20,31,155,183]. While CRPS impacts all aspects of patients' life [147,273], its pathophysiology has not been fully elucidated and is considered multifactorial, including anatomical and functional changes at peripheral (e.g., neurogenic inflammation and vasomotor dysfunction) and central levels (e.g., maladaptive plasticity) [26,30,77]. Additionally, animal models support the involvement of autoimmune

processes [114]. Cognitive symptoms are increasingly recognized as a typical feature of CRPS [102]: body representation disturbances and perceptual deficits have been consistently documented using questionnaires and neuropsychological testing procedures [39,78,253]. However, they are not included yet in the diagnostic criteria.

There is growing evidence of potential subgroups among CRPS patients [35,64,89,138,214]. A recent systematic review identified seven possible classifications (with a total of 12 potential subtypes) [138]. These classifications are based on the presence or absence of a major peripheral nerve lesion, central sensitization, dystonia, skin temperature changes, inflammation biomarkers, familial history of CRPS, or condition duration. It is supposed that various phenotypes reflect differing pathophysiological mechanisms [88], which may account for the variable treatment responses and would enable personalized, mechanism-based therapeutic management [77,88]. Subgroup identification could also clarify why some patients progress to chronic, disabling forms [37,18,14]. However, studies exploring CRPS subtypes typically focused on only one aspect of the biopsychosocial model (e.g., symptoms/signs or quantitative sensory testing [QST] values), without simultaneously integrating clinical observations, QST, cognitive changes and psychosocial variables.

Regarding CRPS duration, the terms *early* and *persistent CRPS* (preferred to *acute* and *chronic*) were clarified in the Valencia consensus, although the definition of early CRPS remains vague due to insufficient data [92]. It is supposed that, after the first 12-18 months, CRPS becomes more difficult to manage (i.e., *persistent*), but it remains unclear whether all CRPS cases diagnosed within the first 12 months should be considered as a homogeneous *early* condition. Moreover, no required duration between the triggering event and CRPS diagnosis has been established [92], although some experts suggest a timeframe of 3 to 6 months. This proposed duration reflects the challenge in distinguishing

between normal post-traumatic healing and the onset of *early* CRPS, which involves greater pain and psychological distress than in patients with fractures that do not develop CRPS [63], as well as a more intense inflammatory response and vasomotor dysfunction than persistent CRPS [26,194]. Few studies have specifically addressed the characteristics of (very) early CRPS, as participants are often grouped into a single cohort due to small sample sizes, making it difficult to assess how duration influences the clinical presentations/outcomes. However, understanding this early phase is essential to characterize the clinical course of this condition [158]. Moreover, while several treatments might be effective and are recommended only at the early stage, not all patients seem to benefit from them [22,77,109].

The aim of the present study is (1) to report key characteristics of (very) early CRPS patients (< 6 months), and (2) to investigate potential subgroups within this population, considering a large array of biopsychosocial factors. This might allow to better understand and manage this heterogeneous population.

3. Methods

The present cross-sectional study is part of an observational longitudinal study, following the STROBE guidelines [55]. The protocol was approved by the local ethic committee (2022/28FEV/093) and was prospectively registered on ClinicalTrials.gov (NCT05337501).

3.1. PARTICIPANTS AND SETTING

Participants were included from May 2022 to December 2023. Potential subjects were referred by French-speaking hospital physicians or general practitioners in Belgium. They were contacted by the same investigator (MHL, first author of the present manuscript) who explained the objectives and procedures of the study and conducted a first screening of eligibility. After this

stage, a screening visit was scheduled, and eligible participants who gave their informed consent to participate in the study were included.

Inclusion criteria were (1) being over 18 years old, (2) meeting the Budapest clinical diagnostic criteria [104], (3) symptoms onset from less than 6 months, (4) CRPS type I or II [92], (5) capacity to understand and voluntarily sign an informed consent. Exclusion criteria were (1) insufficient French language skills to answer questionnaires, (2) personal previous history of CRPS at the same limb[30], (3) post-stroke CRPS type I (*shoulder-hand* syndrome), (4) severe psychiatric or neurological disorders that would interfere with the participants' ability to complete the study tasks.

Concerning CRPS duration, we did not specify a minimum time between trauma and inclusion (as in other studies, e.g., [2]), for the following reasons. First, there is no specific recommendation concerning the minimum delay required between initial physical trauma and establishment of diagnosis [92,109]. Second, it can be difficult to distinguish the onset of CRPS and the *normal* slow recovery from high-energy trauma and/or a long period of immobilization. However, the cut-off is clearer for minor trauma (such as ankle sprain or elective surgery). Finally, it is recommended to identify and diagnose CRPS as early as possible for better management, at least for therapeutic education [91,92]. Knowing that a number of patients with CRPS will recover spontaneously within a few months and that we are currently unable to explain this variable prognosis,

[30] The exclusion of patients with a prior CRPS in the same limb was based on the consideration that a previous episode could alter the natural course of the condition, analogous to how a recurrent ankle sprain may influence recovery in the same foot. Patients with a history of CRPS in a different limb, however, were **not** excluded, as excluding them would have unnecessarily reduced the sample size. These cases could be recorded and accounted for in the analysis, enabling the evaluation of whether prior CRPS in another limb influences clinical presentation or outcomes. In hindsight, these criteria might appear somewhat contradictory, and an alternative approach could have been to include all patients while carefully documenting the previously affected limb.

the inclusion of *very early* CRPS seemed relevant to achieve our research objectives.

As there is no consensus on the definition of early CRPS [91], we choose to use a duration <6 months for *early* CRPS, and <3 months for *very early* CRPS.

3.2. PROCEDURES

Participants were invited to attend the assessment as soon as possible. They were then included in a 1-year prospective follow-up study (the data of which is not covered by the present manuscript; completion date is scheduled for December 2024). The study investigator (MHL) collected demographic and clinical data, performed Quantitative Sensory Testing (QST) [225], and a visuospatial perception task (Temporal Order Judgement task [TOJ] [78]) in a session of about two hours. To reduce the risk of bias, the testing room and the investigator were identical for each participant. The participants received financial compensation for their participation (€25). If a participant was unable to attend, a phone interview was conducted, and he/she was proposed to complete the survey at home.

The day after the experimental session, the participants were invited to complete a set of questionnaires at home. They were informed that questionnaires should preferably be completed in one session. A personal link to the questionnaires was provided by e-mail to the participants using the REDCap platform. Subjects who wished to avoid using an online platform received the paper versions of the questionnaires at the end of each assessment, with a pre-stamped envelope to send it back within one week.

3.3. MEASURES

3.3.1. Demographic variables

- Age, sex, Body Mass Index (BMI), limb dominance, participant-reported comorbidities and related treatments, addictions (smoking [currently smoking and pack-year], alcohol [units per week], narcotic abuse),
- Education level (number of school years completed after age 12).[31]

3.3.2. Work-related variables

- Professional status, work type based on the Work Demands Coding System [290];
- Medico-legal conflict with employer or insurance company, work injury.

3.3.3. CRPS history

- Family history of CRPS (1st and 2nd level);
- Triggering event: as described in our preregistered protocol (NCT05337501), we had initially chosen to assess the physical severity of the initiating event using a 4-point ordinal scale: spontaneous, elective surgery, low energy trauma, and high energy trauma. The distinction between *low* and *high* energy trauma was based on a scale designed for emergency medicine (available in the *Supplementary materials 1 [methodS1]*, [244]). However, we observed a ceiling effect – almost all traumas were considered as *low* energy. We have therefore chosen to use another 5-point scale previously used in CRPS research [14]: minor incident/no known tissue injury, soft tissue injury, minor surgical procedure (i.e., elective surgery), fracture not requiring surgical repair, and major injury requiring surgical repair.

[31] Additional contextual information, such as ethnicity, place of residence (urban vs. others) , and socioeconomic status, would also have been relevant.

- Potential immobilization, type (splint vs. cast) and duration of strict immobilization[32];
- CRPS duration at inclusion, i.e. since the beginning of the symptoms and the duration since the initial event. In case of presumed symptoms onset during cast immobilization, we added two weeks after the cast removal to determine the date of the CRPS onset. The aim was to ensure that removal of the cast had not altered the symptoms;
- Bone scintigraphy results (if performed [positive vs. no argument for CRPS diagnosis]). Although bone scan is not recommended for diagnosing CRPS [92], it is commonly used by some clinicians (despite the presumed poor sensitivity, inducing false negative and misunderstanding [280]).

3.3.4. CRPS clinical variables

- Localization, and spreading of the initial localization to another part of the body, as defined by Goebel et *al*. [92];
- Research Budapest criteria and CRPS severity score (CSS) [108];
- Neuropathic signs [92]: hypoalgesia, allodynia (to touch, pressure, cold, and joint mobilisation), hyperalgesia to pinprick stimulus;
- Vasomotor signs: skin temperature difference between the affected and contralateral limb (mean of 3 measures at the same point using a digital

[32] As outlined in the introduction (6.1.4. Onset and Risk Factors for CRPS onset), the concept of immobilization is likely broader than the simple use of external devices: it also encompasses the reduced voluntary or unconscious use of the limb. Pain, fear of movement, or avoidance behaviours driven by anxiety may lead to a form of "functional disuse" that can, in some cases, be more restrictive than the duration of casting itself. In our study, this measure was assessed retrospectively and is therefore subject to bias. An alternative approach would have been to evaluate current limb inactivity through actimeters or other wearable motion sensors, allowing objective and dynamic tracking of activity levels. While such a method could provide a more precise quantification of immobilization, it would also require considerable resources in terms of cost, logistics, and patient adherence.

infrared thermometer [Tempett, SENSELab, Sweden]), skin color asymmetry (reddish, pale, bluish, or mottled);

- Sudomotor signs: swelling or sweating asymmetry;
- Trophic signs: skin disturbance (e.g., ulcer), hyper/hypotrichosis, increased/decreased growth of fingernails;
- Motor signs: tremor, dystonia, restricted passive range of motion (RoM), weakness (defined as a Medical Research Council [MRC] scale < 5/5). We also quantitatively measured muscle strength using a Jamar dynamometer for upper extremity (UE) CRPS, and a hand-dynamometer (quadriceps strength, isometric position at 60°) for lower extremity (LE) CRPS. Grip testing of upper extremity is commonly assessed in CRPS research(e.g., [101]), we followed the instruction of the American Society of Hand Therapists [216]. For LE, it has been shown that lower limb CRPS present a deficit of the knee extensor, even if this joint is not directly involved (e.g. CRPS of the ankle) [185]. We therefore choose to assess quadriceps strength, which is essential for walking ability and gait control. The highest value of three trials was recorded. Then, we computed a percentage relative to the unaffected side. These two continuous measures were added after the start of the study and were therefore not collected for all participants;
- Current treatment.

3.3.5. Revised-Bath-Complex Regional Pain Syndrome-Body Perception Disturbance Scale (r-B-CRPS-BPDS)

During the evaluation session, the participants filled in the French-Canadian version [14] of the recently revised B-CRPS-BPDS perceptual abnormalities of the painful limb [148]. As the investigator had to draw the mental representation of the participant's limbs, the questionnaire was completed exclusively during the face-to-face assessment.

3.3.6. Quantitative Sensory Testing (QST)

A Quantitative Sensory Testing (QST) was performed based on the German Research Network on Neuropathic Pain (DFNS) protocol (version 2.1 – 08.07.2010) [186,224]. The instructions were freely translated and adapted to French-speakers. We measured the following parameters on the most painful area of the affected limb and on the homologous area of the contralateral limb: Cold Detection Threshold (CDT), Warm Detection Threshold (WDT), Thermal Sensory Limen (TSL) Paradoxical Heat Sensation (PHS), Cold Pain Threshold (CPT), Heat Pain Threshold (HPT), Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Mechanical Pain Sensitivity (MPS), Dynamic Mechanical Allodynia (DMA), Vibration Detection Threshold (VDT), and Pressure Pain Threshold (PPT).

QST was assessed using: (1) a contact heat and cold stimulator (TCS II, QST.Lab, Strasbourg, France) with a 10-cm^2 probe (T06, QST.Lab, Strasbourg, France) for thermal stimuli, (2) a standardized set of modified von Frey hair (Optihair2-Set, MRC Systems GmbH, Heidelberg, Germany) for MDT, (3) a set of weighted pinprick stimuli with fixed stimulus intensities (the PinPrick; MRC Systems GmbH, Heidelberg, Germany) for MPT, MPS and WUR, (4) a cotton wisp (∼3mN), a cotton wool tip fixed to an elastic strip (∼100mN) and a brush (∼200–400mN) for DMA, (5) a Rydel–Seiffert tuning fork (64Hz, 8/8 scale) for VDT, and (6) a calibrated pressure gauge device (FDIX50, Wagner Instruments, Greenwich, CT, USA) for PPT.

3.3.7. Temporal Order Judgement (TOJ) task

The participants performed a visual TOJ task, that consists of discriminating the temporal order of two lateralized visual stimuli presented in a rapid temporal succession (see *Supplementary materials 2. TOJ procedure [methodS2]* for a detailed description). Those psychophysical tasks are classically used to

investigate perceptual abilities and were recently used to evidence perceptual biases in CRPS patients [79,102]. They are based on the idea that paying attention to a stimulus facilitates its detection.

The materials and procedures were the same as those used in [78,79] with the exception that visual stimuli were presented near the feet for patients with lower extremity CRPS. Two parameters of the psychometric function used to fit participants' performance were analysed, its threshold and its slope. The threshold measures the point of subjective simultaneity (PSS) and is used to index whether the participants' judgments are biased to the advantage of the visual stimulus presented in one particular side of space. The slope relates to the precision of the participants' responses (for furthers explanations, see [80]).

3.3.8. Survey at home

At home, the participants completed several questionnaires assessing functional, psychological and social variables:

- (1) Disability (QuickDASH for upper limb [19], Lower Extremity functional scale [LEFS] for lower limb [115]),
- (2) Quality of Life (QoL)-Participation (EuroQol-5 dimensions – 5 levels [EQ-5D-5L] [25]),
- (3) Pain severity and interference (Brief Pain Inventory-short form [BPI-SF] [133]),
- (4) Pain-related fear of movement (Tampa Scale of Kinesiophobia-11 [TSK-11] [284]),
- (5) Anxiety and depressive disorders (Hospital Anxiety and Depression Scale [HADS] [289]),
- (6) Psychosocial factors associated with chronification of common MSK pain, also known as "yellow flags" (French version of the Örebro Musculoskeletal Pain Screening Questionnaire-short form [ÖMPSQ-SF] [193]),

- (8) Coping strategies to deal with pain (Coping Strategies Questionnaire-French version [CSQ] [127]),
- (7) Perceived social support (Social Support Questionnaire-short form [SSQ6] [211]),
- (9) "General" pain sensitivity (Pain Sensitivity Questionnaire [PSQ] [68]).

3.4. STATISTICAL ANALYSIS

Study data were collected and managed using REDCap electronic data capture tools hosted at the Saint-Luc University Hospital. Statistical analyses were conducted using IBM SPSS Statistics 28, Latent Gold 6.0, and R software (R × 64 version 4.2.3). A p-value < 0.05 was considered statistically significant. The study was preregistered in ClinicalTrial.gov (NCT05337501), but the analysis plan of the inclusion data was decided at the end of the inclusion phase. The script used to analyse QST results is available at: https://github.com/vladaron/CRPS_QST.

We used descriptive statistics to present the characteristics of the cohort. For continuous variables, we reported mean and standard deviation (SD), while categorical variables were described using numbers and percentages.

Concerning the variables, temperature asymmetry was calculated as the difference (Δ) between the affected and the contralateral side. Asymmetric temperature was defined as a $\Delta \geq 1°C$ or $\leq -1°C$. Quantitative strength deficit between the limbs was computed as the relative percentage between affected side and contralateral (affected side strength divided by contralateral strength). For unaffected upper extremity strength, we made an adjustment of 10% based on the dominant side (+10% for non-dominant, -10% for dominant) [216]. Disability was reported as a score from 0 ("no disability") to 80 or 100 ("most possible disability*"*), for lower or upper extremity respectively. EQ-5D index was computed according to the EQ-5D-5L value set for Belgium. Pain severity corresponded to the 5th item of the BPI-SF ("your pain on the average over the

last 24 hours"). Pain interference was computed as the mean value of the seven last items of the BPI-SF [49]. Psychosocial risk of chronification was determined using reference values of the French-version of the ÖMPSQ-SF: low (≤38), medium (39 to 49), and high (≥50). Anxiety or depressive disorders were defined as probable for HADS scores ≥ 11, potential as ≥ 8 [116] or absent if <8. Coping dimension scores were computed as the mean score of the items related to each dimension (1: never, to 4: very often) [127]. Availability dimension of the SSQ6 was computed as the sums of the number of available persons by items (0 to 9). The satisfaction dimension was the sums of satisfaction score for each item (0: very unsatisfied; 6: very satisfied) [211]. Pain sensitivity score was calculated as the average of all PSQ items, with the exception of the three non-painful (item 5, 9 and 13), minor score was computed as the average of items 3, 6, 7, 10, 11, 12, and 14 [68].

Regarding QST data, the results were log transformed except for CPT, HPT, PHS, DMA, and VDT [186,224]. As recommended, we did not compute WUR in participants reporting no pain for single 256-mN pinprick stimulation (n = 25) [224]. We reported the values by limb and sex, using mean and SD. We then computed Z-scores. First, we related the individual values of the affected and contralateral site to the normative values ($Z = [\text{individual value} - \text{mean}_{\text{database}}] / \text{SD}_{\text{database}}$) grouping by extremity, sex, and age [162] Z-values above ‘‘0’’ indicate hyperfunction, which means that the limb was more sensitive compared to the contralateral side (lower thresholds), whereas z-scores below ‘‘0’’ indicate hypofunction and therefore lower sensitivity (higher thresholds). We then computed t values to examine differences between our cohort and the normative values as recommended by Magerl et *al.* [162].

For the TOJ, participants' data were excluded from statistical analyses when the threshold and the slope of the psychometric function could not be reliably estimated during the 40 trials of at least one block, suggesting that their

performance was too inconsistent or below chance level (see *Supplementary materials 2. TOJ procedure [methodS2]*, and [80] for a more detailed discussion of the potential contribution of responses biases in TOJ tasks). This criterion led to the exclusion of the data of five of the 78 tested participants. To facilitate statistical analyses of TOJ results, PSS values, initially encoded in terms of temporal order between left and right sides of space, were recoded to correspond to the side of the affected limb and that of the contralateral limb. Accordingly, data from patients affected by right-sided CRPS were transformed (multiplied by −1) to allow comparison with left-sided CRPS. Positive values correspond to a perceptual bias to the advantage of visual stimuli presented on the side of the affected limb. Potential systematic bias towards the affected or the contralateral side was investigated comparing mean PSS values to 0 using a one-sample t- test.

We assessed the homogeneity of our sample by investigating significant differences between participants who completed only the home survey and the other participants. Continuous variables were compared between these two groups using a Student T test or a Mann-Whitney U test according to their distribution (histograms and normal QQ plots). Proportions between categorical variables were compared with a Pearson's Chi-squared test. The same statistical tests were used to explore potential differences between subgroups in our cohort. For ≥ 2 groups comparisons, continuous variables were compared using the Kruskal-Wallis test. Correlations between TOJ results and body perception disturbances were tested using Pearson coefficient. Each statistically abnormal result was reported.

To identify potential phenotypes (i.e., subgroups), we performed a LCA, a statistically robust method which is a type of mixture modelling. The aim is to identify unobservable (latent) profiles among heterogeneous group of patients [240,278]. This analysis requires to include variables that are *a priori* thought to be implicated in CRPS physiopathology, to identify mechanism-based subgroups.

Two literature reviews [77,88] identify several categories of pathophysiological mechanisms; for each of these mechanisms we selected a potentially relevant measure. The presence or absence of sensitization was assessed using the allodynia (sign) and PPT (Z-score of the affected side, normalized by the normative values), psychosocial indicators of the risk of chronification were measured using the ÖMPSQ-SF score, disturbed body scheme was evaluated with the r-CRPS-bath-BPDS, presumed inflammatory response was indirectly inferred from the physical severity of the triggering event, and vasomotor dysfunction was evaluated using the difference in skin temperature between the affected and contralateral limb. Only subjects with no missing data were included. Collinearity between variables was assessed using Variance Inflation Factor (VIF) (> 4). For further explanations related to the LCA procedure, see *Supplementary materials 6. Latent class analysis – statistical considerations [tableS14].*

4. Results

4.1. PARTICIPANTS CHARACTERISTICS

Figure 3.1 shows the flowchart of the participant selection procedure. In total, 158 patients were contacted. Finally, 113 participants were included in the study, 21% of them performed only the online session. Consequently, some data were only collected for part of the cohort: clinical assessment (n = 89), QST (n = 85), and TOJ procedure (n = 78).

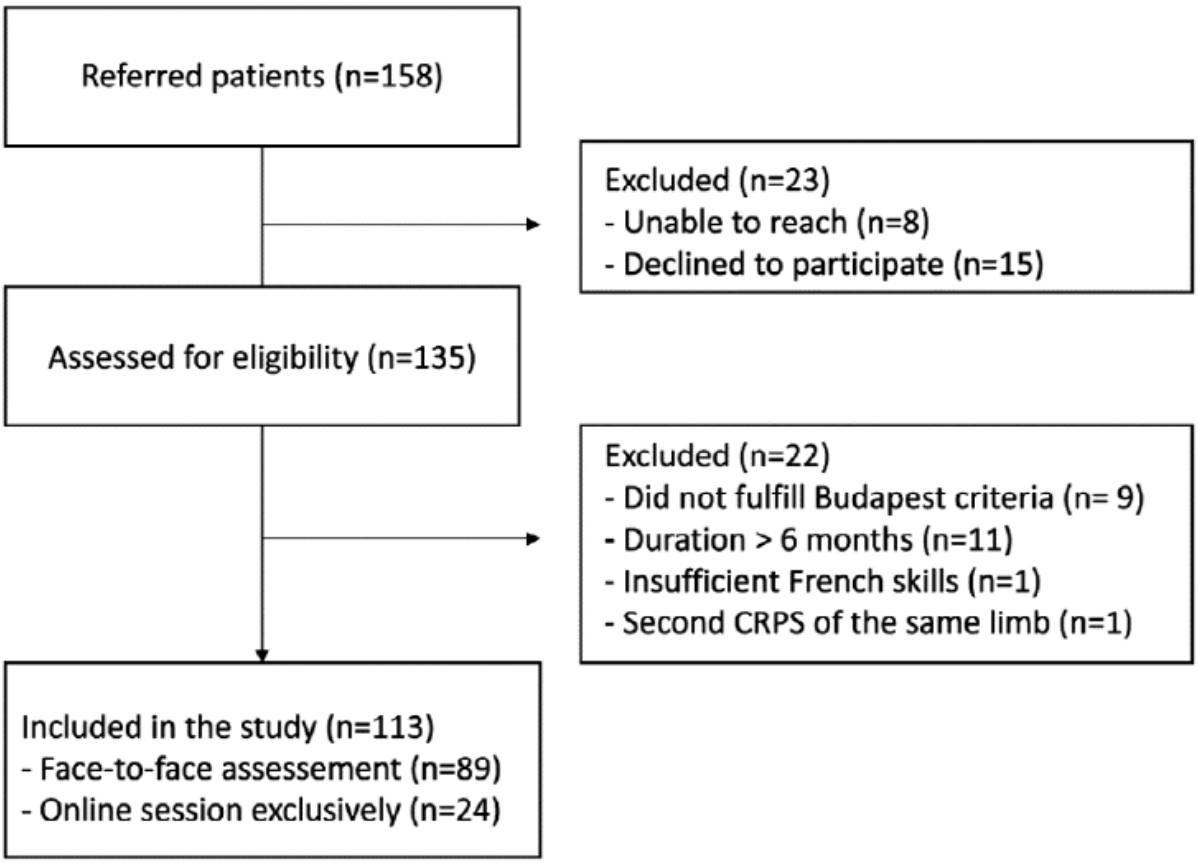

Figure 3.1. Flowchart of the participant selection

Table 3.1 shows the main characteristics of the cohort at baseline. Participants who were only assessed remotely did not significantly differ from the rest of the cohort in terms of demographic or clinical data ($p>0.05$; data not shown). The sample was predominantly female (77%), with a mean age of 53 years. About a quarter of the cohort had a family or personal (at another limb) history of CRPS. Regarding social variables, 68% were working before the onset of the condition. Among them, 18% reported a work injury and only 30% had already returned to work.

Variables			*n* (%) or Mean ± SD (*n* = 113)
Sex (women)			87 (77.0)
Age (years)			52.9 ± 13.3
BMI (kg/m^2)			26.2 ± 4.9
Smoking	Currently		24 (21.2)
	Pack-year		8.5 ± 14.3
Alcohol (units per week)			3.0 ± 7.2
Education level (years)			7.8 ± 2.8
History of CRPS	Only personal		13 (11.5)
	Only family		13 (11.5)
	Both		1 (0.9)
Working before CRPS			77 (68.1)
Work type (*n* = 77)	Not applicable		3 (3.9)
	Minimal physical demands (mentally demanding work)		20 (26.0)
	Mixed physically and mentally demanding work		19 (24.7)
	Light physically demanding work		30 (39.0)
	Heavy physically demanding work		5 (6.5)
Professional status at inclusion	Workers		19 (16.8)
	Medical part-time		5 (4.4)
	Pensioner		23 (20.4)
	Unemployed		5 (4.4)
	Student		2 (1.8)
	Sickness – invalids' beneficiary		59 (52.2)
Work injury			15 (13.3)
Medico-legal conflict with the employer or insurance company			15 (13.3)
Specialisation of physician referring participant	Orthopaedic		57 (50.4)
	Physical medicine		43 (38.1)
	General practice		13 (11.5)
Participant-reported comorbidities	Chronic pain		18 (15.9)
	Anxiety		5 (4.4)
	Depression		3 (2.7)
	Insomnia		5 (4.4)
	Asthma		4 (3.5)
	Migraine	With aura	6 (5.3)
		Without aura	4 (3.5)
	Diabetes	Type I	2 (1.8)
		Type II	3 (2.7)
	Inflammatory diseases		0 (0)

Table 3.1. ***Baseline characteristics of participants.*** *The physical demand for work ("type of work") only concerns people who were working before the onset of CRPS. If participants retired after the onset of CRPS, the type of work was considered "not applicable". Abbreviations: BMI, body mass index; CRPS, complex regional pain syndrome; n, number of participants; SD, standard deviation.*

Concerning CRPS features, the proportion of upper extremity CRPS was greater (59%) than lower extremity CRPS (**Table 3.2**). Only one participant did not report a triggering event, while the others described soft tissue injury (13%), elective surgery (23%), fracture not requiring surgical repair (30%), and major injury requiring surgical repair (33%). The initial event occurred on average 120 days before the inclusion, while the mean CRPS symptoms duration was 76 days. Most of the subjects reported immobilization, with a mean duration of 5 weeks.

Nearly all the participants reported skin colour asymmetry (90%), swelling (99%), and motor disturbances (100%). However, only 36% reported sweating asymmetry, and 55% trophic disturbances. Concerning the clinical features of CRPS, sensory signs were found in 78% of the assessed participants, more frequently hyperalgesia to pinprick (61%) than allodynia (47%). Nearly half of the assessed participants presented asymmetric limb temperature with a range of difference of –3.0 to 5.2°C. Among them, 41% presented colder limb. Most participants exhibited swelling, while sweating was only observed in 19% of the subjects. Trophic disturbances were observed in half of the cohort, principally hypertrichosis or fingernails abnormalities. Only 6% of the participants did not suffer from restricted RoM, and 8% from weakness. Mean CSS was 11.5. Participants varied greatly regarding body perception disturbances (range: 1 to 35/47). Treatments were standard, based on analgesics and physiotherapy. Some patients also benefited from multidisciplinary management (including occupational therapy).

Variables		*n* (%) or mean ± SD (*n* = 113)
Localization	UE	67 (59.3)
	– Elbow	1 (0.9)
	– Hand/wrist	63 (55.8)
	– Only fingers	3 (2.6)
	LE	46 (40.7)
	– Knee	3 (2.7)
	– Foot/ankle	43 (38.0)
Triggering event	Minor incident/no known tissue injury	1 (0.9)
	Soft tissue injury	15 (13.3)
	Elective surgery	26 (23.0)
	Fracture not requiring surgical repair	34 (30.0)
	Major injury requiring surgical repair	37 (32.7)
CRPS symptoms duration (days)		75.8 ± 44.1
Duration from triggering event (days)		120.0 ± 51.1
Strict immobilisation	None	15 (13.3)
	Cast	76 (67.3)
	Only splint	22 (19.5)
	Duration (weeks) Median [min to max]	4.7 ± 3.0 5 [0 to 15]
CRPS type II		11 (9.7)
CRPS symptoms	Continuing pain	113 (100.0)
	Hyperalgesia or allodynia	95 (84.1)
	Temperature asymmetry	94 (83.2)
	Skin colour asymmetry	102 (90.3)
	Sweating asymmetry	41 (36.3)
	Swelling asymmetry	112 (99.1)
	Trophic disturbances	62 (54.9)
	Motor disturbances	113 (100.0)
Sensory signs (*n* = 89)	Hyperalgesia to pinprick	54 (60.7)
	Allodynia (any type)	42 (47.2)
	Allodynia to touch	14 (15.7)
	Allodynia to light pressure	26 (29.2)
	Allodynia to cold	8 (9.0)
	Allodynia to joint mobilisation	15 (16.9)
	Tactile hypoesthesia	10 (11.2)
	None	20 (22.5)
Temperature sign (*n* = 89)	Normal	49 (55.1)
	Warmer (≥ 1°C)	24 (27.0)
	Colder (≤ −1°C)	16 (18.0)
	Absolute value (°C) [min to max]	0.2 ± 1.4 [−3.0 to 5.2]

(Continues)

Variables			*n* (%) or mean ± SD (*n* = 113)
Skin colour sign (*n* = 89)	Normal		17 (19.1)
	Reddish		43 (48.3)
	Pale		3 (3.4)
	Bluish		14 (15.7)
	Mottled		12(13.5)
Sudomotor sign (*n* = 89)	Swelling		80 (89.9)
	Sweating		17 (19.1)
Trophic signs (*n* = 89)	None		39 (43.8)
	Skin disturbance		13 (14.6)
	Hypertrichosis		27 (30.3)
	Hypotrichosis		3 (3.4)
	Fingernails abnormalities		28 (31.5)
	Ulcer		1 (1.1)
Motor signs (*n* = 89)	None		2 (2.2)
	Tremor		7 (7.9)
	Dystonia		2 (2.2)
	Restricted RoM		84 (94.4)
	Weakness		82 (92.1)
	Relative strength of the affected side (%)	UE (*n* = 34)	0.38 ± 0.28
		LE (*n* = 26)	0.68 ± 0.23
CRPS severity score (/16) (*n* = 89)			11.5 ± 2.2
Fulfil Budapest research criteria			89 (78.8)
r-CRPS-Bath-BPDS (/47) (*n* = 89)			15.1 ± 8.2
Scintigraphy (*n* = 56)	Positive		48 (85.7)
	No argument for CRPS		8 (14.3)
Visuospatial test (*n* = 73)	PSS (ms)		3.3 ± 22.3
	Slope		0.043 ± 0.044
Treatment	Paracetamol or NSAIDS		70 (61.9)
	Weak opioids		28 (24.8)
	Strong opioids		3 (2.7)
	Atypical analgesics		15 (13.3)
	Topical analgesics		3 (2.7)
	Glucocorticoids		12 (10.6)
	Bisphosphonates		6 (5.3)
	Active physiotherapy		72 (63.7)
	Passive physiotherapy		91 (80.5)
	Mirror therapy		17 (15.0)
	Multidisciplinary management		12 (10.6)
	Interventional therapy		1 (0.9)

Table 3.2. ***Clinical presentation of early CRPS****. Atypical analgesics mean antidepressants and antiepileptics with proven effect on pain. Multidisciplinary management was considered if the participant benefited from multidisciplinary management in a rehabilitation centre, including medical management and at least two of the following healthcare professionals: physiotherapist, occupational therapist, psychologists. Abbreviations: CRPS, complex regional*

pain syndrome; LE, lower extremity; n, number of participants; PSS, point of subjective simultaneity; SD, standard deviation; UE, upper extremity.

Table 3.3 shows the results from the questionnaires. The participants reported variable levels of disability and pain. Most of the cohort described impaired QoL and self-rated health. Around a third of the cohort presented with probable anxiety disorders, and a quarter with depressive disorders (HADS subscales ≥ 11). The psychosocial risk of chronification was assessed as high for half of the cohort (ÖMPSQ-SF ≥ 50).

Variables			*n* (%) or mean ± SD (*n* = 113)
Disability	UE (/100) *n* = 67		62.6 ± 19.3
	LE (/80) *n* = 46		47.2 ± 15.6
Pain intensity (/10)			4.7 ± 2.3
Pain interference (/10)			4.9 ± 2.3
Quality of life	EQ-index (/1)		0.51 ± 0.30
	EQ-VAS (/100)		53.0 ± 21.5
General self-rated health (*n* = 105)	Excellent		4 (3.8)
	Very good		9 (8.6)
	Good		36 (34.3)
	Fair		31 (29.5)
	Poor		25 (23.8)
Pain-related fear of movement (/44)			31.0 ± 6.7
HADS anxiety	Potential disorder (score ≥ 8)		70 (61.9)
	Probable disorder (score ≥ 11)		43 (38.1)
	Score (/21)		9.4 ± 4.3
HADS depression	Potential disorder (score ≥ 8)		48 (42.5)
	Probable disorder (score ≥ 11)		29 (25.7)
	Score (/21)		7.2 ± 4.4
OMPSQ-SF	Total score (/100)		49.6 ± 17.9
	Psychosocial risk of chronification	Low	34 (30.1)
		Medium	20 (17.7)
		High	59 (52.2)
Coping strategies to deal with pain	Distraction (/4)		2.7 ± 0.7
	Catastrophizing (/4)		1.9 ± 0.6
	Ignoring painful sensations (/4)		2.1 ± 0.6
	Distancing from pain (/4)		1.7 ± 0.7
	Praying (/4)		1.9 ± 0.9
Perceived social support	Availability (0 to 54)		24.9 ± 14.4
	Satisfaction (6 to 36)		29 ± 7.3
Pain sensitivity	Total score (/10)		4.8 ± 3.8
	Minor score (/10)		1.9 ± 2.0

Table 3.3. Questionnaires filled at home*. Abbreviations: CRPS, complex regional pain syndrome; EQ, EuroQol; HADS, hospital anxiety depression scale; LE, lower extremity; n, number of participants; ÖMPSQ-SF, Örebro Musculoskeletal Pain Screening Questionnaire-short form; PSS, point of subjective simultaneity; SD, standard deviation; UE, upper extremity; VAS, visual analogic scale.*

4.2. TEMPORAL ORDER JUDGMENT TASK

We did not observe any systematic bias in visuospatial perception for the entire cohort as well as for upper or lower limb respectively. Complete results are available in the Supplementary materials (*3. TOJ results [tableS1]*). Furthermore, we did not find any significant correlation between the computed PSS and the r-Bath-CRPS-BPDS score (ρ=-0.91, p=0.45).

4.3. QST RESULTS

Depending on the CRPS localization, the area most frequently assessed were the dorsum of the hand (90%, for upper extremity) and of the foot (94%, for lower extremity). For other participants, we tested the palmar side of the wrist (n = 2), the palmar side of the hand (n = 2), the extensors of the elbow (n = 1), and the medial face of the knee (n = 2). PPT were always tested at the same area (thenar eminence for upper limb, and abductor hallucis for lower limb) except for knee (n = 2) and elbow (n = 1) CRPS.

The sensory profile of 80 participants was fully assessed. For some others (n = 5), it was only possible to collect part of the QST data (for logistic reasons).

Figures 3.2 and **3.3** summarize the sensory profiles of early CRPS patients (mean and CI95). Tables showing raw values according to sex, and CRPS localization, as well as Z-scores of each modality are presented in the supplementary section. Compared to the German normative database [162], both sides showed similar disturbances, overall more pronounced for the affected limb than for the contralateral side. More specifically, we observed a loss of function for the detection of thermal (CDT, WDT, TSL) and mechanical stimuli (MDT, and VDT [which was not significant after Bonferroni correction]), and a gain of function for thermal and blunt pressure painful stimuli (CPT, HPT and PPT). Some parameters appear to be unaffected by the condition (MPT, MPS, WUR).

Figures showing mean and SD or SEM of the Z-scores are also available in the Supplementary materials [figures S1 & S2).

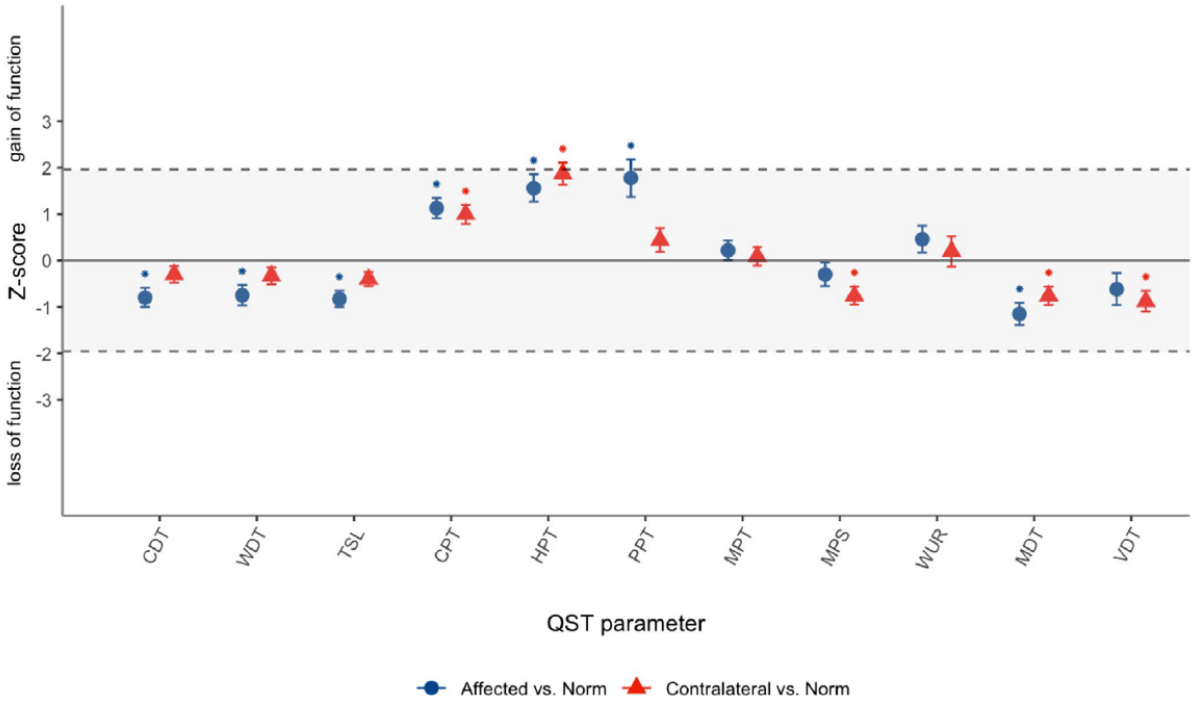

Figure 3.2. ***Z-scores (normative values), for each QST parameter.***

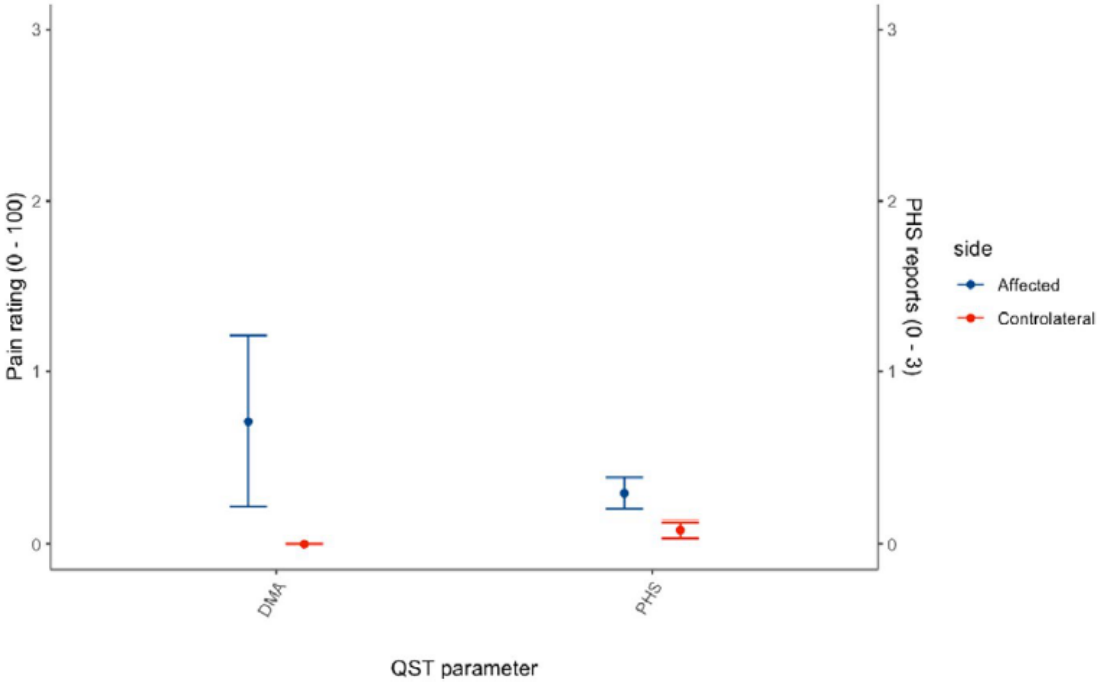

Figure 3.3. DMA and PHS parameters (raw values).

4.4. DIFFERENCES BASED ON REPORTED CLASSIFICATIONS

We first examined whether the collected variables differed significantly between several potential classifications described in the literature [138]. For the sake of brevity, we only report statistically significant differences ($p<0.05$) in **Table 3.4**. Complete results are available in the *Supplementary materials 5. Potential classifications: statistical results [tableS4 to S13]*.

4.4.1. Sex

Only upper extremity disability was significantly higher among females (n = 87) than males. Two social variables differed in both sexes (alcohol consumption and education level).

4.4.2. Family or personal history of CRPS

No differences were observed between the participants reporting a family history of CRPS (n = 14) and the others. Subjects with a personal history of CRPS at another limb (n = 14) reported a higher mean disability score for UE, more sweating symptoms, and more allodynia to joint mobilization.

4.4.3. Triggering event

Participants whose initial event was a minor trauma (n = 16) were younger, presented more allodynia to touch or pressure, while the lower extremity was more often involved than in the rest of the cohort. Interestingly, these subjects presented higher ÖMPSQ-SF score, and higher depressive disorder score than other participants. In cases of fracture or trauma requiring surgical intervention (n = 71), participants reported lower pain intensity and interference, they were also immobilized longer than other participants. Subjects with CRPS induced by surgical procedures (elective or post-trauma, n = 63) reported significantly more skin disturbances than those with other initial events. Some QST variables differed according to the triggering event: we observed a higher gain of function

in blunt pressure and MPS for minor trauma and elective surgery in comparison with fracture or trauma requiring surgical repair.

4.4.4. Historical CRPS subtypes / major peripheral nerve lesion

We observed a higher proportion of skin disturbance signs in CRPS type II (n = 11) than in CRPS type I. All CRPS type II were triggered by surgery (elective or post-trauma), while only 51% of subjects with CRPS type I had been operated. Interestingly, none of the QST parameters were different between these two subgroups.

4.4.5. Involved limb

Participants with lower limb CRPS (n = 46) were younger, presented more allodynia, but less skin disturbances than upper extremity CRPS. They reported more pain interference. The physical intensity of the triggering event differed, with more minor traumas for lower limb and more traumas requiring surgery for upper limb CRPS. Temperature of the contralateral side was significantly different between upper and lower extremity. We also observed more asymmetric temperature (warmer or colder) in lower than in upper extremity, and more asymmetric skin colour. Therefore, CSS was significantly higher in lower than upper limb CRPS. Regarding QST values, lower extremity CRPS presented higher gain of function for thermal painful stimuli.

4.4.6. Research Budapest criteria

Participant fulfilling the Research Budapest criteria (n = 89) were younger, presented higher body perception disturbances, reported more pain (intensity and interference), higher disability (upper and lower extremity), ÖMPSQ-SF score, pain-related fear of movement, HADS scores, and impaired QoL than participants whose symptoms did not completely meet the research criteria. Those 89 subjects reported poorer general self-rated health and higher catastrophizing CSQ

subscale. As expected, they had higher CSS, with significantly more vasomotor symptoms, asymmetric colour, and neuropathic disturbances (symptoms and signs).

4.4.7. Skin temperature changes

Participants with colder skin (n = 16) were younger, presented significantly more allodynia to touch than participants with warmer (n = 24) or neutral skin temperature (n = 49). The colour of the skin was significantly different between the three subgroups, with more reddish skin for warmer, and more bluish skin for colder skin temperature. As expected, mean CSS was statistically higher for warmer and colder skin than neutral.

4.4.8. Very early CRPS

CRPS participants with symptoms duration < 90 days (n = 75) presented significantly higher mean temperature asymmetry, and upper extremity disability score than other participants. They reported and presented more trophic disturbances.

4.4.9. Smoking habits

Smokers (n = 24) described more temperature asymmetry, reported higher pain interference, depressive disorders, ÖMPSQ-SF score, and presented higher catastrophizing CSQ subscale. We observed more hypertrichosis. MPS was also lower in smokers than others (minor loss of function).

Variables differing between subgroups		Potential subtypes										
		Sex	Family history	Personal history	Triggering event	Historical CRPS subtype	Limb involved	Budapest research criteria	Skin temperature	CRPS duration	Smoking habits	LCA profiles
Age					**		***	***	*			*
Educational level		*			*						*	
Alcohol consumption		***										
Affected limb					*		/					
Triggering event					/	*	**					***
Duration of immobilisation					***							
CRPS symptoms	Hyperalgesia or allodynia							***				**
	Asymmetric colour							***				
	Asymmetric temperature							***			*	
	Sweating			**								
	Skin disturbances				*							
CRPS signs	Hyperalgesia to pinprick							***				
	Allodynia Any type						*	**				***
	To touch				*		*		**			**
	To pressure				*		**	*				*
	To cold			*								**
	Skin colour asymmetry						**	*	***			
	Skin temperature asymmetry						**		/	*		
	Trophic disturbances					**				*	*	
	Weakness						*					

(Continues)

Variables differing between subgroups		Potential subtypes										
		Sex	Family history	Personal history	Triggering event	Historical CRPS subtype	Limb involved	Budapest research criteria	Skin temperature	CRPS duration	Smoking habits	LCA profiles
CRPS severity score							*	***	*			***
Budapest research criteria								/				**
r-CRPS-BATH-BPDS								***				***
Disability	UE	*		***			/	*		*		***
	LE						/	*				*
EQ-index					*			***				***
EQ-VAS								**				***
General self-rated health								*				**
Pain intensity					*			**				***
Pain interference					**		**	**			*	***
Pain-related fear of movement					*			**				
HADS anxiety								*				
HADS depression					**			***			**	***
OMPSQ-SF					**			**			**	***
Availability of support							*					*
Coping strategies, catastrophizing								**			*	***
Coping strategies, distancing from pain		**						**				
Coping strategies, ignoring pain sensations					*							
Coping strategies, praying												*
Cold pain threshold (*Z*-score)							*					
Heat pain threshold (*Z*-score)							**					
Mechanical detection threshold (*Z*-score, affected)		*										
Mechanical pain sensibility (*Z*-score, affected)											*	**
Pressure pain threshold (*Z*-score, affected)												***
Dynamic mechanical allodynia (log-transformed values, affected)												*

(Continues)

	Potential subtypes										
Variables differing between subgroups	Sex	Family history	Personal history	Triggering event	Historical CRPS subtype	Limb involved	Budapest research criteria	Skin temperature	CRPS duration	Smoking habits	LCA profiles
Pressure pain threshold (Z-score, contralateral)											*
Point of subjective simultaneity (ms)											**

Table 3.5. Exploratory subgroups analysis*. Note: We reported variables statistically differing in at least one subgroup. For instance, age did not significantly differ between males and females, but education level and alcohol consumption did. Historical subtypes correspond to CRPS type I and II. /, not tested. Abbreviations: EQ, EuroQol; HADS, hospital anxiety depression scale; LCA: latent class analysis; LE, lower extremity; ÖMPSQ-SF, Örebro Musculoskeletal Pain Screening Questionnaire-Short Form.; r-CRPS-Bath-BPDS, revised-CRPS-Bath-Body perception disturbance scale questionnaire; UE, upper extremity; VAS, visual analogic scale. *p < 0.05; *p < 0.01; ***p < 0.001.*

4.5. LATENT CLASS ANALYSIS

No collinearity was observed between the variables. The skin temperature did not distinguish participants and was thus removed from the model. The best fit was a 4-profile model (for details, see *Supplementary materials 6. Latent class analysis – statistical considerations [tableS14]*). Characteristics of each profile are summarized in **Table 3.5**, while **Figure 3.4** illustrates the variables used to classify subjects, and **Figure 3.5** the differences between subgroups. No significant differences were observed in terms of CRPS duration (onset of symptoms or trauma), temperature, or classic CRPS features (symptoms or signs used in the Budapest criteria), except for sensory features.

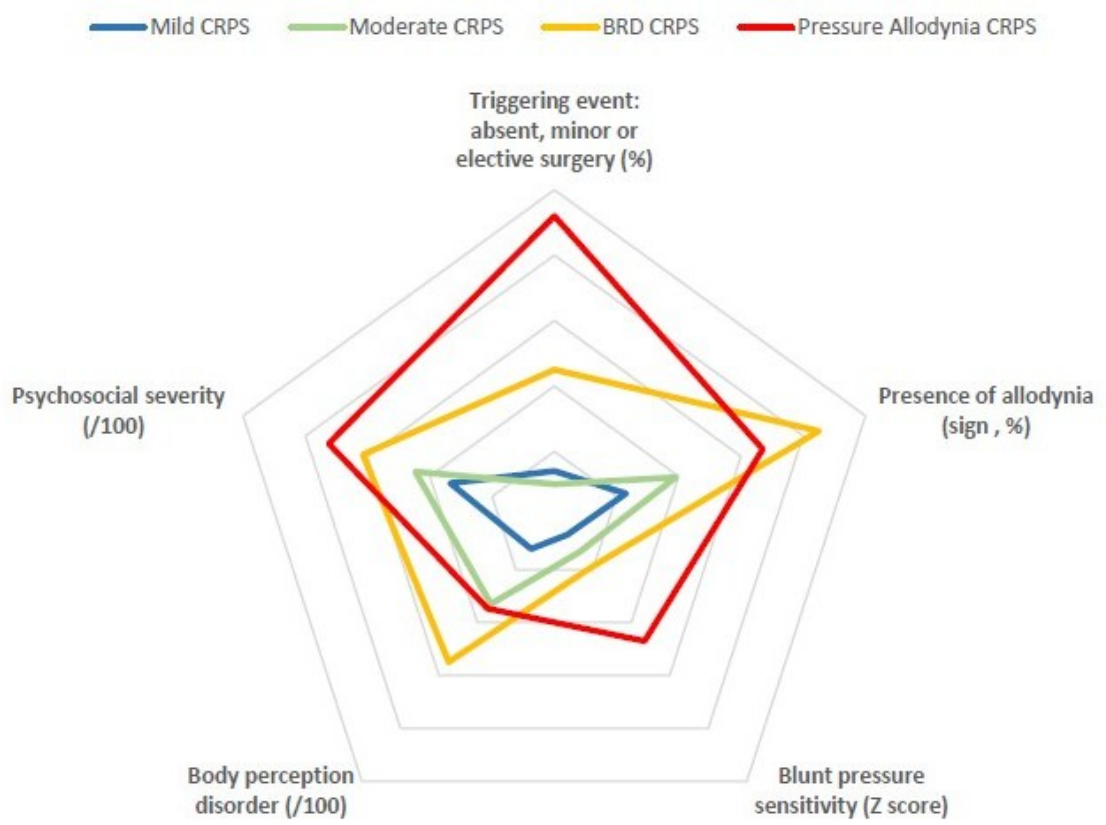

Figure 3.4. ***Results of the latent class analysis (LCA): variables determining the different profiles.*** *Presented on a 0 (centre) to 100 scale for each profile (expressed by a mean or proportion). Triggering events were dichotomized between absent/minor trauma/elective surgery vs. fracture/major trauma requiring surgical repair. The presence of allodynia (sign, any stimulus) is expressed as a rate within each profile. ÖMPSQ-SF score was used to indicate the psychosocial severity, mean pressure pain threshold (Z score, contralateral values normalized by the norms) was multiplied by 10, while body perception disorder corresponds to the mean r-bath-CRPS-BPDS normalized on a /100 scale (original score multiplied by 2.13). Abbreviations ÖMPSQ-SF, Örebro musculoskeletal pain questionnaire – short form; r-B-CRPS-BPDS, revised-Bath-complex regional pain syndrome-body perception disturbance scale.*

A first group (*Mild CRPS*, n = 22) was composed of older people than in the other subgroups. The initiating event was either a fracture or a major trauma requiring surgical repair. In comparison to the other profiles, this *Mild CRPS* subgroup presented a milder condition in all measures: less allodynia, CSS, body perception disorders, disability, depressive scores, pain ratings. They reported

better QoL and general self-rated health. The catastrophizing subscale was lower, as was the ÖMPSQ-SF score. Social support was higher than in the three other subgroups. The average gain in function for PPT was the lowest of four profiles, while there was a loss of function for MPS compared to healthy subjects [162]. Half of these patients did not fulfil the research Budapest criteria.

The second profile (*Moderate CRPS*, n = 31) mainly consisted of subjects whose CRPS was triggered by a major trauma or some fractures. In comparison to the other participants, this subgroup seemed to present a moderate condition, with more impairments than the first profile but fewer than the two others in terms of sensory signs, disability, QoL, general self-rated health, pain ratings, and depressive scores. *Moderate CRPS* patients presented a significant impairment in body perception and an increased pain sensitivity to blunt pressure in comparison to the normative values [162]. This profile showed a significant systematic perceptual bias during TOJ, suggesting that participants paid more attention to the unaffected limb than to the affected limb (see **Table 3.5** and *Supplementary materials 3. TOJ results [tableS1]* for statistical results).

LCA identified two last profiles of *severe* CRPS: *body representation disturbance (BRD) CRPS* (n = 20) and *Pressure allodynia CRPS* (n = 12). In comparison with the two first profiles, they both reported poorer outcomes in all measures. The *BRD CRPS* profile was composed of CRPS triggered by various events, but mostly by elective surgery. Allodynia was highly prevalent, and CSS score was high. Those participants presented the highest body perception disturbances score and pain sensitivity to mechanical stimuli (MPS) in our sample. The *Pressure Allodynia CRPS* profile is composed of younger subjects than the other subgroups. The physical intensity of the initial event was low (almost exclusively minor traumas or elective surgeries). Allodynia to cold and pressure were often found. They presented similar body perception disturbances than the *Moderate CRPS* profile. ÖMPSQ-SF score was the highest of the four

profiles. Those 12 participants presented a major sensitivity to blunt pressure (on both sides), and a significant increase of DMA. In contrast to *Moderate CRPS* profile, the TOJ task identified a spatial bias to the detriment of the perception of visual stimuli occurring in the contralateral side, suggesting that patients paid more attention to the affected limb than to the unaffected limb (see **Table 3.5** and Supplementary materials 3 [tableS1]).

Overall, the presence of allodynia, higher psychosocial risk of chronification, higher body perception impairment, low physical intensity initiating event, and lower PPT were associated with poorer outcomes.

Variables		n (%) or mean ± SD (n = 85)				
		Profile 1 (n = 22)	Profile 2 (n = 31)	Severe CRPS (n = 32)		
				Profile 3 (n = 20)	Profile 4 (n = 12)	
		Mild CRPS	Moderate CRPS	BRD CRPS	Pressure allodynia CRPS	p
Age (years)		58.1 ± 11.5	50.8 ± 14.3	50.4 ± 13.5	47.8 ± 12.1	0.050
Triggering event	Spontaneous or minor trauma	4 (4.5)▪	1 (3.2)§	2 (10.0)	6 (50.0)▪,§	< 0.001
	Elective surgery	2 (9.1)▪	2 (6.5)§	7 (35.0)	5 (41.7)▪,§	
	Fracture without surgery	11 (50.0)▪	9 (29.0)§	5 (25.0)	1 (8.3)▪,§	
	Trauma requiring surgical repair	8 (36.4)▪	19 (61.3)§	6 (30.0)	0 (0.0)▪,§	
CRPS symptoms	Hyperalgesia or allodynia	13 (59.1)†,ᵣ	28 (90.3)†	19 (95.0)ᵣ	11 (91.7)	0.004
CRPS signs	Allodynia (any stimulus)	5 (22.7)ᵣ	12 (38.7)#	17 (85.0)ᵣ,#	8 (66.7)	< 0.001
	Allodynia to touch	1 (4.5)	2 (6.5)	7 (35.0)	4 (33.3)	0.007
	Allodynia to pressure	3 (13.6)▪	7 (22.6)	9 (45.0)	7 (58.3)▪	0.017
	Allodynia to cold	0 (0.0)▪	1 (3.2)§	3 (15.0)	4 (33.3)▪,§	0.006
	Skin temperature (°C)¤	0.3 ± 1.5	0.3 ± 1.3	0.1 ± 1.2	0.3 ± 1.9	0.997
CRPS severity score (/16)		10.1 ± 2.2†,ᵣ	11.2 ± 2.0▪	13.1 ± 1.3ᵣ,▪	12.4 ± 1.8†	< 0.001
Budapest research criteria		11 (50.0)†,ᵣ	27 (83.9)†	18 (90.0)ᵣ	10 (83.3)	0.008
r-Bath-CRPS-BPDS (/47)		5.7 ± 2.6†,ᵣ,▪	15.5 ± 2.9†,§	25.8 ± 3.5▪,§,#	16.3 ± 8.3ᵣ,#	< 0.001
Disability	UE (/100)	52.6 ± 20.2†,ᵣ	62.4 ± 19.2	78.5 ± 8.6†	80.5 ± 4.1ᵣ	0.001
	LE (/80)	24.0 ± 15.3†,ᵣ	44.9 ± 12.8	53.6 ± 14.4†	52.1 ± 10.8ᵣ	0.013
HADS depression (/21)		3.9 ± 3.6†,ᵣ,▪	7.1 ± 4.4▪	9.0 ± 3.4†	10.3 ± 2.7ᵣ	< 0.001
Pain intensity (/10)		3.2 ± 2.1†,ᵣ	4.1 ± 2.5§	6.1 ± 2.1†	6.8 ± 2.0ᵣ,§	< 0.001
Pain interference (/10)		3.0 ± 2.1†,ᵣ	4.4 ± 2.0▪,§	6.4 ± 1.5†,▪	6.6 ± 1.3ᵣ,§	< 0.001
OMPSQ-SF (/100)		33.4 ± 15.8†,ᵣ	44.6 ± 12.8▪,§	61.5 ± 8.6†,▪	72.5 ± 11.5ᵣ,§	< 0.001
CSQ-catastrophizing (/4)		1.5 ± 0.5†,ᵣ	1.8 ± 0.4	2.2 ± 0.7†	2.2 ± 0.5ᵣ	< 0.001
CSQ-praying (/4)		1.7 ± 0.8	1.6 ± 0.8†	1.9 ± 0.8	2.5 ± 1.0†	0.010
Social support (satisfaction, /36)		32.9 ± 3.9†	27.4 ± 7.6†	29.0 ± 5.4	29.6 ± 5.3	0.012

(Continues)

Variables		n (%) or mean ± SD (n = 85)				
		Profile 1 (n = 22)	Profile 2 (n = 31)	Severe CRPS (n = 32)		
				Profile 3 (n = 20)	Profile 4 (n = 12)	
		Mild CRPS	Moderate CRPS	BRD CRPS	Pressure allodynia CRPS	p
EQ-index (/1)		0.76 ± 0.18†,ˇ,▪	0.54 ± 0.26†	0.34 ± 0.23▪	0.24 ± 0.30ˇ	< 0.001
EQ-VAS (/100)		67.5 ± 18.4†,ˇ	55.7 ± 19.5▪,§	38.3 ± 19.0†,§	32.6 ± 13.4▪,ˇ	< 0.001
General self-rated health	Excellent	1 (4.5)ˇ,▪	2 (6.5)§	0 (0)ˇ	0 (0)▪,§	0.004
	Very good	4 (18.2)ˇ,▪	2 (6.5)§	0 (0)ˇ	1 (9.1)▪,§	
	Good	10 (45.5)ˇ,▪	15 (48.4)§	4 (23.5)ˇ	2 (18.2)▪,§	
	Fair	6 (27.3)ˇ,▪	9 (29.0)§	4 (23.5)ˇ	1 (9.1)▪,§	
	Poor	1 (4.5)ˇ,▪	3 (9.7)§	9 (52.9)ˇ	7 (63.6)▪,§	
Mechanical pain sensitivity (Z-score, affected)		−0.79 ± 1.02	−0.68 ± 1.12	3.03 ± 1.44	0.78 ± 1.62	0.004
Dynamic mechanical allodynia (log-transformed values, affected)		0.1 ± 0.26	0.1 ± 0.01	0.58 ± 1.29	5.08 ± 8.44	0.019
Pressure pain threshold (Z-score, affected)		0.68 ± 1.55†	1.33 ± 1.26ˇ	1.91 ± 2.08	4.70 ± 3.14†,ˇ	< 0.001
Pressure pain threshold (Z-score, contralateral)		−0.22 ± 1.29†	0.60 ± 1.12	0.33 ± 1.39	1.44 ± 1.92†	0.013
PSS (ms)		8.7 ± 24.1 (n = 22)	−9.0 ± 19.9 (n = 25)▪	7.1 ± 18.1 (n = 16)	15.9 ± 17.8 (n = 10)▪	0.003

Table 3.5. ***Characteristics of the four profiles identified by latent class analysis in the cohort.***

Note: With the exception of skin temperature, only statistically significative variables were reported. The p-values correspond to Kruskal–Wallis or Chi-squared test. Abbreviations: BRD, body representation disturbance; CRPS, complex regional pain syndrome; CSQ, coping strategies questionnaire; EQ, EuroQol; HADS, hospital anxiety depression scale; LE, lower extremity; n, number of participants; ÖMPSQ-SF, Örebro musculoskeletal pain questionnaire – short fort; PSS, Point of subjective simultaneity; r-Bath-CRPS-BPDS, revised-Bath-CRPS-Body perception disturbances scale; SD, standard deviation; UE, upper extremity; VAS, visual analogic scale. ¤, not significative; † or ˇ or ▪ or § or #, significant pairwise comparisons (adjusted by the Bonferroni correction).

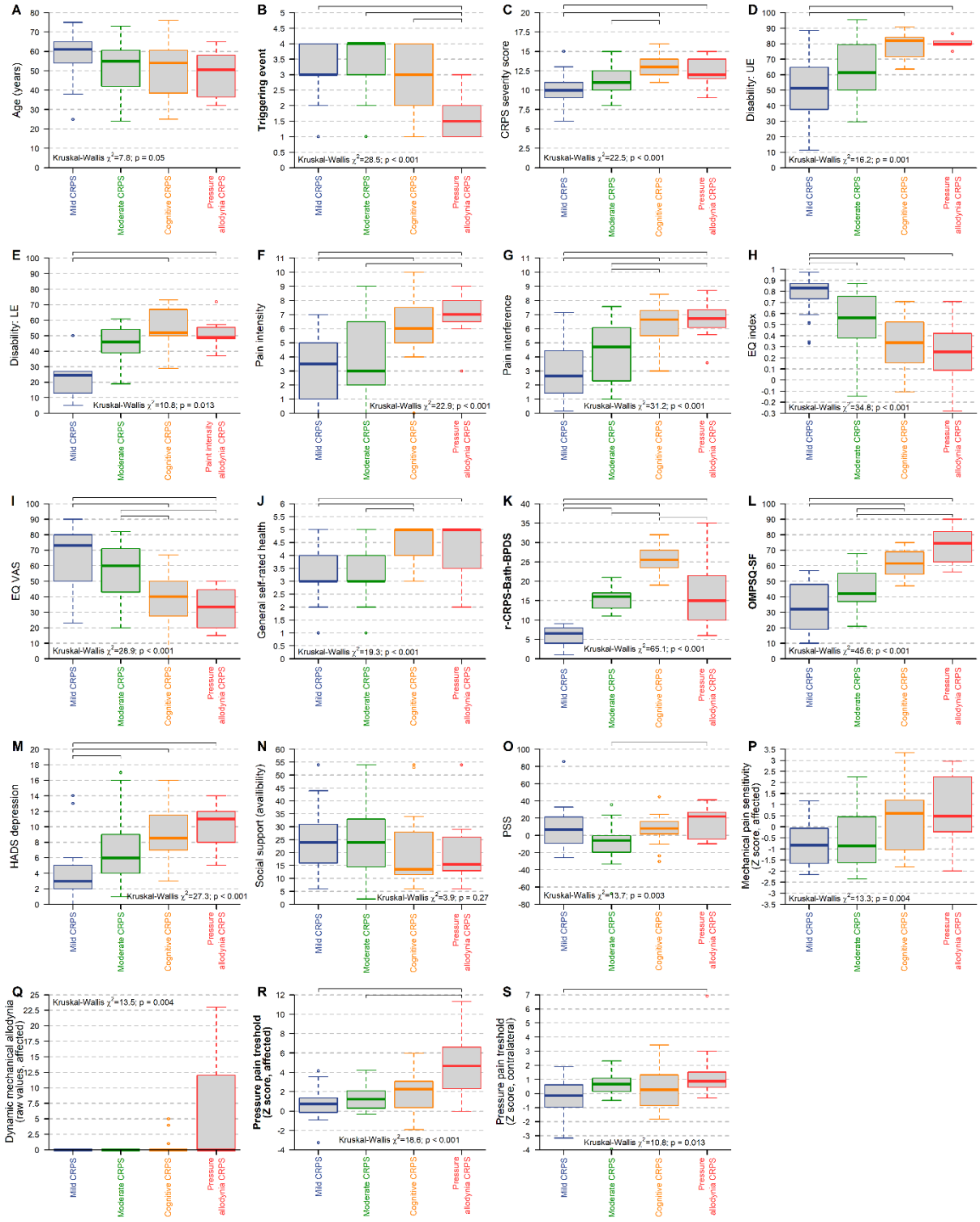

Figure 3.5. ***Distribution of patient's CRPS characteristics according to the four profiles created in latent class analysis.***

5. Discussion

This study, evaluating the biopsychosocial characteristics of 113 subjects suffering from (very) early CRPS (< 6 months), confirmed the heterogeneity of clinical presentations. Overall, the CSS score was high, function and QoL were considerably impaired. While no significant visuospatial bias was observed at the level of the entire cohort, many participants reported alterations in body perception. QST results showed similar, but milder, abnormalities than previous studies [89,245]. Interestingly, neither the duration of the condition nor skin temperature significantly affected the CRPS features and outcomes, suggesting the absence of a required minimum duration for diagnosis.

Using LCA (n = 85), four profiles were identified. *Mild* and *Moderate CRPS* were characterized by high intensity triggering events contrasting with moderate perturbation of outcomes (more pejorative in *Moderate* than in *Mild CRPS)*. Both severe CRPS subgroups showed poorer outcomes than the two other profiles. *BRD CRPS* displayed the most severe body perception disturbances, highest MPS, and rate of allodynia. *Pressure allodynia CRPS* were mostly triggered by events of low physical intensity, had the highest psychosocial severity, and displayed a dramatic reduction in PPT values. *Moderate CRPS* and P*ressure allodynia CRPS* displayed attentional bias in opposite directions during the TOJ task. The identification of these four profiles, based on an uncontrolled statistical analysis not relying on condition duration, confirmed the heterogeneity among (very) early CRPS patients, probably subtended by different mechanisms.[33]

[33] An important limitation to consider when interpreting these findings is the absence of data on participants' status prior to CRPS onset. Consequently, the observed differences between patients should not be attributed exclusively to distinct manifestations of CRPS. Some of these variations may instead reflect pre-existing traits or vulnerabilities, which could influence both the development and the clinical expression of the condition.

5.1. INTERPRETATION IN THE LIGHT OF THE LITERATURE

5.1.1. Clinical features

In a large retrospective cohort [194], early CRPS (< 6 months) was associated with swelling and warmer skin than the contralateral limb, while persistent CRPS presented colder skin. The authors found similar reduction of muscle strength (60%) and RoM (approximatively 47%) between these two subgroups. Our results show that early CRPS can also present colder skin temperature. In line with our data, another prospective early CRPS cohort [14,15] observed weakness and restricted RoM in the majority of this population (>90%). They also found similar proportions of other symptoms and signs, pain rating, and pain-related fear of movement [14,15].

5.1.2. Neurocognitive deficits

Regarding spatial perception, previous research suggested that CRPS patients might present perceptual biases affecting their ability to perceive visual stimuli in the side of space corresponding to their affected limb [39,78,184]. However, no such systematic biases could be evidenced here at the level of the entire cohort (n = 73), corroborating more recent studies [79,102,254] and challenging the hypothetical role of visuospatial biases in CRPS pathophysiology. This does not exclude the possibility that other factors might be involved in visuospatial biases in CRPS [79]. In support of this hypothesis, we identified significant spatial biases for two subgroups. *Moderate CRPS* participants seem to pay more attention to the side of the unaffected limb, while *Pressure allodynia CRPS* participants seem to preferentially direct attention to the affected side. The reason behind this finding still needs to be explored.

Using r-B-CRPS-BPDS results, our sample shows similar body perception disturbances than those of the cohort used to design the revised version of this

questionnaire, composed mainly of patients with persistent CRPS [253]. This suggests that early and persistent CRPS share similar body perception disorders, and therefore that these disturbances are not simply a consequence of long-lasting symptoms. This raises the question of the pathological role of body perception disturbances in triggering and/or maintaining CRPS.

5.1.3. Potential classifications discussed in the literature

The current literature about subtyping CRPS is based on statistical analyses that might lack reliability and reproducibility [70], such as t-test/non-parametric equivalent statistics (n = 19), or classical clustering algorithms, e.g. k-means (n = 3) and TwoStep Cluster (n = 3) [138].

Using t-tests or equivalents, we did not observe any differences based on a family or personal history of CRPS, or CRPS type. This last observation is in line with current consensus suggesting that the historical division of CRPS in types I and II is probably clinically irrelevant [92], even though this was recently discussed [138].

Patients who met the research Budapest criteria appeared to experience a more severe condition (e.g., pain, disability, QoL). Studies that include CRPS patients using research Budapest criteria might therefore select a more severe cohort of CRPS, reducing the external validity of their findings. As discussed by [104], the advantage of the research vs. clinical Budapest criteria appears to be minimal.

Concerning other potential subtypes, our results do not confirm those of other studies showing that cold CRPS was associated with poorer clinical outcomes, loss of function on QST assessment, and signs of central sensitization [138].

Our data did not allow us to investigate other reported classifications (biomarkers of inflammation, CRPS duration [early vs. persistent], whereas dystonia was too rare to allow statistical analysis [n = 2]) [138].

5.1.4. Pathophysiological mechanisms potentially underlying CRPS profiles

The heterogeneity of CRPS presentations and outcomes suggests the existence of unobservable (i.e., latent) subgroups [77]. As discussed above, previously reported classifications do not adequately account for this variability in our cohort, but the LCA distinguished CRPS patients with different clinical characteristics and outcomes, potentially subtending distinct pathological patterns. One of the advantages of LCA is that the analysed parameters were chosen *a priori* as proxies for several categories of putative physiopathological mechanisms of CRPS (sensitization, psychosocial distress, disruption of the body scheme, presumed abnormal inflammatory response, and vasomotor changes). However, it must be noted that these parameters have not been validated for this purpose (see methods and supplementary sections for further explanations) and that their relationship to the putative mechanisms is often indirect.

Regarding sensory profiles, a lower PPT on the affected side is considered a potential distinguishing feature of CRPS [89]. In our LCA, an increase in sensitivity to blunt pressure was associated with the more severe profiles. Gaynor and colleagues also associated higher pressure pain sensitivity with more severe chronic pain disorders (including fibromyalgia, temporomandibular disorder, irritable bowel syndrome, ...). In a longitudinal study, higher pressure pain sensitivity predicted a higher risk of still meeting the research Budapest criteria at 12-month follow-up [222]. However, the predictive value of PPT appears to be low in other MSK pain syndromes [87,117,206].

Several observations suggest a greater involvement of central / systemic mechanisms with more severe CRPS profiles (BRD and Pressure allodynia CRPS). First, higher body perception impairment, probably caused by central mechanisms [102], was associated with poorer outcomes.

Second, the more severe profiles were triggered by less intense events than the mild and moderate CRPS subgroups. In addition to a different (abnormal) inflammatory response [77], a greater implication of maladaptive neuroplasticity might be hypothesized [64] in severe CRPS following low intensity trauma. It should be noted however that other studies showed a positive association between the physical intensity of the trauma and the severity of the outcomes [158] or the risk of CRPS incidence [155,202,208,223].

Third, the presence of allodynia might indicate central sensitization [51,163,285], although it could also be explained by peripheral sensitization [9]. Fourth, the higher pressure pain sensitivity on the contralateral side associated with severe profiles is strongly suggestive of systemic mechanisms [245]. Finally, psychosocial factors are important contributors to the development and maintenance of central sensitization [48,171]. In our LCA analysis, higher psychosocial severity (as measured by ÖMPSQ-SF, but also catastrophizing and depressive scores) is associated with the two severe subgroups and poorer outcomes. In the aforementioned MSK pain study [84], the most important parameters to determine the severity of the condition were psychosocial factors. Many other studies stress the importance of psychosocial variables for the evolution of MSK pain [117,122,153].

In line with the hypothesis of central maladaptive changes, Dimova and colleagues [64] identified three potential phenotypes in persistent CRPS patients: a "*central phenotype*" (minor trauma, allodynia, motor disturbances and sensory deficits), a "*peripheral phenotype*" (temperature asymmetry, edema, sweating, skin color, and trophic changes) and a "*mixed phenotype*" (associating both characteristics). However, in contrast to these data, our LCA results did not identify subgroup differences according to "peripheral" CRPS characteristics whereas our profiles were strongly linked to different outcomes. The difference might be explained by the clustering method, the variables introduced into the

model and/or a different population. Consequently, it suggests that the presence or absence of CRPS features (with the exception of sensitive signs) assessed by the Budapest criteria might not be relevant for subgroup classification.

5.2. LIMITATIONS

A first limitation of this study is related to the small proportion of patients who were not subjected to a face-to-face assessment, while the CRPS diagnosis requires physical examination [92]. However, the subjects who were assessed exclusively by telephone had a typical clinical history and classic CRPS symptoms, and we observed no significant difference between these participants and those who were assessed physically. In addition, patients were referred by experienced clinicians, using the Budapest criteria. Finally, a preliminary analysis of longitudinal data (at 6- and 12-month follow-up, n = 91) showed no different outcomes (pain, CSS, Budapest clinical criteria, disability or QoL) based on this criterion (*data not shown*).

The selection of (very) early CRPS participants might be hampered by the difficulty of distinguishing signs and symptoms that are "*normal*" after a trauma from those that indicate early CRPS. As explained in the methods section, no specific recommendation can be found in the literature concerning this question and "normal" evolution after trauma can take days or weeks depending on trauma severity. Therefore, we suggest that "very early CRPS" diagnosis is possible when the evolution does not follow the expected pattern. Furthermore, we did not identify any difference in our sample between *very* early CRPS (< 3 months) and 3-6 months CRPS. Finally, our preliminary analysis of longitudinal data at 1 year suggests that *very early* CRPS did not differ in terms of the aforementioned outcomes, and that the duration of CRPS or since the triggering event was not associated with any of these outcomes (univariate analysis in a mixed-effects model, unpublished preliminary results).

All measurements, including temperature, were taken at only one point in time. However, CRPS symptoms are variable over time [92]. Therefore, a single measure might not be sufficient to detect change.

Our sample size was relatively small to perform LCA, even though clear recommendations do not exist [240]. In the future, it will be important to reproduce our findings with an external dataset to validate the identified profiles. It would also be interesting to evaluate whether the parameters selected for the LCA do really reflect the putative pathophysiological mechanisms that were hypothesized.

5.3. CONCLUSIONS

This study contributes to a nuanced understanding of (very) early CRPS and highlights that this population can be divided into subgroups, presenting different outcomes. These profiles did not depend on the duration of the condition, suggesting the absence of minimum delay required to diagnose CRPS. Furthermore, it does not seem relevant to distinguish *early* CRPS based on skin temperature. Our results challenge some traditional CRPS classifications, suggesting that current diagnostic criteria may not fully capture the complexity of the disorder. LCA results point to the potential role of central / systemic mechanisms in severe conditions. The clinical implication of the identified phenotypes should be further investigated.

VI. CHAPTER 3. CRPS Evolution is Determined by Both Biological and Psychosocial Factors – a 1-Year Prospective Observational Study

Reference: Louis, Marc-Henri; Legrain, Valéry; Aron, Vladimir; Filbrich, Lieve; Mouraux, André; Henrard, Séverine; Guillaume, Laurent; Mouraux, Dominique; Barbier, Olivier; Libouton, Xavier; Berquin, Anne. *Complex regional pain syndrome evolution is determined by both biological and psychosocial factors: a 1-year prospective observational study.* Pain. 2025 Oct 8. doi: 10.1097/j.pain.0000000000003815. PMID: 41065599.

Presented *in annual CRPS SIG meeting (04/2025), EFIC Congress (commented poster, 05/25).*

1. Abstract

Complex regional pain syndrome (CRPS) is a challenging condition with unpredictable clinical evolution. Identifying early prognostic factors could transform patient management and improve outcomes. This prospective study followed 113 patients with early CRPS (<6 months) over one year to assess clinical evolution and investigate key predictors of chronification. Participants underwent repeated clinical assessments, quantitative sensory testing, and self-reported evaluations at four time-points until one year. Multivariable mixed effect models were used to identify independent early prognostic factors. Despite some improvement, 35% of the participants still met Budapest criteria at one year, with persistent pain, disability, and impaired quality of life. Sensory profiles appeared to stabilize after a few months, while body perception disturbance scores did not change during the follow-up period. Psychosocial factors, such as baseline disability, psychosocial severity, and social support, but also body mass index and allodynia were predictors of long-term outcomes. Biopsychosocial Early CRPS (*BE-CRPS*) profiles defined through a latent class analysis carried out on the basis of data measured at inclusion revealed distinct clinical trajectories and showed stronger prognostic value than previously suggested CRPS classifications (e.g.,

based on skin temperature). These findings highlight the importance of an early assessment incorporating biopsychosocial elements to stratify risk and tailored interventions. Our study paves the way for the development of a clinical tool to predict CRPS evolution, potentially enabling tailored treatments. Future research should validate these predictive models and explore their integration into routine practice, potentially improving the management of early CRPS.

2. Introduction

CRPS is an important cause of chronic pain and disability but remains a poorly understood condition [92], despite recent interesting findings [77]. However, its prognosis is still debated.

Early CRPS describes a stage of the condition potentially easier to manage and more likely to improve than *persistent CRPS* [92]. However, no clear consensus exists regarding the exact timepoint distinguishing these two stages, with proposed cut-offs typically ranging between 12 and 18 months after symptom onset [92] . As a result, the term early CRPS is often applied to a broad and somewhat imprecise timeframe.

Whereas older research suggested a favourable evolution of early CRPS, with a majority of patients experiencing spontaneous recovery [291], more recent prospective studies and systematic reviews showed rare complete remissions and poor rate of RtW [18,128]. Some data show similar outcomes at one and eight years, suggesting the absence of resolution after 12 months [43]. All these elements highlight the importance of investigating early factors influencing the evolution, and therefore the risk of CRPS chronification. Yet, this topic remains largely unexplored as shown in a recent systematic review [158] where only six studies were found, most considered at a high risk of bias. Among the identified potential predictors, six were supported by moderate evidence: anxiety, pain,

disability, pain-related fear of movement, sex, and physical intensity of the triggering event.

The literature on CRPS prognosis originally considered biological factors [38,279], such as skin temperature and sensory disturbances, as predictors. In contrast, psychological factors (commonly called *yellow flags*) have come to the fore more recently [16] as in many other pain conditions such as LBP or adhesive capsulitis [112,178,189].

The identification of these factors in MSK disorders has led to the development of short questionnaires, allowing clinicians to quickly assess the prognosis of early conditions [119,153]. Furthermore, some of these tools were designed with the aim of adapting the therapeutic management and improving outcomes, with varying degrees of success [120,122].

A similar approach in CRPS has never been tried, probably because of the lack of established prognostic factors. Importantly, no prospective study has simultaneously included biological, psychological and social factors. In addition, we recently identified four profiles of early CRPS patients characterized by distinct clinical features and outcomes [157], suggesting the existence of multiple pathophysiological mechanisms associated with different clinical trajectories. Their relevance and value in a longitudinal setting have not been assessed yet.

The purposes of the present study were (1) to assess the clinical evolution of early CRPS (defined in this study as < 6 months) during the 12 months following the onset, (2) to investigate potential early prognostic factors covering the span of the biopsychosocial model, potentially leading to the development of a tool allowing clinicians to predict patients' prognosis.

3. Methods

This observational longitudinal study followed the STROBE guidelines [55]. The protocol was approved by the local ethic committee (2022/28FEV/093) and was prospectively registered on ClinicalTrials.gov (NCT05337501). The present study corresponds to the follow-up data of an early CRPS cohort (N = 113) previously published [157].

3.1. PARTICIPANTS

The inclusion procedure was extensively described in [157]. Participants were referred from 28 French-speaking Belgian clinical centres, contacted by phone (MHL) and then included from May 2022 to December 2023, the last follow-up being performed in December 2024.

Inclusion criteria were (1) over 18 years old, (2) meeting the Budapest clinical diagnostic criteria [104], (3) symptoms onset from less than 6 months, (4) CRPS type I or II [92], (5) ability to understand and voluntarily sign an informed consent. Exclusion criteria were (1) insufficient French language skills to answer questionnaires, (2) personal previous history of CRPS at the same limb, (3) post-stroke CRPS type I (*shoulder-hand syndrome*), (4) severe psychiatric or neurological disorders that would interfere with the participants' ability to complete the study tasks.

3.2. PROCEDURES

Most participants were assessed four times in total, at inclusion and during three other sessions respectively at 4.5, 6, and 12 months following the onset of the condition, except for participants included after 4.5 months of condition duration who were assessed three times only (see Fig 1.). Each assessment session lasted approximately 2 hours and involved identical procedures including collection of demographic and clinical data, quantitative sensory testing [225],

and a visuospatial perception task (Temporal Order Judgement task [78]). To reduce the risk of bias, the testing room and the investigator (MHL) were identical for each participant. The subjects received financial compensation for their participation (€25 for each session). If a participant was unable to attend, a phone interview was conducted, and it was proposed to complete the survey at home.

The day after each experimental session, the participant was invited to complete a set of questionnaires at home. He/she was informed that the questionnaires should preferably be completed in one session.

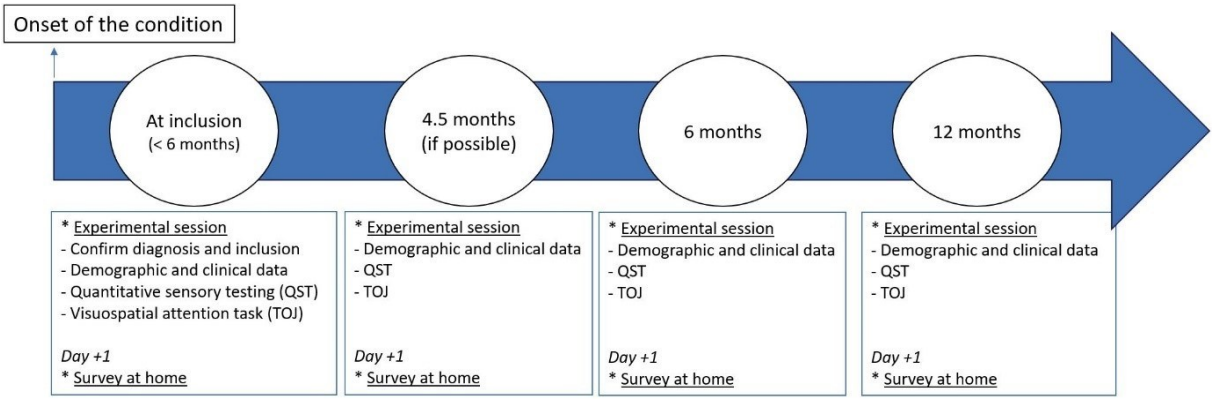

Figure 4.1. ***Study design***.

3.3. MEASURES

The collected data was extensively described in [157]. Briefly, it included (1) demographical data (age, sex, Body Mass Index [BMI], limb dominance, participant-reported comorbidities and related treatments, addictions, education level), (2) work-related variables (professional status, work type [290], medico-legal conflict, work injury), (3) CRPS history (family or personal history of CRPS, physical intensity of the triggering event [14], potential immobilization type and duration, CRPS duration at inclusion, i.e., from the beginning of the symptoms and from the initial event, bone scan results), (4) CRPS clinical variables (localization, and spreading [92], research Budapest criteria [108], CRPS severity score [CSS] [108], neuropathic signs [92], vasomotor signs, sudomotor signs, trophic signs, motor signs, current treatment), (5) revised-Bath-Complex

Regional Pain Syndrome-Body Perception Disturbance Scale (r-B-CRPS-BPDS) [253], (6) Quantitative Sensory Testing (QST) [186,224], (7) Temporal Order Judgement (TOJ) task (point of subjective simultaneity [PSS] and slope [78]).

After each session, participants completed several questionnaires at home to assess functional, psychological and social variables: (1) disability (QuickDASH for upper extremity [19], Lower Extremity functional scale [LEFS] for lower extremity [115]), (2) quality of Life (QoL) (EuroQol-5 dimensions – 5 levels [EQ-5D-5L] [25]), (3) pain severity and interference (Brief Pain Inventory-short form [BPI-SF] [133]), (4) pain-related fear of movement (Tampa Scale of Kinesiophobia-11 [TSK-11] [284]), (5) anxiety and depressive disorders (Hospital Anxiety and Depression Scale [HADS] [289]), (6) psychosocial factors associated with chronification of common MSK pain, labelled in this study *psychosocial severity* (French version of the Örebro Musculoskeletal Pain Screening Questionnaire-short form [ÖMPSQ-SF] [193]), (8) pain coping strategies (Coping Strategies Questionnaire-French version [CSQ] [127]), (7) perceived social support (Social Support Questionnaire-short form [SSQ6] [211]), and (9) "general" pain sensitivity (Pain Sensitivity Questionnaire [PSQ] [68]).

We also categorized patients using profiles determined in our previous study [157] using a latent class analysis [240] based on five baseline characteristics: physical intensity of the triggering event, pressure pain threshold (PPT), r-B-CRPS-BPDS, presence of allodynia (sign), and ÖMPSQ-SF score.

These parameters were chosen to reflect potentially relevant pathophysiological mechanisms of CRPS. The analysis yielded four *Biopsychosocial Early CRPS (BE-CRPS) profiles*, labelled based on their initial characteristics*: Mild CRPS*, *Moderate CRPS*, *Body representation disturbance [BRD] CRPS* and *Pressure allodynia CRPS* (n = 85). While *Mild* and *Moderate CRPS* differed mainly in baseline outcomes (poorer for *Moderate CRPS* than for *Mild CRPS*), *BRD* and

Pressure allodynia CRPS showed the worst clinical profiles, distinguishing across all five LCA variables (Fig. 2, see [157] for details).

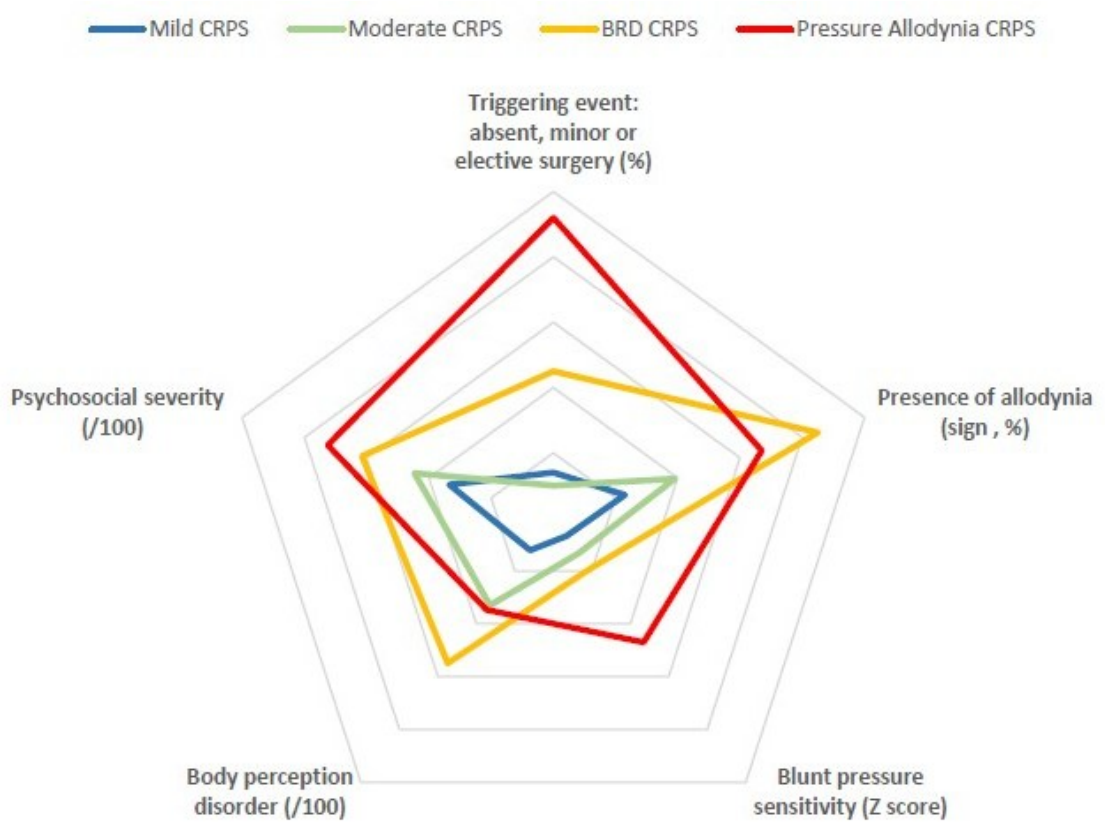

Figure 4.2. Variables entered in the latent class analysis*. Presented on a 0 (centre) to 100 scale for each profile (expressed by a mean or proportion). Triggering events were dichotomized between absent/minor trauma/elective surgery vs. fracture/major trauma requiring surgical repair. The presence of allodynia (sign, any stimulus) is expressed as a rate within each profile. ÖMPSQ-SF score was used to indicate the psychosocial severity, mean pressure pain threshold (Z score, contralateral values normalized by the norms) was multiplied by 10, while body perception disorder corresponds to the mean r-bath-CRPS-BPDS normalized on a /100 scale (original score multiplied by 2.13). Abbreviations ÖMPSQ-SF, Örebro musculoskeletal pain questionnaire – short form; r-B-CRPS-BPDS, revised-Bath-complex regional pain syndrome-body perception disturbance scale.*

3.4.OUTCOMES

The outcome parameters were selected to assess the three components of the ICF [141]: *body function and structure* (CSS, Budapest clinical criteria, pain

intensity), *activity* (pain interference, disability), and *participation* (QoL and RtW). As per the aim of the ICF, the primary outcome was defined as the disability score. RtW outcome was only assessed among participants working prior to CRPS onset (n = 77).

The outcomes were prospectively chosen, except for meeting the Budapest clinical criteria, which was added after the onset of the study, as it was thought to be a relevant add-on to CSS.

3.5. STATISTICAL ANALYSIS

Study data were collected and managed using REDCap electronic data capture tools hosted at the Saint-Luc University Hospital. Statistical analyses were conducted using IBM SPSS Statistics 28, and R software (R × 64 version 4.2.3). A p-value <0.05 was considered statistically significant. The script used to analyse QST results is available at https://github.com/vladaron/CRPS_longitudinal.

Characteristics of the participants were presented using mean and standard deviation (SD) for continuous variables, frequency and percentages for categorical variables. The computation methods of the variables are detailed in the appendix.

TOJ data were excluded from statistical analyses when parameters of the psychometric function could not be reliably estimated during the 40 trials of at least one of the two blocks, suggesting that the participant's performance was too inconsistent or below chance level (see *supplementary section, 3. TOJ procedure*). Accordingly, data from 9 sessions were discarded (inclusion: 5/78; 4.5 months: 1/50; 6 months: 2/69; 1 year: 1/72).

Threshold values were recoded so that the measure of perceptual simultaneity was expressed relative to the affected limb vs. contralateral limb (rather than left vs.

right limb); positive values indicate a perceptual bias to the advantage of visual stimuli presented on the side of the affected limb, negative values to the contralateral limb. Potential systematic bias towards the affected or the contralateral side was investigated comparing mean PSS values to 0 using a one-sample t- test.

We assessed the homogeneity of our sample by investigating significant differences between participants who completed only the home survey and the other participants (all variables at the inclusion, and outcomes at last follow-up). Continuous variables were compared between these two groups using a Student T test or a Mann-Whitney U test according to their distribution, examined with histograms and normal QQ plots. Proportions of categorical variables were compared with a Pearson's Chi-squared test. The same statistical tests were used to explore potential differences between the participants who still met the Budapest clinical criteria and the others at last follow-up. Correlations were assessed using Pearson coefficient.

Differences between time-points were assessed using linear mixed models (LMMs) or generalized LMMs (random intercept for participants, no random slope), depending on the dependent variable (discrete or categorial). For prognostic models, we imputed the missing values (see below). As the aim of the study was to assess the role of early prognostic factors, only baseline value of the predictors was included in those models. An example is provided in the supplementary data section of the chapter (*5. Example of participants' characteristics used in the prognostic models*).

3.5.1. Missing data management for prognostic models

We used a multiple imputation to replace the missing values [151,219] (considered as *missing at random*, i.e., likelihood of being missing is consistent within groups determined by the observed data) of each predictor at the inclusion.

Hence, seventy-five datasets were created using the mice R package [41] and the imputed values were used to compute predictive multivariable models, pooled in a single output.

3.5.2. Building prognostic models

Included variables were selected based on a backward elimination procedure. It was performed with mice for logistic regression and with mitml R package [99] for LMMs, as mice does currently not provide such approach for these models. A complete explanation of the statistical method is available in the supplementary section (*4. Explanation of the building prognostic models method*).

4. Results

Figure 4.3 shows the flowchart of the study. In total, we contacted 158 patients. Eventually, 113 participants performed the inclusion session, while 107 were assessed at the 1-year follow-up (drop-out rate: 5%). The participants were referred by general practitioners (12%, 5 centres), orthopaedists (50%, 9 centres), and physical medicine doctors (38%, 14 centres). During the study, some assessments were only performed remotely (see Fig 2.). Consequently, some data were only collected for part of the cohort: clinical assessment, QST, and TOJ procedure. Participants who were assessed remotely did not significantly differ from the rest of the cohort in terms of demographic or clinical data at the inclusion or in terms of outcomes at 1 year ($p>0.05$; *data not shown*).

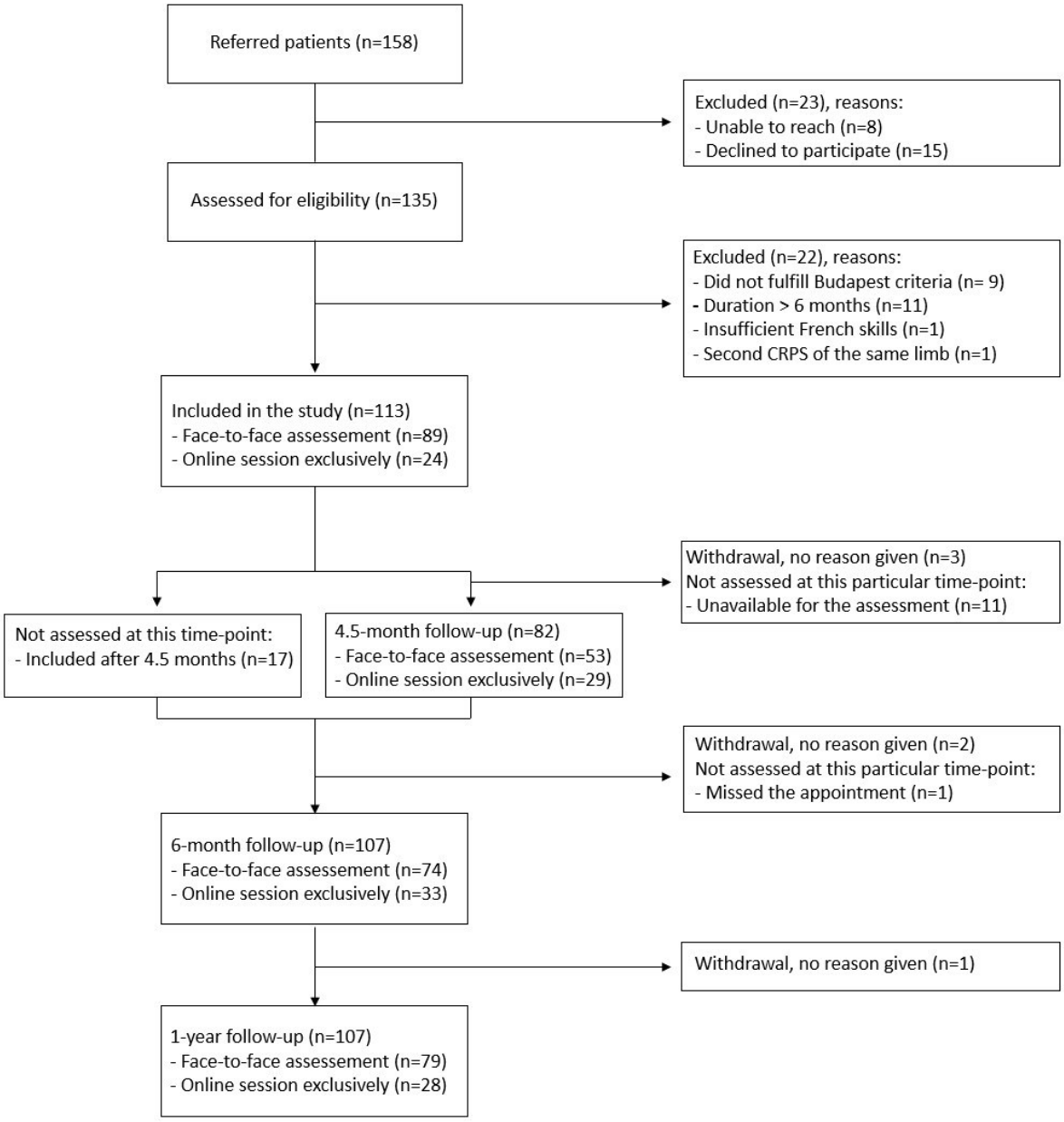

Figure 4.3. ***Flowchart of the study.*** *Note: The number of participants assessed at 6 and 12 months is identical despite one more participant being lost to follow-up at 12 months, due to the inclusion of another participant who was not assessed at the 6-month time point.*

4.1. PARTICIPANTS CHARACTERISTICS

4.1.1. Demographical inclusion variables

An extensive description and analysis of the demographic and inclusion characteristics of the participants is available in [157]. They are briefly summarized in **Table 4.1**.

Variables		***n (%) or mean ± SD (n = 113)***
Sex (women)		87 (77.0)
Age (years)		52.9 ± 13.3
BMI (kg/m^2)		26.2 ± 4.9
Smoking	Currently	24 (21.2)
	Pack-year	8.5 ± 14.3
Alcohol (units per week)		3.0 ± 7.2
Education level (years)		7.8 ± 2.8
History of CRPS	Only personal	13 (11.5)
	Only family	13 (11.5)
	Both	1 (0.9)
Working before CRPS		77 (68.1)
Work type	Not applicable	28 (24.8)
	Minimal physical demands (mentally demanding work)	23 (20.4)
	Mixed physically and mentally demanding work	23 (20.4)
	Light physically demanding work	33 (29.2)
	Heavy physically demanding work	6 (5.3)
Professional status at inclusion	Workers	19 (16.8)
	Medical part-time	5 (4.4)
	Pensioner	23 (20.4)
	Unemployed	5 (4.4)
	Student	2 (1.8)
	Sickness – invalids' beneficiary	59 (52.2)

Work injury			15 (13.3)
Medico-legal conflict with the employer or insurance company			15 (13.3)
Specialization of physician referring participant	Orthopaedic		57 (50.4)
	Physical medicine		43 (38.1)
	General practice		13 (11.5)
Participant-reported comorbidities (previously to CRPS onset)	Chronic pain		18 (15.9)
	Anxiety		5 (4.4)
	Depression		3 (2.7)
	Insomnia		5 (4.4)
	Asthma		4 (3.5)
	Migraine	With aura	6 (5.3)
		Without aura	4 (3.5)
	Diabetes	Type I	2 (1.8)
		Type II	3 (2.7)
	Inflammatory diseases		0 (0)
Localization	UE		67 (59.3)
	- Elbow		- 1 (0.9)
	- Hand / wrist		- 63 (55.8)
	Only fingers		3 (2.6)
	LE		46 (40.7)
	- Knee		- 3 (2.7)
	Foot / ankle		43 (38.0)
Triggering event	Minor incident/no known tissue injury		1 (0.9)
	Soft tissue injury		15 (13.3)
	Elective surgery		26 (23.0)
	Fracture not requiring surgical repair		34 (30.0)
	Major injury requiring surgical repair		37 (32.7)
CRPS duration (days)			75.8 ± 44.1
Duration since triggering event (days)			120.0 ± 51.1
Strict immobilization	None		15 (13.3)
	Cast		76 (67.3)

	Only splint	22 (19.5)
	Duration (weeks) Median [min to max]	4.7 ± 3.0 5 [0 to 15]
CRPS type II		11 (9.7)
Early CRPS profile[1]	Mild CRPS	22 (25.9)
	Moderate CRPS	31 (36.5)
	Body representation disturbance CRPS	20 (23.5)
	Pressure allodynia CRPS	12 (14.1)
Scintigraphy (n = 56)	Positive	48 (85.7)
	No argument for CRPS	8 (14.3)
	Uptake ratio (affected/contralateral) (n = 48)	1.74 ± 0.53

Table 4.1. Baseline characteristics of participants. *Abbreviation: CRPS: complex regional pain syndrome; SD, standard deviation; n, number of participants; BMI, body mass index; UE, upper extremity; LE, lower extremity; [1], based on Louis MH et al. European journal of pain (London, England) vol. 29,2 (2025): e4785. doi:10.1002/ejp.4785.*

4.1.2. Clinical evolution

Table 4.2 shows the CRPS features of the cohort at each assessment. At one year, about 40% of the participants still described constant pain. The most prevalent features were motor changes (85%), while only 22% still reported sweating asymmetry or trophic changes. Regarding the clinical presentation, sweating was rarely observed (4%). However, weakness or reduction of RoM were still found in 75% of the cohort at 12 months. Concerning body perception, participants still presenting an *active* state (i.e., meeting clinical Budapest criteria) reported similar disturbances to the early condition (i.e., mean of the whole cohort at inclusion) or to persistent CRPS [253] (see supplementary section, *6. Supplementary tables - Table S1*).

We did not observe any influence of time on individual r-B-CRPS-BPDS score for participants still meeting the Budapest clinical criteria at 1 year (*effect of the time as a predictor in a univariate LMM: $p > 0.05$, data not shown*). For the whole

cohort, time had a significant effect only at early stages (*effect of time as a predictor in a univariate LMM: $p < 0.05$; post hoc Bonferroni correction: $p < 0.05$ only between inclusion and 6–12 months assessments, data not shown*).

The few participants (n = 11) who underwent surgery of the affected limb during follow up showed similar outcomes than the other patients (*chi-squared and independent t-test, data not shown*).

	Variables		*n (%) or mean ± SD*			
			Inclusion (n=113)	***4.5 months (n=64)***	***6 months (n=86)***	***1 year (n=105)***
Fulfil Budapest research criteria			89 (78.8)	25 (39.1)	38 (44.2)	25 (23.8)
CRPS symptoms	Continuing pain		113 (100.0)	39 (60.9)	49 (57.0)	41 (39.0)
	Hyperalgesia or allodynia		95 (84.1)	41 (64.1)	50 (58.1)	53 (50.5)
	Temperature asymmetry		94 (83.2)	39 (60.9)	48 (55.8)	41 (39.0)
	Skin colour asymmetry		102 (90.3)	45 (70.3)	56 (65.1)	40 (38.1)
	Sweating asymmetry		41 (36.3)	18 (28.1)	22 (25.6)	23 (21.9)
	Swelling asymmetry		112 (99.1)	55 (84.6)	68 (79.1)	65 (61.9)
	Trophic disturbances		62 (54.9)	30 (46.9)	22 (25.6)	26 (24.8)
	Motor disturbances		113 (100.0)	59 (92.2)	83 (96.5)	89 (84.8)
			n=89	*n=53*	*n=74*	*n=79*
Sensory signs	Hyperalgesia to pinprick		54 (60.7)	19 (35.8)	34 (45.9)	24 (30.4)
	Allodynia (any type)		42 (47.2)	11 (20.8)	16 (21.6)	17 (21.5)
	Allodynia to light touch		14 (15.7)	5 (9.4)	6 (8.1)	9 (11.4)
	Allodynia to pressure		26 (29.2)	5 (9.4)	11 (14.9)	15 (19.0)
	Allodynia to cold		8 (9.0)	2 (3.8)	4 (5.4)	9 (11.4)
	Allodynia to joint mobilization		15 (16.9)	3 (5.7)	5 (6.8)	7 (8.9)
	Tactile hypoesthesia		10 (11.2)	4 (7.5)	7 (9.5)	10 (12.7)
	None		20 (22.5)	29 (54.7)	34 (31.5)	46 (58.2)
Temperature sign	Normal		49 (55.1)	33 (62.3)	51 (68.9)	66 (83.5)
	Warmer (≥ 1°C)		24 (27.0)	9 (17.0)	13 (17.6)	6 (7.6)
	Colder (≤ -1°C)		16 (18.0)	11 (20.8)	11 (14.9)	7 (8.9)
	Absolute value (°C) [min to max]		0.2 ± 1.4 [-3.0 to 5.2]	0.0 ± 1.2 [-3.0 to 3.0]	0.5 ± 1.2 [-6.0 to 3.0]	-0.09 ± 0.8 [-3.4 to 2.7]
	Normal		17 (19.1)	19 (35.8)	39 (52.7)	62 (78.5)
Skin colour sign	Reddish		43 (48.3)	18 (33.3)	17 (23.0)	8 (10.1)
	Pale		3 (3.4)	3 (5.6)	5 (6.8)	2 (2.5)
	Bluish		14 (15.7)	8 (14.8)	9 (12.2)	4 (5.1)
	Mottled		12 (13.5)	6 (11.1)	4 (5.4)	3 (3.8)
Sudomotor sign	Sweating		17 (19.1)	3 (5.7)	5 (6.8)	3 (3.8)
	Swelling		80 (89.9)	41 (75.5)	48 (64.9)	34 (43.0)
Trophic signs	None		39 (43.8)	29 (54.7)	54 (73.0)	66 (83.5)
	Skin disturbance		13 (14.6)	8 (15.1)	7 (9.5)	5 (6.3)
	Hypertrichosis		27 (30.3)	10 (10.4)	4 (5.4)	4 (5.1)
	Hypotrichosis		3 (3.4)	2 (3.8)	3 (4.1)	1 (1.3)
	Fingernails abnormalities		28 (31.5)	14 (26.4)	12 (16.2)	7 (8.9)
	Ulcer		1 (1.1)	1 (1.9)	1 (1.4)	0 (0)
Motor signs	None		2 (2.2)	3 (5.7)	7 (6.5)	20 (25.3)
	Tremor		7 (7.9)	1 (1.9)	2 (2.7)	1 (1.3)
	Dystonia		2 (2.2)	0 (0.0)	0 (0)	1 (1.3)
	Restricted RoM		84 (94.4)	48 (90.6)	65 (87.8)	56 (70.9)
	Weakness		82 (92.1)	39 (73.6)	51 (68.9)	44 (55.7)
	Relative strength of the affected side (%)	UE	0.38 ± 0.28 (n=34)	0.62 ± 0.24 (n=24)	0.63 ± 0.27 (n=36)	0.74 ± 0.30 (n=47)
		LE	0.68 ± 0.23 (n=26)	0.84 ± 0.21 (n=12)	0.85 ± 0.21 (n=26)	0.87 ± 0.27 (n=31)
r- Bath-CRPS-BPDS (/47)			15.1 ± 8.2	11.2 ± 8.0	10.5 ± 8.8	9.9 ± 9.4
Visuospatial test	PSS (ms)		3.3 ± 22.3 (n=73)	3.5 ± 29.1 (n=49)	0.5 ± 23.5 (n=67)	5.1 ± 28.9 (n=71)
	Slope		0.04 ± 0.04 (n=73)	0.05 ± 0.06 (n=49)	0.13 ± 0.77 (n=67)	0.05 ± 0.05 (n=71)
			n=113	*n=65*	*n=86*	*n=106*
Treatment	No treatment		0 (0)	8 (12.3)	16 (18.6)	48 (45.3)
	Paracetamol or NSAIDS		70 (61.9)	21 (32.3)	30 (34.9)	21 (19.8)
	Weak opioids		28 (24.8)	9 (13.8)	9 (10.5)	8 (7.5)
	Strong opioids		3 (2.7)	2 (3.1)	2 (2.3)	2 (1.9)

	Atypical analgesics	15 (13.3)	7 (10.8)	10 (11.6)	11 (10.4)
	Topical analgesics	3 (2.7)	4 (6.2)	5 (5.8)	3 (2.8)
	Glucocorticoids	12 (10.6)	0 (0)	1 (1.2)	1 (0.9)
	Bisphosphonates	6 (5.3)	4 (6.2)	3 (3.5)	2 (1.9)
	Physiotherapy (any modality)	104 (92.0)	47 (72.3)	57 (66.3)	42 (39.6)
	Active physiotherapy	72 (63.7)	47 (72.3)	57 (66.3)	32 (30.2)
	Passive physiotherapy	91 (80.5)	42 (64.6)	43 (50.0)	31 (29.2)
	Mirror therapy	17 (15.0)	13 (20.0)	8 (9.3)	6 (5.7)
	Psychotherapy	2 (1.8)	4 (6.2)	7 (8.1)	7 (6.6)
	Multidisciplinary management	12 (10.6)	12 (18.5)	12 (14.0)	8 (7.5)
	Interventional therapy	1 (0.9)	0 (0)	0 (0)	0 (0)
Surgery of the initially affected limb		2 (1.8)	/	/	11 (10.5)

Table 4.2. ***Clinical evolution of CRPS****. For participants assessed remotely, research Budapest criteria were considered when they reported at least one symptom in the four categories of the IASP criteria. Abbreviations: CRPS: complex regional pain syndrome; SD, standard deviation; n, number of participants; UE, upper extremity; LE, lower extremity; r-Bath-CRPS-BPDS, revised-Bath-CRPS-Body perception disturbance scale; PSS, point of subjective simultaneity.*

Table 4.3 shows the biopsychosocial variables from the self-completed questionnaires at each time-point (excluding outcomes, presented in the following section). Most variables improved over time (*effect of the time in univariate LMMs: $p<0.05$*).

Variables			***n (%) or mean ± SD***				
			Inclusion (n=113)	*4.5 months (n=82)*	*6 months (n=107)*	*1 year (n=105)*	*P-value*
General self-rated health (n=105 for inclusion)	Excellent		4 (3.8)	3 (3.8)	5 (4.7)	3 (2.8)	<.001
	Very good		9 (8.6)	15 (18.8)	20 (18.7)	24 (22.4)	
	Good		36 (34.3)	26 (32.9)	33 (30.8)	38 (35.5)	
	Fair		31 (29.5)	26 (32.9)	33 (30.8)	26 (24.1)	
	Poor		25 (23.8)	9 (11.4)	16 (15.0)	16 (15.0)	
Pain-related fear of movement (/44)			31.0 ± 6.7	28.8 ± 7.5	28.7 ± 7.9	26.8 ± 8.4	<.001
HADS anxiety	Potential disorder (≥8)		70 (61.9)	43 (52.4)	53 (49.5)	49 (45.8)	<.001
	Probable disorder (≥11)		43 (38.4)	25 (30.5)	33 (30.8)	32 (29.9)	NS
	Score (/21)		9.4 ± 4.3	8.4 ± 4.2	8.0 ± 4.2	7.7 ± 4.2	<.001
HADS depression	Potential disorder (≥8)		48 (42.5)	33 (40.2)	33 (30.8)	30 (28.3)	0.002
	Probable disorder (≥11)		29 (25.7)	17 (20.7)	22 (20.6)	12 (11.3)	<.001
	Score (/21)		7.2 ± 4.4	6.2 ± 4.4	6.4 ± 4.5	5.7 ± 4.4	<.001
OMPSQ-SF	Total score (/100)		49.6 ± 17.9	42.6 ± 20.1	43.4 ± 19.6	38.8 ± 21.1	<.001
	Psychosocial risk of chronification	Low	34 (30.1)	35 (42.7)	44 (41.5)	56 (52.3)	<.001
		Medium	20 (17.7)	15 (18.3)	19 (17.9)	15 (14.0)	
		High	59 (52.2)	32 (39.0)	43 (40.6)	36 (33.6)	
Coping strategies to deal with pain	Distraction (/4)		2.7 ± 0.7	2.8 ± 0.7	2.7 ± 0.7	2.8 ± 0.7	NS
	Catastrophizing (/4)		1.9 ± 0.6	1.8 ± 0.6	1.9 ± 0.7	1.8 ± 0.7	<.001
	Ignoring painful sensations (/4)		2.1 ± 0.6	2.3 ± 0.7	2.2 ± 0.7	2.4 ± 0.8	<.001
	Distancing from pain (/4)		1.7 ± 0.7	1.7 ± 0.7	1.7 ± 0.7	1.8 ± 0.7	NS
	Praying (/4)		1.9 ± 0.9	1.8 ± 0.9	1.8 ± 0.9	1.7 ± 0.9	<.001
Perceived social support	Availability (0 to 54)		24.9 ± 14.4	25.1 ± 14.9	23.6 ± 14.6	23.7 ± 14.3	NS
	Satisfaction (6 to 36)		29.0 ± 7.3	29.0 ± 7.5	28.8 ± 7.7	29.1 ± 7.3	NS
Pain sensitivity	Total score (/10)		5.0 ± 1.9	5.0 ± 1.9	5.4 ± 2.0	5.0 ± 2.0	.040
	Minor score (/10)		3.8 ± 2.0	3.8 ± 2.0	4.2 ± 2.2	3.8 ± 2.1	.024

Table 4.3. ***Questionnaires filled at home (with the exception of outcomes).*** *P-value expressed the significance of the factor "time" (corresponding to each time-point) in simple mixed effect models only including the time as predictors. Abbreviations: CRPS: complex regional pain syndrome; SD, standard deviation; n, number of participants; UE, upper extremity; LE, lower*

extremity; EQ, EuroQol; VAS, visual analogic scale; HADS, hospital anxiety depression scale; ÖMPSQ-SF, Örebro Musculoskeletal Pain Screening Questionnaire-short form; NS, not significant.

For the sake of completeness, comparisons between patients still meeting Budapest clinical criteria at 1 year with other patients for CRPS features and self-reported variables are available in the supplementary section (*6. Supplementary tables*).

4.1.3. QST results through 1-year

The sensory profile was fully assessed in 274 sessions (inclusion: n = 80; 4.5 months: n = 51; 6 months: n = 69; 12 months: n = 74). For logistic reasons, it was only possible to collect part of the QST data for some other sessions (n = 15).

Figure 4.4 summarizes the sensory profiles of participants at each time-points. **Table 4.4** presents the normalized QST values by modality, and the potential effect of time, side, and their interaction on the different QST variables.

For the sake of brevity, results from 4.5 months follow-up were not presented in the tables and figures (but included in the LMMs). The raw values of each time-point are also available in the appendix, with the number of participants for each assessment and modality.

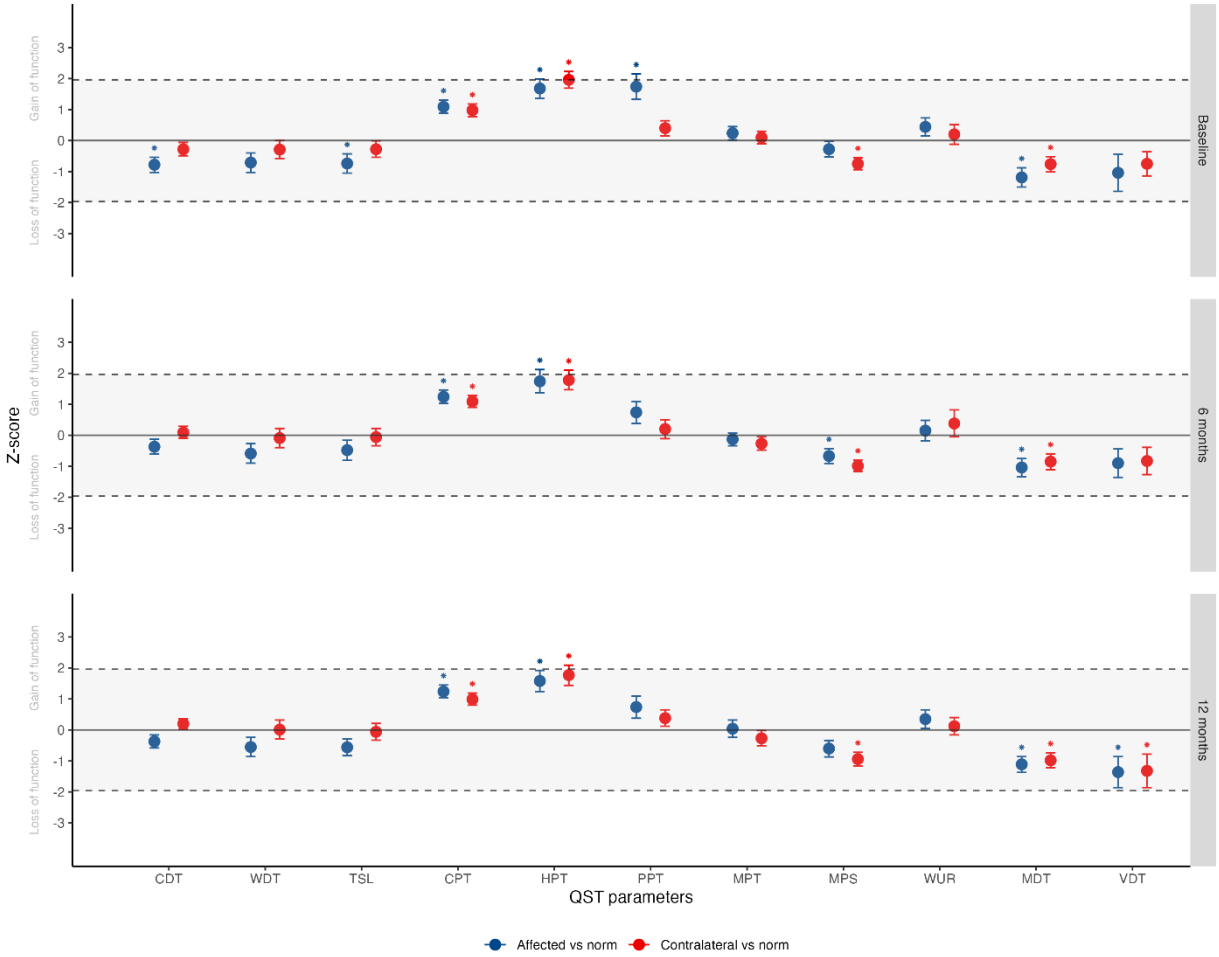

Figure 4.4. ***Sensory profiles of participants in comparison with healthy volunteers (German normative values), at different time-points****. Mean and CI95 (Z-scores). Values from the affected limb and the contralateral side were normalized by the normative values (in blue and red, respectively)* [162]. *Abbreviations: *, p value < 0.05 after Bonferroni correction; CDT, Cold detection threshold; WDT, Warm detection threshold; TSL, Thermal sensory limen; PHS, Paradoxical heat sensation; CPT, Cold pain threshold; HPT, Heat pain threshold; MDT, Mechanical detection threshold; MPT, Mechanical pain threshold; MPS, Mechanical pain sensitivity; DMA, Dynamic mechanical allodynia; WUR, Wind-up ratio; VDT, Vibration detection threshold; PPT, Pressure pain threshold.*

Globally, participants, in comparison to normative data from healthy subjects [162], were characterized by increased sensitivity to thermal painful stimuli (CPT and HPT) and blunt pressure (PPT), as well as a reduced sensitivity to non-painful thermal stimuli (CDT, WDT, and TSL) and to some mechanical stimuli (MPS, MDT, and VDT).

QST modalities		T1 (n=80)		T3 (n=69)		T4 (n=74)		Time	Side	Time X Side
		Aff	Cont	Aff	Cont	Aff	Cont			
		Mean ± SD						*p-value*		
CDT		-0.78 ± 1.37	-0.28 ± 1.18	-0.37 ± 1.17	0.09 ± 0.97	-0.37 ± 1.08	0.2 ± 0.86	**<.001**	**<.001**	.890
WDT		-0.71 ± 1.73	-0.29 ± 1.59	-0.59 ± 1.61	-0.09 ± 1.57	-0.55 ± 1.6	0.01 ± 1.59	**.024**	**<.001**	.858
TSL		-0.74 ± 1.65	-0.28 ± 1.44	-0.48 ± 1.63	-0.06 ± 1.4	-0.56 ± 1.39	-0.06 ± 1.41	**.009**	**<.001**	.963
PHS (%)		11.2%	8.7%	17.4%	1.4%	11%	5.5%	.815	**<.001**	.180
CPT		1.09 ± 1.19	0.98 ± 1.15	1.24 ± 1.1	1.09 ± 0.95	1.24 ± 1.07	0.99 ± 1.02	.148	**.004**	.833
HPT		1.68 ± 1.75	1.96 ± 1.5	1.74 ± 1.9	1.78 ± 1.59	1.58 ± 1.76	1.77 ± 1.71	.645	**.017**	.766
MDT		-1.19 ± 1.7	-0.76 ± 1.33	-1.04 ± 1.49	-0.85 ± 1.27	-1.11 ± 1.33	-0.98 ± 1.26	.243	**.001**	.238
MPT		0.24 ± 1.15	0.1 ± 1.1	-0.13 ± 1.03	-0.27 ± 1.08	0.04 ± 1.45	-0.27 ± 1.3	**.007**	.067	.535
MPS		-0.28 ± 1.38	-0.75 ± 1.07	-0.67 ± 1.22	-0.99 ± 0.94	-0.6 ± 1.41	-0.94 ± 1.16	**.002**	**<.001**	.684
DMA	(log)	-0.85 ± 0.50	-1 ± 0	-0.89 ± 0.47	-1 ± 0	-0.87 ± 0.51	-1 ± 0	.766	**<.001**	.141
	(%)	12.3%	0%	5.7%	0%	6.7%	0%	.151	**<.001**	**.017**
WUR		0.44 ± 1.29	0.2 ± 1.27	0.15 ± 1.3	0.38 ± 1.56	0.35 ± 1.19	0.12 ± 1.01	.820	.436	.127
VDT		-1.04 ± 3.32	-0.75 ± 2.16	-0.9 ± 2.36	-0.83 ± 2.27	-1.36 ± 2.63	-1.32 ± 2.86	**<.001**	.737	.523
PPT		1.74 ± 2.28	0.4 ± 1.38	0.74 ± 1.85	0.2 ± 1.59	0.74 ± 1.89	0.38 ± 1.41	**<.001**	**<.001**	**.002**

Table 4.4. Z-scores of each QST modality at different time-points*. PHS and DMA are expressed as a proportion of subjects showing abnormalities, other values correspond to mean and standard deviation of CRPS participants, normalized using normative values of healthy subjects* [162]*. P values expressed the potential effect of time (as a factor), side, and their interaction on the different QST variables (mixed effect models with random intercept and fixed slope, using the four time-point assessments, without imputation). Abbreviations: QST, quantitative sensory testing; T1, inclusion; T3, 6 months; T4, 1 year; n, number of participants with fully assessed QST. Part of modalities were collected for 15 others. Aff, affected side; Cont, contralateral side; Time X Side, interaction between time and side; CDT, Cold detection threshold; WDT, Warm detection threshold; TSL, Thermal sensory limen; PHS, Paradoxical heat sensation; CPT, Cold pain threshold; HPT, Heat pain threshold; MDT, Mechanical detection threshold; MPT, Mechanical pain threshold; MPS, Mechanical pain sensitivity; DMA, Dynamic mechanical allodynia; WUR, Wind-up ratio; VDT, Vibration detection threshold; PPT, Pressure pain Threshold.*

The LMMs results showed that thermal pain thresholds, MDT, DMA, and WUR were stable over the one-year period. Conversely, time significantly influenced the individual values of CDT, WDT, TSL, MPT, MPS, VDT, and PPT. In post-hoc analyses, we only observed a significant difference between the inclusion values and some other time-points, mostly at 1 year follow-up (at 4.5

months: CDT, TSL; at 6 months: CDT, MPT, MPS, PPT; at 12 months: CDT, WDT, TSL, MPT, MPS, VDT and PPT). No difference between any other time-points was found.

Regarding the effect of side (CRPS limb versus contralateral limb), most of the QST modalities differed significantly between the affected and the contralateral limb, regardless of the time-point (exceptions: HPT, MDT, and WUR).

Finally, only PPT and DMA (presence vs. absence of abnormal value) were significantly impacted by a different effect of time depending on side. In pairwise comparisons, we observed a significant difference between the PPT values at inclusion and the three other time-points for the affected side (reduction of the gain of function), but no significant difference for the contralateral side. Similarly, we observed different rates of abnormal DMA between the inclusion and 4.5 months, but not for the control side.

4.1.4. Temporal order judgment task

As in our inclusion data [157], we did not observe any systematic bias in visuospatial perception (whole cohort, upper or lower limb groups) for any of the follow-up time-points (*$p>0.05$, data not shown*). At follow-ups, none of the early CRPS profiles exhibited significant bias (*$p>0.05$, data not shown*). Furthermore, we did not find any significant correlation between the computed PSS values and the r-Bath-CRPS-BPDS score for any time-point. Eventually, the individual scores were stable at follow-up (*effect of time as factor in a univariate LMM: $p>0.05$, data not shown*).

4.2. CRPS OUTCOMES AT 12 MONTHS

Table 4.5 and **Figure 4.5** summarize the evolution of each outcome (except for RtW, see below). It should be noted that participants included during the 3

months following CRPS onset did not report different outcomes at any follow-ups than those included between 3 and 6 months (*independent t-test without correction: p>0.05; data not shown*). A comparison of outcomes according to the presence or absence of Budapest clinical criteria at 1 year is available in the supplementary section (*6. Supplementary tables – Table S3*).

On average, we observed a progressive improvement of CRPS, although complete resolution was not achieved in most of the participants. At 1 year, 35% of the cohort still met the clinical Budapest criteria, with a mean CSS of 5.8. The average reported pain (either intensity or interference) remained above 3/10. Disability scores showed persistent impairment at the cohort level, and overall, QoL remained affected. Lastly, the large SD for each outcome underlines the considerable variability among CRPS patients' outcomes.

Variables			***n (%) or mean ± SD***			
			Inclusion (n=113)	*4.5 months (n=82)*	*6 months (n=107)*	*1 year (n=107)*
Body function and structures	**CRPS severity score (/16)**		11.5 ± 2.2 (n=89)	8.9 ± 2.9 (n=53)	8.1 ± 3.2 (n=74)	5.8 ± 4.0 (n=79)
	Meeting Budapest clinical criteria		113 (100.0)	35 (53.8) (n=64)	43 (50.0) (n=86)	37 (34.9) (n=105)
	Pain intensity (/10)		4.7 ± 2.3	4.1 ± 2.3	4.2 ± 2.4	3.8 ± 2.6
Activities	**Pain interference (/10)**		4.9 ± 2.3	3.6 ± 2.5	3.8 ± 2.7	3.2 ± 2.7
	Disability	**Z-score**	0 ± 1	-0.79 ± 1.13	-0.94 ± 1.14	-1.46 ± 1.13
		UE (/100)	62.6 ± 19.3 (n=67)	49.2 ± 20.7 (n=47)	45.5 ± 21.2 (n=64)	34.8 ± 21.6 (n=63)
		LE (/80)	47.2 ± 15.6 (n=46)	32.9 ± 18.8 (n=35)	31.2 ± 18.9 (n=43)	23.9 ± 17.9 (n=44)
Participation	**Quality of life**	**EQ index (/1)**	0.51 ± 0.30	0.64 ± 0.28	0.68 ± 0.26	0.74 ± 0.24
		EQ VAS (/100)	53.0 ± 21.5	63.5 ± 19.7	64.7 ± 21.0	69.8 ± 19.6

Table 4.5. Evolution of the outcomes over 1-year period. *Abbreviations: CRPS: complex regional pain syndrome; SD, standard deviation; n, number of participants; UE, upper extremity; LE, lower extremity; EQ, EuroQol; VAS, visual analogic scale.*

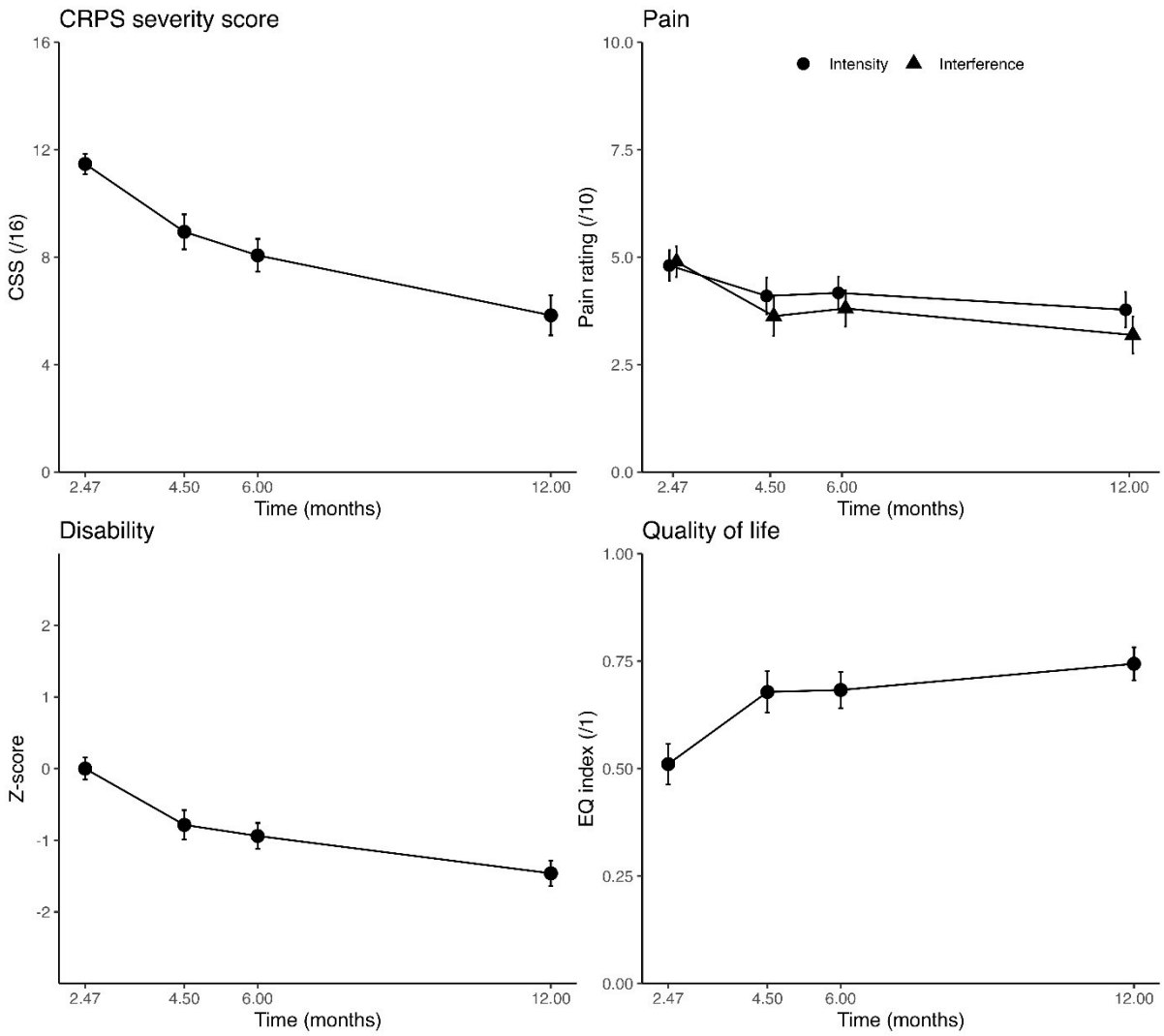

Figure 4.5. Evolution of the different continuous outcomes for the whole sample*. Mean and CI95. For graphical representation, the starting point was considered as the mean CRPS duration at the inclusion (2.47 months).*

To better characterize the impact of CRPS on QoL, we compared EQ-5D-5L results from our cohort (both at baseline and at the 1-year follow-up) with Belgian normative data [266], and with a cohort of patients with chronic pain (symptom duration >12 months) followed in primary care settings [156] (see supplementary material, Table S11).

Compared to normative values, all CRPS subgroups (early, persistent, and whole cohort at 12 months) showed significantly worse outcomes across all EQ-5D-5L dimensions, EQ-index, and EQ-VAS ($p < 0.001$; *Chi-squared test and*

independent t-test). When compared to primary care chronic pain patients, early and persistent CRPS participants reported greater difficulties in self-care and usual activities ($p < 0.001$, *Chi-squared test*) than chronic pain patients. At 12 months, the EQ-5D-5L dimensions of the whole CRPS QoL were similar to those of the chronic pain cohort, except for lower pain/discomfort and anxiety/depression. EQ-index and EQ-VAS scores remained lower in early and persistent CRPS compared to other chronic pain patients ($p < 0.05$, *independent t-test*), whereas the overall 12-month CRPS cohort showed no significant difference, suggesting partial recovery over time.

Regarding working status (Table 4.6), 61.5% of people who had been active before CRPS onset had returned to work at 6 months, and 69% (n = 48/70) at 1 year. Among participants back to work, 13% (n = 6) had reduced the physical demands of their work, and two took a part-time job due to CRPS.

Variables		***n (%) or mean ± SD***			
		Inclusion (n=77)	4.5 months (n=55)	6 months (n=65)	1 year (n=70)
Has returned to work (%)		23 (29.9)	29 (52.7)	40 (61.5)	48 (68.6)
Working status (%)	Worker	18 (23.4)	25 (45.5)	34 (52.3)	46 (65.7)
	Medical part-time	5 (6.5)	4 (7.3)	6 (9.2)	2 (2.9)
	Pensioner	3 (3.9)	0 (0)	1 (1.4)	2 (2.9)
	Student	2 (2.6)	2 (3.6)	1 (1.4)	2 (2.9)
	Unemployed	1 (1.3)	2 (3.6)	1 (1.5)	2 (2.9)
	Sickness	48 (62.3)	22 (40.0)	22 (33.8)	16 (22.9)

Table 4.6. Work status of participants previously working before CRPS onset, during the follow-up period*. Abbreviations: CRPS: complex regional pain syndrome; SD, standard deviation; n, number of participants assessed at particular time-point (among those working prior the CRPS onset).*

Finally, we investigated the clinical evolution of CRPS participants according to their *BE-CRPS profiles* formerly identified with a LCA analysis [157], represented in **Figure 4.6**. **Table 4.7** presents the outcomes of participants at 12 months, depending on this classification.

First, we observed a similar improvement for all outcomes (i.e., similar slopes) regardless of the profile (*effect of the interaction of time x outcomes in LMMs: $p>0.05$*). Second, their outcomes remain distinct at every time-point (*Kruskal-Wallis Test for every outcome at each time-point: $p<0.05$*). At 12 months, this difference was most prominent between the *Mild* profile and the severe profiles (i.e. *BRD* and *Pressure allodynia CRPS), the latter profiles* reporting the poorest outcomes at 1 year, still more pejorative than the values of *Mild* or even *Moderate CRPS* profiles at inclusion (see **Table 4.7**).

It should be noted that the proportion of participants who returned to work at 12 months was not significantly different between the profiles.

Variables			*n (%) or mean ± SD*				*p-value*
			Mild CRPS (n=21)	*Moderate CRPS (n=31)*	*Severe CRPS (n=30)*		
					BRD CRPS (n=18)	*Pressure allodynia CRPS (n=12)*	
Body function and structures	**CRPS severity score (/16)**		3.4 ± 3.1†˟ (n=21)	5.6 ± 3.7 (n=29)	7.7 ± 3.5† (n=17)	9.0 ± 4.8˟ (n=10)	**<.001**
	Clinical Budapest criteria		2 (9.5)†˟	6 (19.4)▪§	12 (66.7)†§	8 (66.7)˟▪	**<.001**
	Pain intensity (/10)		2.7 ± 2.0†˟	3.2 ± 2.5▪§	5.4 ± 2.7†§	5.8 ± 2.1˟▪	**<.001**
Activities	**Pain interference (/10)**		2.0 ± 2.1†˟	2.4 ± 2.6▪§	4.5 ± 2.4†§	5.0 ± 2.3˟▪	**<.001**
	Disability	**Z-score**	-2.24 ± 0.93†˟	-1.66 ± 0.81▪	-0.69 ± 1.28†	-0.56 ± 0.88˟▪	**<.001**
		UE (/100)	24.1 ± 19.2†˟ (n=15)	31.9 ± 17.7 (n=18)	50.7 ± 23.5† (n=10)	55.9 ± 8.1˟ (n=5)	**.004**
		LE (/80)	2.7 ± 3.3†˟ (n=10)	19.5 ± 10.3 (n=13)	35.0 ± 22.4† (n=8)	36.0 ± 17.3˟ (n=7)	**.002**
Participation	**Quality of life**	**EQ index (/1)**	0.89 ± 0.16†˟	0.80 ± 0.18	0.57 ± 0.28†	0.59 ± 0.29˟	**<.001**
		EQ VAS (/100)	78.7 ± 16.4˟	69.4 ± 22.1	68.1 ± 17.6	56.9 ± 20.5˟	**.013**
	Return to work		12 (80.0) (n=15)	17 (73.9) (n=23)	8 (66.7) (n=12)	2 (28.6) (n=7)	.093

Table 4.7. Outcomes at 1 year according to early CRPS profiles*. The p-values correspond to Kruskal-Wallis or Chi-squared test. Abbreviations: † or ˟ or ▪, significant pairwise comparisons (adjusted by the Bonferroni correction); CRPS, complex regional pain syndrome; SD, standard deviation; n, number of participants; BRD, body representation disturbance; UE, upper extremity; LE, lower extremity; EQ, EuroQol; VAS, visual analogic scale.*

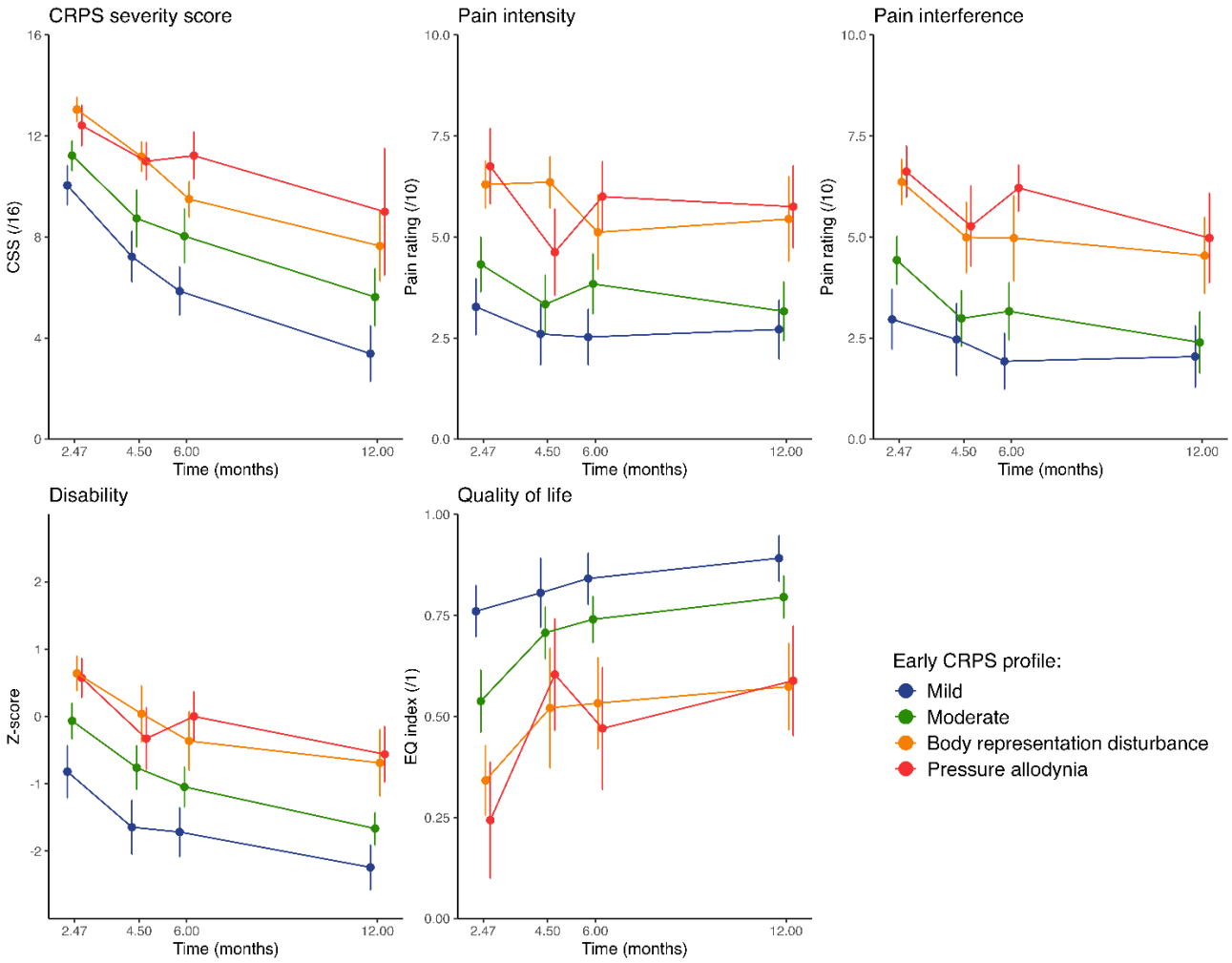

Figure 4.6. ***Evolution of each Biopsychosocial Early CRPS (BE-CRPS) profile.*** *Mean and CI95. For graphical representation, the starting point was considered as the mean CRPS duration at the inclusion (2.47 months).*

4.3. EARLY PROGNOSTIC FACTORS IN CRPS

4.3.1. General considerations

Due to its length, the description of the potential predictive value of each variable in a simple multivariable model (see methods section for further details) is available upon request or via the following link (https://osf.io/5qz2w/?view_only = 7d52ddac7e124297ab38c0b1f463bcd4). In the following sections, we only present the final multivariable models (**Table 4.8**).

Given their potential subtending pathophysiological mechanisms and clinical applications (e.g., therapeutic targets), we choose to include the *BE-CRPS profiles* into the multivariable analyses. Therefore, the five variables used to design the profiles (ÖMPSQ, r-B-CRPS-BPDS, presence of allodynia, physical intensity of the triggering event, and PPT of the affected limb) were not considered as separate potential predictors. It should be noted that many biopsychosocial variables were highly associated with CRPS evolution in the *univariate* analyses (e.g., pain-related fear of movement, catastrophizing, ÖMPSQ, depressive and anxiety disorders, pain, general self-rated health, EQ index and EQ VAS, etc.). Since ÖMPSQ has been already used to create the profiles, the disability score was chosen as an *umbrella* variable for biopsychosocial factors, gathering several concepts and strongly correlated with others meaningful biopsychosocial predictors. Furthermore, it was put forward as a potential early prognostic factor in previous research [158].

Regarding early treatment, our protocol was not designed to assess the potential predictive value of therapeutic modalities [219]. For instance, some analgesics were associated with poorer outcomes (as already described in [16]); it was probably a reflection of the severity of the condition rather than a prognostic factor in itself. Surprisingly, vitamin C (n = 55) was associated with a reduced pain over time in the simple multivariable models, while participants doing

physiotherapy (n = 104) at the inclusion presented an improvement of certain outcomes over time in comparison to the other subjects. More specifically, this association was observed with strengthening and stretching modalities rather than TENS or passive physiotherapy (e.g., massage). Other early therapeutic modalities showed no impact on the prognosis (e.g., glucocorticoids [n = 12], bisphosphonates [n = 6], mirror therapy [n = 17], or multidisciplinary management [n = 12]). Nevertheless, due to the inherent bias in the assessment method (self-reporting, assessed a specific time-point), and the potential confounding effect with other predictors, the treatment variables were not included in the final multivariable analyses.

Prognostic factors (values at T1)		Outcomes																									
		Body structure and function											*Activities*								*Participation*						
		CRPS severity score				**Clinical Budapest criteria**			**Pain intensity**				**Pain interference**				**Disability**				**Quality of life**				**Return to work** (ÖMPSQ model)		
		***β*^{Std}**	***β***	***SE***	***P***	***OR***	***95CI***	***P***	***β*^{Std}**	***β***	***SE***	***P***	***β*^{Std}**	***β***	***SE***	***P***	***β*^{Std}**	***β***	***SE***	***P***	***β*^{Std}**	***β***	***SE***	***P***	***OR***	***95CI***	***P***
Time (months)		/	-.729	.134	**<.001**		*Not included*		/	-.181	.080	**.024**	/	-.314	.080	**<.001**	/	-.252	.028	**<.001**	/	.051	.008	**<.001**		*Not included*	
Time² (months²)		/	.018	.010	**<.001**		*Not included*		/	.007	.006	.251	/	.012	.006	**.033**	/	.009	.002	**<.001**	/	-.002	.001	**<.001**		*Not included*	
Age (year)		-.010	-.003	.015	.862	1.01	.97 – 1.05	.590	.026	.005	.008	.513	.039	.008	.011	.462	.012	.001	.004	.775	-.111	-.001	.001	.285	.97	.92 – 1.03	.329
Sex (ref=female)		/	.473	.471	.315	1.26	.37 – 4.34	.717	/	-.390	.243	.113	/	.127	.329	.698	/	-.021	.123	.862	/	-.034	.030	.262	1.13	.17 – 7.52	.150
Limb (ref=UE)		/	.252	.410	.538	.87	.40 – 3.30	.793	/	.029	.214	.904	/	.076	.296	.798	/	.022	.111	.842	/	-.033	.027	.213	.89	.90 – .97	.401
Baseline values																											
Outcome variable		.162	.294	.098	**.003**	/	/	/	/	.504	.570	.052	**<.001**	.592	.592	.077	**<.001**	.718	.818	.051	**<.001**	.618	.494	.058	**<.001**	/	/	/	/
Disability		.177	.706	.229	**.002**																	-.158	-.038	.017	**.024**		*Not included*	
Early CRPS profiles (ref=Mild CRPS)	Moderate CRPS	/	.587	.533	.271	1.85	.40 – 9.19	.454	/	.180	.287	.530	/	.208	.400	.603											
	BRD CRPS	/	1.450	.650	**.026**	11.58	2.15 – 62.22	**<.001**	/	.896	.330	**.007**	/	.899	.481	.062										*Not included*	
	Pressure allodynia CRPS	/	1.834	.720	**.011**	9.49	1.58 – 56.80	**.016**	/	.853	.377	**.024**	/	1.302	.533	**.015**											
BMI						1.21	1.01 – 1.24	**.031**	.100	.053	.022	**.012**					.108	.025	.010	**.014**	-.123	-.006	.003	**.019**			
CSQ ignoring painful sensations									-.099	-.427	.171	**.015**															
SSQ availability																	-.114	-.009	.004	**.011**							
HADS anxiety score																					-.143	-.008	.003	**.013**			
ÖMPSQ score		*Not included*				*Not included*			*Not included*				*Not included*				*Not included*				*Not included*				.96	.93 – .99	**<.001**
R² (MVP)		**0.482**				/			**.505**				**.447**				**.664**				**.538**				/		

Table 4.8. ***Early prognostic factors identified in multivariable analyses.*** *Linear mixed models with random intercept and time, time², age, sex, and limb and relevant variable(s) (see methods section for selection) as fixed factor in each model; with the exception of binary outcome where a binary logistic regression was performed. Time was therefore not included as covariate in these two models. The "outcome variable" corresponded to the baseline value of the investigated outcome (e.g., for pain intensity, the baseline pain intensity; see Methods section for details). "Blank section" referred to variables that were removed during the selection stage. Abbreviations: T1, inclusion; β^{Std}; estimate standardized; β,*

estimate; SE, standard error; p: p-value in final multivariate model; OR, odds ratio; 95CI, 95% confidence interval (lower – upper); RtW, return to work; ref, reference value; UE, upper extremity; BMI, body mass index; CSQ, coping strategies questionnaire; SSQ, social support questionnaire; HADS, hospital anxiety depressive scale; ÖMPSQ, Örebro musculoskeletal pain screening questionnaire; Not included, not included in the multivariate model for theorical and statistical reasons (see methods section for further explanations); UE, upper extremity; R2 (MVP): proportion of variance of the dependent variable explained by the model.

4.3.2. Predictors of CSS and clinical Budapest criteria (body function and structure in ICF classification)

The following variables were independently associated with CSS regardless of the time-point: *baseline CSS*, *baseline disability*, and *BE-CRPS profiles*. The model explained 48% of the variance of the dependent variable. In brief, *severe BE-CRPS profiles*, higher *CSS* and *disability* at an early stage were associated with higher CSS at every time-point.

For the presence or absence of clinical Budapest criteria at 12 months, *BE-CRPS profiles* (severe profiles [*BRD* or *Pressure allodynia CRPS*] in comparison with *Mild CRPS*), and *BMI* were independent predictors of this dichotomic outcome in a logistic regression model. In summary, *higher BMI* and *severe BE-CRPS profiles* were linked to a greater likelihood of still meeting Budapest criteria after one year.

4.3.3. Predictors of pain intensity (body function and structure in ICF classification)

Baseline pain intensity score, *BE-CRPS profiles*, *BMI*, and *baseline CSQ ignoring painful sensations* appeared to be independent early prognostic factors in multivariable model. Fifty percents of pain intensity variance was explained by these variables. In short, individuals with *Mild CRPS profile*, *lower BMI*, and a *tendency to disregard painful sensations* reported lower pain ratings at each assessment.

4.3.4. Predictors of pain interference (activities in ICF classification)

Two variables were enough to explain 45% of the variance of pain interference evolution regardless of the time-point: *baseline pain interference score* and *BE-CRPS profiles*.

4.3.5. Predictors of disability (activities in ICF classification)

Baseline disability score, *BMI*, and *social support (availability)* were identified as independent early prognostic factors. The model achieved to explain 66% of the disability variance through the four time-points. To put it succinctly, *higher disability*, *BMI* and *lower social support* at baseline were associated with higher disability during 1-year follow-up.

4.3.6. Predictors of quality of life (participation in ICF classification)

Four variables were independently associated with the QoL whatever the time-point: *BMI*, *baseline EQ index*, *disability*, and *anxiety scores*. The model explains 54% of the QoL variance. Overall, a *lower EQ index*, along with *higher disability*, *anxiety*, and *BMI*, were predictors of reduced quality of life at each time point.

4.3.7. Predictors of return to work (participation in ICF classification)

As the *BE-CRPS profiles* were not influencing RtW in the *univariate* logistic regression model, we included the variables initially used to create the profiles (if they were significant in preliminary simple multivariable models). We identified that the baseline *ÖMPSQ score* was the only independent variable associated with the likelihood of returning to work during the first year following the CRPS onset.

4.3.8. Models without biopsychosocial early CRPS profiles

To evaluate if the *BE-CRPS profiles* had an added value to predict evolution when compared with more *classical* predictors, we also ran the analysis where profiles data were replaced by the five variables used to generate the *BE-CRPS profiles*. For the sake of completeness, we have presented these models in the supplementary sections (*6. Supplementary tables – Table S9*). We observed a significant predictive value of the *ÖMPSQ score* for all outcomes, and of the

presence of allodynia for some. The identified prognostic factors and percentage of explained variance were similar to the models including the *BE-CRPS profiles*.

4.3.9. Variables with an absence of evidence

In **Table 4.9**, we regrouped the variables with an absence of significative prognostic value (p>0.010), in simple multivariable models for any of the tested outcomes. Among others, initial *skin temperature* was not associated with any outcome.

Demographical variables	Age (among adults)
	Sex
	Smoking habits (pack-year)
CRPS features	CRPS duration (onset or since triggering event, in days)
	CSS sign temperature (abnormal vs. normal)
	Skin temperature (continuous)
	CSS sign skin color (abnormal vs. normal)
	CSS sign motor (present vs. absent)
Neurocognitive features	TOJ PSS
CRPS classifications	Family history of CRPS
Psychosocial variables	CSQ distraction
	PSQ minor
	PSQ total score
Early treatments	Bisphosphonates (n=6)
	Glucocorticoids (n=12)
	Acetylcysteine (n=18)
	Vitamin D (n=38)
	Contrast baths (n=32)
	Mirror therapy (n=17)
	Passive physiotherapy (n=89)
	Multidisciplinary management (n=12)
QST modalities (Z-scores)	CDT (control side)
	WDT (control side)
	TSL (control side)
	HPT (affected and control sides)
	MDT (affected and control side)
	MPT (affected and control sides)
	WUR (affected and control sides)
	VDT (control side)

Table 4.9. Variables with an absence of evidence in simple multivariate models. *Abbreviations: QST, quantitative sensory testing; CRPS, complex regional pain syndrome; N,*

number of subjects presenting this characteristic in the inclusion cohort; CSS, CRPS severity score; TOJ, temporal order judgement task; PSS, point of subjective simultaneity; CSQ, coping strategies questionnaire; PSQ, pain sensitivity questionnaire; CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical painful threshold; WUR, wind-up ratio; VDT, vibration detection threshold.

5. Discussion

We conducted a comprehensive, prospective, observational analysis of 113 early CRPS patients from different clinical practices, over a one-year period, with repeated assessments of various biopsychosocial variables. With a high follow-up rate (95%), our findings confirm the evolution described in prior studies [14,18,128]. Prognosis may be influenced by limited number of independent early factors, including *BMI*, *baseline disability*, *allodynia*, and *ÖMPSQ scores*. Incorporating the latter two, the *BE-CRPS profiles* were strongly associated with multiple outcomes.

5.1. CLINICAL EVOLUTION

At 1 year, 35% of participants still met the clinical Budapest criteria, and only two-thirds had resumed professional activity (substantially lower than the 89% RtW rate in LBP [53]). Compared to Belgian norms, QoL remained reduced across the whole cohort at 12 months [266], while persistent CRPS patients reporting worse outcomes than those from a Belgian chronic pain sample managed in primary care [156]. No spreading [92] was observed, and outcomes were similar irrespective of surgery on the affected limb (n = 11), suggesting there is no clear contraindication for performing surgery on a limb with a history or active state of CRPS, provided it is deemed medically necessary.

Interestingly, CRPS duration at baseline did not significantly affect outcomes at any time-point, implying that early-stage CRPS (up to six months) remains

relatively homogeneous based on this criterion, without a minimum time threshold required for diagnosis.

Body perception disturbances remained stable over the one-year period for participants still meeting Budapest criteria at 1 year, while some variation was observed between baseline and 6 or 12 months in the whole cohort. These results suggest that, for participants who are developing a persistent condition, such disturbances are present from the outset.

Repeated QST assessments showed that most of the sensory modalities changed little over time. Indeed, the only significant differences were found between the measured values at baseline and those at other sessions (4.5, 6, and 12 months) but not between these latter time-points, indicating sensory changes mostly concern the first months of CRPS. Previous research, conducted with smaller sample sizes, has suggested that the sensory profile of CRPS patients remains stable over time [73,215].

Given that both of these studies included patients with longer CRPS durations, our findings align with their results. This suggests that individual sensory profiles tend to quickly stabilize independently of the condition's evolution (i.e., resolves or becomes persistent), limiting the utility of repeated QST assessments as biomarkers of the CRPS evolution.

5.2. EARLY PROGNOSTIC FACTORS

In the past, CRPS prognosis research has primarily focused on biological factors, as illustrated by the conclusion of a 2011 Delphi survey [38]. Forty-nine items, such as sensory or motor changes, were deemed to be associated with poorer outcomes. Conversely, only three social factors were considered relevant and psychological factors were surprisingly not mentioned at all.

More recent studies particularly-have highlighted the crucial role of psychological factors in the development of persistent CRPS [16,43]. There are also numerous

studies associating unfavourable psychosocial variables with a more serious state [4,17,75]. It is, however, essential to emphasize that individuals who develop CRPS do not present a distinct psychological profile [20], and the so-called "*yellow flags*" reflect normal psychological responses to pain rather than underlying psychopathology. As illustrated by the fear-avoidance [275] and pain interpretation bias models [259], it is the *intensity* and *persistence* of these reactions over time that increase the risk of chronification. Both models support that early interventions might reduce the transition from acute to chronic conditions [129,258].

Our results show that it might be possible to predict CRPS evolution based on early factors. As for LBP, prognosis appears to be primarily influenced by psychosocial variables — captured by the ÖMPSQ — and additional factors such as BMI or social support rather than some CRPS-specific features (historical classification [type I vs. II], CSS, or skin temperature). Moreover, the presence of allodynia and body perception disturbances, both included in the *BE-CRPS profiles*, also emerged as key prognostic factor. Our results are globally consistent with the existing literature [158].

However, whereas previous studies have linked high-energy trauma to a poorer prognosis [158], our findings indicate the opposite: patients with more intense initial trauma tended to have better outcomes, as suggested by the *BE-CRPS profiles* (where *Mild* and *Moderate* profiles were associated with better outcomes and higher intense traumatic event) [157] and preliminary simple multivariable analyses.

BMI emerged as a relevant prognostic factor in both our study and Román's cohort [226]. While obesity is frequently linked to chronic pain, the exact nature of this relationship remains debated [118,167,192]. In CRPS, two possible explanations might be proposed: (1) higher BMI directly contributes to a worse prognosis, potentially due to chronic low-grade inflammation present in obese

patients [233], and/or (2) higher BMI reflects a more complex psychosocial burden, not fully captured by including psychosocial measures, despite our extensive assessment of these variables in multivariable models.

The *BE-CRPS profiles* [157] were associated with different outcomes and might independently participate in prognosis. ÖMPSQ score (and, in a minor way, the presence of allodynia) were also strong predictors of CRPS evolution, explaining similar variance in multivariable models.

However, considering the *BE-CRPS profiles* as prognostic factor might add information compared to the ÖMPSQ categories alone. For instance, some participants classified as high risk based on ÖMPSQ were assigned to the *Mild CRPS* profile, while *BRD CRPS* (one of the severe profiles, associated with the poorest outcomes) had a ÖMPSQ score comparable to *Moderate CRPS*. This suggests that relying solely on the ÖMPSQ may be an oversimplified approach to prognostic stratification.

5.3. CLINICAL AND RESEARCH PERSPECTIVES

Our results show that CRPS patients presenting an initial severe condition are at greater risk of developing a persistent condition. Current data do not allow us to conclude that the use of our *BE-CRPS* profiling has a greater clinical interest than that of each of the variables used to construct these profiles [35]. For clinicians seeking a quick screening, assessment of ÖMPSQ and the presence of allodynia might be sufficient. For the researcher however, we suggest that classifying patients using these early profiles – and thus incorporating physical intensity of the triggering event, body perceptions disturbances and deep tissue sensitivity as additional variables – offers valuable opportunities to advance mechanistic understanding and guide personalized interventions, considering the underlying pathophysiological hypotheses and potential therapeutic targets [157].

Figure 4.7 illustrates a putative and unvalidated stratified early management based on *BE-CRPS profiles*, inspired by last guidelines [77,91,109]. In particular, the two severe profiles may benefit from early intensive therapies, including cognitive multisensory interventions targeting body perception disturbances [11] for *BRD CRPS profile*, while patients belonging to *Pressure Allodynia CRPS profile* might respond better to cognitive behavioural therapy or exposure therapy because of the initial higher ÖMPSQ score. However, these two profiles showed comparable characteristics at 12 months, suggesting that this distinction may be more theoretical than clinically actionable. Therefore, rather than targeting psychotherapy to a single profile, we advocate for individualised early psychological support in both severe profiles (even though we expect a greater effect in *Pressure allodynia CRPS*).

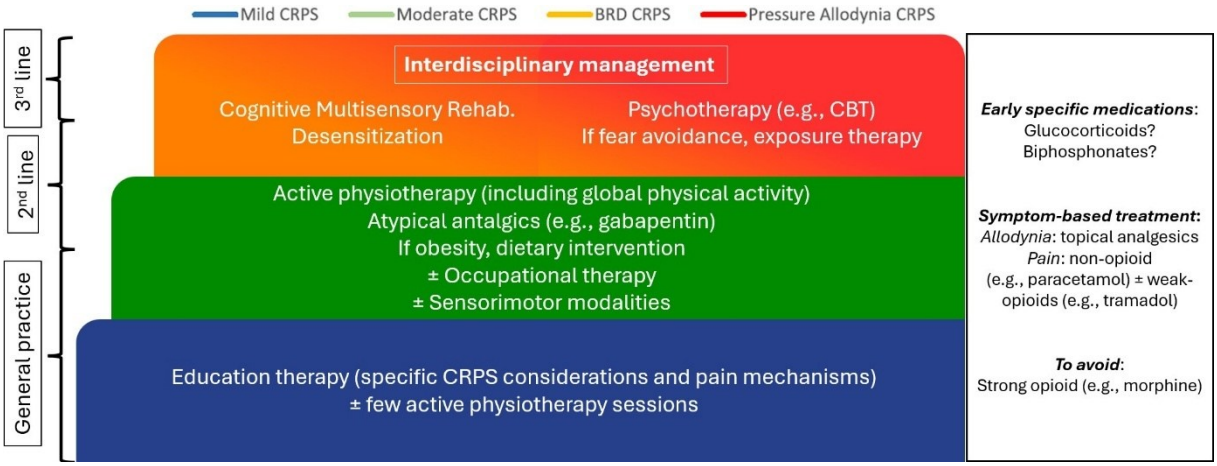

Figure 4.7. Potential early stratified and personalized management approach based on BE-CRPS profiles.[34] *This stratification approach aims to optimize healthcare use — enhancing outcomes in more severe cases through early referral and intensive rehabilitation, while avoiding overtreatment in Mild CRPS, where conservative general practice may suffice*[35]*. Based on guidelines* [77,91,109]*, all patients receive a core treatment package (corresponding*

[34] This figure is further discussed in the general discussion of the thesis ("VII. 3.1. Potential stratification tool").

[35] It should be noted that the term 1st line should be more accurate than "general practise", as most of the initial care is provided by physiotherapists rather than general practitioners, depending on the setting or country.

to Mild CRPS, in blue), while additional therapeutic resources are directed to more severe profiles. Although BRD and Pressure Allodynia CRPS were defined by distinct early features, they showed similar characteristics at 12 months. Thus, the distinction may be more theoretical than clinically actionable. Both severe profiles may benefit from personalized, multimodal rehabilitation tailored to individual clinical features rather than fixed, profile-based protocols. Some treatments (e.g., glucocorticoids, bisphosphonates) are not assigned to specific profiles but may be beneficial in early CRPS; further research is needed to support routine use [22,77]. *Likewise, first- and second-line analgesics should be adapted to patient needs and preferences, while strong opioids are not recommended for chronic pain conditions. Abbreviations: CRPS, complex regional pain syndrome; BE-CRPS profiles, biopsychosocial early CRPS profiles; BRD, body representation disturbances; Rehab., rehabilitation; CBT, cognitive behavioural therapy.*

To support the implementation of early CRPS profiling, we have made the subgrouping equation publicly available. Researchers and clinicians can input five easily assessed parameters to estimate the probability of a patient belonging to each profile (https://github.com/vladaron/CRPS_longitudinal).

5.4.STRENGTHS AND LIMITATIONS

This study presents several strengths: (1) very small drop-out rate (5%), (2) large multicentre cohort performing a comprehensive biopsychosocial assessment, capturing multiple dimensions of the CRPS experience, (3) unsupervised and rigorous selection of potential prognostic factors investigating numerous biopsychosocial concepts, (4) use of transparent and advanced statistical techniques, such LMMs and multiple imputation, (5) inclusion of early CRPS profiles in the analyses, potentially more relevant than traditional CRPS subtypes.

One of the limitations concerns the diagnosis of CRPS[36], which, in a part of the cohort, was not based on direct physical assessment by the investigator. This could have created discrepancies between included participants, as CRPS diagnosis is based on clinical expertise. However, this risk was mitigated by several elements: participants were referred by experienced clinicians using Budapest criteria, presented typical CRPS history and symptoms, and outcomes were consistently collected across all subjects by online questionnaires (except for CSS). Furthermore, no significant differences were found in baseline variables or outcomes at 1 year between participants who were assessed remotely and those who underwent face-to-face assessment.

While sample size is relatively small for exploring a wide range of prognostic factors, the statistical design (LMMs and multiple imputation) enhances confidence in the identified factors. However, it is possible that some predictors deemed insignificant in the multivariable analyses might explain small parts of the variability between participants. The clinical relevance of these predictors remains debatable, given their potential marginal impact on outcomes.

Eventually, the *BE-CRPS profiles* and prognostic factors identified in this study need to be validated in external cohorts. Replication of the findings in larger, independent samples is necessary to confirm their generalizability and utility in clinical practice. Implications for clinical management and secondary prevention of subjects suffering from early CRPS remain to be discussed and explored.

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[36] It is important to emphasize that the diagnosis of CRPS in Chapter 2 and 3 did not rely solely on the judgment of the investigator (MHL), but rather on the converging expertise of several clinicians involved in the patients' care pathways (general practitioners, surgeons, pain specialists, physiotherapists). This collaborative approach enhanced diagnostic reliability by incorporating multiple clinical perspectives. In addition, any doubtful cases were systematically discussed with AB, a clinician with recognized expertise in CRPS, ensuring rigorous and consistent validation of patient inclusion.

5.5. CONCLUSIONS

In this comprehensive prospective study of early CRPS patients, we aimed to identify early prognostic factors and assess the clinical evolution of the condition over a one-year period. Our findings confirm the generally prognosis associated with CRPS and suggest that a combination of psychosocial assessments, including the ÖMPSQ, alongside basic clinical evaluations, could offer a practical and efficient means of identifying patients at higher risk of more severe outcomes. Future research should focus on refining these early prognostic models, incorporating both biological and psychosocial factors, to enable more personalized and effective management strategies for CRPS

VII. Discussion of the Thesis

1. Summary

The present thesis aimed to identify early prognostic factors in patients with CRPS and to examine whether clinically meaningful subgroups can be distinguished to guide stratified management.

In the first study (*Chapter 1*), a systematic review of the literature identified only six relevant studies addressing early prognostic factors in CRPS, most of which suffered from substantial methodological limitations and risk of bias [158]. Despite these constraints, moderate evidence supported six early predictors of poor prognosis: higher pain intensity, self-rated disability, anxiety, pain-related fear of movement, a high-energy triggering event, and, to a lesser extent, female sex. This synthesis highlighted the paucity of high-quality prognostic research in CRPS and established the need for more robust, well-characterized prospective studies.

The second study (*Chapter 2*) confirmed that early CRPS is a highly heterogeneous condition, with clinical variability not adequately explained by traditional CRPS classifications [157]. To address this, we recruited a well-defined cohort of CRPS individuals with symptom onset < 6 months (n = 113). We evaluated differences between participants based on those classifications. As they failed to explain the observed variance between early CRPS individuals, we performed a LCA, based on five characteristics thought to reflect pathophysiological mechanisms, and identified four distinct biopsychosocial profiles, referred to as *BE-CRPS profiles*:

- *Mild CRPS* (high-intensity triggering events, low allodynia rate, r-B-CRPS-BPDS score, low psychosocial severity, high PPT): patients with relatively low pain intensity and functional impairment and limited psychological distress.

- *Moderate CRPS* (high-intensity triggering events, moderate allodynia rate, moderate r-B-CRPS-BPDS score, moderate psychosocial severity, moderate PPT): patients with intermediate levels of pain, disability, and psychological burden.
- *BRD CRPS* (low and high-intensity triggering events, highest allodynia rate, highest r-B-CRPS-BPDS score, moderate psychosocial severity, moderate PPT): patients characterized by pronounced allodynia and body representation disturbances, suggesting potential alterations in central mechanisms.
- *Pressure allodynia CRPS* (only low-intensity triggering events, high allodynia rate, moderate r-B-CRPS-BPDS score, highest psychosocial severity, lowest PPT): patients with features suggestive of prominent (neuro)inflammatory processes.

The two last profiles (*BRD* and *Pressure allodynia CRPS*) showed similar outcomes and could therefore be considered as severe profiles. They may also reflect higher involvement of systemic/central processes (by higher body perception disturbances/allodynia for *BRD*, and higher psychosocial severity and deep tissue sensitivity for *Pressure allodynia CRPS*). Further details relating to these hypotheses are available in *Chapter 2. 5.1. interpretation in the light of the literature*.

The third study followed early CRPS patients over 1 year, with repeated assessments across biological, psychological, and social domains. A substantial proportion of patients continued to experience pain, disability, and impaired QoL at 12 months compared to Belgian normative values (see Table S11, Chapter 3). Prognostic analyses demonstrated that some biological factors (e.g., allodynia) were independent predictors of the evolution but the strongest predictors appear to be early psychosocial factors, including psychosocial severity (ÖMPSQ), maladaptive coping strategies, and anxiety. These factors are shared with other MSK pain conditions and, crucially, are potentially modifiable, underscoring their

importance as targets for early intervention. Importantly, the *BE-CRPS profiles* (incorporating the psychosocial severity) were strongly predictive of long-term outcomes.

Taken together, the different chapters of this thesis provide evidence that prognosis in CRPS is determined not solely by biological or demographic characteristics, but rather by a complex interplay of biopsychosocial factors. It demonstrates that early stratification into clinically meaningful subgroups is feasible and may reflect different underlying mechanisms.

These insights pave the way for the development of stratified and personalized treatment approaches, whereby patients are matched to interventions targeting their specific risk profile, with the overarching aim of preventing the transition from early to persistent CRPS.

2. Interpretations - Early Prognostic Factors in CRPS

In the following section, we discuss in detail each identified prognostic factor. To avoid redundancy with *Chapter 3*, elements already thoroughly addressed above will be only briefly revisited.

The factors are presented in two categories: *non-modifiable factors*, referring to variables that cannot be modified by therapeutic interventions, and *potentially modifiable factors*, referring to variables that clinicians may be able to influence through targeted treatment strategies.

2.1. NON-MODIFIABLES FACTORS

2.1.1. Age

In adults, *age* at the onset of the condition is not influencing the prognosis ([158] and *Chapter 3*). It should be noted that paediatric CRPS seems different

from adult CRPS in many aspects, and no study has already assessed the prognosis in this particular population [3,8].

2.1.2. Sex

One cohort reported that *being a female* was associated to higher CSS (poorer outcome) [16,43]. However, this result was not reproduced in our cohort (*Chapter 3*), whereas *sex* was not associated to any other outcomes in the rest of CRPS literature (e.g., pain, disability, QoL) [158,226]. Based on the ICF classification [141], CSS appears to be a less relevant outcome than other more functional outcomes. Given all these elements, the *biological sex* is probably not a meaningful predictor of CRPS evolution.

2.1.3. Limb dominance (CRPS affecting dominant vs. non-dominant side)

Although our initial hypothesis was that CRPS affecting the dominant limb would cause greater functional impairment than when the non-dominant limb is involved, *limb dominance* showed only a limited association with RtW in our cohort. CRPS of the dominant limb was even associated with higher odds of RtW at 12 months (OR = 1.83, simple multivariable model). However, this effect did not persist after adjustment for other relevant variables.

To date, no other CRPS studies have specifically investigated the impact of limb dominance on clinical outcomes. In the MSK literature, some studies report slightly greater disability when the dominant limb is affected, but the results are not clinically significant [161], while others report no significant difference [47,132]. Similarly, no significant impact of limb dominance on RtW has been observed in other studies [2,262].

2.1.4. Localization (CRPS affecting upper vs. lower limb)

Earlier expert opinions and low-quality studies have suggested that lower limb CRPS is associated with a poorer prognosis than upper extremity CRPS

[38,158,279]. In our simple multivariable models, *lower extremity involvement* was indeed linked to greater pain interference. However, this association did not persist in the fully adjusted models, indicating that lower extremity localization was not an independent predictor of pain interference when accounting for other relevant factors ([16] and *Chapter 3*).

The potential impact of the affected limb in MSK condition (upper vs. lower) has not been thoroughly investigated in the MSK literature. We identified only one retrospective study (n = 181) conducted in an emergency department setting, which reported that lower limb involvement was associated with greater disability and higher levels of absenteeism compared to upper limb injuries [242].

2.1.5. Physical[37] intensity of the triggering event

Higher-intensity triggering events have been associated with an increased risk of developing CRPS [208]. Similarly, based on previous expert opinion [38] and findings from three low-quality studies [158], CRPS cases triggered by more severe injuries have been linked to a poorer prognosis than CRPS cases due to minor trauma. However, this association has been challenged.

Bean et *al*. [16] found no prognostic value of the *severity of the triggering event*. Interestingly, our findings suggest an opposite trend: in our cohort, more intense triggering events were associated with more favourable outcomes, based on results from simple multivariable LMMs (where we observed an association with each outcome except RtW, see **Table 4.8**) and *BE-CRPS profiles*.

[37] The term "physical" was added to avoid confusion with psychological intensity of the trauma (reaction of the individual / psychological impact such as post-traumatic stress disorder). Even if psychological intensity could probably play an important role (e.g., increase prevalence of post-traumatic stress disorder has been found in CRPS population [248]), no data is available regarding their impact on long-term outcomes or CRPS incidence.

Several hypotheses could explain the association between low-intense physical trauma and poorer outcomes:

- Differential pathophysiological mechanisms may be involved. CRPS has been shown to involve dysimmune susceptibility and genetic predispositions [94,114,238], which may render certain individuals vulnerable to developing the condition following low-intensity injuries. In such cases, even minor trauma may elicit a disproportionate (inflammatory) response, triggering the pathological cascade of CRPS. In contrast, individuals without such predispositions may require more severe trauma to initiate the syndrome, potentially resulting in a more localized and self-limiting response.
- Psychological and social factors may also contribute. Patients experiencing CRPS after relatively minor injuries may face a discrepancy between the apparent triviality of the initial trauma and the severity of their symptoms, leading to psychological distress. This mismatch can result in invalidation or misunderstanding from family, healthcare providers, or within medico-legal contexts. Such experiences may exacerbate emotional distress, increase stigmatization, and ultimately contribute to the chronification of the condition.

2.1.6. CRPS duration

In previous research, longer *CRPS duration* has consistently been associated with poorer clinical outcomes [37,181]. However, in our cohort — exclusively composed of early CRPS cases — we found no prognostic value of condition duration, whether measured from the triggering event, the symptom onset, or when comparing patients with CRPS of less than 3 months to those with 3 to 6 months of evolution. This finding and its implication are extensively discussed in *Chapters 2* and *3*.

2.1.7. Family or personal history of CRPS

A genetic predisposition to CRPS is considered likely [238], and some authors have even proposed classifying patients with a family history of CRPS as a distinct clinical subtype [138]. However, in our study, neither *familial history* (n = 13) nor *personal history of CRPS* (i.e., prior CRPS at a different anatomical site, theoretically indicating increased susceptibility, n = 13) were associated with distinct early clinical features [157], or with prognostic differences (*Chapter 3*).

These findings suggest that while genetic vulnerability may contribute to CRPS susceptibility, it might not significantly influence the initial clinical presentation or early course of the condition. However, this conclusion should be interpreted with caution due to the relatively small number of participants with a personal or family history of CRPS (25 out of 113).

2.1.8. Work injury / medicolegal conflict / perceived injustice

The *presence of a medicolegal* context has been associated to poorer outcomes in several MSK conditions (for instance, in whiplash injury [231]). Such conflicts — defined in our study as reports of work-related injuries or disputes with employers or insurance providers — were initially associated in our cohort with some outcomes in simple multivariable LMMs (disability, QoL, RtW) (*Chapter 3*).

However, this variable did not retain statistical significance in the adjusted models and was ultimately excluded. Notably, it was the last variable removed from the model predicting RtW, suggesting it may explain some of the variability in this outcome. The limited sample size for this subgroup analysis (n = 70 at 12 months), combined with the strong predictive value of the ÖMPSQ (which is specifically designed to assess work-related prognosis), likely contributed to its exclusion.

In a cross-sectional analysis, Baum et *al*. found that CRPS patients reported higher levels of perceived injustice compared to individuals with chronic MSK pain [13]. In both groups, higher pain intensity was indirectly associated with stronger perceptions of injustice, mediated by increased pain catastrophizing. These findings suggest that perceived injustice may be one of the pathways through which medicolegal contexts influence CRPS outcomes. Unfortunately, this concept was not directly assessed in our study.

Relatedly to perceived injustice and the lack of recognition, an insightful article explored the belief (held by some researchers and clinicians) that CRPS is not a "real" condition — a stance that can lead to the invalidation of patients' distress, the denial of appropriate treatment, and worse clinical outcomes [23]. The authors reviewed nine studies that questioned various aspects of CRPS, including (1) the legitimacy of the diagnosis, (2) the proposed pathophysiology, (3) the validity of diagnostic criteria, (4) the role of psychological factors, and (5) the general quality of CRPS research. They systematically refuted these criticisms using extensive scientific evidence, concluding that the rejection of CRPS as a valid clinical entity is based on weak or flawed arguments.

2.1.9. Education level

To the best of our knowledge, our study is the first to investigate the predictive value of *education level* in CRPS. Although education showed interesting associations in each simple multivariable model, it was excluded from all more complex adjusted models, suggesting it did not contribute to explaining additional variance beyond the other variables included.

The relationship between education level and chronification remains underexplored across many conditions. Cross-sectional studies have consistently shown that lower educational attainment is associated with higher levels of pain. For example, a large and recent United States survey found that disparities in joint

pain by education level exist in every state, with particularly large gaps in some regions — mainly due to higher pain prevalence among individuals with lower education levels [124]. These results suggest that, in terms of pain-risk, lower educational level may increase vulnerability to adverse contextual factors at the state level. Conversely, higher education may offer some protection against these unfavourable factors. Still, even individuals with college degrees are more likely to experience joint pain if they reside in states with greater educational disparities. In other words, state-level educational inequality appears to negatively affect pain outcomes across all educational groups, though the impact is disproportionately greater among those with lower levels of education.

Similarly, a large Danish study reported that higher education is associated with reduced MSK pain and less function limitations in older adults [103]. In Belgium, a national survey found that lower education levels negatively impacted nearly all dimensions of the EQ-5D-5L (except anxiety/depression), underscoring the broader influence of education on overall QoL, not just pain [266].

2.1.10. Scintigraphic results

To our knowledge, this is the first study to investigate the potential prognostic value of *bone scan* in CRPS (notably based on the uptake ratio, n = 48). Overall, scintigraphic findings did not demonstrate prognostic relevance, with the exception of a marginal association observed in a simple multivariable LMM, where higher uptake ratios were linked to lower pain interference ($p = 0.049$). However, this association did not remain significant after adjustment for other variables.

Therefore, bone scan should not be recommended for prognostic assessment in CRPS [280].

2.1.11. Pain sensitivity (assessed by the pain sensitivity questionnaire)[38]

Self-reported pain sensitivity, as assessed by PSQ, has been suggested as an early prognostic factor in a prospective study (univariate analysis), though the findings were limited by significant methodological biases [158,222]. In our cohort, we found no prognostic value of the PSQ scores.

A recent systematic review and meta-analysis reported a correlation between PSQ scores and acute postoperative pain (r = 0.28, 95% CI 0.15–0.41; five studies; n = 608) but not with chronic post-surgical pain. Notably, the association with acute pain lost significance in adjusted analyses [286].

These findings suggest that the clinical relevance of the PSQ in predicting postoperative pain remains uncertain and is limited in CRPS, particularly when considering the opportunity to assess more relevant concepts.

2.1.12. Sensory profiles

First, it is important to emphasize that all *QST modalities*, assessing specific components of the somatosensory system, are psychophysical in nature. This means they are influenced by individual factors that affect sensory perception, such as emotional state, attention, and reaction time.

Studies with surgical models have suggested that patients with heightened pain sensitivity to some stimuli may be more prone to developing chronic pain. In line with this hypothesis, Petersen *et al*. conducted a systematic review to examine the predictive value of QST — and thereby, sensory profiles — for chronic post-

[38] The decision to classify pain sensitivity (reported by questionnaire) as a non-modifiable variable may be controversial. Since the patient is asked to "imagine yourself in certain situations. You should then decide if these situations would be painful for you and if yes, how painful they would be. Please try as much as possible not to allow your fear or aversion of the imagined situations affect your assessment of painfulness," we estimate that this is relatively an intrinsic, unchangeable characteristic of the individual.

surgical pain [205]. Among the 25 studies included, the majority focused on joint-related surgeries (N = 16) and abdominal or gynaecological procedures (N = 4). The most frequently investigated QST parameters were PPT, temporal summation of pain, and conditioned pain modulation (CPM), with the last two showing the most consistent predictive value. However, CPM protocols varied significantly across studies, and the reliability of CPM (considered as a measure of descending nociceptive inhibitory pathways of the central nervous system) remains debated [134].

Regarding other QST parameters, the same systematic review [205] reported that: (1) thermal modalities were generally not predictive of chronic post-surgical pain — whereas one study found that WDT and HPT predicted higher chronic pain after total knee arthroplasty in patients with osteoarthritis, this was not replicated in four other studies. CDT and CPT were not predictive in six studies; (2) MDT and MPT were also not predictive across five studies; (3) deep tissue sensitivity showed inconsistent associations: PPT was predictive in only 3 out of 11 studies; pressure tolerance threshold was not predictive in any of three studies; cuff-induced pain detection threshold showed a predictive value in one out of three studies, and cuff-induced pressure tolerance threshold in none; (4) electrical pain stimuli were predictive in only one of two studies.

A 2022 systematic review focusing specifically on QST in total joint arthroplasty echoed these findings, reporting similar inconsistencies in predictive value [198].

We also sought to identify studies exploring the prognostic value of sensory profiles for pain chronification in clinical contexts beyond surgery. A systematic review published in 2016 examined the predictive utility of QST measures in individuals with LBP [169]. The authors identified only three eligible studies, all of which were rated as having a high risk of bias. Importantly, none demonstrated

a significant association between QST parameters and LBP outcomes. No more recent systematic reviews on this topic were found.

However, we identified a new study that assessed whether the sensory profile could predict symptoms of central sensitization in patients with acute LBP [96]. While potentially relevant, this study did not investigate the predictive value of QST for more relevant outcomes such as pain intensity, disability, or QoL.

Concerning CRPS, the condition is classically associated with alterations in QST parameters when compared to healthy controls (see [246] for a comprehensive review). However, the prognostic value of the sensory profile in CRPS — i.e., whether early sensory characteristics can predict persistent CRPS — has not yet been evaluated.

Our cohort is the first to assess the sensory profiles of patients with early CRPS and track their progression over a one-year period. In terms of prognostic factors, **Table 5.1** summarizes the results of the simple multivariable models.

Although some QST modalities showed predictive value in simple multivariable analyses, none remained significant in the final adjusted multivariable models.

QST modalities		CSS	CRPS diagnosis	Pain intensity	Pain interference	Disability	QoL	Rtw
CDT	*Aff*	*		**	**	**	**	
	Cont							
CPT	*Aff*							
	Cont							*
WDT	*Aff*	*		*		*		
	Cont							
TSL	*Aff*	**		***	*	**	*	
	Cont							
HPT	*Aff*		*					
	Cont							
MDT	*Aff*							
	Cont							
MPT	*Aff*							
	Cont							
MPS	*Aff*	***	**	***	*	***		
	Cont		*	**		**		
WUR	*Aff*							
	Cont							
VDT	*Aff*	*		**			*	
	Cont							
PPT	*Aff*	***	**	*	**	***	*	
	Cont							

Table 5.1. ***Early predictive value of each QST modality in linear mixed-effects models****. Each model includes fixed effects for time, time², age, sex, pain localization, and the Z-score of the respective QST modality (standardized using German normative reference values* [162]*). None of the variable remains statistically significant in the final multivariable models after variables selection. Abbreviations: *, p<.05; **, p<.01; ***, p<.001; CSS, CRPS severity score; CRPS diagnosis, still meeting clinical Budapest criteria at 1 year; QoL, quality of life; RtW, return to work after 12 months; Aff, affected side; Cont, contralateral side; CDT, Cold detection threshold; WDT, Warm detection threshold; TSL, Thermal sensory limen; PHS, Paradoxical heat sensation; CPT, Cold pain threshold; HPT, Heat pain threshold; MDT, Mechanical detection threshold; MPT, Mechanical pain threshold; MPS, Mechanical pain sensitivity; DMA, Dynamic mechanical allodynia; WUR, Wind-up ratio; VDT, Vibration detection threshold; PPT, Pressure pain Threshold.*

2.2. POTENTIALLY MODIFIABLE FACTORS

2.2.1. Psychosocial severity

In our cohort, the *ÖMPSQ score* — including components such as anxiety and depressive disorders, pain-related fear of movement, catastrophizing and other *yellow flags* — emerged as a strong predictor across all outcomes in the final multivariable models.

For instance, when comparing two individuals with identical age, sex, CRPS localization, and baseline outcome values, a 20-point[39] higher ÖMPSQ score was associated with a 1.2-point increase in CSS, a 0.44-point increase in pain intensity, a 0.88-point increase in pain interference, a 0.24-point higher disability score (Z-score), and a 0.06-point decrease in QoL (EQ-5D index) at each follow-up time point. Moreover, it nearly quadrupled the odds of still meeting the clinical Budapest criteria 1 year after onset (OR = 3.87) and reduced the likelihood of returning to work at 12 months by 56% (OR = 0.44).

These findings, discussed in *Chapter 3*, highlight the consistent and substantial negative prognostic impact of psychosocial distress in early CRPS.

Unlike fixed demographic or injury-related factors, these variables are potentially modifiable. Evidence from MSK pain research suggests that early identification and targeted intervention on psychosocial risk factors (e.g., cognitive-behavioural strategies, multidisciplinary rehabilitation, patient education) can reduce the risk of chronification. In CRPS, the strong predictive value of psychosocial severity observed in our cohort underscores its relevance as a primary target for secondary prevention strategies and as a key dimension for patient stratification.

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[39] Broadly corresponding to the SD of this score at each time-point of our prospective study.

2.2.2. BE-CRPS profiles

Comparing participants who differ only by their *BE-CRPS profile* in adjusted models, those with *Pressure Allodynia CRPS* — compared to *Mild CRPS* — had significantly higher CSS scores (1.83 points greater) at each time-point and were over nine times more likely to meet the clinical Budapest criteria at 12 months (OR = 9.49, 95% CI: 1.58–56.80). Additionally, they reported increased pain intensity (+0.85), greater pain interference (+1.30), higher disability levels (+0.38), and showed a trend toward reduced QoL[40].

These results underscore the prognostic value of *BE-CRPS profiles*, showing that this early classification can meaningfully predict long-term outcomes. Similarly to ÖMPSQ, their interest has been discussed in *Chapter 3*.

Beyond their predictive capacity, the *BE-CRPS profiles* provide a framework for clinical stratification. Identifying patients belonging to high-risk subgroups such as *Pressure Allodynia CRPS* at an early stage could enable clinicians to prioritize more intensive or tailored interventions. Conversely, patients in the *Mild CRPS* subgroup — who display relatively favorable outcomes — might benefit from less resource-intensive approaches.

As with psychosocial severity assessed by the ÖMPSQ, the strong and consistent associations of *BE-CRPS profiles* with clinical outcomes highlight their importance as both a research tool and a potential clinical decision aid.

[40] Here, we choose to report the impact on disability and QoL in final multivariable models to illustrate the clinical relevance of the *BE-CRPS profiles*, even though this variable was removed during the final steps of model selection.

2.2.3. Disability

In our preliminary analysis, *disability* was associated with each outcome and remained significant in final models predicting disability and QoL (see **Table 5.2** for summary). Similarly, another cohort study identified disability as a significant predictor of long-term CSS and pain intensity in CRPS [43].

As proposed by Cave et *al*. [43], higher disability may reflect immobilization of the affected limb (with or without cast or splint), which in turn could act as a reinforcing factor contributing to CRPS pathophysiology (potentially through maladaptive cortical changes [102], but also inflammation [100]) and to its persistence over time. Additionally, this association may be influenced by individuals' perceptions of their condition and their resulting behavioural responses.

Given the prognostic relevance of disability, early interventions aimed at minimizing immobilization and reducing the impact of CRPS on daily functioning could improve long-term outcomes and prevent chronification [43]. It should be noted that it remains unclear whether disability operates as an independent prognostic factor that actively influences outcomes, or if it merely reflects a more complex clinical presentation encompassing biological, psychological, and social components.

2.2.4. Pain

Higher pain intensity following trauma is widely recognized as a key predictor of CRPS onset [77]. Similarly, *pain* (severity and interference) emerged as noteworthy predictors of all outcomes in simple multivariable analyses. However, due to methodological considerations[41] detailed in *Chapter 3* (Methods and

[41] In short, pain was too highly correlated (Pearson coefficient or principal component analysis) with disability or ÖMPSQ to be simultaneously included into the different models.

Results), these variables were not retained in the final multivariable models. As with disability, pain intensity has been previously associated with long-term outcomes such as CSS and disability [43], in CRPS as in other chronic pain conditions [71].

Cave et *al*. [43] proposed several mechanisms that may underlie this association: (1) higher baseline pain might exacerbate CRPS symptoms via neurogenic inflammation and autonomic dysregulation, contributing to clinical signs such as oedema and temperature asymmetries, (2) elevated pain levels may foster maladaptive behavioural patterns, including avoidance behaviours, (3) according to Leventhal's self-regulatory model of illness perception[42], pain severity can influence cognitive and emotional representations of illness, which have been shown to predict functional outcomes in both CRPS [6] and general chronic pain populations [28], (4) elevated pain might reflect early sensitization processes.

Another plausible hypothesis is that higher pain reported at early stages may reflect pre-existing heightened pain sensitivity (either peripheral or central), predisposing individuals to the pathophysiological mechanisms that contribute to CRPS chronification, possibly even before symptoms onset.

As with disability, one could hypothesize that interventions targeting pain reduction (either pharmacological or non-pharmacological) may improve CRPS prognosis. It is also possible that high pain levels merely reflect a more severe underlying condition, and that modifying this symptom alone may not significantly alter the course of CRPS.

[42] which posits that higher pain intensity leads to more severe illness appraisals, thereby increasing self-reported disability [12].

2.2.5. CRPS symptoms and signs

CRPS symptoms and signs, gathered in CSS, were initially thought to have an important prognostic value [38]. Both the existing literature [158] and our findings (*Chapter 3*) contrast this assumption. While several CSS variables displayed predictive associations in simple multivariable models (illustrated in **Table 5.2**), none — except allodynia — remained significant in the final multivariable analyses (*Chapter 3*, supplementary data Table S12)[43].

We further tested the historical CRPS classification (type I vs. type II) and the vasomotor/sudomotor-based subtypes proposed by Bruehl et *al*. [35]. Neither of these classifications showed independent prognostic value once other biopsychosocial factors were accounted for.

These results suggest that the traditional clinical descriptors of CRPS do not adequately capture the complexity or prognostic heterogeneity of the condition. The fact that allodynia — but not other CSS features — was retained as a significant predictor underlies particular pathophysiological mechanisms, such as peripheral sensitization or maladaptive central processing, associated with poorer evolution. This is consistent with the identification of the *BRD profile*, which showed particularly poor outcomes (*Chapter 3*).

Taken together, these findings indicate that while the CSS remains interesting for clinical characterization, its individual components (beyond allodynia) have limited value for prognosis. More nuanced, multidimensional approaches — such as biopsychosocial profiling — appear necessary to understand and predict

[43] The rationale behind this selection is detailed in *Chapter 3*. Briefly, to reduce the number of potential prognostic variables, CSS was included in models incorporating *BE-CRPS profiles*. However, due to a high correlation between CSS and ÖMPSQ, it was excluded from supplementary models that did not include *BE-CRPS profiles*. In these latter models, each individual CRPS sign was analysed separately instead.

condition trajectories in early CRPS. These points are discussed in detail in *Chapter 3*.

Early CRPS features		*Outcomes*						
		CSS	CRPS diagnosis	Pain intensity	Pain interference	Disability	QoL	Rtw
Hyperalgesia or allodynia	*Sympt*	***		***	**	**	**	
Hyperalgesia	*Sign*		*	**				
Allodynia	*Sign*	***	**	***	***	***	***	
Skin temperature	*Sympt*	***				*	*	*
	Sign							
	Continuous							
Skin colour	*Sympt*							
	Sign							
Sweating	*Sympt*	**	**	*	**	**	*	
	Sign	*					*	
Sweeling	*Sympt*							
	Sign	**						
Trophic	*Sympt*	*						
	Sign	**						
Motor	*Sympt*							
	Sign							
CRPS severity score		***	***	***	*	***	***	
Historical CRPS type		*						
Research Budapest criteria		***		*		*	*	
CRPS subtypes[a]	*Warm*							
	Cold	*	*					

Table 5.2. ***Early predictive value of each CRPS symptom and sign in simple multivariable linear mixed-effects models***. *Each model includes fixed effects for time, time², age, sex, pain localization, and the CRPS symptom/sign or CSS. None of the variable remains statistically significant in the final multivariable models after variable selection.* [a]*, CRPS subtypes correspond to the classification proposed by Bruehl et al.* [35]*; the p-value is computed in comparison to neutral subtype (not meeting the criteria for warm [red and warm skin] or cold*

*[cold and bluish skin] CRPS). Abbreviations: *, p<.05; **, p<.01; ***, p<.001; Sympt, symptom; Continuous, delta between affected skin temperature and contralateral side.*

2.2.6. Body perceptions disorders

The *r-B-CRPS-BPDS* was associated with all outcomes in simple multivariable models (except RtW). However, in fully adjusted models, its predictive effect did not account for significant variance in any outcome and was systematically excluded. This finding is consistent with previous results from Bean and colleagues, where body perception disturbances demonstrated promising predictive value in univariate analyses but failed to remain significant in multivariable models [16,43].

Nevertheless, our analyses revealed that body perception disturbance emerged as a key determinant of the *BE-CRPS profiles*. This suggests that while it may not independently predict long-term outcomes once other biopsychosocial factors are considered, it plays an important role in shaping the clinical heterogeneity of CRPS. In particular, altered body representation has been linked to mechanisms of maladaptive neuroplasticity that may interact with psychological distress and sensory abnormalities (i.e., allodynia) to define specific subgroups, such as the *BRD CRPS profile*.

Therefore, body perception disturbances appear less relevant as standalone prognostic markers, but highly informative as part of a multidimensional stratification approach. The implications of this finding are further explored in *Chapters 2* and *3*.

2.2.7. Social support

Perceived social support (availability or satisfaction) is one of the numerous concepts surrounding the social dimension [130]. A recent systematic review highlighted that, in chronic pain, (1) perceived social support was positively

associated with QoL and negatively associated with depression, (2) social support satisfaction was inversely associated with depression, (3) spousal responses were positively associated with pain intensity, pain interference, and depression [220]. However, most findings were drawn from cross-sectional designs and correlational analyses. As noted by the authors, social support is often treated as a global concept, despite the importance of clearly specifying which type is being measured.

To our knowledge, *Chapter 3* corresponds to the first study to examine the predictive value of perceived social support in CRPS. Satisfaction with support showed limited prognostic relevance, predicting only pain interference in simple multivariable analyses. In contrast, availability was associated with CSS, pain interference, disability, and QoL in simple multivariable models — and remained significantly associated with disability in the final multivariable model (**Table 4.8**). In brief, individuals with a higher number of available social contacts showed greater improvement in disability over time. It should be noted that this individual score remained stable across follow-up (*effect of time as factor in univariate LMM predicting perceived social support: $p>0.05$*), suggesting that social support availability does not increase or decrease among people experiencing chronification.

2.2.8. Body mass index

In our study, *BMI* emerged as a significant factor influencing multiple outcomes in the final multivariable models. A 10-point increase in BMI was associated with 6.25-fold higher odds of meeting CRPS diagnostic criteria at 12 months. In early CRPS patients, the same increase was linked to consistently worse outcomes across time points: approximately 0.5 points higher pain intensity, a 0.25-point higher disability Z-score, and a 0.06-point lower EQ-5D index per time point. Although these effects are modest, they were observed in

models adjusted for baseline outcome values, indicating an independent contribution of BMI to CRPS prognosis. This effect has not been consistently reported in prior research [158], with the exception of [226].

As discussed in *Chapter 3*, several hypotheses may explain the influence of BMI on CRPS outcomes, but it remains uncertain whether weight reduction would meaningfully alter prognosis. In another study involving chronic pain patients in primary care [156], we found that the impact of individual lifestyle factors on pain chronification was probably small; however, the accumulation of multiple healthy habits appeared to improve outcomes. Thus, weight loss — particularly when combined with other lifestyle changes such as increased weekly physical activity — could potentially yield clinically relevant benefits.

2.2.9. Physical demands of the job

We observed a significant association between the *physical demands of work* and RtW rates at 1 year in simple multivariable logistic regression model. In details, participants with low physically demanding jobs had an 84.4% lower likelihood of returning to work at 12 months compared to those with minimally demanding jobs (OR = 0.156; 95% CI [0.05; 0.48]). Notably, six participants (13%) reported having reduced the physical demands of their job.

This finding aligns with the results of Bean et *al*., who identified work-related physical demands as a key factor influencing sick leave approximately 2 months after CRPS onset (see *Chapter 1* for details). Nevertheless, in our cohort, the variable did not explain sufficient variance in final multivariable models and was therefore removed (see Methods section in *Chapter 3*).

Much of the existing literature on the relationship between physical job demands and RtW originates from studies of orthopaedic conditions, though findings remain conflicting. For example, in patients undergoing hip or knee arthroplasty, physical demands of the job were not predictive of time to RtW,

whereas flexible working conditions showed a positive association [170]. In contrast, one other study reported that jobs involving lifting or stair climbing are associated with lower RtW rates after knee arthroplasty, and that physically demanding occupations or roles requiring prolonged standing independently predicted delayed RtW [287]. Among patients undergoing arthroscopic rotator cuff repair, time to RtW varied significantly according to job demands — averaging 3.8 ± 3.1 months for sedentary workers versus 5.8 ± 2.8 months for those in very physically demanding roles [76]. Despite these findings, no review has yet synthesized the evidence across orthopaedic interventions to clarify these relationships.

In LBP, a systematic review identified moderate evidence supporting the role of physical job demands as a barrier to RtW in subacute or chronic cases [257]. This highlights the potential utility of workplace interventions aimed at modifying job demands. For instance, a randomized controlled trial investigated the added value of a structured meeting between the physiotherapist, employer, and patient, alongside standard physiotherapy care (also provided to the control group) [237]. The meeting aimed to establish a coordinated action plan that recommended workplace adjustments and changes to the patient's daily activities to improve work ability and support RtW. The intervention significantly increased the odds of maintaining work ability at 12-month follow-up, suggesting that such workplace-focused interventions may be effective strategies to reduce long-term absenteeism.

2.2.10. General self-rated health

In a previous general practise cohort [156], we demonstrated that *general self-rated health* was an important predictor of the pain chronification. In simple multivariable models, this parameter was highly associated to every outcome (except RtW). In final multivariable analyses, this variable did not explain

additional variance and was therefore removed. However, given its simplicity and effectiveness, probably gathering several concepts, questioning patients about their perceived health could be interesting in clinical practice, before asking more focused questions (for a more detailed discussion, see [156]).

2.3. SUMMARY

We propose the following table (**Table 5.3**), which summarizes the predictive value of demographic characteristics, social context, CRPS-specific features, sensory profiles, and biopsychosocial factors tested in our longitudinal cohort (*Chapter 3*).

Baseline characteristics	**Outcomes**						
	CSS	CRPS diagnosis	Pain intensity	Pain interference	Disability	QoL	Rtw
Demographic characteristics							
Age							
Sex							
BMI	O	X	X		X	X	
Smoking				O			
Social context							
Educational level		O	O	O	O	O	O
Medicolegal conflict					O	O	O
Physical demand of the job							O
Social support (availability)	O			O	X	O	
Social support (satisfaction)				O			
CRPS specific features							
Localisation				O			
Limb dominance							O
Physical intensity of the triggering event	O	O	O	O	O	O	
Duration of strict immobilization							
Historical CRPS type (I and II)	O						
Personal or family history of CRPS							
Scintigraphic results				O			
CRPS duration							
CRPS symptoms and signs (except allodynia; see Table 5.2)	O	O	O	O	O	O	
Allodynia (sign)	X	O	O	O	X	X	
Research Budapest criteria (vs. only meeting clinical Budapest criteria)	O		O	O	O	O	
Relative strength					O		

CRPS subtype (warm vs. cold vs. neutral)[a]	X						
Body perception disturbances	O	O	O	O	O	O	
BE-CRPS profiles[b]	X	X	X	X	O	O	
Sensory profiles							
QST (see Table 5.1)	O	O	O	O	O	O	
Biopsychosocial factors							
Pain°	O	O	X	X	O	O	O
ÖMPSQ	X	X	X	X	X	X	X
Disability	X	O	O	O	X	X	O
QoL°	O	O	O	O	O	X	O
Anxiety			O	O		X	
Depression*	O	O	O	O	O	O	O
GSRH	O	O	O	O	O	O	
CSQ prayer					O	O	O
CSQ ignoring painful sensations			X	O	O	O	
CSQ catastrophisation*	O	O	O	O	O	O	O
CSQ distraction							
Kinesiophobia*	O		O	O	O	O	O
Pain sensitivity (questionnaire)							

Table 5.3. Summarizing of the predictive value of each potential prognostic factors in our longitudinal study. *Abbreviations:* ***baseline predictors*** *in bold, potentially modifiable variables at CRPS onset; X, significant in multivariable models; O, only significant in univariate models; *, These variables were not included in any multivariable models (including BE-CRPS profiles or ÖMPSQ) for methodological reasons (see Chapter 3); °, these variables were only included in multivariable models predicting their own evolution for methodological reasons; [a], based on* [35]*; [b], based on* [157]*; CSS, CRPS severity score; BMI, body mass index; BE-CRPS profiles, biopsychosocial early CRPS profiles; ÖMPSQ, Örebro Musculoskeletal Pain Screening Questionnaire; QoL, quality of life; GSRH, general self-rated health; CSQ, coping strategies questionnaire.*

3. Implications - Towards a Stratified and Personalized Management in CRPS?

Identifying early prognostic factors in a condition offers multiple benefits: it deepens our understanding of underlying mechanisms, reveals potential therapeutic targets, and supports educational interventions. However, identification alone is not sufficient. To generate real clinical value, such insights must translate into modified clinical strategies that meaningfully improve condition/disease trajectories. A widely accepted approach involves adapting standard care by introducing interventions that specifically address factors linked to poorer outcomes.

By identifying early variables impacting CRPS prognosis, our work lays the foundation for a more personalized approach to management. One further step would be to investigate whether targeting these modifiable factors could effectively alter the clinical course of CRPS.

3.1. POTENTIAL STRATIFICATION TOOL

Based on the modifiable predictors identified, we propose the following stratified and personalized management approach (upon condition of validation). The principle is to use the *BE-CRPS profiles* to stratify patients according to their risk of chronification and tailor therapeutic strategies accordingly, based on both published guidelines on the topic [77,91,109] and pathophysiological mechanisms potentially underlying the different profiles. An application has been designed to facilitate their utilisation in further research (https://github.com/vladaron/CRPS_longitudinal).

While all patients would receive a core treatment package, additional therapeutic resources and modalities would be allocated to the more severe profiles, directly at the start of treatment (i.e., without the four-week delay suggested in Ferraro's algorithm [77]).

Furthermore, as proposed in *Chapters 2* and *3*, the lack of patient selection for specific interventions may partly explain the limited effectiveness observed for certain therapeutic modalities. In CRPS studies, we hypothesize that tailoring interventions based on *BE-CRPS profiles* could help address this limitation and improve treatment outcomes for some modalities in specific patient subgroups.

This proposal, inspired from the SBT work [119,122] is summarized in **Figure 5.1** (briefly presented in *Chapter 3*). Before detailing the proposed stratified management approach, several considerations must be acknowledged. First, the figure reflects a potential management pathway within a specific healthcare setting, largely shaped by the Belgian system but also influenced by an idealized model in which general practitioners/physiotherapist can provide appropriate CRPS- and pain-related education. In practice, however, access to certain interventions varies considerably. For example, psychotherapy and occupational therapy are positioned as second- or third-line options due to limited availability and associated costs, despite their recognized relevance in many chronic pain conditions. By contrast, physiotherapy is presented as a first-line intervention in this model, though accessibility to physiotherapists may be restricted in other healthcare systems.

Second, it is important to emphasize that these treatment options are putative and hypothetical. Their purpose is to illustrate potential implications of this work and, most importantly, to stimulate discussion. This is not an established treatment protocol. Although addressing modifiable early prognostic factors has been attempted in multiple conditions, targeting individually identified prognostic factors may not necessarily improve outcomes in CRPS (particularly if some of these predictors reflect stable traits rather than modifiable states), and we remain far from having a validated tool to guide treatment strategies in clinical practice.

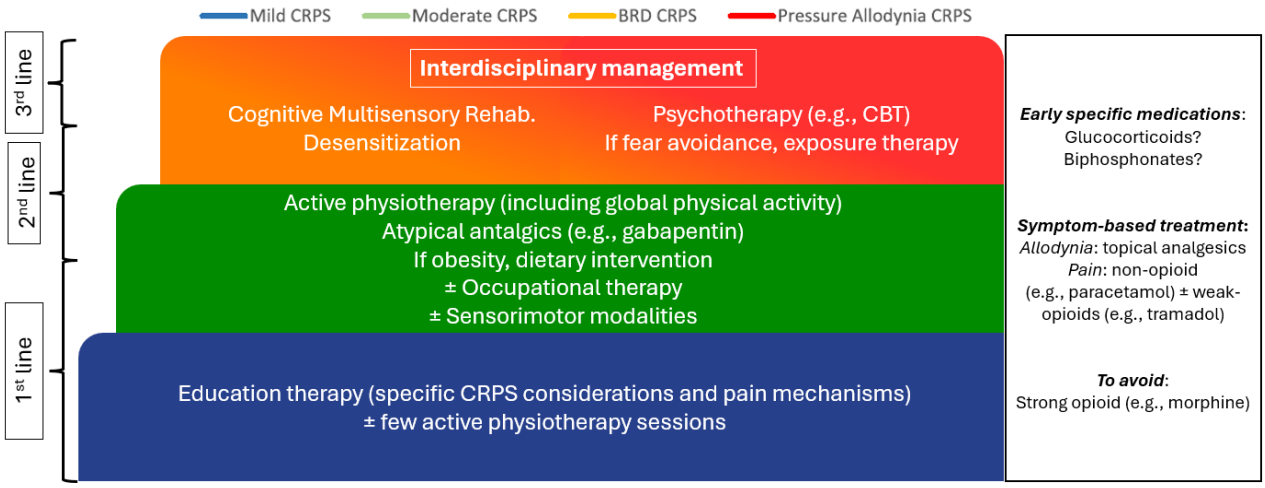

Figure 5.1. ***Potential early CRPS stratified management according to BE-CRPS profiles****. Abbreviations: CRPS, complex regional pain syndrome; BE-CRPS profiles, biopsychosocial early CRPS profiles; BRD, body representation disturbances; Rehab., rehabilitation; CBT, cognitive behavioural therapy.*

3.1.1. General considerations and treatment modalities common to all profiles

As emphasized by Ferraro et *al*. [77], all patients diagnosed with CRPS should receive comprehensive education about the condition. This begins with clearly stating a formal diagnosis using the term *complex regional pain syndrome* (rather than *algodystrophy* or "*causalgia*" for instance), which helps validate the patient's experience and provides a framework for understanding their symptoms.

Specific CRPS education should include:

- A plain language *explanation of CRPS pathophysiology and typical symptoms*, such as vasomotor disturbances, pain-related distress, and altered limb perception — reassuring patients that these symptoms are common and do not indicate condition progression or worsening prognosis.
- *Reassurance* about the (1) non-life-threatening nature of the condition, emphasizing that CRPS does not compromise vital prognosis, (2) its evolution — while the long-term outcome remains uncertain, it is reasonable to expect a gradual reduction in pain and disability over the

coming months, even if the extent of improvement cannot be precisely predicted.

- *Encouragement to remain as active as possible*, clarifying that movement — even if painful — is part of the treatment, in contrast to other conditions like fractures where rest is recommended. Among others, it is thought that moving contribute to alleviate inflammation [100], one of the key components of early CRPS pathophysiology (see Introduction section). For instance, a recent systematic review investigated the effectiveness of exercise in reducing inflammatory markers in autoimmune diseases [160]. The authors reported that regular physical activity was associated with a modest reduction in C-reactive protein, IL-6, and TNF-α. Although early CRPS is not typically marked by elevated CRP levels, its pathophysiology appears to involve autoimmune mechanisms, including a potential role for TNF-α. These findings suggest a possible benefit of encouraging global physical activity in CRPS management.

Additionally, patients should receive *education on pain mechanisms* more broadly, framed within a biopsychosocial model. This includes helping them understand how thoughts, emotions, behaviours, and the social environment interact with the pain experience. Educational content should also address practical aspects such as activity pacing, management of flare-ups, and the development of adaptive coping strategies. In line with the importance of "yellow flags," specific attention should be given to maladaptive psychological processes related to pain (e.g., catastrophizing, fear of movement). Such information can be delivered by general practitioners, pain specialists, or physiotherapists with training in psychological aspects of pain management, thereby ensuring that education is both accurate and integrated into routine care.

Moreover, patients should be offered *analgesic treatment* — ranging from first- to second-line medications — tailored to individual needs and preferences.

Long-acting formulations may help manage background pain, while short-acting or *as-needed* treatments can support movement and functional rehabilitation. Similarly, extrapolated from neuropathic pain treatment guidelines [247], some topical analgesics (i.e., capsaicin and lidocaine) may be considered in the management of CRPS, particularly to target sensory symptoms like light-touch allodynia. Although the *BRD CRPS* profile was associated with a higher prevalence of allodynia, it would not be appropriate to restrict this therapeutic approach solely to that subgroup. Addressing allodynia should remain a symptom-based strategy, applicable across profiles depending on individual clinical presentation.

Bisphosphonates and *glucocorticoids* are also not allocated to particular profiles. Both seem to be effective in early CRPS, but further investigations are needed to systematically recommend their utilization [22,77]. As a stronger inflammatory response might be hypothesized in severe profiles (particularly in *Pressure allodynia CRPS*, see *Chapter 2*), glucocorticoids may perform better among these subjects. Nevertheless, we are currently lacking valuable studies to support this hypothesis.

Given the unclear rationale underlying most rehabilitation techniques [98], we avoided advice recommending specific methods. The primary goal remains to promote active mobilisation and alleviate symptoms.

3.1.2. Mild CRPS

In cases classified as *Mild CRPS*, clinicians should emphasize the generally favourable prognosis and the likely reduction in both pain and disability over time. Alongside education and analgesia, some physiotherapy sessions may be beneficial. These sessions should focus on addressing patient concerns, reinforcing movement strategies (especially regarding the restricted RoM and weakness, observed in nearly all early CRPS patients), and guiding the

progressive resumption of normal activity based on the patient's specific context and functional goals.

We suggest that this subgroup can be effectively managed by the general practitioner and, if needed, a physiotherapist, with the option of a single consultation with a physician experienced in CRPS. This visit would serve to confirm the diagnosis and ensure the patient receives appropriate explanations and guidance.

3.1.3. Moderate CRPS

For individuals of the *Moderate CRPS* profile, the main therapeutic strategy should be intensive rehabilitation led by a physiotherapist. Depending on the general practitioner's clinical judgment, referral to secondary care — for instance, to a specialist in physical medicine and rehabilitation (as commonly practiced in Belgium) — may be appropriate to initiate a multidisciplinary rehabilitation program. This program may include occupational therapy when functional impairments interfere with activities of daily living or work-related tasks.

Given its safety profile, ease of implementation, and the possibility of self-training, sensorimotor modalities (e.g., mirror therapy) could be introduced as a complementary approach for patients where a full active program is not possible yet[44], or those describing body representation disorder. It should be noted that the evidence related to the effectiveness of these modalities is very limited or even contradictory [196,243]. In addition to targeted rehabilitation of the affected limb, patients should be encouraged to engage in general physical activity, including both aerobic and resistance exercises.

[44] Mostly due to movement-induced pain.

Increasing overall physical activity may not only positively influence body composition (and thus BMI) but also help modulate systemic inflammation, which may play a role in maintaining CRPS symptoms (see *3.1.1. General considerations and treatment modalities common to all profiles* for references and explanations).

As increased BMI appears to be associated with poorer CRPS prognosis, strategies to reduce body fat should be considered. While promoting physical activity is essential in all CRPS cases, a nutritional intervention may offer added value. Referral to a dietitian should therefore be considered for patients with overweight or obesity. While this approach is primarily proposed for the *Moderate* and *severe profiles* to optimize cost-effectiveness within a stratified care model, it may also be a valuable adjunct in *Mild CRPS* cases, given the broader health benefits of addressing elevated BMI.

In terms of pharmacological management, the early introduction of atypical analgesics — such as tricyclic antidepressants or anticonvulsants (gabapentin, pregabalin) — may be considered at this stage, without the need to wait for several weeks of persistent pain. We hypothesize that this proactive approach could enhance symptoms control, thereby facilitating participation in rehabilitation sessions and ultimately potentially reducing the risk of pain chronification.

3.1.4. Severe CRPS – BRD and Pressure allodynia CRPS

While the two severe profiles were defined based on distinct early characteristics, they did not show significant differences in clinical presentation or outcomes at 1 year (*non-adjusted Chi-squared and Wilcoxon tests: $p > 0.05$*). Therefore, we propose for both groups the immediate initiation of intensive multidisciplinary rehabilitation, involving physiotherapists, occupational therapists, and, when indicated, psychologists.

In practice, both subgroups would likely benefit from a personalized, multimodal rehabilitation program, rather than rigidly adhering to a predefined profile-based protocol. However, the existence of two distinct profiles[45] suggests differences in pathophysiological mechanisms and, hence, tailored therapeutic modalities.

3.1.4.1. Severe CRPS – BRD CRPS

The *BRD profile* was characterized by the highest body perception disturbances and an important probability of presenting allodynia. Therefore, it might be interesting to include Cognitive Multisensory Rehabilitation (including discrimination tasks)[46] [11] and desensitization (which could also help patients "to perceive their limb in a more normal way" [149]) into the interdisciplinary management. Furthermore, we expect that sensorimotor modalities (e.g., mirror therapy) might be more effective for these patients.

3.1.4.2. Severe CRPS – Pressure allodynia CRPS

Given the elevated ÖMPSQ scores observed in the *Pressure allodynia CRPS* subgroup (which means, higher psychosocial severity), psychological support appears particularly important for those patients. The goal is to address maladaptive cognitive and emotional processes that may contribute to pain chronification.

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[45] Identified through LCA and therefore statistically different at inclusion.

[46] As summarized by Batalla et *al*., "Cognitive Multisensory Rehabilitation (CMR) focuses on the perception and integration of different sensory modalities (e.g. somatosensory, visual, etc.) and body to produce purposeful, effective, and accurate movements facilitating appropriate interactions with the surrounding environment" [11]. CMR tasks engage brain areas involved in sensorimotor integration, body awareness, and pain processing — functions that may be altered in CRPS patients exhibiting body perception disturbances [264].
In practice, the CMR protocol typically involves 35 minutes of sensory discrimination tasks performed during functional movements (mostly with eyes closed), followed by 10 minutes applying the learned strategies to activities of daily living in each treatment session [11].

For instance, within the framework of the pain interpretation bias model — a likely driver of catastrophizing — tailored cognitive-based therapies have been shown to modify these biases and significantly improve outcomes compared to sham interventions [258].

Furthermore, exposure-based therapies, particularly in patients with kinesiophobia, show promising effects in reducing pain and disability, and in facilitating a more progressive return to movement and daily activities [77]. Given the time- and resource-intensive nature of these interventions, it seems especially relevant to target this subgroup of patients, who is not only at higher risk of chronification but also more likely to respond positively to such therapies.

3.1.5. Stratified CRPS management – summary

The approach proposed above specifically targets early CRPS (i.e., within 6 months of symptom onset). Although this strategy has yet to be tested, refined, and validated in prospective studies, it represents a first attempt at a stratified and personalized management model for early CRPS.

This putative model pursues several objectives: (1) to provide a rationale for tailoring treatment modalities based on patient characteristics and prognosis, (2) to improve outcomes in more severe cases via early referral and intensive rehabilitation, and (3) to optimize healthcare resource utilization by reducing unnecessary medical procedures in all CRPS patients, long-term work absenteeism in severe profiles, and overtreatment in patients with *Mild CRPS* — for whom a more conservative approach may be sufficient.

Despite its promise, it is important to acknowledge that this approach may not ultimately modify the clinical course. This could be due either to the limited modifiability of the identified prognostic factors or because these factors reflect underlying severity without being causally involved, in which case targeting them may not influence long-term outcomes.

4. Research and Clinical Implications

We showed that CRPS is a condition that substantially impacts all dimensions of life. As summarized in *Chapter 3*, a significant proportion of CRPS patients continue to experience pain and disability 1 year after onset, underlining the need for continued research and clinical attention.

With regard to CRPS diagnostic criteria — and given the lack of evidence for a significant influence of symptom duration on clinical outcomes — it is important to reconsider the notion that a minimum duration is required before a CRPS diagnosis can be made. Rather than increasing the risk of overdiagnosis, clarifying that no minimum duration is required would help to recognize and validate patient suffering early, thereby preventing therapeutic delays and promoting timely, appropriate interventions.

In fibromyalgia, for example, receiving a diagnosis has not been shown to negatively impact long-term outcomes [282]; on the contrary, it may provide a helpful framework, reduce unnecessary investigations, and avoid repeated hospitalizations. In CRPS, we hypothesize that early diagnosis and patient education may positively influence prognosis — or at the very least, limit confusion and prevent unnecessary, potentially costly or even harmful, medical procedures.

Just as the outdated “three stages” model has been abandoned [92], it may also be time to let go of rigid distinctions such as "warm" vs. "cold" CRPS or type I vs. type II (absence or presence of a demonstrated peripheral neurological lesion) — or at least avoid placing undue clinical emphasis on them.

Our work highlights several variables that should be considered as potential confounders in future CRPS research. Ideally, we recommend incorporating *BE-CRPS profiles* as a stratification or adjustment factor in studies involving early CRPS populations, to test its accuracy in different settings.

More broadly, the systematic inclusion of psychosocial variables — as assessed by tools such as the ÖMPSQ — along with the presence of allodynia and BMI, appears both clinically relevant and time-efficient. These factors may significantly influence outcomes and should be accounted for (i.e., used as cofounding variables) in order to improve the interpretability of future findings in (early) CRPS research.

As psychosocial factors are key predictors in most MSK conditions, we could hypothesize that common mechanisms are implicated into chronification of CRPS and MSK disease, such as LBP. As summarized in the *Introduction section*, these mechanisms are still poorly understood.

One of the key lessons we have drawn from four years of working on this CRPS project is the urgent need to improve practitioner education. Too often, we have witnessed colleagues unfamiliar with CRPS, or, worse, conveying inaccurate and sometimes harmful information to patients.

The following examples illustrate this observation:

- relying on the outdated three-stage model to predict future disease course;
- requiring bone scintigraphy for diagnosis or, conversely, refusing to diagnose CRPS in the absence of positive imaging;
- offering patients overly optimistic prognoses tied to arbitrary timelines (e.g., a patient was told that CRPS "only lasts 12 months" which, at 11.5 months, was still suffering as on the first day, yet fully expecting the condition to resolve within two weeks);
- refusing surgery for unrelated conditions on an affected limb solely due to a history of CRPS;
- or making stigmatizing comments such as "It's all in your head", "CRPS is a disease of civil servants", "You could tell in advance this patient would

develop CRPS — look at their personality", or "I hope you're including PSYCHOLOGICAL variables in your study".

Such misconceptions and attitudes not only perpetuate stigma but can directly harm patients by delaying appropriate care or invalidating their experience. As such, practitioner education – including tools for appropriate communication – should remain a central priority in CRPS management and research moving forward.

4.1. FUTURE RESEARCH

Based on our observations made during our work, several paths warrant further exploration.

First, extending the follow-up of early CRPS patients beyond the 1-year boundary of our cohort would be highly valuable. Such an extension could confirm the findings by Cave et al. [43], who observed minimal clinical improvement between 6 months, 1 year, and 8 years of follow-up, suggesting that outcomes tend to stabilize early in the condition course. Reassessing participants previously included in our cohorts would provide crucial insights into the persistence or evolution of the identified prognostic relationships and help determine whether early (bio)psychosocial factors continue to influence long-term outcomes.

Second, our prognostic findings should be replicated in a larger and independent cohort. Incorporating biomarkers related to inflammatory processes and genetic predispositions — two aspects not directly explored in *Chapter 3* — could yield new insights into CRPS pathophysiology.

Third, external validation of the BE-CRPS profiles in an independent cohort is essential to ensure that this classification is both reproducible and clinically applicable in early CRPS populations. Combining this validation with the integration of biological markers such as TNF-α and its soluble receptor (sTNF-

RII), alkaline phosphatase, and osteoprotegerin could yield valuable complementary insights. This approach would enable the exploration of potential mechanistic links between distinct *BE-CRPS profiles* and specific inflammatory or bone metabolism pathways, thereby bridging clinical phenotype with biological mechanisms. However, the clinical feasibility of such profiling must remain a priority, relying on variables that can be easily and rapidly assessed in everyday practice.

Future studies should also investigate whether the *BE-CRPS profiles* reflect distinct underlying pathophysiological processes, such as heightened central or systemic sensitization in the more severe subgroups.

Finally, the clinical and economic impact of a stratified management approach based on *BE-CRPS profiles* remains to be evaluated. A randomized controlled trial could assess whether stratified care improves outcomes and cost-effectiveness in early CRPS. However, several preliminary steps are required before implementing such an approach in practice:

- Reproducing the *BE-CRPS* classification and confirming its external validity.
- Establishing a clearer consensus on standard-of-care management for early CRPS, particularly regarding the use of glucocorticoids, bisphosphonates, and specific interventions such as cognitive multisensory rehabilitation.
- Conducting an initial prospective, single-arm feasibility study with a limited number of participants to assess the acceptability of a stratified approach among patients and clinicians, as well as its practical feasibility in preventing chronification.

Together, these steps would lay the foundation for a future stratified randomised control trial aimed at translating the findings of this thesis into a validated, personalized management strategy for early CRPS.

4.2. STRATIFICATION MANAGEMENT OF EARLY CRPS: A STUDY DESIGN

Building on our previous findings and the recognized need for further advancement in this field, we propose the conceptual design of a randomized controlled trial aimed at improving the understanding and management of early CRPS. The overarching objective of such a study would be to determine whether a stratified management approach, tailored to early prognostic profiles, can prevent chronification and improve long-term outcomes.

As previously discussed, several crucial steps must precede the implementation of such a trial. Chief among these is the external validation of the *BE-CRPS profiles*, ensuring their reproducibility and clinical applicability across independent cohorts. Furthermore, methodological development is required to design practical, clinician-friendly tools for accurate profile classification and to identify the most suitable therapeutic strategies for each subgroup.

The intention of presenting this proposed design is not to outline a finalized protocol but rather to stimulate discussion and provide a roadmap for future research. Ultimately, this approach aims to bridge the gap between early prognostic assessment and personalized intervention, establishing whether stratified care can meaningfully alter the clinical trajectory of early CRPS.

4.2.1. Aims

The aim of this study would be to assess the added value of a personalized, stratified treatment approach based on those *BE-CRPS profiles* during the early phase of the condition.

4.2.2. General study design

The study will be conducted as a multicentre randomized controlled trial with a 2:1 allocation ratio (intervention:control)[47], summarized in **Figure 5.2**.

Participants with early CRPS will be enrolled and assessed as soon as possible after symptoms onset, then randomized into two groups:

- an intervention group, receiving treatment tailored to their *BE-CRPS profile*, and
- a control group, receiving treatment as usual without stratification.

Four follow-up assessments will be scheduled:

- at 6 to 8 weeks post-inclusion, and at
- 6-, 9-, and 12-months following symptom onset.

Recruitment will be built on the clinical network established during our previous longitudinal study (see *Chapters 2* and *3*). The intervention will be delivered at two sites: Cliniques Universitaires Saint-Luc and CHU UCL Namur, site Godinne.

A longer follow-up period (e.g., 2 years) could provide valuable insights into the long-term course of CRPS. However, such an approach would likely require substantial additional resources and may be associated with higher drop-out rates. Moreover, current evidence suggests that CRPS outcomes tend to stabilize after the first year [43], reducing the added value of extending follow-up beyond this timeframe.

[47] The choice of such ratio is justified by ethical considerations (offering the supposed best treatment for more patients) and the need to gather more information on the interventional group.

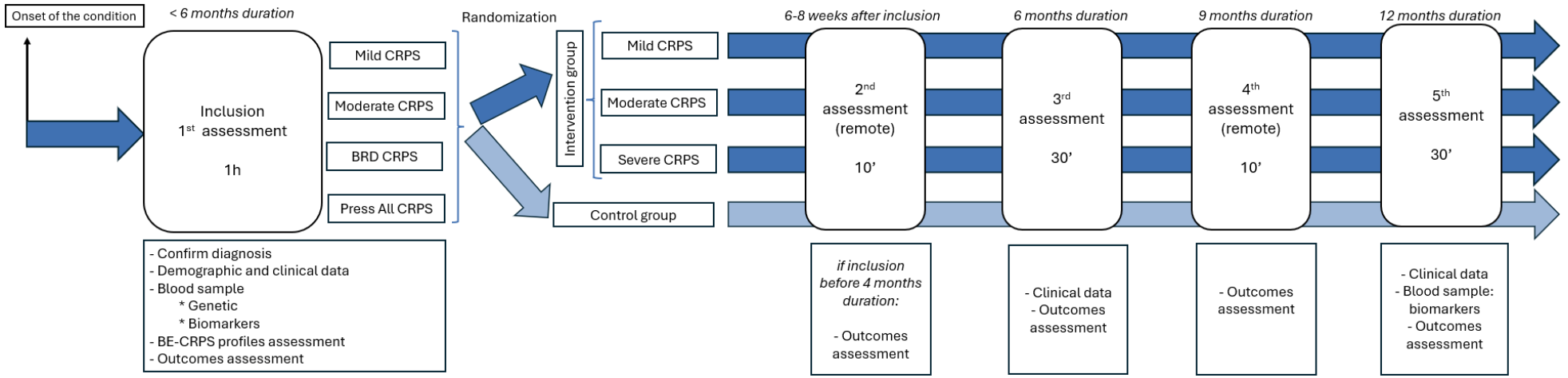

Figure 5.2. ***Study design of a randomized controlled trial investigating the added-value of a stratified management based on BE-CRPS profiles in individuals with early CRPS****. Participants with early CRPS (i.e., < 6 months since symptom onset) are included as soon as possible. Following the determination of their BE-CRPS profile, they are randomized into two groups.*

In the intervention arm, treatment is tailored to their BE-CRPS profile, whereas in the control group, standard care is provided without stratification. All other parameters are intended to remain consistent between groups.

Abbreviations: CRPS, comp lex regional pain syndrome; BE-CRPS profiles, Biopsychosocial early CRPS profiles; BRD, body representation disturbances; Press All, Pressure Allodynia.

4.2.3. Hypotheses

While we hope that the stratified and personalized approach based on *BE-CRPS profiles* may broadly enhance care for all early CRPS patients — particularly by educating and raising awareness among caregivers — *s*uch effects may not be detectable in this initial randomized study, as the control group will receive optimal management based on the most recent guidelines, likely exceeding typical early CRPS management and broadly corresponding to the treatment of *Moderate CRPS*. Furthermore, evidence suggests the effectiveness of such stratified interventions is mainly driven by improvements in patients with severe profiles [54,122]. Therefore, we hypothesize the following:

- (1) Patients in the two severe subgroups (*BRD* and *Pressure Allodynia CRPS*) will show significantly greater improvements in the intervention group compared to the control group, due to early referral to a specialized team delivering tailored treatments.
- (2) The moderate subgroup will achieve outcomes similar to or slightly better than those of *Moderate CRPS profile* in the control group.
- (3) Patients in the mild subgroup will have comparable outcomes across both groups, but with lower resource use in the intervention arm. Given the low incidence and societal cost of CRPS, this objective is considered secondary.

4.2.4. Participants and inclusion criteria

The following table (**Table 5.4**) presents the proposed inclusion and exclusion criteria to recruit the participants.

Inclusion criteria	Exclusion criteria
• Adults (≥ 18 years old) • Early CRPS (< 6 months duration since symptoms onset) • Meet clinical Budapest criteria [104] • CRPS type I or II [92] • Capacity to understand and voluntarily sign an informed consent	• Age < 18 years old • Post-stroke CRPS ("shoulder-hand syndrome") • Insufficient French language skills to answer questionnaires • Personal previous history of CRPS at the same limb • Severe psychiatric or neurological disorders that would interfere with the participants' ability to complete the study tasks

Table 5.4. ***Inclusion and exclusion criteria of the potential randomized trial investigating the effectiveness of a stratified management in early CRPS patients based on the BE-CRPS profiles.***

Participants for which the distance between their homes and the centres performing the intervention corresponds to a major barrier would be invited to participate in the control group.

4.2.5. Inclusion session and variables collected

The study will consist of five sessions, each designed to collect specific variables.

The first session will be an inclusion session conducted by the investigator as early as possible, and within the six months of CRPS symptom onset. During this session, the following variables will be collected:

- *Demographic variables*: age, sex, BMI, limb dominance, participant-reported comorbidities and related treatments, addictions, education level,
- *Work-related variables*: professional status, work type based on the Work Demands Coding System [290];

- *Medico-legal context*: conflict with employer or insurance company, work injury, perceived injustice.
- *CRPS history*: family history of CRPS (1st and 2nd level), triggering event and its physical intensity, potential immobilization (type [splint vs. cast] and duration of strict immobilization), CRPS duration at inclusion (since the onset of the symptoms and the triggering event).
- *Scintigraphic results* if performed
- *CRPS clinical variables*: localization, potential spreading, Research Budapest criteria, CSS, CRPS signs and symptoms (including skin temperature difference and grip strength), current treatment, notably using the Medication Quantification Scale [110].
- *Body perception disturbances*: R-Bath-CRPS-BPDS
- *Deep tissue sensitivity*: PPT
- Some *self-reported questionnaires*, based on CRPS recommendations [97], assessing: (1) disability, (2) QoL, (3) pain severity and interference, (4) pain-related fear of movement, (5) anxiety and depressive disorder, (6) psychosocial severity (ÖMPSQ), (7) pain catastrophizing, and (8) perceived social support.
- In addition to the previous study, we would like to evaluate thanks to a blood sample from the arm of the unaffected side:
    - *Some biomarkers*: TNF-α and its soluble receptor (sTNF-RII), alkaline phosphatases, and osteoprotegerin. Additional biomarkers may be considered based on cost-effectiveness and expert recommendations[48].
    - *Genetic background*: HLA-DQ8 and four relevant SNPs (see Introduction. Physiopathology section for details).

[48] Notably, we plan to solicit input from the CRPS SIG forum of the IASP.

4.2.6. Randomisation

The allocation process will use dynamic randomisation[49], adjusting assignment based on the sex, CRPS duration (< 2 months, 3 to 4 months, 5-6 months)[50], and *BE-CRPS profiles* [50].

4.2.7. Study *follow-ups sessions*

Six to 8 weeks after the inclusion[51], participants will complete a brief online survey with outcome questionnaires. A short phone call with the investigator will assess CRPS symptoms. This timepoint will only apply to participants included before 4 months of symptom duration.

At 6 months, participants will attend an in-person follow-up visit during which the investigator will review current and past treatments, conduct a physical examination, and complete outcome questionnaires.

At 9 months, participants will again complete a brief online survey with outcome questionnaires, followed by a phone call from the investigator to assess CRPS symptoms.

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[49] We plan to apply biased-coin minimisation, using *MinimPy* application [229].

[50] Although our observational cohort suggested that CRPS duration does not significantly influence outcomes in early CRPS, this finding requires replication as it has only been reported once. To minimize potential confounding, we therefore prefer to stratify randomisation by CRPS duration rather than risk detecting both a treatment effect and an unintended imbalance across groups. This approach also reduces the need to adjust for CRPS duration in statistical models, thereby limiting the number of covariates and increasing statistical power.

[51] This timeframe is based both on clinical experience in rehabilitation and on the European guidelines, which recommend waiting approximately two months before considering referral to specialized care if no substantial reduction in pain or improvement in disability is observed [91]. Accordingly, we consider 6–8 weeks to be an appropriate window to distinguish between the effects of natural recovery and those of the intervention.

At 12 months (final follow-up), the investigator will collect the same data as at the six-month visit and obtain a second blood sample to allow comparison of early vs. 12-month biomarkers.

4.2.8. Blinding and methods to reduce the risk of bias

Investigators conducting inclusion and follow-up sessions will not provide therapeutic follow-up for any participant, regardless of group allocation. Participants will remain blinded to their allocation. In the control group, caregivers will not be informed of the individual's *BE-CRPS profile*.

4.2.9. Treatment modalities depending on the groups

In the intervention group, participants will be treated according to their BE-CRPS *profile*, assessed at the inclusion session (see *3.1. Potential stratification tool* in discussion section for details). Profile-based recommendations and a treatment algorithm will be provided to their caregivers, who will be specifically trained before trial onset[52].

Conversely, in the control group, *BE-CRPS profile* variables will be recorded, used for randomization but not to guide therapy. Only general treatment recommendations will be provided, corresponding to the "best standard of care," which broadly aligns with the *Moderate CRPS* profile.

Both groups will receive standardized educational therapy at the inclusion session, with information summarized in a prospectus to ensure equal access to education. If hospital-based therapeutic modalities are required (e.g., for severe profiles and some *Moderate CRPS* participants in the intervention group), both arms will be referred to the same limited pool of physiotherapists, occupational therapists, and psychologists specifically trained in CRPS management.

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[52] The duration and the modalities of this training still need to be defined.

4.2.10. Endpoints

We are planning to investigate several outcomes at each time-point, based on ICF [141].

- Body structure and functions:
  - CSS
  - Budapest clinical criteria
  - Pain severity (Patient Reported Outcomes Measurement Information System 29-item Health Profile [PROMIS-29 profile])
- Activity
  - Pain interference (PROMIS-29 profile)
  - Disability (*primary endpoints*): quickDASH and LEFS. The PROMIS-29 profile is also investigating the "physical function" but only based on four questions, with a demonstrated ceiling effect in upper limb conditions [21].
- Participation
  - QoL (EQ-5D-5L)
  - Ability to participate in social role (PROMIS-29)
  - RtW
  - Patient's global impression of change
  - Successful recovery, self-reported by the participant (yes/no)[53].

[53] There is currently no consensus on what constitutes 'recovery' in CRPS. While simple cut-offs (e.g., pain intensity < 3/10) or definition (e.g., not meeting Budapest criteria anymore) could be used, they do not adequately capture the multidimensional nature of recovery. For instance, a patient may report an absence of pain yet still experience substantial disability in daily life.
A qualitative study showed that, after trauma, patients described successful recovery as a return to 'normal,' though the definition of 'normal' was highly individual [177]. Conducting a qualitative survey with both early and persistent CRPS patients to explore the concept of recovery would therefore be an important step for the field.

In terms of statistical analyses, we will perform a LMM with repeated measures for each outcome, incorporating relevant confounding variables (e.g., BMI and baseline value of the outcome) to evaluate whether assignment to the intervention group significantly influences outcome trajectories over time. The intention to treat principle will be respected, where missing data are accounted for under the missing at random assumption (using multiple imputation [151], similarly to *Chapter 3*).

To assess group-specific costs, quality-adjusted life years (commonly called QALYs) will be calculated using the EQ-5D-5L questionnaire. At each follow-up, we will also record treatments, medical procedures, and (para)medical appointments to estimate healthcare costs attributable to CRPS for each participant.

4.2.11. Sample size

Using data from our observational cohort, we calculated the required sample sizes ($\alpha = 0.05$; power = 0.80; two-sample comparison; 2:1 allocation ratio) based on the following hypotheses:

- (1) The intervention will result in a significant improvement in disability across the entire cohort, compared to its natural course (statistical comparison: means and SD from inclusion to last follow-up using the values of the entire observational cohort).
- (2) The intervention will lead to a significant improvement in disability for the severe subgroup compared to its natural course (statistical comparison: means and SD from inclusion to last follow-up using the values of the two severe profiles from the observational cohort).

Nevertheless, we expect that the use of this dichotomous outcome in our study will already provide valuable preliminary insights.

The most statistically demanding scenario (hypothesis 2) required 76 participants, assuming that individuals with severe profiles will represent approximately 37% of the cohort, as observed in our previous study (see *Chapters 2* and *3*).

To account for a conservative 20% dropout rate (despite the low attrition observed in our previous study [5%]), we increased the target sample size to 90 participants (60 in the intervention group, 30 in the control group).

VIII. Conclusion

This thesis demonstrates that early CRPS is not a uniform condition but rather a syndrome marked by substantial heterogeneity in presentation, mechanisms, and prognosis. This phase requires a biopsychosocial perspective to be fully understood.

By combining a systematic review and a prospective cohort offering a deep analysis of the early period as well as a longitudinal follow-up, this work advances three main propositions:

First, psychosocial severity should be recognized as a central prognostic construct in CRPS. Consistently associated with CRPS diagnosis, pain, disability, QoL, and RtW, psychosocial distress emerged as the strongest predictor across all outcomes. Crucially, these factors are modifiable, creating opportunities for early and targeted interventions. This supports the development of screening and management pathways similar to those implemented in LBP, with the aim of reducing the risk of chronification.

Second, early CRPS should be conceptualized as a heterogeneous syndrome defined by distinct subgroups. The identification of four *BE-CRPS profiles — Mild*, *Moderate*, *BRD*, and *Pressure Allodynia CRPS* — provides prognostic insight and may reflect different underlying mechanisms. These profiles offer a framework for stratification, with direct implications for both patient care and clinical trial design.

Third, future research and clinical trials should integrate emerging key predictors such as psychosocial severity or/and *BE-CRPS profiles*. Incorporating these factors may reduce heterogeneity, improve prognostic accuracy, and clarify the true efficacy of therapeutic interventions. In practice, this would enable personalized care, where low-risk patients could be managed conservatively, while high-risk subgroups such as *Pressure Allodynia* or *BRD CRPS* receive early

multidisciplinary treatment. Large-scale, longitudinal studies are now essential to refine prognostic models and validate stratification tools.

Taken together, this thesis supports a shift in CRPS research and management — away from an exclusive focus on biological markers and toward an integrative, stratified, and personalized framework. Such an approach holds promise not only to improve outcomes for individual patients but also to strengthen the methodological foundations of CRPS research and open new avenues for targeted therapeutic innovation.

IX. Annexes

1. Supplementary materials

1.1.CHAPTER 1

Available at https://onlinelibrary.wiley.com/doi/10.1002/ejp.4785 in "Supporting information".

1.2.CHAPTER 2

Available at https://onlinelibrary.wiley.com/doi/10.1002/ejp.4785 in "Supporting information".

1.3.CHAPTER 3

Available at https://journals.lww.com/pain/fulltext/9900/complex_regional_pain_syndrome_evolution_is.1035.aspx in "Supplemental Digital Content".

2. Articles Published During the Thesis Period but Not Included in the Chapters

2.1. Facteurs pronostiques précoces dans le syndrome douloureux régional complexe : une revue systématique (French translation of Chapter 1)

Louis Marc-Henri, Meyer Caroline, Legrain Valéry, Berquin Anne. *Facteurs pronostiques précoces dans le syndrome douloureux régional complexe : une revue systématique*. Douleur et analgésie. 2023 Sept; Vol. 36, no. 3, p. 133-47. doi: 10.3166/dea-2022-0267.

2.2. Fattori precoci prognostici, biologici e psicologici, della sindrome dolorosa regionale complessa : una review sistematica (Italian translation of Chapter 1)

Louis Marc-Henri, Meyer Caroline, Legrain Valéry, Berquin Anne. *Fattori precoci prognostici, biologici e psicologici, della sindrome dolorosa regionale complessa : una review sistematica.* Dolore: Aggiornamenti Clinici. 2023. n. 2, p. 5-18.

2.3. Do lifestyle factors influence pain prognosis? A 1-year follow-up study

Louis Marc-Henri, Berquin Anne, Steyaert Arnaud. *Do lifestyle factors influence pain prognosis? A 1-year follow-up study.* Br J Pain. 2023 Jun;17(3):293-305. doi: 10.1177/20494637231152975. Epub 2023 Jan 19. PMID: 37342394; PMCID: PMC10278450.

2.4. Syndrome douloureux régional complexe : comprendre, diagnostiquer et traiter une pathologie méconnue (French version)

Louis, Marc-Henri ; Berquin, Anne. *Syndrome douloureux régional complexe : comprendre, diagnostiquer et traiter une pathologie méconnue*. In: Ortho-Rhumato, Vol. 23, no.2, p. 18-22 (2025) http://hdl.handle.net/2078.1/301107

2.5. Complex regionaal pijnsyndroom : een miskende ziekte begrijpen, diagnosticeren en behandelen (Dutch version)

Louis, Marc-Henri ; Berquin, Anne. *Complex regionaal pijnsyndroom : een miskende ziekte begrijpen, diagnosticeren en behandelen*. In: Ortho-Rheumato, Vol. 23, no.2, p. 18-22 (2025) http://hdl.handle.net/2078.1/301108

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