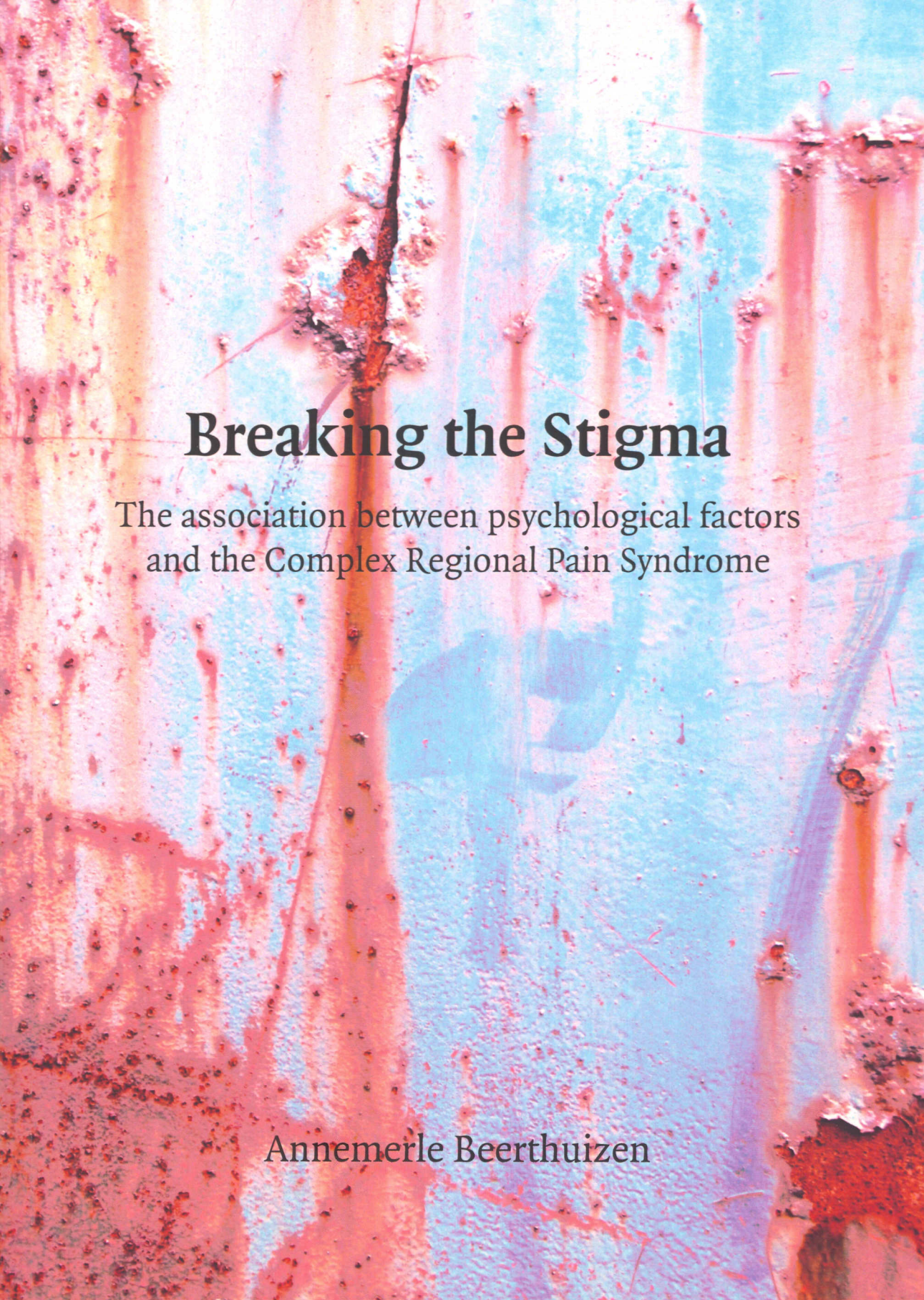

Breaking the Stigma

The association between psychological factors and the Complex Regional Pain Syndrome

Annemerle Beerthuizen

Breaking the Stigma

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The work presented in this thesis was performed at the Department of Anesthesiology and the Department of Medical Psychology and Psychotherapy of the Erasmus MC, Rotterdam.

The study presented in this thesis was funded by the Stichting Erasmus Fonds Pijnbestrijding and the Department of Anesthesiology of the Erasmus MC, Rotterdam.

This thesis was printed with the financial support of the Department of Anesthesiology, Erasmus MC, the Erasmus University, Rotterdam, Nederlandse Vereniging van Posttraumatische Dystrofie Patiënten, and the Stichting Esperance.

ISBN 978-90-8559-427-7

Cover
Dick Ederveen & Monique van Gurp

Lay-out and type setting
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Printed by
Optima Grafische Communicatie, Rotterdam

Breaking the Stigma

The association between psychological factors and the Complex Regional Pain Syndrome

Het stigma doorbroken

De relatie tussen psychologische factoren en het Complex Regionaal Pijn Syndroom

Proefschrift
ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 19 november 2008 om 13:45 uur

door
Annemerle Beerthuizen

geboren te Nijmegen

Promotiecommissie

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Voor mijn ouders

CONTENTS

CHAPTER 1

General introduction

WHAT IS THE COMPLEX REGIONAL PAIN SYNDROME?

In 1900, Sudeck[1] first described a post-traumatic pain syndrome with edema and trophic changes. This syndrome, known as Sudeck atrophy, was later called sympathetic reflex dystrophy and in 1994 renamed Complex Regional Pain Syndrome (CRPS). CRPS usually develops after a minor trauma such as an injury or fracture or after surgery, but spontaneous development of CRPS type 1 (CRPS1) has also been described[2, 3]. There are two types of CRPS described; CRPS1 arises without an obvious, detectable nerve lesion, and type 2 (CRPS2) manifests with an obvious, detectable lesion.

The observation that only certain patients develop CRPS1 after a common trauma has led to the idea that some patients are susceptible to developing CRPS1. There are indications for a genetic susceptibility for CRPS1[29-33], and there is growing evidence for immunological attainment of this syndrome, but a definitive conclusion cannot yet be made[34-39].

The International Association for the Study of Pain (IASP) defines CRPS1 as a variety of painful conditions following injury that appears regionally and has a distal predominance of abnormal findings. The symptoms exceed in both magnitude and duration the expected clinical course of the inciting event, often resulting in significant impairment of motor function and showing variable progression over time[4]. The diagnosis of CRPS1 is based on criteria, and several criteria sets have been developed. The most often used are those of Veldman[5], of IASP[4], and of Bruehl[6]. Pain is the most common symptom used in these criteria, and other symptoms include allodynia, hyperalgesia, abnormal skin color, temperature change, abnormal sudomotor activity, edema, tremor, dystonia, and motor/trophic disturbances[4, 5, 7].

Sarangi et al.[8] found that 22% of CRPS1 patients still reported symptoms at one year after trauma. Several authors concluded that CRPS1 has a severe impact on quality of life, with substantial interference in daily life activities[9, 10]. CRPS1 is a disabling pain syndrome. In a study by Geertzen et al.[10], 26% of patients with CRPS1 had to change jobs, and 30% of the patients with CRPS1 had to quit their job for more than a year. Large, prospective studies on the incidence of CRPS1 in an at-risk population are scarce. The overall limitations of studies on the incidence of CRPS1 are that they analyze a relatively small source population, are single-center studies, employ restricted follow-up, include only one type of fracture, do not measure signs, and either provide no information on the criteria used to diagnose CRPS1 or use a self-made instrument. Reports on the incidence of CRPS1 are therefore inconclusive.

DIAGNOSTIC CRITERIA

Criteria sets used to diagnose CRPS1 are not completely comparable to one another. Although the criteria of Veldman are internationally accepted, there is no psychometric information yet available for these criteria, and there has been much debate about how to apply them. The IASP criteria have a sensitivity of 0.98 and a specificity of 0.36[6], and the criteria of Bruehl have a sensitivity of 0.70 and a specificity of 0.94[6]. The IASP criteria are considered the most appropriate for clinical situations because of the high sensitivity, and the Bruehl criteria are considered the best choice for research purposes because of the high specificity. In our study, all three criteria sets are evaluated; however, the criteria of Bruehl are preferred.

THE ASSOCIATION BETWEEN PSYCHOLOGICAL FACTORS AND CRPS1

The pathophysiology of CRPS1 is not yet understood. The literature yields several hypotheses, and they can be divided into peripheral mechanisms that concern an exaggerated (neurogenic) inflammation[11, 12] and central mechanisms such as central sensitization and the influence of psychological factors in the onset of CRPS1[13-15]. Some researchers have suggested that "psychologically peculiar" patients have an increased risk for developing CRPS1[13, 16].

An indication that psychological factors may play a role in the development of CRPS1 is that the symptoms sometimes spread from the initial affected site, even to a different limb, without the occurrence of a new trauma[17]. Other indications for the involvement of psychological factors are the reported high response rate to placebo therapies[18]. Also, some case reports suggest a relationship between conversion and CRPS1[19-22].

Several authors have suggested pathways between psychological factors and the development of CRPS1. Some authors have stated that certain patients are prone to developing CRPS1 because of personality[23, 24]; however, others disagree with this conclusion[25-27]. Therefore, the main research question that this thesis addresses is as follows: Is there an association between psychological factors and the development and/or maintenance of CRPS1?

THESIS OUTLINE

Figure 1.1 outlines the chapters in this thesis that address different aspects of CRPS1.

Chapter two of this thesis gives a systematic review of the existing literature on the association between psychological factors and CRPS1. Epidemiological data from large, prospective studies on the incidence of

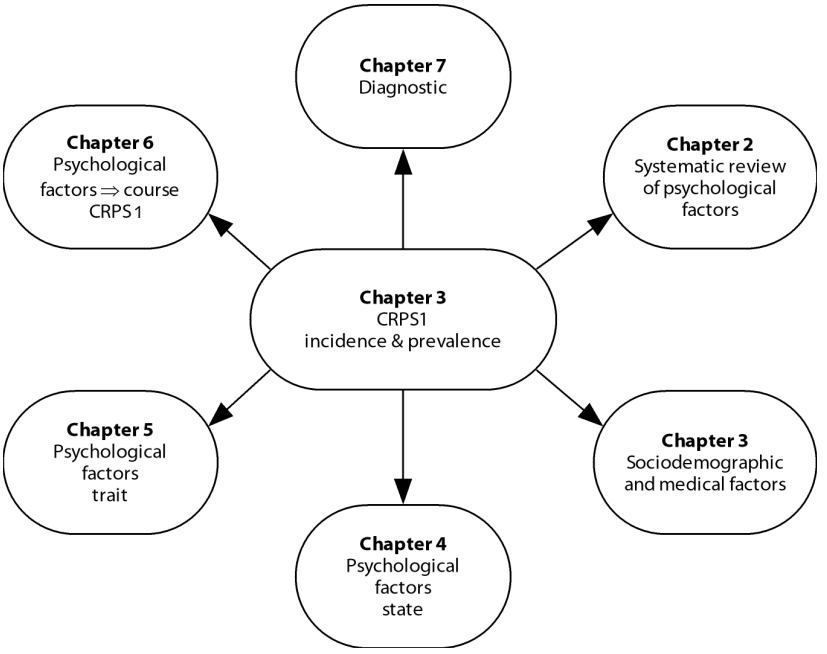

Figure 1.1 Aspects of CRPS1 and the corresponding chapters of this thesis

CRPS1 in patients with a fracture are scarce. Therefore, chapter three presents the incidence of CRPS1 in our study. This chapter concerns the following questions:

- What is the incidence of CRPS1 in patients after a fracture?
- What is the prevalence of CRPS1 in patients after a fracture at 3 and 12 months after trauma?
- Are there demographic (sex, age, level of education) differences between patients with a fracture who develop CRPS1 and those who do not?
- Are there differences in the following medical variables between CRPS1 patients and those who do not develop CRPS1: occurrence of CRPS1 in the past, number of comorbidities, type of fracture/fracture location, intra-articular fracture, dominant hand reductions of the fracture, type of treatment, and duration in plaster?
- To what extent can CRPS1 be predicted by demographic and medical variables?
- Is there a difference in quality of life between patients with a fracture without CRPS1 and patients with a fracture with CRPS1?

Chapters four and five answer the main question of this study, namely: Is there an association between psychological factors and the development of CRPS1? Chapter four is concerned with the association between psycho-

logical states and CRPS1, while chapter five addresses the association between psychological traits and CRPS1. Chapter six discusses the relationship between psychological factors (kinesiophobia, catastrophizing, and depression) and the course of disuse-related CRPS1 symptoms. This chapter It provides the basis for psychological interventions in the chronification of CRPS1.
Chapter seven discusses the application of an objective diagnostic tool in patients with CRPS1 (i.e., infrared thermography to register skin surface temperature), and chapter eight provides an overview of the results of the studies described in this thesis, discussing the implications of research on CRPS1. In addition, this final chapter includes recommendations for future studies.

CRPS: A MODEL DISEASE

CRPS1 is a model disease in which the functioning of the nervous system in patients with chronic pain can be studied. Therefore, information on CRPS1 can also be of importance for other diseases, such as rheumatoid arthritis, in which inflammation and central sensitization can also play an important role[28]; this response of the nervous system in patients with CRPS is more pronounced and therefore easier to study.

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CHAPTER 2

Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1)? A systematic review

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R. de Wit

Invited review submitted to Pain

ABSTRACT

Background and aims Complex Regional Pain Syndrome type 1 (CRPS1) is a complication arising after trauma or surgery, although spontaneous development has also been described. Its pathophysiology is still a matter of debate, but psychological factors have been suggested to play a role, although their influence is unclear. The aim of this study was to investigate the evidence for the influence of psychological factors on CRPS1.

Methods In a systematic literature review, articles were selected using Cochrane, Pubmed/Medline, Psychinfo, and Cinahl since 1980. Only original articles and empirical studies were included. Based on these selection criteria, a total of 31 articles were identified. Studies were evaluated and weighted using a quality assessment instrument.

Results The few prospective studies do not report a relationship between CRPS1 and depression, anxiety, neuroticism, or anger. The results of the retrospective/cross-sectional studies seem to yield contradictory results regarding psychological problems in patients with CRPS1. A majority show no association, and studies with a higher methodological quality lean to a conclusion of no relationship between psychological factors and CRPS1. The majority of included studies (N = 24; 77%) had only a poor to moderate methodological quality.

Conclusions Although many patients with CRPS1 are stigmatized as being "psychologically peculiar," this literature review identified no relationship between CRPS1 and depression, anxiety, hysteria, hypochondria, obsessive-compulsive behavior, somatization, neuroticism, interpersonal sensitivity, dependency, hostility/anger, extraversion/introversion, insomnia, or paranoia. Only life events seemed to be associated: patients who experienced more life events appeared to have a greater chance of developing CRPS1. More studies with greater methodological quality and more participants should be performed on the association between psychological factors and the development and course of CRPS1.

INTRODUCTION

Complex Regional Pain Syndrome type 1 (CRPS1) is a complication after trauma or surgery, although spontaneous development of the disorder has also been described. Pain is the most common symptom; less commonly reported symptoms are allodynia, hyperalgesia, abnormal skin color, temperature change, abnormal sudomotor activity, edema, and motor/ trophic disturbances[1-3]. The symptoms of CRPS1 patients usually occur in an extremity and are disproportional to the inciting event[2].

The pathophysiology of CRPS1 is poorly understood, as reflected in the wide range of explanatory theories, including an unregulated sympathetic nervous system[4], an exaggerated neurogenic inflammation[4], a genetic predisposition[5,6], and immobilization of the limb (disuse)[7,8]. Apart from these somatically oriented explanations, it has been suggested that "psychologically peculiar" patients have an increased risk for developing CRPS1[9]. Others, however, refute this influence[10, 11]. Hendler[12] stated that doctors use the label "psychogenic pain" when patients do not respond to medical or surgical treatment, or when patients display behavior that doctors find difficult to cope with.

An indication that psychological factors may play a role in the development of CRPS1 is that some case-reports suggest a relationship between conversion and CRPS1[13-16]. Other authors suggest that psychological factors play a role in the course of CRPS1 rather than in its development or suggest that the long-lasting symptoms result in a change in the psychological make-up of patients. Monti et al.[17] stated that the long-lasting, intense pain of a trauma results in an exaggeration of maladaptive personality traits and coping styles. Zucchini et al.[18] concluded that CRPS1 patients lack motivation to rehabilitate because they profit from secondary gain as a chronic patient.

The conclusions of several reviews on the role of psychological factors in CRPS1 are contradictory[9, 11, 19-33]. Some reviews included (single) case studies, while others reviewed a small number of studies. Therefore, the results are difficult to interpret.

To clarify the role of psychological factors in CRPS1, we performed a systematic review of the existing literature on the association of these factors with CRPS1 in adult patients.

METHODS

Selection of studies

A computer-assisted search in the Cochrane, Pubmed/Medline, Psychinfo, and Cinahl databases was performed using the keywords "complex regional pain syndrome," reflex sympathetic dystrophy," "posttraumatic dystrophy," "algodystrophy," and "sudeck" in combination with

"psych*". The reference lists of the included articles were also searched for additional references. Only original articles describing empirical studies and written in Dutch or English were included. A further selection was made based on the following criteria: publishing dates between January 1980 and June 2007; focus on a study population of adults; use of clinical interviews or (validated) questionnaires; and inclusion of data about the influence of psychological factors on the development and/or course of CRPS1. Single case reports, letters, and editorials were excluded.

Methodological quality assessment

The methodological quality of the studies was assessed using the criteria of De Vet et al. (see Table 2.1)[34]. The score ranges from 0 to 99 for randomized controlled trials, and from 0 to 38 for those studies that were not randomized, controlled trials. For individual studies, the percentage of the maximal score obtainable for that study was calculated (e.g., for studies that were not randomized and controlled, a study with 19 points scored 50%). We classified the studies as follows: excellent (75% or higher), good (50% to 75%), moderate (25% to 50%), and poor (less than 25%). Two observers assessed the studies independently, blinded to the authors of the study, journal title, and year of publication. Discrepancies were resolved by discussion until consensus was reached.

Instruments

The instruments used in the included studies have different goals. Table 2.2 presents an overview of the instruments used in the included studies, classified by probability of psychiatric diagnosis, severity of psychological distress, (pathological levels of) personality traits, psychological distress, and life events (e.g. divorce, death of a spouse, vacation).

Statistical analyses

Because of the methodological, clinical, and statistical heterogeneity of the studies and a lack of comparable endpoints, pooling of the data was not possible. Thus, the data are qualitatively instead of quantitatively summarized.

RESULTS

The included studies evaluated a wide range of psychological factors in relationship to CRPS1. The results for each psychological factor are summarized below. To increase the readability of this review, we present the results in two groups: studies that found no or a limited role of psychological problems in patients with CRPS1 and studies that found a substantial

role for psychological factors in patients with CRPS1. Furthermore, when prospective studies are available, prospective and retrospective/cross-sectional studies are summarized separately.

Thirty-one studies fulfilled the inclusion criteria (Table 2.3). The following psychological factors were included in this review: depression, anxiety, somatization, (psycho)neuroticism, life events, hysteria, hypochondria, obsessive-compulsive behavior, (interpersonal) sensitivity, dependency, hostility/anger, extraversion, introversion, and paranoia.

Depression

Prospective studies

In five studies, the relationship between depression and CRPS1 was investigated prospectively. Van Spaendonck et al.[35] compared 12 CRPS1 patients with the reference group of the Zung depression questionnaire. They found no significant difference between these two groups. Daviet et al.[36] found that depression did not predict the severity of CRPS1. Puchalski and Zyluk[37] also found no significant differences in depression scores between patients with a distal radius fracture who developed CRPS1 and patients with a distal radius fracture without CRPS1. The mean quality of these three studies is moderate (30%; range: 5%–50%).

Feldman et al.[38] studied the reciprocal relationship between depression and pain in patients with CRPS1. They found that pain led to an increase in depressed mood and that a depressed mood resulted in an increase in pain. The quality of this study is good (55%). Harden et al.[39] found a non-significant trend for higher preoperative depression scores to be associated with the diagnosis of CRPS1 one month after the surgery. However, depression scores at baseline did not predict the presence of CRPS1 at 3 and 6 months. The quality of this study is moderate (32%).

Retrospective/cross-sectional studies

Nineteen retrospective/cross-sectional studies investigated the influence of depression on CRPS1. Two studies showed that CRPS1 patients are less depressed than headache patients and facial pain patients[40, 41]. Eight studies did not find higher depression scores for CRPS1 patients compared with several control groups (see Table 2.3 for a specification of the control groups[17, 35, 42-48]. Greipp[49] reported that 57% of patients never experienced depression. The mean methodological quality of the 11 studies described above is moderate (39%, range: 8%–76%).

In contrast, two other studies found that patients with CRPS1 reported higher depression scores than controls[18, 50]. Furthermore, Van Houdenhove et al.[51] showed that CRPS1 patients reported higher depression scores than cardiac patients but lower depression scores than psychiatric out-patients. Of the patients with CRPS1, 27% scored in the range of a severe clinical depression. The scores were comparable with those of a group of chronic idiopathic pain patients, significantly higher than those

of a group of organic pain patients, and significantly lower than those of two groups of depressed patients. The mean methodological quality of these three studies is poor (20%, range 11%–32%).

Four studies reported the prevalence of (chronic) depression in CRPS1 patients. In these studies, prevalence rates ranged from 31% to 96%[52-55]. It should be noted that in the study of Szeinberg-Arazi et al., for 10 of the 12 participants, the affected limb was amputated[54]. The mean methodological quality of these studies is moderate (29%, range: 5%–50%).

Anxiety

Prospective studies

Two prospective studies investigated the relationship between anxiety and CRPS1. Feldman et al.[38] studied the reciprocal relationship between anxious mood and pain in patients with CRPS1. Increased pain caused an increase in anxious mood, but increased anxiety did not lead to an increase in pain. The methodological quality of this study is good (55%). Harden et al.[39] found that higher levels of anxiety prior to surgery were associated with the prevalence of CRPS1 at the 1-month follow-up. However, anxiety at baseline did not predict the presence of CRPS1 at 3 and 6 months of follow-up. The methodological quality of this study is moderate (32%).

Retrospective/cross-sectional studies

Ten retrospective/cross-sectional studies explored the relationship between anxiety and CRPS1. Eight studies, with moderate mean methodological quality (39%, range: 16%–76%), reported no difference in cognitive, somatic, phobic or general anxiety, or in panic disorders between CRPS1 patients and several control groups[17, 40, 42-47]. Two studies reported that CRPS1 patients are more anxious and agoraphobic than other somatic patients, i.e., patients with a hand injury or cardiac patients[50, 51]. However, Van Houdenhove et al [51] also found that CRPS1 patients are more anxious than a non-CRPS1 population but less anxious than psychiatric patients. Bruehl et al.[43] found that CRPS1 patients have a higher score on phobic anxiety compared to patients with low back pain but comparable scores to patients with limb pain. The mean methodological quality of these three studies is moderate (36%, range 18%–56%).

Life events

Eight studies investigated the influence of life events on CRPS1. Two studies, with poor (8%)[35] and moderate (29%)[17] methodological quality, found no differences in reported life events before the development of CRPS1. Three studies, with moderate mean methodological quality (29%, range 18%–39%), reported that CRPS1 patients had experienced more stressful life events than the controls[42, 45, 51]. Three studies, with poor mean methodological quality (22%, range: 5%–42%), found high percentages

of patients with CRPS1 reporting adverse life events preceding the disease. The percentages ranged from 49% to 100%[53, 56, 57].

Hysteria/hypochondria

Eight studies investigated the influence of hysteria and/or hypochondria on CRPS1. Nelson and Novy[41] (methodological quality: 74%) found that CRPS1 patients score lower on both the hysteria and hypochondria scales of the Minnesota Multiphasic Personality Inventory (MMPI) than patients with fascial pain. Shiri et al.[47] (quality: 16%) found no differences in the hysteria or the hypochondriasis subscales of the MMPI between conversion disorder patients and CRPS1 patients. The mean methodological quality of these two studies is moderate (45%). Zucchini et al.[18] reported that CRPS1 patients scored higher on both the hysteria and hypochondria scales of the MMPI than controls with brachial plexus lesions (methodological quality: 11%). Van Hilten et al.[58] found an elevated score for both the hysteria and hypochondria subscales of the MMPI in patients with CRPS1-related dystonia (quality: 13%). The mean methodological quality of these two studies is poor (12%).

Two studies reported only prevalence rates in CRPS1 patients, without comparing these rates with other populations. Subbarao and Stillwel[52] and Grunert et al.[59] reported prevalences of hysteria and hypochondria in patients with CRPS1 of 42% and 90%, respectively. Van Houdenhove[53] found histrionic traits in 44% of the CRPS1 patients, while the diagnosis "conversion hysteria" was made in 40% of these patients. Finally, Szeinberg-Arazi et al.[54] reported that CRPS1 patients showed hysterical behavior, without providing percentages. The mean methodological quality of these four studies is moderate (26%, range: 5%–50%).

Obsessive-compulsive behavior

Seven studies reported on the influence of obsessive-compulsive behavior on CRPS1. DeGood et al.[40] concluded that CRPS1 patients show less obsessive-compulsive behavior than headache patients. Also, van Houdenhove et al.[51] found that CRPS1 patients show less obsessive-compulsive behavior than psychiatric patients (difference not significant). In four studies, no difference was found between CRPS1 patients and several groups of control patients[17, 43, 46, 50]. The mean methodological quality of these six studies is moderate (42%, range: 18%–76%). Van Houdenhove[53] reported histrionic traits in 12.5% of the CRPS1 patients (poor methodological quality: 18%).

Somatization

Nine studies explored the effect of somatization on CRPS1. Three studies found that CRPS1 patients show less somatization than controls[40, 44, 46]. Four studies did not find a difference between CRPS1 patients and controls

regarding somatization[42, 44-46]. The mean methodological quality of these five studies is moderate (42%, range: 18%–76%). However, three studies reported that CRPS1 patients more often express psychological problems as somatic complaints than other patient groups[43, 50, 51]. The methodological quality of these studies is moderate (29%, range: 18%–58%). De Vilder[60] reported a somatization prevalence rate of 64% in patients with CRPS1. The methodological quality of this study is poor (21%).

Neuroticism

Prospective studies

Two prospective studies evaluated the role of neuroticism in the development of CRPS1. Puchalski and Zyluk[37] found no significant differences in neuroticism between CRPS1 patients and controls. The methodological quality of this study was moderate (34%). Van Spaendonck et al.[35] concluded that patients who did develop CRPS1 after a wrist fracture are not more neurotic than patients with a wrist fracture without CRPS1. Both patients with CRPS1 and patients without CRPS1 showed an increased score on neuroticism compared to the general population, and similar scores as psychiatric patients. The methodological quality of this study is poor (5%).

Retrospective/cross-sectional studies

Six retrospective/cross-sectional studies reported on the influence of neuroticism on CRPS1. Four studies, with moderate methodological quality (38%, range: 18%–58%), found no differences in neuroticism between CRPS1 patients and controls[42, 43, 45, 46]. However, Van Spaendonck et al.[35] concluded that CRPS1 patients showed fewer neurotic characteristics than psychiatric patients but more than the normal population. In the same study, female patients with CRPS1 showed fewer neurotic characteristics than female patients with functional complaints. In a study by Van Houdenhove et al.[51], CRPS1 patients had a significantly higher score for psychoneuroticism than a reference group of cardiac patients. Furthermore, in two studies that overall found no differences between CRPS1 patients and the control group, female CRPS1 patients showed higher scores on neuroticism[42] and were more unstable than female hand pathology patients waiting for elective hand surgery[45]. The mean methodological quality of these four studies is poor (24%, range: 8%–39%).

(Interpersonal) Sensitivity

Six studies explored the effect of (interpersonal) sensitivity on CRPS1. Two studies found that CRPS1 patients report fewer symptoms of interpersonal sensitivity than the control groups[40, 51]. No differences were found in three studies concerning sensitivity between CRPS1 patients and the controls[43, 45, 46]. The mean methodological quality of these five studies is moderate (45%, range: 18%–76%).

However, two studies, with a moderate mean methodological quality (39%), reported that CRPS1 patients have a higher score on the (interpersonal) sensitivity subscale than the control groups of patients with a hand injury without CRPS1, and low back pain patients, respectively[43, 50].

Dependency

Two studies addressed the prevalence of dependent behavior in patients with CRPS1. Van Houdenhove[53] found that in 28% of CRPS1 patients, a dependent personality was observed. The methodological quality of this study is poor (18%). However, Monti et al.[17] found dependent behavior in only 4% of patients with CRPS1 (compared with 8% of the control group with chronic low back pain). The methodological quality of this study is moderate (29%).

Hostility/anger

Prospective studies

One prospective study investigated the reciprocal relationship between anger and pain. Feldman et al [38] found that "a high-pain day" was predictive for an increase in anger. An increase in anger was not predictive of an increase in pain. The methodological quality of this study was good (55%).

Retrospective/cross-sectional studies

Seven retrospective/cross-sectional studies investigated the influence of hostility/anger on CRPS1. Two studies found that CRPS1 patients had a significantly lower score on hostility than the control groups[40, 51]. Four studies reported that there was no difference in hostility between patients with CRPS and controls[40, 43, 45, 46]. The mean methodological quality of these five studies is moderate (45%, range: 18%-76%). Van Houdenhove et al.[51] however, stated that CRPS1 patients reported significantly more hostility symptoms than cardiac patients. The methodological quality of this study is moderate (32%).

One study investigated the relationship between anger and pain. Bruehl et al.[61] found an interaction effect of anger expression and diagnostic group: in patients with CRPS1, greater expression of anger was related to a higher intensity of pain, while in non-CRPS1 limb-pain patients, greater expression of anger was related to a lower intensity of pain. The methodological quality of this study is moderate (34%).

Van Houdenhove[53] reported that 13% of the CRPS1 patients showed passive-aggressive personality traits. The methodological quality of this study is poor (18%).

Extraversion/introversion

Prospective studies
Two prospective studies explored the effect of extraversion/introversion on CRPS1. Puchalski and Zyluk[37] found no difference in extraversion between CRPS1 patients and control groups, with moderate methodological quality (34%). In contrast, Van Spaendonck et al.[35] concluded that patients with CRPS1 after a wrist fracture have a higher score on extraversion than the general population (quality: 5%, poor).

Retrospective/cross-sectional studies
A study by Van Spaendonck et al.[35] with poor methodological quality (8%) found no statistically significant difference in extraversion/introversion between patients with CRPS1 and both control groups.

De Vilder[60] concluded that 19% of CRPS1 patients scored higher than average on the extraversion scale. The methodological quality of this study is poor (21%).

Insomnia

Five studies involved the relationship between insomnia and CRPS1. Two studies, with moderate mean methodological quality (47%), found no significant difference in insomnia between CRPS1 patients and controls[40, 45]. On the other hand, two studies, also with moderate methodological quality (34%), found more sleeping problems in CRPS1 patients than in controls[46, 51].

Greipp[49] concluded that insomnia was never a problem in 43% of the CRPS1 patients, occasionally a problem in 43%, and is a severe problem for 14%. The methodological quality of this study is poor (14%).

Paranoia

Five studies explored the effect of paranoia on CRPS1. Four studies found no significant difference in paranoia between CRPS1 patients and the control groups[40, 41, 43, 47]. Monti et al.[17] made the diagnosis paranoia once (4%) in the control group of chronic low back pain patients and in none of the CRPS1 patients. The mean methodological quality of these five studies is good (50%, range: 16%–76%).

DISCUSSION

The objective of the present study was to review the literature on the influence of psychological factors on CRPS1. The majority of included studies (n = 24, 77%) have only a poor to moderate methodological quality.

Two main results emerge from this review. First, most prospective stud-

ies found no relationship between a diagnosis of CRPS1 and depression, anxiety, neuroticism, hostility/anger, or extraversion/introversion. Second, the results of the retrospective/cross-sectional studies seem to yield contradictory results regarding psychological problems in patients with CRPS1. A majority of studies found no association between psychological factors and CRPS1. For nine out of the 13 psychological factors in this review (paranoia, hysteria/hypochondria, obsessive-compulsive behavior, somatization, insomnia, hostility/anger, interpersonal sensitivity, neuroticism, and dependency), studies with a relatively high methodological quality found no association with CRPS1. For three other factors (depression, anxiety, and extraversion/introversion), the majority of studies also found no association, but the methodological quality of these studies was equal to or worse than the quality of the studies that found an association with CRPS1.

For life events, the evidence seems to indicate a relationship with the development of CRPS1. Life events may lead to CRPS1 because a repeatedly triggered sympathetic system develops an altered local catecholamine responsiveness resulting in a prolonged increased autonomic arousal[19, 33, 39, 45, 62]. Furthermore, the somewhat more obscure results regarding insomnia may partly be explained by the fact that CRPS1 may lead to sleeping problems (leading to increased scores on the insomnia subscale).

It can be concluded that there is no evidence for a relationship between CRPS1 and depression, anxiety, neuroticism, anger, obsessive-compulsive behavior, somatization, hostility/anger, interpersonal sensitivity, extraversion/introversion, or paranoia. This conclusion finds further confirmation from the fact that several studies included only patients attending a specialized pain clinic[40, 43, 44]. As Covington[63] stated, pain clinic patients represent a biased sample because these patients report more intense pain that is more constant and associated with greater functional impairment. They also have a higher chance of experiencing depression, withdrawal, and substance abuse[64]. Therefore, any existing relationship between psychological factors and CRPS1 is expected to be clearly present in this biased population. Moreover, when no relationship is found in this biased population, it is even more probable that no relationship exists.

When we compare our results with those of previous reviews, our findings are more robust and therefore of enhanced value for a few reasons[9, 11, 19-33]. First, we focused solely on psychological factors. In addition, we included more studies, and we weighted those studies based on their methodological quality.

However, several limitations also must be considered. First, in terms of a best-evidence-synthesis method, the evidence is limited or inconclusive because of a lack of high-quality studies and because of inconsistent outcomes and non-comparable study designs[65]. Therefore, our conclusions should be interpreted with some caution. Second, the criteria of de Vet[34] were used because of the absence of a validated methodological quality instrument for studies that are not randomized, controlled trials, at the time this article was written.

An explanation for the inconclusive results found in the included studies could be the use of different diagnostic criteria for CRPS1. For instance, the criteria sets of the International Association for the Study of Pain[2], Bruehl[66], and Veldman[1] yield different prevalence rates in the same study group[67]. In addition, existing criteria sets originate from different medical disciplines and/or countries, emphasizing different symptoms in the diagnosis[68]. An obvious recommendation based on this difference is to improve diagnostic rigor by using criteria that have proven discriminative power[69].

The same concern applies to the diagnosis of psychological problems: several slightly different definitions are used across diagnostic instruments in the included studies. This difference implies that it is difficult to make comparisons across studies of the prevalence of psychological problems and their influence on the development of CRPS1. A fourth point of concern is that the time since diagnosis of CRPS1 varies largely across the studies, from weeks[51] to more than 6 years[38]. The same is true for the duration of psychological problems and the duration of pain. Bruehl and colleagues[43] suggested that patients who have pain for a longer period either adapt well or suffer from increased distress. Measuring psychological problems in such a group may lead to an overestimation (or an underestimation) of the prevalence of these problems. Because of the variance in duration of complaints, the nature, number, and duration of medical and/or psychological treatments presumably also differs across the studies.

A fifth point of concern might be the differences in the initiating event varying across studies, such as fractures or surgery. In the literature, it is unclear whether the type of trauma leading to CRPS1 influences the role of psychological factors. However, the overall finding across studies of no relationship between psychological factors and CRPS1 makes it unlikely that this issue is of concern.

A final point is that no psychological theory or framework was used in the included articles, and in some studies, only a portion of the included patients participated in the psychological study, which may have led to a selection bias.

In summary, studies with a higher methodological quality suggest no relationship between psychological factors and CRPS1. More prospective studies with high-quality methodology should be performed on the association between psychological factors and the development or maintenance of CRPS1, respectively. No firm conclusion can be drawn from the literature on the assocation between psychological factors and the maintenance of CRPS, and our review identified no direct relationship between psychological factors and the development of CRPS1, with the possible exception of life events. Research showed that there is no justification for stigmatizing patients with CRPS1 as being "psychologically peculiar."

Acknowledgements
The authors would like to thank J. Beerthuizen, M.Sc. for his valuable contribution to the quality assessment of the articles included in this review.

Table 2.1. Criteria list for methodological assessment[34]

Criterion		Answer options (weights)*			
A. SELECTION AND RESTRICTION	1. Description of inclusion and	o	?	+ (2)	
	2. Restriction to a homogeneous study population	o	?	+ (2)	–
B. TREATMENT ALLOCATION	1. Randomization	yes		no	
	2. Allocation procedure adequate	o	?	+(10)	–
	3. Blinded allocation procedure	o	?	+ (5)	–
C. STUDY SIZE	1. Smallest group >25 participants	o	?	+ (4)	
	2. Smallest group >50 participants	o	?	+ (4)	
	3. Smallest group >75 participants	o	?	+ (4)	
D. PROGNOSTIC COMPARABILITY (9 points total)	1. Duration of the complaint	o	?	+	–
	2. Baseline scores for outcome measures	o	?	+	–
	3. Age	o	?	+	–
	4. Recurrence status (number of relapses) at baseline	o	?	+	–
	5. Radiating pain	o	?	+	–
E. DROP-OUTS	1. No drop-outs or	o	?	+(12)	–
	2. Number of drop-outs given in each group	o	?	+ (2)	
	3. Reasons for withdrawal (of drop-outs) given in each group	o	?	+ (2)	
	4. Drop-outs not leading to bias (less than 5%)	o	?	+ (8)	–
F. LOSS TO FOLLOW-UP	1. Less than 20% loss to follow-up in all groups	o	?	+ (2)	
	2. Less than 10% loss to follow-up in all groups	o	?	+ (2)	
	3. Loss to follow-up not leading to bias	o	?	+ (8)	–
G. INTERVENTION # 1 = experimental (6 point total)	1. Type of intervention	o	?	+	
	2. Intensity of intervention parameters	o	?	+	
	3. Duration of each treatment session	o	?	+	
	4. Treatment frequency	o	?	+	
	5. Number of treatment sessions	o	?	+	
	6. Compliance presented	o	?	+	–
G. INTERVENTION #2=placebo or other control (6 points total)	1. Type of intervention	o	?	+	
	2. Intensity of intervention parameters	o	?	+	
	3. Duration of each treatment session	o	?	+	
	4. Treatment frequency	o	?	+	
	5. Number of treatment sessions	o	?	+	
	6. Compliance presented	o	?	+	–

Table 2.1. Criteria list for methodological assessment[34] (*continued*)

Criterion		Answer options (weights)*			
H. EXTRA TREATMENTS	1. No co-interventions or	o	?	+ (2)	–
	2. Co-interventions comparable between groups	o	?	+ (2)	–
I. BLINDING OF PATIENT	1. Attempt at blinding or naïve patient	o	?	+ (2)	–
	2. Blinding evaluated and successful	o	?	+ (2)	–
J. BLINDING OF THERAPIST	1. Attempt at blinding	o	?	+ (2)	–
	2. Blinding evaluated and successful	o	?	+ (2)	–
K. BLINDING OF OBSERVER	1. Attempt at blinding	o	?	+ (2)	–
	2. Blinding evaluated and successful	o	?	+ (2)	–
L. OUTCOME MEASURES (6 points total)	1. Pain	o	?	+	
	2. Global measure of improvement	o	?	+	
	3. Functional status	o	?	+	
	4. Mobility	o	?	+	
	5. Medical consumption	o	?	+	
	6. Life-events	o	?	+	
M. FOLLOW-UP PERIOD	1. Timing comparable	o	?	+ (1)	
	2. Measurement just after the last treatment	o	?	+ (1)	
	3. Measurement 3 months or longer after randomization (if relevant)	o	?	+ (1)	
N. SIDE EFFECTS	1. Description of side effects in each group	o	?	+ (1)	
O. ANALYSIS AND PRESENTATION OF DATA	1. Frequencies or mean/standard deviation or median/quartiles (for most important measurements)	o	?	+ (1)	
		o	?	+ (1)	
	2. Intention to treat analysis or	o	?	+ (3)	
	3. Adequate corrections for baseline differences or drop-outs	o	?	+ (3)	

* + = Description of this item is informative, and the presence of bias is unlikely for this item
– = Description of this item is informative, but the study is flawed on this item
? = Description of this item is unclear or incomplete and therefore impossible to interpret
o = No information about this item is given in the paper

Table 2.2. Categories of instruments used across the included studies

Category	Instrument	
Probability of psychiatric diagnosis	Symptom Checklist[70]	SCL-90
	Symptom Checklist, revised[71]	SCL-90R
	Brief Symptom Inventory[72]	BSI
	Hopkins Symptom Checklist[73]	HSCL
	Beck Depression Inventory[74]	BDI
	Clinical (psychodynamic) interview	
	Montgomery-Asberg Depression Rating Scale[75]	MADRS
	Zung depression scale[76]	
	Yesavage's Geriatric Depression Scale[77]	GDS
Severity of psychological distress	Cognitive – Somatic Anxiety Questionnaire[78]	CSAQ
	State Trait Anxiety Inventory[79]	STAI
	Anger Expression Inventory[80]	AEI
	Survey tool constructed by author of study	
	Affect Balance Scale[81]	ABS
Personality traits	Amsterdam Biographic Index[82]	ABV
	Minnesota Multiphasic Personality Inventory – Dutch version[83]	NVM
	Minnesota Multiphasic Personality Inventory[84]	MMPI
	Dutch Personality Questionnaire[85]	DPQ
	Eysenck Personality Questionnaire – revised[86]	EPS
	Personality Diagnostic Questionnaire – revised[87]	PDQRL
Life events	Social Readjustment Rating Scale[88]	SRRS
	Recent Life Change Questionnaire – Dutch version[89]	VRMG
	Investigation of the personal history (life events)	

Table 2.3. Characteristics of the studies per factor

Factor	Authors	N CRPS1 patients	Measurement tool	Design
DEPRESSION – prospective	Van Spaendonck et al.[35]	12	Zung	Cohort
	Feldman et al.[38]	109	ABS	Cohort
	Daviet et al.[36]	24	MADRS	Cohort
	Harden et al.[39]	16	BDI	Cohort
	Puchalski & Zyluk[37]	9	BDI & GDS	Cohort
DEPRESSION – retrospective/cross-sectional	Subbarao & Stillwell[52]	45	MMPI & psychiatric evaluations	Cross-sectional
	Van Houdenhove[53]	32	Psychodynamic interviews	Cross-sectional
	Hardy & Merritt[50]	9	HSC	Cross-sectional
	Zucchini et al.[18]	13	MMPI	Cross-sectional
	Van Spaendonck et al.[35]	160	ZUNG	Cross-sectional
	Szeinberg-Arazi et al.[54]	12	DSM-III-R	Survey
	DeGood et al.[40]	71	SCL-90R	Case-control
	Geertzen et al.[42]	24	SCL-90	Survey
	Van Houdenhove et al.[51]	66	SCL-90 & BDI	Cross-sectional

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
Reference group questionnaire	(5%) poor	No difference between CRPS1 patients and controls
No	(55%) good	Pain increased depressed mood; depressed mood contributed to an increase in pain in CRPS1 patients
No	(50%) good	Depression not a prognostic factor for CRPS1 severity
Patients without CRPS1 after total knee arthroplasty (n = 61)	(32%) moderate	Preoperative depression almost significantly correlated with presence of CRPS1 at 1 month
Patients with a distal radius fracture without CRPS1 (n = 41)	(34%) moderate	CRPS1 patients are not more depressed than controls
No	(50%) good	31% of CRPS1 patients are depressed
No	(18%) poor	In 15 CRPS1 patients (47%), a diagnosis of manifest or masked depression was made
Patients with a hand injury, without CRPS1 (N\n = 8)	(18%) poor	CRPS1 patients are more depressed than controls
Patients with brachial plexus lesions (= 23)	(11%) poor	CRPS1 patients are more depressed than controls
Reference group questionnaire	(8%) poor	CRPS1 patients are not more depressed than controls
No	(5%) poor	Several patients demonstrated primary neurotic depressive traits with immature dependent behavior and narcissism
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	CRPS1 patients are less depressed than controls
Patients who underwent elective hand surgery, without CRPS1 (n = 42)	(39%) moderate	CRPS1 patients are not more depressed than controls
SCL-90: reference groups questionnaire BDI: (1) Idiopathic pain/masked depression (n = 18); (2) organic pain patients (n = 16): (3) pain with depression (n = 15); (4) depression without pain (n = 13)	(32%) moderate	SCL-90: CRPS1 patients report significantly more depression than cardiac patients and less depression than psychiatric patients. BDI: Depression scores are comparable to the control group 1, higher than 2, and lower than 3 & 4

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
	Nelson & Novy[41]	58	MMPI	Cross-sectional
	Bruehl et al.[43]	34	BSI	Survey
	Ciccone et al.[44]	25	BDI	Survey
	Monti et al.[17]	25	Structured psychiatric diagnostic interview (DSM-III-R)	Cross-sectional
	Geertzen et al.[45]	24	SCL-90	Survey
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
	Rauis[55]	100	Psychiatric examination	Cross-sectional
	Greipp[49]	14	Survey tool made by author	Cross-sectional
	Shiri et al.[47]	17	MMPI & standardized semi-structured psychological interviews	Survey
	Kocabas et al.[48]	40	BDI	Cohort
ANXIETY - prospective	Feldman et al.[38]	109	ABS	Cohort
	Harden et al.[39]	16	STAI	Cohort
ANXIETY – retrospective/cross-sectional	Hardy & Merritt[50]	9	HSC	Cross-sectional

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
Myofascial pain syndrome patients (n = 214)	(74%) good	CRPS1 patients are less depressed than controls
Non-CRPS1 limb pain (n = 50) and low back pain patients (n = 165)	(58%) good	No difference in depression between CRPS1 patients and both control groups
Patients with chronic back pain (n = 44) and patients with local neuropathy (n = 21)	(55%) good	CRPS1 patients are not more depressed than controls
Chronic low back pain patients from disc-related radiculopathy (n = 25)	(29%) moderate	CRPS1 patients are not more depressed than controls
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	CRPS1 patients are not more depressed than controls
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	CRPS1-dystonia patients are not more depressed than controls
No	(37%) moderate	Prevalence of chronic depression is 96%
No	(29%) moderate	Overwhelming depression was not reported (57% never experienced depression, 29% rarely, 14% occasionally)
Conversion disorder patients (n = 20)	(16%) poor	One-third of patients in both the CRPS1 (35%) and the conversion disorder groups (30%) suffered from Axis 1 disorders, mostly from depression and PTSD
CVA patients suffering from a cardiovascular accident without CRPS1 (n = 42)	(66%) good	No differences in depression between CRPS1 patients and controls
No	(55%) good	Pain led to an increase in anxious mood; anxiety did not contribute to an increase in pain in patients with CRPS1
Patients without CRPS1 after total knee arthroplasty (n = 61)	(32%) moderate	Preoperative anxiety is significantly correlated with the presence of CRPS1 1 month after surgery
Patients with a hand injury, without CRPS1 (n = 8)	(18%) poor	CRPS1 patients are more anxious than controls

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
	DeGood et al.[40]	71	SCL-90R	Case-control
	Geertzen et al.[42]	24	STAI	Survey
	Van Houdenhove et al.[51]	66	SCL-90 & STAI	Cross-sectional
	Bruehl et al.[43]	34	BSI	Survey
	Ciccone et al.[44]	25	CSAQ	Survey
	Geertzen et al.[45]	24	SCL-90	Survey
	Monti et al.[17]	25	Structured psychiatric diagnostic interview (DSM-III-R)	Cross-sectional
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
	Shiri et al.[47]	17	MMPI & standardized semi-structured psychological interviews	Survey
LIFE-EVENTS	Van Houdenhove[53]	32	Psychodynamic interviews	Cross-sectional

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	CRPS1 patients are less anxious than controls No significant differences in phobia between the three groups
Patients who underwent elective hand surgery, without CRPS1 (n = 42)	(39%) moderate	No differences in anxiety between CRPS1 patients and controls
Reference groups questionnaires	(32%) moderate	STAI: CRPS1 patients have significantly higher scores on anxiety than the normal population, but lower than psychiatric patients SCL-90: CRPS1 patients report significantly more anxiety & agoraphobia than cardiac patients but both less than psychiatric patients
Reference group questionnaire	(58%) good	No differences in anxiety between CRPS1 patients and both controls CRPS1 patients have a higher score on phobic anxiety than low back pain patients, but no difference on this subscale between CRPS1 patients and non-CRPS1 limb pain
Patients with chronic back pain (n = 44) and patients with local neuropathy (n = 21)	(55%) good	No difference between CRPS1 patients and controls in (cognitive & somatic) anxiety
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	No differences between CRPS1 patients and the controls when comparing the total groups on anxiety and agoraphobia Males with CRPS1 are significantly more anxious than male controls
Chronic low back pain patients from disc-related radiculopathy (n = 25) (29%)	moderate	No difference in the number of patients with a panic disorder in the CRPS1 group and controls
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	No difference in anxiety and phobic anxiety between CRPS1-dystonia patients and controls
Conversion disorder patients (n = 20) and a medically ill control population of the MMPI	(16%) poor	Low anxiety scores are present in CRPS1 and conversion disorder patients
No	(18%) poor	21 CRPS1 patients (66%) experienced an affective loss together with the provoking physical factor that caused CRPS1

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
	Egle & Hoffmann[56]	8	Interview	Cross-sectional
	Van Spaendonck et al.[35]	160	SRRS	Cross-sectional
	Geertzen et al.[42]	24	SRRS	Survey
	Van Houdenhove et al.[51]	66	VRMG	Cross-sectional
	Geertzen et al.[45]	24	SRRS	Survey
	Geertzen et al.[57]	65	SRRS	Cross-sectional
	Monti et al.[17]	25	Structured psychiatric diagnostic interview (DSM-III-R)	Cross-sectional
HYSTERIA	Subbarao & Stillwell[52]	45	MMPI	Cross-sectional
	Van Houdenhove[53]	32	Psychodynamic interviews	Cross-sectional
	Zucchini et al.[18]	13	MMPI	Cross-sectional
	Grunert59	20	Structured clinical interview & MMPI	Cross-sectional
	Szeinberg-Arazi et al.[54]	12	DSM-III - R	Survey
	Nelson & Novy[41]	58	MMPI	Cross-sectional
	Van Hilten et al.[58]	10	MMPI-2	Cross-sectional
	Shiri et al.[47]	17	MMPI & standardized semi-structured psychological interviews	Survey

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
No	(5%) poor	All patients were going through a very difficult period in their lives at the time of trauma or operation and the development of CRPS1 afterwards
Reference group questionnaire	(8%) poor	CRPS1 patients do not have elevated scores for life events
Patients who underwent elective hand surgery, without CRPS1 (n = 42)	(39%) moderate	CRPS1 patients have experienced more life events than controls
Reference group questionnaire (railway personnel)	(32%) moderate	CRPS1 patients mentioned significantly more life events (mean 12.74) than controls (mean 6.14)
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	Life events were significantly more present in CRPS1 patients compared to controls
No	16 (42%) moderate	Social life event with a Life Change Unit > 35 was present in 32 patients with CRPS1
Chronic low back pain patients from disc-related radiculopathy (n = 25)	(29%) moderate	No relationship between life events and the development of CRPS1
No	(50%) good	Prevalence of hysteria and hypochondria is 42%
No	(18%) poor	14 CRPS1 patients (44%) showed histrionic traits, and in 13 CRPS1 patients (41%) the diagnosis of conversion hysteria was made
Patients with brachial plexus lesions (n = 23)	(11%) poor	CRPS1 patients suffer more from hysteria than the controls
No	(32%) moderate	Prevalence of hypochondria and hysteria is 90%
No	(5%) poor	CRPS1 patients showed hysterical behavior
Myofascial pain syndrome patients (n = 214)	(74%) good	CRPS1 patients are less hysterical than the controls
No	(13%) poor	Elevated score on hysteria in patients with CRPS1-dystonia
Conversion disorder patients (n = 20) and a medically ill control population of the MMPI	(16%) poor	CRPS1 and conversion disorder patients exceeded normal scores on the MMPI hysteria scale (no significant differences between the two groups)

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
HYPOCHONDRIA	Subbarao and & Stillwell[52]	45	MMPI	Cross-sectional
	Zucchini et al.[18]	13	MMPI	Cross-sectional
	Grunert[59]	20	Structured clinical interview & MMPI	Cross-sectional
	Nelson & Novy[41]	58	MMPI	Cross-sectional
	Van Hilten et al.[58]	10	MMPI-2	Cross-sectional
	Shiri et al.[47]	17	MMPI & standardized semi-structured psychological interviews	Survey
OBSESSIVE-COMPULSIVE BEHAVIOR	Van Houdenhove[53]	32	Psychodynamic interviews	Cross-sectional
	Hardy & Merritt[50]	9	HSC	Cross-sectional
	DeGood et al.[40]	71	SCL90-R	Case-control
	Van Houdenhove et al.[51]	66	PDQRL	Cross-sectional
	Bruehl et al.[43]	34	BSI	Survey
	Monti et al.[17]	25	Structured psychiatric diagnostic interview (DSM-III-R)	Cross-sectional
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
SOMATIZATION	Hardy & Merritt[50]	9	HSC	Cross-sectional
	De Vilder[60]	42	NVM	Cross-sectional

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
No	(50%) good	Prevalence of hysteria and hypochondria is 42%
Patients with brachial plexus lesions (n = 23)	(11%) poor	CRPS1 patients suffer more from hypochondria than the controls
No	(32%) moderate	Prevalence of hypochondria and hysteria is 90%
Myofascial pain syndrome patients (n = 214)	(74%) good	CRPS1 patients had significantly lower scores on hypochondriasis
No	(13%) poor	Elevated score on hypochondriasis in patients with CRPS1-dystonia
Conversion disorder patients (n = 20) and a medically ill control population of the MMPI	(16%) poor	No significant differences between the CRPS1 patients and conversion disorder patients on the hypochondria subscale
No	(18%) poor	Obsessional traits were present in 4 (12.5%) of the CRPS1 patients
Patients with a hand injury, without CRPS1 (n = 8)	(18%) poor	No difference between CRPS1 patients and controls
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	CRPS1 patients show less obsessive-compulsive behavior than controls
Reference group questionnaire	(32%) moderate	CRPS1 patients show less obsessive-compulsive behavior than psychiatric patients (not significant)
Reference group questionnaire	(58%) good	No difference in obsessive-compulsive behavior between CRPS1 patients and both control groups
Chronic low back pain patients from disc-related radiculopathy (n = 25)	(29%) moderate	No difference in obsessive-compulsive behavior between CRPS1 patients and controls
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	No difference in compulsive behavior between CRPS1-dystonia patients and controls
Patients with a hand injury, without CRPS1 (n = 8)	(18%) poor	CRPS1 patients express psychological problems as somatic complaints more frequently than controls
No	(21%) poor	Prevalence of somatization is 64.3%

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
	DeGood et al.[40]	71	SCL-90R	Case-control
	Geertzen et al.[42]	24	SCL-90	Survey
	Van Houdenhove et al.[51]	66	SCL-90	Cross-sectional
	Bruehl et al.[43]	34	BSI	Survey
	Ciccone et al.[44]	25	CSAQ	Survey
	Geertzen et al.[45]	24	SCL-90	Survey
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
NEUROTICISM – prospective	Van Spaendonck et al.[35]	12	ABV	Cohort
	Puchalski & Zyluk[37]	9	EPQ-R	Cohort

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	CRPS1 patients express psychological problems as somatic complaints less frequently than controls
Patients who underwent elective hand surgery, without CRPS1 (n = 42)	(39%) moderate	CRPS1 patients do not somatize more than controls
Reference groups questionnaire	(32%) moderate	SCL-90: CRPS1 patients report significantly more somatization symptoms than cardiac patients but less than psychiatric patients
Non-CRPS1 limb pain (n = 50) and low back pain patients (n = 165)	(58%) good	CRPS1 patients somatize more than low back pain patients and non-CRPS1 limb pain patients
Patients with chronic back pain (n = 44) and patients with local neuropathy (n = 21)	(55%)good	CRPS1 patients report fewer non-specific medical symptoms than back pain patients. No differences in number of non-specific medical symptoms between CRPS1 and local neuropathy patients
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	No differences in somatization between CRPS1 patients and controls
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	No differences in somatization between CRPS-dystonia patients and the reference group female population CRPS1-dystonia patients express psychological problems as somatic complaints less often than rehabilitation patients
Reference group questionnaire	(5%) poor	Patients with CRPS1 after a wrist fracture (1) are more neurotic than the general population; (2) have similar scores on neuroticism compared with psychiatric patients; and (3) have comparable scores on neuroticism with patients with a wrist fracture without CRPS1
Patients with a distal radius fracture without CRPS1 (n = 41)	(34%) moderate	No significant differences in neuroticism between CRPS1 patients and controls 25 CRPS1 patients (50%) were classified as emotionally balanced, 20 (40%) as moderately balanced, and 5 (10%) as neurotic (emotionally unbalanced)

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
NEUROTICISM – retrospective/cross-sectional	Van Spaendonck et al.[35]	160	ABV	Cross-sectional
	Geertzen et al.[45]	24	DPQ & SCL-90	Survey
	Van Houdenhove et al.[51]	66	SCL-90 & PDQRL	Cross-sectional
	Bruehl et al.[43]	34	BSI	Survey
	Geertzen et al.[45]	24	SCL-90	Survey
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
(INTERPERSONAL) SENSITIVITY	Hardy & Merritt[50]	9	HSC	Cross-sectional
	DeGood et al.[40]	71	SCL-90R	Case-control
	Van Houdenhove et al.[51]	66	SCL-90	Cross-sectional
	Bruehl et al.[43]	34	BSI	Survey

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
Reference group questionnaire	(8%) poor	Patients with CRPS1 have a higher neuroticism score than the general population but comparable with psychiatric patients; women with CRPS1 have a lower neuroticism score than women with nervous-functional complaints
Patients who underwent elective hand surgery, without CRPS1 (n = 42)	(39%) moderate	DPQ: No differences in neurotic complaints between CRPS1 patients and controls SCL-90: No differences in psycho-neuroticism between CRPS1 patients and controls; female CRPS1 patients showed a high score of psycho-neuroticism
Reference groups questionnaires	(32%) moderate	SCL-90: CRPS1 patients have a significantly higher score on psychoneuroticism than cardiac patients but a significantly lower score than psychiatric patients PDQRL: CRPS1 patients have significantly lower scores on psychoneuroticism than psychiatric patients
Non-CRPS1 limb pain (n = 50) and low back pain patients (n = 165)	(58%) good	No difference in psychoticism between CRPS1 patients and controls
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	CRPS1 patients are not more emotionally unstable than controls Female CRPS1 patients are significantly more emotionally unstable than women in the control group
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	No difference in psychoneuroticism behavior between CRPS1-dystonia patients and controls
Patients with a hand injury, without CRPS1 (n = 8)	(18%) poor	CRPS1 patients had a significantly higher score on interpersonal sensitivity compared with controls
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	CRPS1 patients have a lower score on interpersonal sensitivity than controls
Reference groups questionnaire	(32%) moderate	CRPS1 patients report significantly more sensitivity symptoms than cardiac patients but less than psychiatric patients
Non-CRPS1 limb pain (n = 50) and low back pain patients (n = 165)	(58%) good	CRPS1 patients have a higher score on interpersonal sensitivity than low back pain patients, but comparable scores with non-CRPS1 limb pain patients

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
	Geertzen et al.[45]	24	SCL-90	Survey
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
DEPENDENCY	Van Houdenhove[53]	32	Psychodynamic interviews	Cross-sectional
	Monti et al.[17]	25	Structured psychiatric diagnostic interview (DSM-III-R)	Cross-sectional
HOSTILITY/ANGER – prospective	Feldman et al.[38]	109	ABS	Cohort
HOSTILITY/ANGER – retrospective/cross-sectional	Van Houdenhove[53]	32	Psychodynamic interviews	Cross-sectional
	DeGood et al.[40]	71	SCL-90R	Case-control
	Van Houdenhove et al.[51]	66	SCL-90	Cross-sectional
	Bruehl et al.[43]	34	BSI	Survey
	Geertzen et al.[45]	24	SCL-90	Survey
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
	Bruehl et al.[61]	34	AEI	Cross-sectional

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	No differences in sensitivity between CRPS1 patients and controls
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	No difference in sensitivity between CRPS1-dystonia patients and controls
No	(18%) poor	A dependent personality was observed in 9 (28%) of the CRPS1-patients
Chronic low back pain patients from disc-related radiculopathy (n = 25)	(29%) moderate	In one patient with CRPS1 (4%) and in two controls (8%) the diagnosis of dependent personality was made
No	(55%) good	Pain predicted increase in anger
No	(18%) poor	In 4 CRPS1 patients (12.5%), the personality trait passive-aggressive was present
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	CRPS1 patients have a significantly lower score on hostility than headache patients No significant difference in hostility between CRPS1 patients and low back pain patients
Reference groups questionnaire	(32%) moderate	CRPS1 patients report significantly higher hostility than cardiac patients but significantly lower than psychiatric patients
Non-CRPS1 limb pain (n = 50) and low back pain patients (n = 165)	(58%) good	No difference in hostility between CRPS1 patients and both control groups
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	No differences in hostility between CRPS1 patients and controls
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	No difference in hostility between CRPS1-dystonia patients and controls
Non-CRPS1 chronic patients experiencing limb pain (n = 50)	(34%) moderate	In patients with CRPS1, more expression of anger was related to a higher intensity of pain; in the control group, more expression of anger was related to a lower intensity of pain

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
EXTRAVERSION/ INTROVERSION prospective	Van Spaendonck et al.[35]	12	ABV	Cohort
	Puchalski & Zyluk[37]	9	EPQ-R	Cohort
EXTRAVERSION/ INTROVERSION retrospective	Van Spaendonck et al.[35]	160	ABV	Cross-sectional
	De Vilder[60]	42	NVM	Cross-sectional
INSOMNIA	DeGood et al.[40]	71	SCL-90R	Case-control
	Van Houdenhove et al.[51]	66	SCL-90	Cross-sectional
	Geertzen et al.[45]	24	SCL-90	Survey
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
	Greipp[49]	14	Survey tool made by author	Cross-sectional
PARANOIA	DeGood et al.[40]	71	SCL-90R	Case-control
	Bruehl et al.[43]	34	BSI	Survey

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

Control group	Quality*	Conclusion
Reference group questionnaire	(5%) poor	Patients with CRPS1 after a wrist fracture have a higher score on extraversion than the general population
Patients with a distal radius fracture without CRPS1 (n = 41)	(34%) moderate	23 CRPS1 patients (46%) were classified as ambivertics, 15 (30%) as introvertics, and 12 (24%) as extrovertics. There was no significant difference on the subscale extroversion between CRPS1 patients and controls
Reference group questionnaire	(8%) poor	Patients with CRPS1 do not have a significantly different score on extraversion compared to both the general population and psychiatric patients
No	(21%) poor	19% of the CRPS1 patients scored higher than average on the extroversion scale
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	No significant difference in sleeplessness between CRPS1 patients and both control groups
Reference groups questionnaire	(32%) moderate	CRPS1 patients report significantly more sleeping problems than both control groups
Hand pathology patients waiting for elective hand surgery within the next 24 hours (n = 42)	(18%) poor	No differences in insomnia between CRPS1 patients and controls
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	Significantly higher scores on insomnia in the female CRPS1-dystonia population compared with the control female population and in the total CRPS1-dystonia population as compared to rehabilitation patients
No	(29%) moderate	Insomnia never a problem in 43% of the CRPS1-patients, 43% reported an occasional problem, and in 14%, it was almost/always a problem
Low back pain (n = 66) and headache patients (n = 51)	(76%) good	No significant difference in paranoia between CRPS1 patients and both control groups
Non-CRPS1 limb pain (n = 50) and low back pain patients (n = 165)	(58%) good	CRPS1 patients do not differ in paranoia compared to both control groups

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

Table 2.3. Characteristics of the studies per factor *(continued)*

Factor	Authors	N CRPS1 patients	Measurement tool	Design
	Nelson & Novy[41]	58	MMPI	Cross-sectional
	Monti et al.[17]	25	Structured psychiatric diagnostic interview (DSM-III-R)	Cross-sectional
	Van der Laan et al.[46]	27	SCL-90R	Cross-sectional
	Shiri et al.[47]	17	MMPI & standardized semi-structured psychological interviews	Survey

* A score of 75% or higher indicates a qualitatively excellent study; a score of 50% to 75% is classified as good; 25% to

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Control group	Quality*	Conclusion
Myofascial pain syndrome patients (n = 214)	(74%) good	No differences in paranoia between CRPS1 patients and controls
Chronic low back pain patients from disc-related radiculopathy (n = 25)	(29%) moderate	Paranoia as a psychiatric diagnosis was made once in the controls (4%) and in none of the CRPS1-patients
Reference group female population (n = 577) questionnaire and control rehabilitation population (n = 56)	(37%) moderate	No difference in compulsive behavior between CRPS1-dystonia patients and controls
Conversion disorder patients (n = 20) and a medically ill control population of the MMPI	(16%) poor	No significant differences between the CRPS1 patients and conversion disorder patients

50% is moderate; and a score less than 25% indicates a study with a poor methodological quality

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CHAPTER 3

Complex Regional Pain Syndrome type 1 (CRPS1): Prospective study on 596 patients with a fracture

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ABSTRACT

Background We investigated the incidence of CRPS1 among patients with a fracture and evaluated the association between demographic and medical factors and CRPS1.

Methods Patients with a single fracture were included (n = 596) from three hospitals. At plaster removal (T1) and at 3 (T2) and 12 (T3) months after trauma, participants completed a CRPS1 symptoms questionnaire and were clinically diagnosed. At baseline (T0), T2, and T3, they completed a questionnaire on demographic and medical variables. Patients were diagnosed according to Bruehl, Veldman, and the International Association for the Study of Pain criteria.

Findings Of the 596 participants at baseline, 42 (7.0%) were diagnosed with CRPS1 according to the Bruehl criteria. Risk factors for CRPS1 included intra-articular fracture (50.0% CRPS1, 29.4% non-CRPS1), rheumatoid arthritis (14.3% vs 5.3% non-CRPS1), ankle fracture (50.0% vs 25.8% non-CRPS1), musculoskeletal comorbidities (54.8% vs 27.6% non-CRPS1), and fracture dislocation (64.3% vs 39.4% non-CRPS1). Ankle fracture and dislocation contributed significantly to the development of CRPS1. No CRPS1-patients were symptom-free at T3. Patients with CRPS1 had significantly more pain than patients without CRPS1 on all three timepoints. Patients with CRPS1 reported a lower quality of life on the physical composite score than patients without CRPS1 at both T0 and T2 ($p < .001$).

Interpretation CRPS1 occurs frequently after a fracture, and all patients continue having symptoms after one year. CRPS1 patients reported musculoskeletal comorbidities and rheumatoid arthritis more often, providing insight into the pathophysiology.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS, formerly known as reflex sympathetic dystrophy) is an invalidating pain syndrome. There are different sets of criteria for diagnosing CRPS type 1 (CRPS1), such as the criteria of Veldman[1], the International Association for the Study of Pain (IASP) criteria[2], and the criteria of Bruehl[3] (see Appendix 1). Pain is the most common symptom used in these criteria sets. Other symptoms used are allodynia, hyperalgesia, abnormal skin color, temperature change, abnormal sudomotor activity, edema, tremor, dystonia, and motor/trophic disturbances[1, 2, 4]. The use of different criteria across studies yields variable results that are difficult to interpret.

Large, prospective studies on the incidence of CRPS1 after a fracture are scarce. The overall limitations of such prospective studies are a relatively small source population[5-10], involvement of a single center and limited types of fracture[5-17], either no information given on the criteria used to diagnose CRPS1 or the use of a self-made instrument[6, 9, 18], and no follow-up[5, 6, 8, 14, 18]. The results of these studies are therefore inconclusive (range of reported incidence: 0.9–37).

Demographic and medical variables may play a role in the development of CRPS1. Patients with a fracture of the upper extremity have a greater chance of developing the disorder[1, 19-22], and the prevalence is higher among women compared with men[1, 22]. There is no consensus in the literature regarding the influence of fracture type on the chance of developing CRPS1. The mean age of patients at onset varies among several studies from 37 to 65 years[1, 20, 23-26].

The purpose of the present study was to describe the onset of CRPS1 after a fracture up to one year after trauma and to study the association between demographic/medical variables and the development of CRPS1.

In CRPS1, the functioning of the nervous system in patients with chronic pain can be studied well because of the pronounced symptoms compared to other diseases. Therefore, further research on this syndrome can also help to unravel other chronic diseases (e.g., rheumatoid arthritis).

The research questions addressed were as follows:

- What is the incidence of CRPS1 in patients after a fracture?
- What is the prevalence of CRPS1 in patients after a fracture at 3 and 12 months after trauma?
- Are there demographic (sex, age, level of education) differences between patients with a fracture who develop CRPS1 and those who do not?
- Are there differences in the following medical variables between CRPS1 patients and those who do not develop CRPS1: occurrence of CRPS1 in the past, number of comorbidities, type of fracture/fracture location, intra-articular fracture, dominant hand, fracture reduction, type of treatment, and duration in plaster?

– To what extent can CRPS1 be predicted by demographic and medical variables?
– Is there a difference in quality of life between patients with a fracture without CRPS1 and patients with a fracture with CRPS1?

PATIENTS AND METHODS

Participants

Patients were recruited from the emergency rooms of three hospitals in Rotterdam, the Netherlands; one university hospital (Erasmus MC) and two general hospitals (Medisch Centrum Rijnmond Zuid, the Clara and Zuider locations). Patients who were 18 years or older with a single fracture of the wrist, scaphoid, ankle, or metatarsal V were included in the study. Patients were treated conservatively with plaster cast (88.1%), with tape (0.7%), or with both plaster and surgery (10.9%). Patients were excluded if they were unable to complete a questionnaire (e.g., because of language problems or cognitive impairments), lived more than 50 km away from the hospital, had a nerve damage that could result in CRPS type 2, or had fractures in more than one extremity.

Design

A prospective, multicenter cohort study was performed.

Procedure

This study was approved by the local medical ethics committee of the Erasmus Medical Centre (MEC 223.922/2003/18). After informed consent, the participants completed a questionnaire by phone within two weeks after trauma (T0, see Figure 3.1) covering demographic variables (age, sex, education level) and medical functioning. Immediately after removal of the plaster (T1), the patients were again interviewed using a form with 23 symptoms related to CRPS1. When a patient fulfilled 4 out of 4 of the IASP criteria[2] and/or at least 4 out of 5 of the Bruehl criteria[3], the patient was referred to a pain specialist with considerable experience with CRPS (F.J.P.M.H.) at the Pain Treatment Centre of the Erasmus MC Rotterdam to confirm the diagnosis. Patients with a positive diagnosis received the standard medical treatment according to the guidelines used in the Netherlands, namely dimethyl sulfoxide cream[27] and physical therapy (to improve functionality, mobility, and muscle strength). Three months after trauma (T2), all patients completed a questionnaire. When a patient did not fulfill the criteria earlier but fulfilled them at T1, this patient was also referred to the Pain Treatment Center to confirm the diagnosis. When confirmed, standard therapy was also started in this patient. All patients diag-

nosed at T2 with CRPS1 according to the IASP criteria and/or the criteria of Bruehl were asked to fill in a short questionnaire one year after trauma (T3) to evaluate symptoms related to CRPS1. Patients not fulfilling the criteria at plaster removal or at T2 but reporting symptoms suspected for CRPS1 at T3 were referred to the Pain Treatment Center (and treated if necessary).

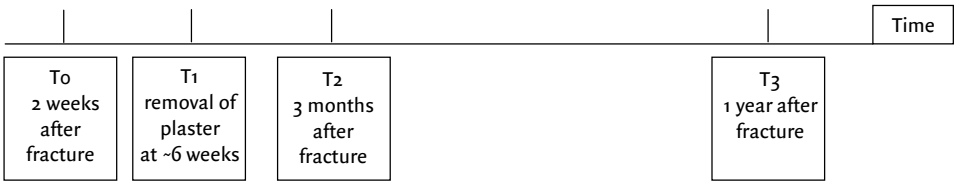


Figure 3.1. Timepoints of measurement

Measurements

Demographic and medical

Age, sex, and education level were analyzed. Medical variables addressed type of fracture/fracture location, intra-articular fracture, fracture reduction, and type of treatment. Medical questions filled in by patients at To covered occurrence of CRPS1 in the past, dominant hand, type of treatment, pain severity (Numeric Rating Scale), and comorbidities. At T1, the number of weeks in the plaster cast was determined.

Health-related quality of life

Health-related quality of life was measured at T2 using the SF-36 scale, which contains the following eight subscales: Physical functioning, role limitations because of physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations because of emotional problems, and general mental health. The SF-36 is a widely used instrument with good validity and reliability (mean alpha coefficient across all subscales = 0.84)[28]. Two composite scores are defined: the physical composite score and the mental composite score.

Diagnosis of CRPS1

In this study, three different sets of criteria for diagnosing CRPS1 were used: the criteria of Veldman[1], the IASP-criteria[2], and the criteria of Bruehl[3] (see Appendix 3.1). In addition, the diagnosis was confirmed by means of a physical examination. A diagnosis of CRPS1 was confirmed when a patient fulfilled all the criteria (symptoms and signs) of Bruehl.

Statistical analysis

Descriptive statistics were used to determine (multiple response) frequencies. Differences between CRPS1 patients and non-CRPS1 patients on continuous variables were analyzed with the Mann-Whitney U tests because of

the skewed distribution of these variables. Differences between CRPS1 patients and non-CRPS1 patients on nominal variables were analyzed using the Pearson chi-Square test. In case of a 2x2 table, the Fisher's exact test was used.

Binary logistic regression analysis (the backward Wald method) was used to evaluate the value of medical variables in the prediction of the development of CRPS1. A significance level of ≤ .10 was used for the final step of the logistic regression analysis. As an outcome variable, the diagnosis of CRPS1 according to the Bruehl criteria was used. Sensitivity and specificity were valued equally.

To analyze the course of the pain ratings, a Manova for repeated measurements using the presence/absence of CRPS1 (group) and the timepoints of measurement (period) as independent variables was performed.

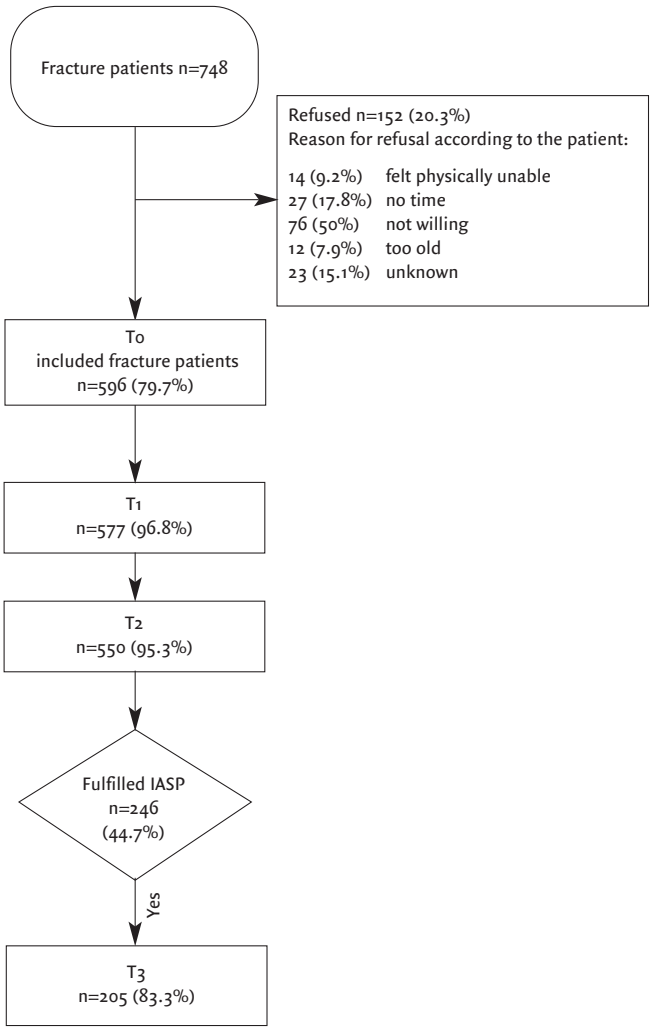
To analyze the differences between the scores of patients with CRPS1 for both composite scores of the SF-36 (physical and mental), a student's t-test was performed for independent samples in cases of normal distribution. When the distribution was not normal, a Mann Whitney U test was performed. Both composite scores are the linear T-score transformation of the aggregated component scores, which resulted in acquiring a mean of 50 and a standard deviation of 10 in the American population.

The analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 14.0.

RESULTS

Patients

From February 2002 until April 2006, 748 consecutive patients fulfilling the inclusion criteria were asked to participate, and 596 (79.7%) agreed (217 [36.4%] male and 379 [63.6%] female; Figure 3.2). The median age was 52.8 years [interquartile range (IQR) 33.4–63.9]. Common education levels were junior (23.8%) or senior vocational education (19.3%). Patients who refused to participate did not differ significantly from the participants in gender or preceding trauma but were older (median age: 61.8 years; range: 18–89; IQR: 37.9–74.1; $p < .001$). In 311 patients (52.2%), the upper extremity was affected and in 285 patients (47.8%) the lower extremity was. Median time in plaster was 42 days (SD: 14.5). At T2, 550 patients participated, and 46 (7.7%) were lost to follow-up. Patients lost to follow-up at T2 did not differ significantly from those completing follow-up at T2 with regard to age, sex, or pain at T0. At T3, 246 patients (44.7%) who met the IASP criteria at T2 were asked to fill in a third questionnaire on symptoms of CRPS1, with a response of 205 patients (83.3%). Patients who participated at T3 were significantly older ($p = .01$; median age: 55.1; IQR: 37.8–66.3) than patients who did not participate at T3 (median age: 52.1; IQR: 31.3–60.7). Patients who participated at T3 were more often female (72.7%) than patients who did not participate at T3 (58.6%) ($p = .001$).



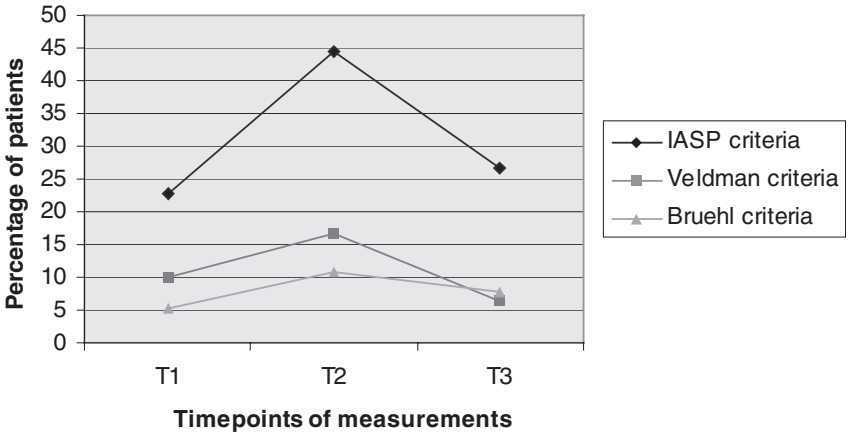
To = baseline, T1 = plaster removal, T2 = 3 months after trauma, T3 = one year after trauma; IASP = criteria of the International Association for the study of Pain

Figure 3.2. Flow chart for patient inclusion

Symptoms of the criteria sets by measurement

Figure 3 shows the number of patients at the different timepoints of measurement per criteria set. When the IASP criteria are used, 289 (48.5%) are diagnosed with CRPS1. With use of the criteria of Veldman, 127 (21.3%) are diagnosed with CRPS1, and when the anamnestic criteria of Bruehl are used, 76 (12.8%) are diagnosed with CRPS1. The peak of CRPS1 is seen at three months after trauma. Of the 293 patients who fulfilled 4 out of 5 of

the criteria of Bruehl and/or the criteria of IASP and were therefore referred to the Pain Treatment Centre, 53 (18.1%) refused or were not able to come. In total, 42 (14.3%) participants met the criteria of Bruehl for CRPS1, or 7.0% of all participants at baseline.



IASP = International Association for the Study of Pain

Figure 3.3. Percentage of patients fulfilling the different sets of criteria by timepoints of measurement

Demographic and medical variables

Table 3.1 shows the differences in demographic and medical variables between the CRPS1 patients and patients without CRPS1.

Of all the factors studied, patients with CRPS1 differed significantly from patients without CRPS1 in fracture location, intra-articular fracture, and dislocation of the fracture. TFurthermore, patients with an ankle fracture more often developed CRPS1 compared to other fracture locations. However, when a distinction was made between the upper and the lower extremities, both groups were equally affected in CRPS1 patients compared to the patients without CRPS1 (10% of patients with a fracture in the lower extremity developed CRPS1 compared to 7.1% with involvement of the upper extremity).

Table 3.1. (Relative) frequencies of demographic and medical factors in patients with CRPS1 compared to patients without CRPS1

	Factor n = 42	CRPS1 n = 453	Non-CRPS1	p
Sex n (%)	Male	11 (26.2)	162 (35.8)	ns
	Female	31 (73.8)	290 (64.2)	
Age		Mean: 54.0 Range: 22–82 IQR: 40.2–67.4	Mean: 49.8 Range: 18–90 IQR: 33.0–63.6	ns
Education level n (%)	No education	1 (2.4)	2 (0.44)	ns
	Primary school	6 (14.3)	41 (9.1)	
	Junior vocational education	10 (23.8)	105 (23.2)	
	Lower general secondary education	8 (19.0)	75 (16.6)	
	Senior vocational education	5 (11.9)	87 (19.2)	
	Higher general secondary education/pre-university education	6 (14.3)	59 (13.1)	
	Bachelor	6 (14.3)	62 (13.7)	
	Master	0 (0.0)	21 (4.6)	
Fracture location n (%)	Ankle	21 (50.0)	117 (25.8)	p = .002
	Foot	3 (7.1)	100 (22.1)	
	Wrist	18 (42.9)	209 (46.1)	
	Hand	0 (0.0)	27 (6.0)	
Dominant hand n (%)		11 (61.1)	108 (45.4)	ns
CRPS1 in the past n (%)		2 (5.1)	8 (1.8)	ns
Intra-articular fracture n (%)		21 (50.0)	131 (29.4)	p = .006
Fracture reduction n (%)		17 (40.5)	122 (27.1)	ns
Dislocation n (%)		27 (64.3)	177 (39.4)	p = .003
Days in plaster		Mean: 47.8 SD: 17.50	Mean: 42.0 SD: 13.64	ns
Type of fracture treatment n (%)	Plaster	35 (83.3)	400 (88.9)	ns
	Surgery and plaster	7 (16.7)	47 (10.4)	
	Tape	0 (0.0)	3 (0.7)	

Binary logistic regression analysis

Table 3.2 presents the results of the binary logistic regression analysis. Dislocation and the location of the fracture (ankle) contributed significantly to the prediction of CRPS1.

The sensitivity was 50.2, specificity was 83.3, and the overall classification was 53.0.

Table 3.2. Prediction of CRPS1

Covariate	B	Exp(B)	p
Dislocation	1.00	2.717	.004
Hand*	–18.272	.000	.998
Foot*	–.788	.455	.221
Ankle*	.944	2.571	.007
Constant	–3.094	.045	< .001

* The wrist was used as the reference location

The median number of comorbidities of patients with CRPS1 was two (IQR: 1–3.25); for those without CRPS1, it was one (IQR: 0–2). This difference is significant (p = .027). Patients with CRPS1 suffered significantly more often from rheumatoid arthritis compared to those without CRPS1 (p = .020). Musculoskeletal comorbidities (back pain and arthrosis) were also significantly more present in patients with CRPS1 compared to those without CRPS1 (p < .001).

The mean number of symptoms of patients with CRPS1 at T2 was 14 (SD = 4.23); the median number of symptoms at T3 was 9 (range: 1–21).

Figure 3.4 shows the mean pain ratings of the preceding week at the different timepoints of measurement for patients with and without CPRS1. There was a significant effect of time ($F_{2,344}$ = 10.73; p < .001), and group ($F_{1,172}$ = 14.32; p < .001). Furthermore, patients with and without CRPS1 did not differ on the severity of the pain they found tolerable.

Concerning quality of life, patients with CRPS1 did not report a different score compared to patients without CRPS1 on the mental composite score of the SF-36 at either T0 or T2. Concerning the physical component score at T0, patients with CRPS1 reported a significantly lower quality of life than patients without CRPS1 (CRPS1: mean 27.3, SD: 7.42; without CRPS1: mean: 34.6, SD: 8.56; $t_{(490)}$ = 5.29; p < .001). At T2, patients with CRPS1 also had a significantly lower physical composite score than patients without CRPS1 (CRPS1: mean 30.8, SD 8.34; without CRPS1: mean 44.9, SD 10.0; p < .001).

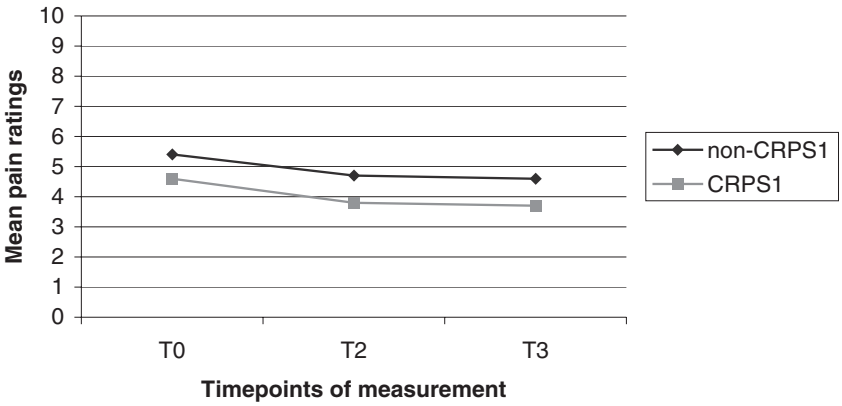


Figure 3.4. Mean pain scores on the different timepoints

DISCUSSION

This investigation is one of the first prospective studies with a large number of patients (n = 596) to describe the incidence and prevalence of patients with CRPS1 after a fracture. CRPS1 based on the Bruehl criteria occurred in 7.0% of the study population. In the literature, the incidence rates of CRPS1 after a fracture vary between 0.9% and 37%[5-18, 26]. The lower incidence in our study compared to other studies might be explained by the use of (objective) diagnostic criteria with a higher specificity (0.94)[3] in our study. The lack of a gold standard for diagnosing CRPS1 leads to different results among studies; as our results indicate, the method used to diagnose CRPS1 largely determines the incidence of CRPS1. Another explanation is the exclusion of communitive fractures in the current study. Other studies have shown that patients with a communitive fracture have a higher chance of developing CRPS1[26, 29, 30]. Also, the different relative frequencies in the distribution of the various types of fractures of the participants in our sample might explain the differences in CRPS1 rates in the literature.

Of the patients with CRPS1, the majority were female (73.8%), which is in accordance with many other studies[21, 22]. However, no significant difference was found in the proportion of women that developed CRPS1 compared to the proportion of men that developed CRPS1. This finding is in accordance with the proposed explanation that the prevalence of wrist fractures in women is the cause of their relatively higher representation among CRPS1 patients[31], although this explanation is inconsistent with the findings of others[26, 32].

The relationship between specific fractures and the occurrence of CRPS1 has also been described. Sarangi et al. reported that 30% of patients with a tibial fracture develop CRPS1. In our study, a similar number was

identified (27.3%). The occurrence of CRPS1 after a (displaced) distal radius fracture varies from 0.9% to 18%[6, 8, 10, 15, 16, 18, 33]. A problem with comparing hazard ratios for developing CRPS1 after distal radius fractures is the fact that different definitions for this type of fracture are used (e.g., colles fracture included or not). In our study, 8.3% of patients with a distal radius fracture (including colles fractures) developed CRPS1. The percentage of CRPS1 patients after a colles fracture ranges from 1–37%[5, 7, 11-14, 17, 34], and in the present study, 14% of patients with a colles fracture developed CRPS1, falling in the middle of the reported range. In our study, the fracture location differed significantly between patients who developed CRPS1 compared to those who did not. Patients with an ankle fracture had a higher chance of developing CRPS1 compared to patients with other fracture locations. However, there was no statistical difference in the chance to develop CRPS1 between the upper and lower extremity. This finding is in contrast with other studies, in which the upper extremity was affected more often than the lower extremity[1, 20-22].

There is no consensus on the influence of the type of fracture on the onset of CRPS1 in the literature. Several studies found no association between fracture type and the probability of developing CRPS1[5, 9, 12]. On the other hand, others concluded that CRPS1 occurs more often after more severe fractures[11, 26]. There is no consensus either on the influence of dislocation of the fracture on the onset of CRPS1. Roumen et al.[14] stated that dislocation does have an effect, but Bickerstaff and Kanis[11] disagree with this statement based on their prospective study on CRPS1 after a colles fracture. Our results support the findings of Roumen et al. Furthermore, patients with CRPS1 had significantly more intra-articular fractures than the patients without CRPS1; this finding supports the results of Zollinger et al.[26] but not the results of others[5, 14, 33, 35].

Furthermore, patients who developed CRPS1 in the current study reported musculoskeletal comorbidities and rheumatiod arthritis relatively more often than those who did not develop this syndrome. In other words, patients with these comorbidities are more susceptible to developing CRPS1. There are some indications for a genetic susceptibility for CRPS1[36-38]. Also, there is growing evidence in the literature for immunological attainment of this syndrome, but definite conclusion cannot be made[39-42]. Several authors have reported a frequent (spontaneous) resolution of (all) the signs and symptoms of CRPS1[11, 20, 43]. In our study the mean number of symptoms between T2 and T3 decreased significantly, but none of the 37 CRPS1 patients who participated at T3 (one year after trauma) reported being symptom free. Sarangi et al.[9] found that 22% of the CRPS1 patients still reported symptoms at one year after trauma.

Already at baseline, patients with CRPS1 rated their pain significantly higher than patients without CRPS1. Their pain ratings remained higher, and therefore pain could be an important predictor of the development of CRPS1.

Concerning quality of life, CRPS1 patients did not score differently on

mental health, but their physical functioning was lower than that of patients without CRPS1 at both To and T2. This difference might be explained by the fact that these patients suffer from more symptoms than patients without CRPS1.

The number of patients fulfilling the CRPS1 criteria one year after trauma is relatively low. One explanation is the fact that several symptoms of these criteria (such as swelling and temperature asymmetry) are related to inflammation, which is less pronounced in chronic CRPS1. This is in accordance with the clinical impression and the findings of Bruehl et al.[44] who defined three subtypes of CRPS1.

Of the patients who were referred to the Pain Treatment Center for diagnosis, 18.1% refused or were not able to come. We assume that not many CRPS cases were missed because patients with only a few symptoms did not feel the need to go to a doctor and the chance that these patients developed CRPS1 is low.

In conclusion, an intra-articular fracture, a fracture of the ankle, rheumatoid arthritis, musculoskeletal comorbidities, and a dislocation of the fracture are risk factors for CRPS1. Furthermore, none of the CRPS1 patients were free of symptoms at one year after trauma, confirming that CRPS1 is an invalidating, long-lasting syndrome.

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APPENDIX 3.1: SETS OF CRITERIA FOR DIAGNOSING CRPS1

Criteria of Veldman[1]: (1) At least four out of five signs or symptoms: pain, differences in skin color, edema, differences in skin temperature, and changes in active range of motion. (2) Signs and symptoms present in an area larger than might be expected for the initial trauma. (3) Increase of signs and/or symptoms during or after exercise.

Criteria of IASP[2]: (1) Type I is a syndrome that develops after an initiating noxious event. (2) Spontaneous pain or allodynia/hyperalgesia occurs, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event. (3) There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event. (4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction. (For the diagnosis of CRPS I, criteria 2–4 must be fulfilled).

Criteria of Bruehl[3]: (1) Continuing pain disproportionate to any inciting event. (2) Presence of at least one symptom in each of the following categories: sensory, vasomotor, sudomotor/edema, or motor/trophic. (3) At least two signs of a sensory, vasomotor, sudomotor/edema, or motor/trophic nature.

CHAPTER 4

The association between psychological factors and the development of the Complex Regional Pain Syndrome type 1 (CRPS1) – a prospective multicenter study

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ABSTRACT

Objective The objective of this study was to investigate the association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1).

Methods A prospective multicenter cohort study was performed involving the emergency room of three hospitals, and patients age 18 years or older, with a single fracture, were included in the study. At baseline (T0) , participants completed a questionnaire covering demographic, psychological (Symptom Checklist-90), and medical variables. At plaster removal (T1) and at three months after trauma (T2), the participants completed a questionnaire addressing symptoms of CRPS1. Psychological factors that were analysed were agoraphobia, depression, somatization, insufficiency, sensitivity, insomnia, and life events.

Results In total, 596 consecutive patients were included in the study, and 7.0% were diagnosed with CRPS1. None of the psychological factors predicted the development of CRPS1. The scores on the Symptom Checklist-90 subscales fell into the range of the general population and were, in most cases, average or below average when compared with those of pain patients or psychiatric patients.

Conclusion No empirical evidence supports a diagnosis of CRPS1 patients as 'psychologically different', and the current results show no relationship between psychological factors and CRPS1.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a complication after surgery or trauma. It presents with several symptoms, including severe pain, allodynia, hyperalgesia, abnormal skin color, temperature change, abnormal sudomotor activity, edema, and motor/trophic disturbances[1-3]. CRPS usually develops after a small trauma such as an injury or fracture or after surgery. There are two types of CRPS; type 1 (CRPS1) occurs without a detectable nerve lesion, and type 2 (CRPS2) is accompanied by a detectable nerve lesion.

One of the controversies about the cause of CRPS1 is the role of psychological factors in its development. Some have described CRPS1 patients as being 'psychologically peculiar'[4], while others have not shared this opinion[5]. Beerthuizen et al.[6] concluded, based on 31 included articles, that the literature shows no relationship between depression, anxiety, hysteria, hypochondria, obsessive-compulsive behavior, somatization, neuroticism, interpersonal sensitivity, dependency, hostility/anger, extraversion/introversion, insomnia, or paranoia on the one hand and CRPS1 on the other. Only life events appear to be related to the development of CRPS1; patients who experienced more life events seemed to have a higher chance of developing CRPS1. However, the majority of included studies (N = 24, 77%) had only poor to moderate methodological quality; most studies used only retrospective or cross-sectional designs. Two hypothetical pathways that could explain the effects of life events on CRPS1 have been described in the literature. The first is an increased nociception resulting in a greater chance of developing CRPS1[4,7]. A second, indirect effect might be a lowered sympathetic response that accounts for an upregulation of the receptors and an increased sensitivity for circulating catecholamines[8-10].

The first aim of the present study was to investigate the contribution of psychological factors in CRPS1. The second aim was to investigate psychological distress in patients with CRPS1 as compared to the different norm groups of the Symptom Checklist-90 (the general population, pain patients, and psychiatric patients).

METHODS

Participants and design

For this prospective multicenter cohort study, patients were recruited from the emergency rooms of three hospitals in Rotterdam, the Netherlands; one university hospital (Erasmus MC) and two general hospitals (Medisch Centrum Rijnmond Zuid, locations Clara and Zuider). Patients who were 18 years or older with a single fracture of the wrist, scaphoid, ankle, or metatarsal V were included in this study after admission to the emergency

room. They were treated with plaster cast (88.1%) or with a combination of surgery and plaster (10.9%). Potential participants were excluded if they were unable to fill out a questionnaire (e.g., because of language problems or cognitive impairments), were living more than 50 km away from the hospital, had a nerve damage that could have caused CRPS type 2, or had fractures in more than one extremity.

Procedure

This study was approved by the local medical ethics committee of the Erasmus Medical Centre (MEC 223.922/2003/18). After informed consent, the participants completed a questionnaire by phone within two weeks after trauma (T0) covering demographic variables and medical and psychological functioning. Immediately after removal of the plaster (T1), the patients were interviewed with a structured questionnaire based on 23 complaints related to CRPS1. Any patient fulfilling the criteria was referred to the Pain Treatment Centre of the Erasmus MC Rotterdam, where the pain specialist was asked to confirm the diagnosis. A diagnosis of CRPS1 was confirmed when a patient fulfilled all of the criteria of Bruehl[11]. Patients with a positive diagnosis received standard medical treatment according to the guidelines used in the Netherlands, namely: dimethyl sulfoxide cream[12] and physical therapy to improve functionality, mobility, and muscle strength. Three months after trauma (T2), all patients were asked to respond to a questionnaire similar to the one that they completed at T1. Any patient who did not fulfil the criteria earlier but fulfilled the criteria at T1 was also referred to the pain specialist for confirmation of a CRPS1 diagnosis. If confirmed, standard therapy was also started for these patients.

Measurements

Demographic and medical

Demographic variables analysed were gender, age, and education level. Medical variables analysed were dislocation of the fracture, fracture location, number of analgesics, and number of symptoms at baseline (T0).

Diagnosis of CRPS1

Patients were interviewed at T1 (by the plaster specialist) and T2 (by phone) using a form with 23 complaints related to CRPS1 based on three sets of criteria: the criteria of Veldman[1], the criteria of the International Association for the Study of Pain[2], and the criteria of Bruehl[11]. When a patient fulfilled 4 out of 4 IASP criteria and/or at least 4 out of 5 Bruehl criteria at T1 or T2, a pain specialist with extensive experience in CRPS (F.J.P.M.H.) at the Pain Treatment Centre of the Erasmus MC Rotterdam was asked to confirm the diagnosis. A diagnosis of CRPS1 was confirmed if a patient fulfilled the Bruehl criteria.

Life Events Inventory
At baseline (To), patients were asked to fill in a questionnaire on life events experienced in the last year. The Life Events Inventory (LEI) was adopted by Cochrane and Robertson[13] from the Schedule of Recent Experience from Hawkins et al.[14]. The LEI is a hierarchical list of stressful life events in which each event has its own score (weight) depending on the degree of disruption that would result when an average person experiences that event[13]. The LEI has been shown to be reliable (Cronbach's alpha, 0.83)[15]. All life events from the LEI with a weight higher than 50 were scored. The influence of the weighted number of life events on CRPS1 was analysed.

Symptom Checklist-90 (SCL-90)
At baseline (To), the participants completed the SCL-90-R, measuring the following dimensions: anxiety, agoraphobia, depression, insufficiency, somatization, interpersonal sensitivity, hostility, and insomnia. The total score is a measure of psychoneuroticism. Validity and reliability of the SCL-90 are good; Cronbach's alphas of the subscales vary from 0.76 to 0.97[16].

In line with Bruehl and Chung[17] who suggested that psychological tests for patients with CRPS1 might include confounded items, we distinguish two types of confounding potentially present. First, some items of the SCL-90 are symptoms of the criteria list used to diagnose CRPS. Second, as proposed by Bruehl and Chung[17], it might be possible that there is a bias in measuring social avoidance; patients with CRPS1 might display extreme social avoidance not because they are agoraphobic, but because they are afraid that someone will bump into their affected arm or leg (agoraphobia, a subscale of the SCL-90, measures social avoidance). Another example of this type of confounding might be that because of the symptoms of CRPS, patients are often restricted in their activities, and motor disturbances such as coordination problems are also present in some cases (these two possible confounded items are components of the subscale insufficiency of the SCL-90). A third example of this confounding might be that, as a consequence of the severe pain that patients with CRPS1 can suffer, sleeping problems can be inherent in the disorder. Therefore, two psychologists determined which items of the SCL-90 are possibly confounded, until consensus was reached. Table 4.1 shows a list of possible confounded items of the SCL-90.

Table 4.1. Possible confounded items of the Symptom Checklist-90 (SCL-90) in patients with complex regional pain syndrome type 1

Subscales of the SCL-90	Possible confounded items
Somatization	Soreness of muscles
	Hot or cold spells
	Numbness or tingling
	Feeling weak in parts of your body
	Heavy feeling in your arms or legs
Agoraphobia	Feeling afraid in open spaces or on the street
	Feeling afraid to travel on buses, subways, or trains
	Feeling uneasy in crowds
Insomnia	Trouble falling asleep
	Awake in early morning
	Restless sleep
Insufficiency	Feeling blocked in getting things done
	Having to do things very slowly to ensure correctness

The scores on the subscales of the SCL-90 (with possible confounded items) of the present study were compared with the scores of the norm groups of the SCL-90: random sample from the general population (n = 2368), consecutive chronic pain patients who were referred to a pain center for the first time (n = 2458), and psychiatric outpatients (n = 5658).

Data analysis

Binary logistic regression analysis (backward Wald method) was used to evaluate whether psychological factors were of value in addition to medical variables in predicting the development of CRPS1. Univariate analyses were performed with a significance level of ≤ .20 The following variables were entered into the model: age, education level, subscales of the SCL-90 (agoraphobia, depression, somatisation, insufficiency, sensitivity, and insomnia), and the sum of the weighted life events. A significance level of ≤ .10 was used for the final step of the logistic regression analysis. As the outcome variable, the diagnosis of CRPS1 according to the Bruehl criteria was used. Sensitivity and specificity were valued as equally important. With a MANOVA for repeated measurements, the differences between CRPS1 patients and patients without CRPS1 on the subscales, leaving out the possible confounded items, were analyzed (see Table 1). Analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 14.0.1.

RESULTS

From February 2002 until April 2006, 748 consecutive patients who fulfilled the inclusion criteria were asked to participate; 596 (79.7%) agreed, consisting of 217 (36.4%) males and 379 (63.6%) females. The median age was 52.8 (range, 18–90; interquartile range, 33.4–63.9).

Patients refusing to participate did not differ significantly from the participants in gender or preceding trauma, but they were significantly older than the participants (median age 61.8, range 18–89; interquartile, 37.9–74.1; $p < .001$). In 311 patients (52.2%), the upper extremity was affected; in 285 patients (47.9%), the lower extremity was involved. The average time in plaster was 43 days. At T2, 550 patients could be evaluated, and 46 (7.7%) refused to participate further or were lost to follow-up. In total, 42 patients (7.0%) developed CRPS1 according to the Bruehl criteria. The mean number of analgesics at baseline was 1.3 (SD = 0.53), and the mean number of symptoms was 4.1 (SD = 4.38).

Table 4.2 presents the results of the logistic regression analysis.

Table 4.2. Prediction of complex regional pain syndrome type 1

Covariate	B	Exp(B)	p
Dislocation	0.979	2.663	.020
Hand*	–17.632	0.000	.998
Foot*	–0.577	0.562	.426
Ankle*	0.900	2.460	.047
Number of analgesics at To	0.132	1.142	.617
Number of symptoms at To	0.188	1.207	< .001
Age	0.023	1.023	.067
Somatisation	0.067	1.069	.038
Constant	–6.737	0.001	<.001

* The wrist was used as a reference location

For CRPS1 at T2, somatisation and age seemed to have had a significant additional predictive power, in addition to medical variables. Greater age resulted in a higher chance of developing CRPS1. Based on this analysis, the following medical variables also contributed significantly to the prediction of CRPS1: dislocation, ankle, and number symptoms (more symptoms heightened the chance of developing CRPS1). The sensitivity (78.9%), specificity (78.1%), and overall classification (78.2%) were high. A cut-off value of 0.8 was used in this analysis.

It appeared that patients scored higher only on the confounded items of Somatisation compared to patients without CRPS1. When the possible confounded items were left out of the binary logistic regression analysis, somatisation was also no longer a significant contributor to the prediction of the development of CRPS1 (Table 4.3).

Table 4.3. Prediction of complex regional pain syndrome type 1 (without possible confounding items from the Symptom Checklist-90)

Covariate	B	Exp(B)	p
Dislocation	0.905	2.471	.029
Hand*	−17.715	0.000	.998
Foot*	−0.364	0.695	.605
Ankle*	0.932	2.539	.039
Number of analgesics at To	0.260	1.297	.300
Number of symptoms at To	0.199	1.220	< .001
Age	0.025	1.025	.042
Constant	−5.908	0.003	< .001

* The wrist was used as a reference location

The sensitivity (78.9%), specificity (76.9%), and overall classification (77.1%) were high. Of the medical/demographic variables included in this analysis, dislocation, ankle as fracture location, number of symptoms, and age significantly contributed to the prediction of CRPS1; more symptoms and an older age increased the chance of developing CRPS1.

Norm groups, SCL-90

A comparison was made between the scores on the SCL-90 at baseline of the patients who later developed CRPS1 and the norm groups of the SCL-90 (general population, patients with chronic pain, and psychiatric outpatients). Table 4.4 shows the percentage of CRPS1 patients with an average or below average score when compared with the norm groups. An average score is defined as a score falling between the mean one standard error measurement. When compared with the norm group of the general population, a relatively large number of patients had an average or below average score (range, 57.1–90.5). The majority of patients with CRPS1 had an average or below average score when compared with either the norm group of the SCL-90 of patients with chronic pain or with the norm group of psychiatric outpatients of the SCL-90.

DISCUSSION

The first aim of this study was to evaluate the role of psychological factors in addition to medical factors in the development of CRPS1. There is no consensus in the literature on the role of psychological factors, such as somatisation, in the development of CRPS1. However, based on the review of Beerthuizen et al.[6], in which methodological quality was taken into account, it seems that psychological factors do not play a role in CRPS1. In this study, the SCL-90 was used to assess psychopathology.

Table 4.4. Percentage of Complex Regional Pain Syndrome type 1 patients with an average or below average score on the Symptom Checklist-90 when compared to different norm groups

	General population N = 2368	Patients with chronic pain N = 2458	Psychiatric outpatients N = 5658
Anxiety	83.3	92.9	96.7
Agoraphobia	64.3	81.0	95.2
Depression	66.7	88.1	97.6
Insufficiency	54.8	78.6	92.9
Somatization	57.1	92.9	92.9
Interpersonal sensitivity	81.0	81.0	95.2
Hostility	90.5	95.2	100
Insomnia	59.5	88.1	88.1
Psychoneuroticism	59.5	85.7	97.6

Bruehl and Chung[17] stated that there might be a bias in the measurement of social avoidance behaviour of patients with CRPS because patients with CRPS1 may show avoidance behaviour that is mistaken for agoraphobia. In an analysis of other subscales of the SCL-90 (somatization, insomnia, and insufficiency), we showed that these scales are affected in the same way. It appeared that patients with CRPS1 score higher on the confounded items of somatization than patients without CRPS1. When the confounded items are left out of the binary logistic regression analysis, however, somatization is no longer a significant contributor to the prediction of the development of CRPS1. These findings are two indications that the abnormal scores on the SCL-90 might be the result of confounding. Therefore, the main conclusion of the present study is that patients with CRPS1 report psychological problems that are comparable to or less than those of the normal population and that psychological factors do not predict the development of CRPS1.

This conclusion is in line with that of the review of Beerthuizen et al.[6], but another finding differs from previous analyses. In the current study, weighted life events did not play a role in the prediction of CRPS1. However, based on eight articles regarding life events[7, 17-23], included in the systematic review by Beerthuizen et al.[18-24], life events might play a role in the development of CRPS1. A possible explanation for the difference in results is that the current study is a prospective well-designed study as opposed to the cross-sectional studies on life events included in the review.

The second aim of this study was to investigate psychological distress in patients with CRPS1 as compared to the norm groups of the SCL-90. In the current study, the included patients had scores on the SCL-90 subscales comparable to those of the general population and lower than those

of both pain patients and psychiatric patients. A relatively large proportion of the CRPS1 patient group had an average or below average score related to psychological functioning when compared with the general population. The number of patients with an average or below average score increased when compared with the scores of pain patients or psychiatric outpatients. Other studies, summarized in the review of Beerthuizen et al.[6], also compared CRPS1 patients with other (patient) groups. The majority of the included studies had only a poor to moderate methodological quality. Our results are comparable with the results of the studies included in that review, except for the studies in which CRPS1 patients were compared with somatic/pain patients. We found that CRPS1 patients as a group score lower than other pain patients, while others report that CRPS1 patients have a score comparable to that of other pain patients (in 60% of the comparisons with other somatic or pain patients).

A general limitation of studies on CRPS1, including the current study, is the lack of a gold standard for diagnosing CRPS1, which results in a comparison of different groups of patients who are all considered CRPS patients. Future research should therefore focus on universal diagnostic criteria. Furthermore, the influence of possibly confounded items on the psychological questionnaires should be studied. In addition, the relationship between psychological factors and the course of CRPS1 has not yet been studied, although different processes might be involved as CRPS1 evolves, something that future research also should address.

Our results indicate that although patients with CRPS1 are stigmatized with a specific psychological profile, psychological problems do not contribute to the prediction of the development of CRPS1.

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CHAPTER 5

The predictive value of personality for the Complex Regional Pain Syndrome type 1 (CRPS1) – a prospective multicenter study

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ABSTRACT

Background The objective of this study was to investigate the relationship between personality factors and the development of the Complex Regional Pain Syndrome (CRPS1). Differences in personality (measured with the Dutch Personality Inventory, DPI) between patients with CRPS1, patients without CRPS1, and the norm group (from the normal population) were studied.

Methods Patients, 18 years or older, with a single fracture were included in this study. A prospective multicenter cohort study was performed at the emergency room of three hospitals. At baseline (T0) and three months after trauma (T2), participants completed a questionnaire on demographic, psychological (Symtom Checklist-90, SCL-90), and medical variables. At plaster removal (T1) and at T2, participants completed a questionnaire on the symptoms of CRPS1. Patients scoring high on the SCL-90 were interviewed by a clinical psychologist.

Results In total, 596 consecutive patients were included in the study. Forty-two patients (7.0%) were diagnosed with CRPS1. Discontentedness and dominance appeared to be predictive of CRPS1. As a group, patients with CRPS1 did not score differently from the normal population on the DPI, except for dominance, where CPRS patients scored lower than other patients. However, for dominance, CRPS1 patients scored around the average of the normal population, while patients without CRPS1 scored above average.

Conclusions There is no evidence in these results for diagnosing CRPS1 patients as having a distinct personality profile at the moment they develop CRPS1. They do not differ from patients without CRPS1, and do not differ from the normal population.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS1) is a complication after surgery or trauma. It is characterized by several symptoms, such as severe pain, allodynia, hyperalgesia, abnormal skin colour, temperature change, abnormal sudomotor activity, edema, and motor / trophic disturbances[1-3]. There is no consensus on the role of personality factors in the development of CRPS1. De Vilder states that 'patients with CRPS1 are often considered by physicians and allied health personnel as having a peculiar personality'[4], p. 252. He describes a discrepancy between the clinical picture of patients with CRPS1 as being dissatisfied with the treatment, and the outcomes of a personality inventory, on which patients with CRPS1 show almost no negativistic attitudes. However, patients with CRPS1 tended to be more rigid and self sufficient (showing little or no interest in other persons and their problems) than the normal population. They also tended to score higher on somatization than the normal population.

The conclusion of a recent systematic review was that the literature can not confirm a direct or indirect relationship between personality factors (e.g. neuroticism) and CRPS1[5]. Some of the reviewed studies found that patients with CRPS1 are more neurotic than a normal comparison group of cardiac patients[6, 7]. Others report no differences between patients with CRPS1 and several control groups[8-12]. However, most studies were of low methodological quality, and used only retrospective or cross-sectional designs. Another recent study reports that, on the level of the individual, there may be higher scores on some personality variables. However, as a group, patients with CRPS1 cannot be characterized by a specific personality profile[13].

Because the previous studies were methodologically flawed, we undertook, and reported in a previous article, a prospective study of the relationship between psychological problems and CRPS1[14]. After correction for confounded items on the subscales somatization, agoraphobia, insomnia and insufficiency, we found that psychological problems have no predictive value over medical variables for who will develop CRPS1 and who will not. In that study, we also evaluated the relationship of a couple of personality characteristics, namely neuroticism, hostility, insufficiency and interpersonal sensivity. Neuroticism is the tendency to react with somatic complaints when confronted with psychological stress. Such a tendency might predispose a patient after a trauma to develop CRPS1. We found no evidence for a relationship between neuroticism or hostility and the development of CRPS1. Other personality factors were not investigated in our previous study.

The aim of the present study is therefore to investigate prospectively the relationship between personality factors as measured with the SCL-90 and the Dutch Personality Inventory (DPI), and the development of CRPS1.

METHODS

Participants

Patients were recruited from the emergency room of three hospitals in Rotterdam, the Netherlands, one university hospital (Erasmus MC), and two general hospitals (Medisch Centrum Rijnmond Zuid, locations Clara and Zuider). Patients, 18 years or older, with a single fracture of the wrist, scaphoid, ankle, or metatarsal V were included in this study. Patients were treated with only a plaster cast (88.1%), or with surgery as well (10.9%). Patients were excluded if: they were unable to fill in a questionnaire (e.g. due to language problems, cognitive impairments); they were living more than 50 kilometres from the hospital; they had a nerve damage which could have caused CRPS1 type 2; or they had fractures in more than one extremity.

Design

A prospective multicenter cohort study was performed.

Procedure

This study was approved by the local Medical Ethical committee of the Erasmus Medical Centre (MEC 223.922/2003/18). After informed consent, the participants completed a questionnaire by phone within two weeks after trauma (T0), on demographic variables, medical variables, and psychological functioning. Immediately after the plaster was removed (T1), the patients were interviewed again using a form with 23 complaints related to CRPS1 (see measurements). If a patient fulfilled the criteria for a diagnosis of CRPS1, he was referred to a pain specialist, well experienced in CRPS1 (F.J.P.M.H.) at the Pain Treatment Centre of the Erasmus MC Rotterdam. The pain specialist was asked to confirm the diagnosis. A diagnosis of CRPS1 was confirmed when a patient fulfilled all the criteria of Bruehl[15]. Patients with a positive diagnosis received a standard medical treatment according to the protocol used in the Netherlands namely: dimethyl sulfoxide (DMSO) cream[16-18], and physical therapy, to improve functionality, mobility and muscle strength. Three months after trauma (T2), all patients were asked to complete a questionnaire, which was similar to the questionnaire completed on T0. If a patient did not fulfil the CRPS1 criteria earlier but fulfilled the criteria at T2, he was also referred to the pain specialist for confirmation of the CRPS1 diagnosis. If positive, standard therapy was also started for this patient.

Patients scoring high or extremely high (compared with the norm group of the normal population) on the SCL-90 subscales, depression and/or anxiety, and/or agoraphobia, and/or with a weighted life-event score of 100 or higher in the past year were invited for a clinical interview

with a psychotherapist. In the interview psychological problems were rated, and, if appropriate, a DSM-IV classification was made. These patients also filled in the Dutch Personality Inventory (DPI)[19] .

Measurements

Demographic
The following demographic variables were analyzed: gender, age, and education.

CRPS1 Diagnosis
Patients were interviewed at T1 and T2, using a form with 23 complaints related to CRPS1. When a patient fulfilled four out of four IASP criteria[2] and/or at least four out of five Bruehl criteria[15] at T1 or T2, a pain specialist, well experienced in CRPS1 (F.J.P.M.H.) at the Pain Treatment Centre of the Erasmus MC Rotterdam, was asked to confirm the diagnosis using Bruehl's criteria. A diagnosis of CRPS1 was confirmed if a patient fulfilled all five Bruehl criteria in his medical history, and at least two out of five Bruehl criteria at physical examination.

Life Events Inventory
At baseline (T0) patients were asked to fill in a questionnaire on life-events experienced in the last year. The Life Events Inventory (LEI) was adopted from the Schedule of Recent Experience (SRE) of Hawkins et al.[20] by Cochrane and Robertson[20]. The LEI is a hierarchical list of stressful life events in which each event has its own score (weight), depending on the degree of disruption that would be caused if an average person experienced it[20]. The LEI has been shown to be reliable[22]. All life-events from the LEI with a weight higher than 50 were scored. This questionnaire was only used to select patients for the interview.

Symptom Checklist – 90 (SCL-90)
At baseline (T0) the participants completed the SCL-90-R, which is a widely used, multidimensional, self-report inventory composed of 90 items. It measures the following dimensions: anxiety, agoraphobia, depression, insufficiency, somatization, interpersonal sensitivity, hostility, and insomnia. The total score is a measure of psychoneuroticism. The SCL-90 has been rigorously evaluated for its psychometric properties, and the reliability and validity of the SCL-90 are good; with the Cronbach's alpha's of the subscales varying from 0.76 to 0.97. Both converging and diverging validity are high. The results of the SCL-90 corresponded reasonably or well with the results of other studies (construct-validity)[23].

Dutch Personality Inventory (DPI)
The DPI is a self-reporting personality questionnaire, consisting of 133 statements that can be endorsed on a three-point scale (agree, ?, do not

agree). The DPI consists of seven scales (i.e. inadequacy (feeling insufficient), social inadequacy (being unhappy in social situations), rigidity (rigidly adhering to rules), discontentedness (distrustful and critical to others), self-satisfaction, dominance and self-esteem. Internal consistency is reasonable to good (coefficient alpha between 0.60 and 0.91). Test – retest stability is good (median 0.87). The scales correlate in the expected direction with other personality scales[19].

Data analysis

Descriptive statistics were used to describe the study population. Differences in personality scores between patients diagnosed with CPRS1 and patients without such a diagnosis were tested with t-tests. Differences in the distribution across the scales of DPV between patients with and without CPRS were tested using Chi-square. Binary logistic regression analysis (Backward Wald method) was used to evaluate whether personality factors were predictive of the development of CRPS1 above medical variables. The following variables were entered in the model: age, education level, and subscales of the DPV. A significance level of ≤ .10 was used for the final step of the logistic regression analysis. As outcome variable, the diagnosis of CRPS1 according to the Bruehl criteria was used. Sensitivity and specificity were valued as equally important.

The analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 15.0.1.

RESULTS

From February 2002 until April 2006, 748 consecutive patients who fulfilled the inclusion criteria were asked to participate; 596 (79.7%) agreed, consisting of 17 (36.4%) males and 379 (63.6%) females. The median age was 52.8 years (range 18-90 years, interquartile range (IQR) 33.4 – 63.9 years).

The patients who refused to participate did not differ significantly from the participants in gender, but were significantly older than the participants (median age 61.8 years, range 18-89 years, IQR: 37.9 – 74.1 years, $p < .001$). In 311 patients (52.2%) the upper extremity was affected, and in 285 patients (47.9%) the lower extremity. The average time in plaster was 43 days.

The mean scores of the DPI and SCL-90 are presented in Tables 5.1 and 5.2.

Table 5.1. Mean scores on the DPI

	CRPS1	No CRPS1	p
Self-satisfaction	3.9	4.2	ns
Self-esteem	3.3	3.7	ns
Inadequacy	3.9	4.2	ns
Social inadequacy	3.6	3.5	ns
Dominance	4.1	4.9	.03
Rigidity	2.8	2.9	ns
Discontentedness	3.4	4.1	ns

Legend: 1 = very low, 2 = low, 3 = below average, 4 = average, 5 = above average, 6 = high, 7 = very high. Reference group: original DPI norm group of normal population

Table 2. Mean scores on the SCL-90

	CRPS1	No CRPS1	p
Insufficiency	17.9	15.4	.03
Interpersonal sensitivity	26.1	23.4	ns
Hostility	7.2	7.7	ns
Neuroticism	140.8	128.1	ns

The mean scores of the patients with CRPS1 were comparable with those of patients without CRPS1, except for dominance. For dominance, patients without CRPS1 scored significantly higher ($t = 2.3$, $df = 86$, $p = 0.03$). Further inspection shows, for that subscale, patients without CRPS1 scored above average, while patients with CRPS1 scored average. In addition, chi-square comparisons show that the distribution of DPI scores across the different levels (1 to 7) was also comparable for the groups with and without CRPS1, with the exception of dominance (data not shown). Patients with CRPS1 scored significantly higher on insufficiency ($t = -2.16$, $df = 198$) than patients without CRPS1. Both groups scored above the mean compared with the normal population. For interpersonal sensitivity and hostility both patients with and without CRPS1 scored comparable with the average of the normal population. For neuroticism patients with CRPS1 scored high, while patients without CRPS1 scored above the average compared with the normal population.

Table 5.3 shows the results of the prediction of CRPS1 based on medical variables and personality variables (scales of the DPI and SCL-90 total score; scales of the DPI and hostility, sensitivity and insuffiency scores of the SCL-90). Dominance of the DPI appeared to have a significant additional predictive value, beyond the included medical variables, to the prediction of CRPS1.

Table 5.3. Prediction of CPRS1

Covariate	B	Exp(B)	p
Dislocation	.51	1.66	.40
Hand*	–18.81	.00	.99
Foot*	–.07	.94	.95
Ankle*	1.37	3.94	.05
Number of analgesics at To	–.40	.67	.39
Number of symptoms at To	.14	1.15	.01
Dominance	–.09	.91	.07
Constant	–1.42	.24	.20

* The wrist was used as a reference location

The sensitivity (80%), specificity (79.3%), and overall classification (79.4%) were high. A cut off value of 0.2 was used in this analysis.

One hundred and twenty-seven patients were invited for an interview, based on their scores on SCL-90 and/or weighted life-events score. Forty-two (33%) patients refused to be interviewed.

The distributions of the DSM-IV scores of the patients willing to be interviewed are presented in Table 5.4, for patients with and without CRPS1.

Table 5.4. Distributions of DSM-IV Axis I and Axis II diagnoses (%)

	CRPS1	No CPRS	Total	p
DSM-IV Axis I diagnosis	9 (53%)	32 (47%)	41 (46%)	ns
No DSM-IV Axis I diagnosis	8 (47%)	36 (53%)	44 (54%)	
DSM-IV Axis II diagnosis	0 (0%)	1 (1%)	1 (1%)	ns
No DSM-IV Axis II diagnosis	17 (100%)	67 (99%)	84 (99%)	

Ns: no significant differences in the distribution of diagnoses across patients with or without CRPS1

About half of the patients (46%) fulfilled the criteria for at least one DMS-IV Axis I classification. There was no difference in the distribution of the patients with or without DSM-IV Axis I diagnosis between patients with or without CRPS1. Only one patient fulfilled the criteria for a DSM-IV Axis II classification. There was no difference in the distribution of patients with or without DSM-IV Axis II diagnosis between patients with or without CRPS1.

DISCUSSION

There is no consensus in the literature on the role of personality factors in the development or course of CRPS1. In this study, the DPI and the scores on the hostility, insufficiency and sensitivity scales of the SCL-90 (or the total score of the SCL-90) were used to assess personality.

We found that dominance has additional predictive value, beyond medical variables. This scale measures whether one is dominant, stimulating, and self-assured. People scoring low on this scale are passive, dependent, and follow others.

A post-hoc explanation could be that dominant patients who, after a trauma, are able to let other people help them instead of helping other people are better off, because in this way they get more rest and the healing process is supported. When, after a trauma, patients still tend to help others and are less able to let others help them, the trauma gets less time to heal. However, final conclusions can not be drawn, especially because our results are opposite to the results presented by De Vilder[4], who reports that patients with CRPS1 score high on self-sufficiency. We did not find elevated scores on the self-satisfaction and self-esteem scales of the DPI. In his discussion, De Vilder suggests that his results cannot be equivocally attributed to CRPS1, and that it remains open how much the fracture, operation and/or immobilization can account for the differences found.

Our results seem to be in accordance with Van Houdenhove[24], who found more dependent behavior in patients with CRPS1.

The results of the present study are incongruent with De Good et al.[25] and Van Houdenhove et al.[26], who reported less hostility in patients with CRPS1 compared with controls. We found no differences in hostility scores between patients with or without CPRS1, and both groups scored comparable with the mean of the normal population. Furthermore, hostility had no predictive value beyond medical variables.

The comparison of the scores of patients with CRPS1 to the scores of patients without CRPS1 on the subscales of the DPI shows no significant differences, except for dominance. However, patients with CRPS1 score average, while patients without CRPS1 score above average. The distribution of scores on the DPI is also comparable for both groups, except for dominance. On the whole, the scores of patients with CRPS1 are almost the same as the average score of the normal population. The scores on the SCL-90 of patients with CPRS are comparable with the normal population for hostility and interpersonal sensitivity and higher for insufficiency and neuroticism. However, in a previous study[14] we argued that the items of this scale may be confounded. The same is true for the score of neuroticism, because this score is the sum of all SCL-90 scales, some of which are confounded as well (i.e. agoraphobia, somatization, and insomnia).

We therefore conclude that patients with CRPS1 do not have a different personality make-up compared with the normal population. This conclusion is in accordance with the results of several other studies, reporting no

differences in personality characteristics (e.g. psychoneuroticism) between patients with CRPS1 and other groups[6, 8-12]. A recent study found that a subgroup of patients with CRPS1 (suffering from severe dystonia) showed that patients with CRPS1 may show differences on some subscales of a personality inventory compared with other groups, but as a group they do not differ from the normal population[13]. Other authors make similar statements[4]. This seems equally applicable for our study.

A general limitation of studies on CRPS1, including the current study, is the lack of a gold standard for diagnosing CRPS1. The use of different criteria sets across studies with different values for sensitivity and specificity limits the comparability of results of these studies. It remains unclear whether the same patients are studied in different studies. In the present study, we used the Bruehl criteria, with high specificity but a lower sensitivity. This could mean that patients in the control group with undetected CPRS mask existing differences. A further possible limitation of this study is the sample selection. It could be that, in a more diverse population, personality variables have more predictive power than in the present homogeneous population. Although final conclusions cannot be drawn, this still seems unlikely for several reasons. First, in a previous publication we showed that psychological problems are not predictive of CRPS1[14]. Second, in our present study, we showed that there is no difference in the prevalence of a psychiatric or personality disorder between patients with and without CRPS1. The results of the present study are concordant with several other studies, as mentioned above. A third limitation is the number of patients with CRPS1 included in this study. Although for a relatively rare illness we have included a large number of patients, statistically the number of patients is rather limited to allow for firm conclusions.

With this third limitation in mind, we still conclude that, as a group, patients with CRPS1 do not differ in personality from the normal population. This conclusion is based on our own results, and the fact that our results are largely concordant with other studies. Future studies should focus on the contribution of personality factors to the maintenance of CRPS1 and other pain syndromes.

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CHAPTER 6

A prospective study on the relation between psychological factors and the course of symptoms related to the Complex Regional Pain Syndrome type 1 – a clinical-empirical exploration

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SUMMARY

Objective To study the relationship between psychological factors and the course of disuse-related CRPS1 symptoms.

Design A prospective multicenter cohort study was performed. At follow-up, three (T2) and 12 months (T3) after trauma, participants completed a questionnaire on symptoms of CRPS1 and were diagnosed by a clinician. At baseline (T0), T2, and T3, the participants completed a questionnaire covering demographic and medical variables. At T2, patients also completed questionnaires on catastrophizing (Pain Coping and Cognition List), depression (Symptom Checklist-90), and kinesiophobia (Tampa Scale of Kinesiophobia).

Setting Participants were recruited from the emergency rooms of two general hospitals and one university hospital in Rotterdam, the Netherlands, directly after trauma.

Participants Patients, 18 years or older, with a single fracture of the wrist, scaphoid, ankle, or metatarsal V, were included in this study (n = 596).

Interventions Patients diagnosed with CRPS1 received treatment according to the guidelines used in the Netherlands.

Main Outcome Measures Course of disuse-related CRPS1 symptoms until 12 months after trauma.

Results Catastrophizing is related to a higher probability that CRPS1 symptoms will persist; the mean score of the patients in the highest quintile of catastrophizing was high, but the number of patients scoring high was small (6.7%).

Conclusions Catastrophizing is an important factor in the maintenance of CRPS1 symptoms for a subgroup of patients. Further research should focus on prevention of chronification of CRPS by treating this psychological risk factor.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS, formerly known as reflex sympathetic dystrophy) is an invalidating pain syndrome. Pain is the most common symptom used in the diagnosis of CRPS type 1 (CRPS1); other symptoms include allodynia, hyperalgesia, abnormal skin color, temperature change, abnormal sudomotor activity, edema, tremor, dystonia, and motor/trophic disturbances[1-3]. For many patients, CRPS1 is a chronic disease. The pathophysiology is still a matter of debate: afferent mechanisms like inflammation, efferent mechanisms such as autonomic disturbances, and more central mechanisms such as psychological disturbances have been described. In a systematic review, Beerthuizen et al.[4] found no evidence for an association between psychological factors and the development of CRPS1. However, the association between psychological factors and the course of CRPS1 remains unclear because of the lack of studies on this topic.

Investigations involving other chronic diseases have clearly established that psychological factors, such as catastrophizing, kinesiophobia (pain-related fear), and depression play an important role in the maintenance of chronic pain and disability[5]. Studies on the course of CRPS1 most frequently concern its possible stages and differences between affected children and adults[6, 7]. Other studies have investigated the effects of a specific treatment (e.g., corticosteroids[8], ketamine[9]). With regard to the psychological consequences of the disease, Monti et al.[10] have asserted that the long-lasting, intense pain of the trauma results in an exaggeration of maladaptive personality traits and coping styles. Zucchini et al.[11] suggested that CRPS1 patients lack the motivation to rehabilitate because they profit from secondary gain as a chronic patient. These studies focused on the psychological consequences of the disease, not on the influence of psychological factors on the maintenance of symptoms. Bruehl and Chung[12] stated that psychological factors can maintain CRPS1, for example, by means of learned disuse and/or stress.

Disuse, catastrophizing, kinesiophobia, and/or depression may be involved in the maintenance of CRPS1. Disuse refers to the physiological and psychological effects of a reduced level of physical activity in daily life[13]. Several symptoms and signs seen in patients with CRPS1 can be a result of disuse (e.g., temperature asymmetry, restricted range of motion, loss of strength, changes in hair and nail growth, and thinner skin). Some authors suggested that immobilization, because of its high frequency among CRPS1 patients, may play a role in the pathogenesis of CRPS1 in a subset of patients[14-16]. Butler[17] presented evidence for the idea that immobilizing a part of the body can produce most signs and symptoms related to CRPS1. The results of animal studies support this suggestion; Guo et al.[18] found in an animal study that casting an intact limb caused warmth, edema, and allodynia. Ushida and Willis[19] reported similar findings.

Kinesiophobia is the fear of using a part of the body because doing so

will hurt or damage the body. Disuse is sometimes difficult to distinguish in behavior from its psychological counterpart, kinesiophobia. We identified only one study on kinesiophobia in relation to CRPS in the literature. De Jong et al.[20] concluded that effective treatment of kinesiophobia results in a decrease in fear, pain, and disability. Nelson et al.[21] reported that fear of injury in patients with CRPS1 can lead to excessive guarding and overprotective behaviors, which may worsen the pain. Kinesiophobia has been extensively studied in patients with low back pain. Several studies concluded that kinesiophobia is predictive of future disability and work status[22-28]. Furthermore, a reduction in kinesiophobia leads to improved functioning and more participation in social activities[27-30]. However, Heneweer et al.[31] concluded that pain is a more important predictor in the chronification of low back pain than kinesiophobia.

Catastrophizing is characterized by tendencies to engage in negative thinking and worry in response to pain[5]. There seems to be a relationship between catastrophizing and kinesiophobia. Linton[32] found in patients with low back pain that catastrophizing and fear of movement are so-called "yellow flags" in the chronification of low back pain. According to Klenerman[22], catastrophizing and avoidance can lead to disuse, disability, and depression, and potentially to chronic pain, creating a vicious circle in patients with low back pain.

Studies on the relationship between catastrophizing and chronic pain have reported that catastrophizing is strongly associated with quality of life of chronic pain patients[33] and is related to poorer adjustment to chronic pain[34]. Furthermore, the reduction of catastrophizing might reduce distress and disability in patients with low back pain[27, 35]. On the other hand, Viane et al.[36] concluded that acceptance of pain is more important in the prediction of mental well-being than pain catastrophizing and pain severity. Catastrophizing has also been studied in patients with fibromyalgia and appeared to be a predictor for more pain and depression and a lower quality of life at 6 months of follow-up in these patients[37].

Depression is a third important psychological factor influencing chronic pain[5]. In a review of the available literature, Beerthuizen et al.[4] concluded, however, that depression is not an important factor in the development of CRPS1. The majority of included studies (N = 24; 77%) in that review had only a poor to moderate methodological quality.

The relationship among disuse, kinesiophobia, catastrophizing, and depression is described in the Fear Avoidance Model (FAM) (Figure 1). This model stresses the influence of catastrophic thinking after an injury on consequent fear and hypervigiliance. These are followed by avoidance of activity, mainly due to the fear that the activity will cause harm and will worsen the pain problem. This avoidance in turn can result in a more general withdrawal from positive reinforcers, leading to mood disturbances such as depression[5].

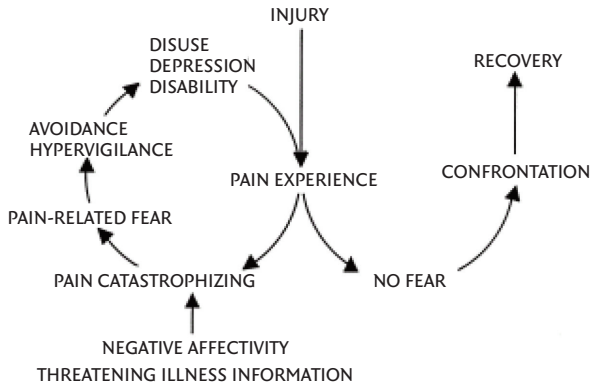

Figure 6.1. The Fear Avoidance Model

In the present study, we tried to clarify the association between kinesiophobia, catastrophizing, and depression on the one hand, and disuse-related symptoms of CRPS1 on the other. The main research question this study addressed was whether or not there is a relationship between psychological factors (kinesiophobia, catastrophizing, and depression) and the course of disuse-related symptoms of CRPS1.

METHODS

Participants

Patients were recruited from the emergency rooms of three hospitals in Rotterdam, the Netherlands; one university hospital (Erasmus MC) and two general hospitals (Medisch Centrum Rijnmond Zuid, the Clara and Zuider locations). Patients 18 years or older with a single fracture of the wrist, scaphoid, ankle, or metatarsal V were included in this study. Patients were treated with a plaster cast (88.1%) or with surgery followed by a plaster cast (10.9%). Patients were excluded if they were unable to fill in a questionnaire (e.g., because of language problems or cognitive impairments) or if they lived more than 50 km from the hospital, had a nerve damage that could result in development of CRPS type 2, or had fractures in more than one extremity.

Design

A prospective multicenter cohort study was performed.

Procedure

This study was approved by the local Medical Ethical Committee of the Erasmus Medical Centre (MEC 223.922/2003/18). All participants provided written informed consent.

Within two weeks of the trauma (T0), patients completed a questionnaire concerning demographic variables and their medical functioning. The timepoint at which the plaster was removed was designated T1. At three months after trauma (T2), all patients completed a questionnaire on demographic variables and medical psychological functioning, together with a questionnaire on symptoms of CRPS1. All patients diagnosed with CRPS1 according to one or more of the criteria sets described below completed a short questionnaire one year after trauma (T3) to evaluate their complaints related to CRPS1.

Measures

Demographic
Age, sex, and education level were analyzed.

Medical
The medical variables included in the model were location of the fracture (wrist, hand, foot, or ankle) and type of treatment. Furthermore, the difference between T2 and T3 in symptoms that could be related to disuse was recorded; these symptoms included temperature and/or color asymmetry (both between the affected and the unaffected side), restricted range of motion, loss of strength, changes in hair growth, changes in nail growth, and thinner skin. The course of these symptoms was divided into four groups for every symptom:

1. No symptoms at either measurement T2 and T3 (T2– T3–)
2. Symptoms only at measurement T2 (T2+ T3–)
3. Symptoms only at measurement T3 (T2– T3+)
4. Symptoms at both measurements (T2+ T3+)

Diagnosis CRPS1
Concerning CRPS1 symptoms, patients were interviewed at T2 and T3 using a form with 23 complaints related to CRPS1 based on three sets of criteria. The three sets of criteria were those of Veldman[1], those of the International Association for the study of Pain (IASP)[2], and those formulated by Bruehl[38].

Depression: Symptom Checklist-90 (SCL-90)
Patients completed the SCL-90[39] at T2. The SCL-90 is a multidimensional, self-report inventory composed of 90 items that measures the dimensions of anxiety, agoraphobia, depression, insufficiency, somatization, interper-

sonal sensitivity, hostility, and insomnia. The total score is a measure of psychoneuroticism (emotional instability).

Pain-related fear: Tampa Scale of Kinesiophobia (TSK)
Patients completed the Dutch version of the Tampa Scale of Kinesiophobia (TSK)[40, 41] at T2. The TSK is an 11-item self-report questionnaire measuring fear of (re)injury due to movement. It contains two subscales: somatic focus and activity avoidance[42]. Each item is scored on a 4-point Likert scale. Scoring possibilities range from "strongly disagree" (score = 1) to "strongly agree" (score = 4). Total score ranges from a minimum of 11 points to the maximum of 44 points. The TSK is a reliable and valid questionnaire to measure kinesiophobia in patients with chronic pain[41, 43, 44].

Catastrophizing: Pain Coping and Cognition List (PCCL)
The Pain Coping and Cognition List consists of 42 items, subdivided into four scales: pain catastrophizing (higher scores denote a higher degree of catastrophizing); pain coping (lower scores denote a lower degree of pain coping); internal pain control (lower scores denote less internal pain control); and external pain control (higher scores denote less external pain control, i.e., more health control by others). Patients completed this questionnaire at T2. Cronbach's alphas of the subscales varying from 0.78 to 0.85 and the internal consistency and construct validity of the PCCL are supported[45].

Statistical analyses

The univariate analyses were described in simpler terms, while the multivariate analyses were examined in terms of multiple correspondence analysis.

Univariate analyses
As measures for central tendency, percentages were estimated when the data were categorical, and means and median were determined when the data were continuous. When distribution of continuous data was normal, the standard deviation was presented; when the distribution was not normal, the interquartile range (IQR) was presented.

Multiple correspondence analysis (MCA)
This method of analysis is descriptive of a process designed to analyze (two-way or multi-way) tables. MCA is basically a principal component analysis for categorical variables. Thus, MCA is quite similar to principal component analysis for continuous variables; however, MCA not only describes the association (similarity) between the variables but also the association (similarity) between the categories. MCA is a generalization of correspondence analysis of a cross-tabulation of two variables to the

cross-tabulation of multiple variables. In MCA, the cells of the bi- or multivariate contingency table are standardized so that the relative frequencies across the cells sum to 1.0. A characteristic is that MCA enables representation of the relative frequencies of the cells in a low-dimensional space, without loss of substantial information. For a comprehensive description of MCA and its applications, see Greenacre[46]; for reference to the roots of this method, which are primarily in France, see Benzécri[47]. More recently, MCA has also become more widely used in English-speaking countries[48, 49]. Simultaneously although independently, similar methods have been developed. They are known as methods for optimal scaling, reciprocal averaging, or homogeneity analysis[50]. Dissimilarities between participants as well as between variables are quantified by calculating Euclidean distances to be represented in a low-dimensional space, usually two-dimensional. Whether the two-dimensional solution is sufficient or not depends on the percentage of variance explained by that solution.

For each variable, the distances between the answer categories reflect the associations: the closer the answer categories, the more similar they are. Projecting the points for one variable onto the vector from the origin to a category point for the other variable defines the association between the variables.

As a proper measure of the overall model fit, the percentage variances explained by the number of dimensions to be extracted (range: 1.0 to 100.0%). Furthermore, the quantification of the answer categories equals to the average scores on the respective dimensions of the participants belonging to this category: the more dissimilar the quantifications of the answer categories within a variable, the higher the differential qualities of these answer categories. If quantifications of answer categories between variables are similar, then these answer categories correspond highly. If these answer categories are dissimilar, then, in contrast, the pertinent categories do not correspond. In this study, the external variables (catastrophizing, depression, and kinesiophobia) were discretized into five categories corresponding to the five quintiles of these variables.

The analyses were performed using the module optimal scaling within the Statistical Package for the Social Sciences (SPSS), version 15.0.

RESULTS

From February 2002 (Erasmus MC) and 2003 (Medisch Centrum Rijnmond Zuid locations Clara and Zuider) through April 2006, 748 consecutive patients who met the criteria were asked to participate, and 596 (79.7%) agreed to do so (217 men, 36.4%; 379 women; 63.6%). The median age was 52.8 years (IQR 33.4–63.9). The group of patients who refused to participate did not differ significantly from the participants in gender, but they were significantly older (median age: 61.8; range: 18–89;

IQR: 37.9–74.1; p < .001). In 311 patients (52.2%), the upper extremity was affected, and in 285 patients (47.9%), the lower extremity. Time in plaster was 43 days on average.

At T2, 550 patients participated, and 46 (7.7%) refused to participate or were lost to follow-up.

At T3, 246 patients who fulfilled the IASP criteria at T2 were asked to fill in a third questionnaire on symptoms of CRPS1, with responses from 205 (83.3%) patients. In total, 42 patients of all the participants at baseline (7.0%) developed CRPS1 according to the Bruehl criteria.

Table 6.1. Description 3 months post trauma of medical/demographic variables

Variable			
Sex	Male	27.3%	
	Female	72.7%	
Age	Median: 55	Range: 18–87	SD 17.07
Location of the fracture	Wrist	40.5%	
	Hand	4.4%	
	Foot	17.1%	
	Ankle	38.0%	
Treatment	Plaster	83.3%	
	Plaster and surgery	16.7%	

Table 6.2. Description at 3 months post trauma of psychological variables

Variable	Range (min–max)	Mean	SD
Depression	16.00–64.00	21.0	7.81
Catastrophizing	1.00–5.58	2.0	0.98
Kinesiophobia	11.00–41.00	23.4	5.84

Tables 6.1 and 6.2 show the descriptive data for the included variables. The mean score on depression (Table 6.2) was comparable to the average score of the reference group of the normal population[39]. The mean depression score of the patients in the highest quintile was high compared with the reference group of the general population. There are no scores or reference groups in the literature for catastrophizing and kinesiophobia.
For the PCCL, a (mean) score of 2.0 (on the subscale catastrophizing) is suggested to be low[45]. The mean score of the patients in the highest quintile was high according to the authors of the questionnaire. The authors of the TSK indicate that a score of 40 or higher can be interpreted as substantial kinesiophobia[20]. The mean score of the patients in the highest quintile of kinesiophobia was still lower than 40 and thus lower than what has been designated as substantial kinesiophobia.

Table 6.3. Course of symptoms at 3 (T2) and 12 (T3) months post trauma (N = 203)*

Symptom†‡ (%)	T2– T3–	T2+ T3–	T2– T3+	T2+ T3+
Temperature asymmetry	47.8	4.9	33.2	13.2
Color asymmetry	46.3	3.4	32.2	17.1
Restricted range of motion	17.1	2.0	50.7	28.8
Loss of strength	18.5	2.4	40.0	38.0
Changes in hair growth	77.6	2.0	17.1	2.0
Changes in nail growth	82.0	3.4	10.7	2.9
Thinner skin	67.3	5.4	20.0	5.4

* Total % lower than 100 indicates missing data.
† Numbers represent row percentages.
‡ T2– T3–: no symptoms at T2 or T3; T2+ T3–: symptoms at T2 but not at T3; T2– T3+: no symptoms at T2 but symptoms present at T3; T2+ T3+: symptoms at both T2 and at T3.

Table 6.3 shows that changes in hair growth and in nail growth were predominantly absent at both moments of measurement (T2 and T3). Temperature asymmetry and color asymmetry were mostly absent (in 50% of the cases) at T2 and T3, and in about one third of the cases they emerged at T3. Furthermore, restricted range of motion and loss of strength were present in 50% of the cases at T3, but almost one third of the cases suffered from these symptoms at both timepoints of measurement.

Multiple contingency table analysis

The method variable principal normalization was applied, meaning that the (dis)similarities between the categories were analyzed. The solution identified turned out to be two-dimensional. The performance of this solution appeared to be good with an explained variance of 68%.

The category quantifications are presented in Figure 6.2. First of all, on average, the four answer categories represented by 1 (i.e., T2– T3–), 2 (i.e., T2+ T3–), 3 (i.e., T2– T3+), and 4 (i.e., T2+ T3+) could be clearly distinguished. The most homogeneous were the categories symbolized by 1 (no symptom change at all). These categories are located at the utmost right side, with z values varying from 0.00 and 1.00 on both dimensions. Also homogeneous was the position of the categories coded by 2; they have z values varying from –1.75 to 1.50 on dimension 1 and –1.50 and 0.00 on dimension 2. Relatively heterogeneous were categories designated by 4, spread over the whole of dimension 1, fluctuating from lower than 3.00 to –0.50, and on the second dimension from 0.00 to 1.25. Last, categories given by 3 were least homogeneous. The majority had to be situated in the area confined by the range –1.00 to 0.00 on dimension 1 and 0.00 and 1.00 on dimension 2. For 3, there were two exceptions; the first was that

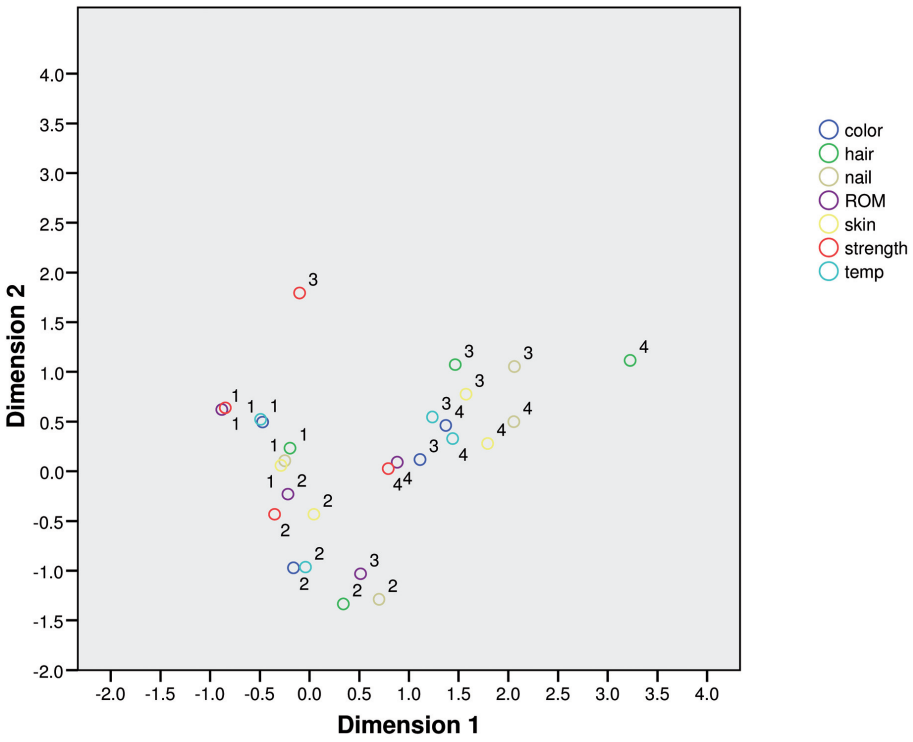

Figure 6.2. The (dis)similarities of the category points (in terms of z-scores), representing (non)change in symptoms [i.e., 1 (T2– T3–), 2 (T2+ T3–), 3 (T2– T3+), and 4 (T2+ T3+)] visualized in a two-dimensional space. ROM = range of motion, temp = temperature asymmetry

change in loss of strength (at T2 no loss of strength while at T3 loss of strength emerged) had to be positioned isolated at the upper right area. The second exception was located near the categories defined by 2. The inference from these findings is that the four groupings of (non)change clearly represent different subgroups of patients (Figure 6.2).
Of the demographic and medical variables (Figure 6.3), only categories given by grouping 2 of diagnosis (fracture of the hand) could be differentiated from the other categories of these variables. This category implies that diagnosis was present at T2 but not T3. The patients belonging to this category were on average located in categories grouped under 2.

Figure 6.4 illustrates the degree to which the psychological variables had differential qualities on the two-dimensional solution of the (non)change of symptoms. It shows that the highest level of catastrophizing could be clearly distinguished from the other categories. Of the psychological variables, catastrophizing was located the farthest to the right, indicating that these patients predominantly belonged to in grouping 4. In other words, these patients suffered from the following symptoms at both

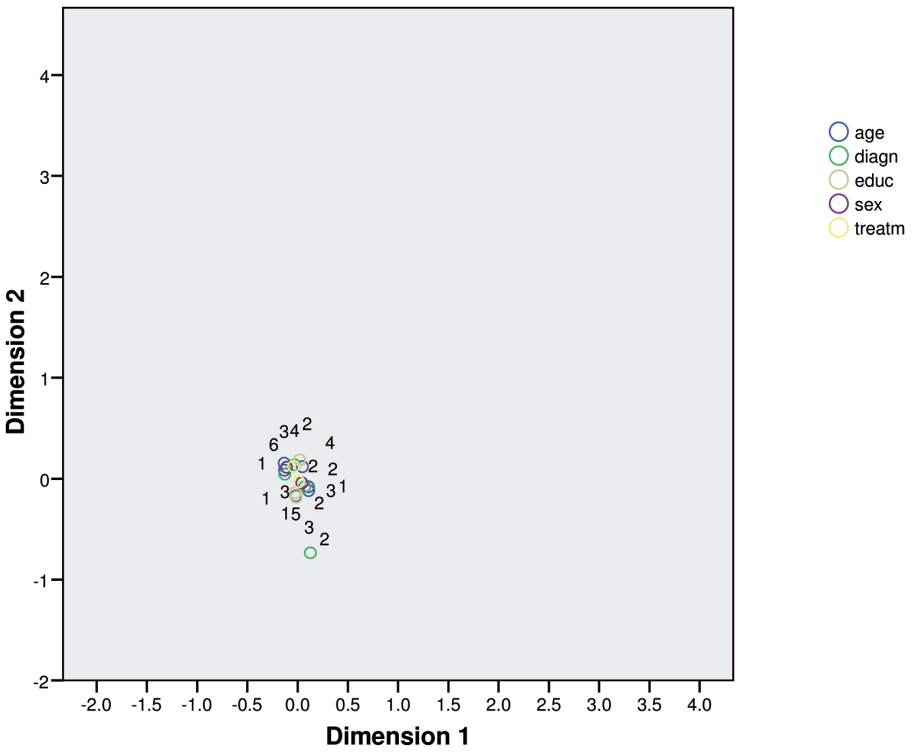

Figure 6.3. The (dis)similarities of the category points (in terms of z-scores) represent the biographic and medical variables on the two-dimensional solution of the (non)change of symptoms.
diagn = diagnosis, educ = education level, treatm = treatment

T2 and T3 (Figure 6.4): temperature asymmetry, color asymmetry, loss of range of motion, and loss of strength. A total of 30.8% scoring in the highest quintile of catastrophizing suffered from temperature asymmetry between the affected and unaffected limb at both T2 and T3. The percentage for color asymmetry was 50.0%, while 69.2% of the highest quintile on catastrophizing was identified as suffering from restricted range of motion. Finally, 69.2% of the highest quintile of catastrophizing suffered from loss of strength. In total, 9 patients had a high score on catastrophizing (6.7% of the 134 patients who filled in the PCCL at T2), of whom 5 were diagnosed as having CRPS1 (71.4%) according to the Bruehl criteria. Two of the nine patients lacked a Bruehl classification.

To a lesser extent, kinesiophobia could also be distinguished from the other categories. Patients with the highest level of kinesiophobia maintained the following symptoms between T2 and T3: loss of range of motion (60.0%) and loss of strength (64.0%). However, only one patient scored higher than the cut-off value for substantial kinesiophobia. Therefore, the clinical relevance of this result is unclear.

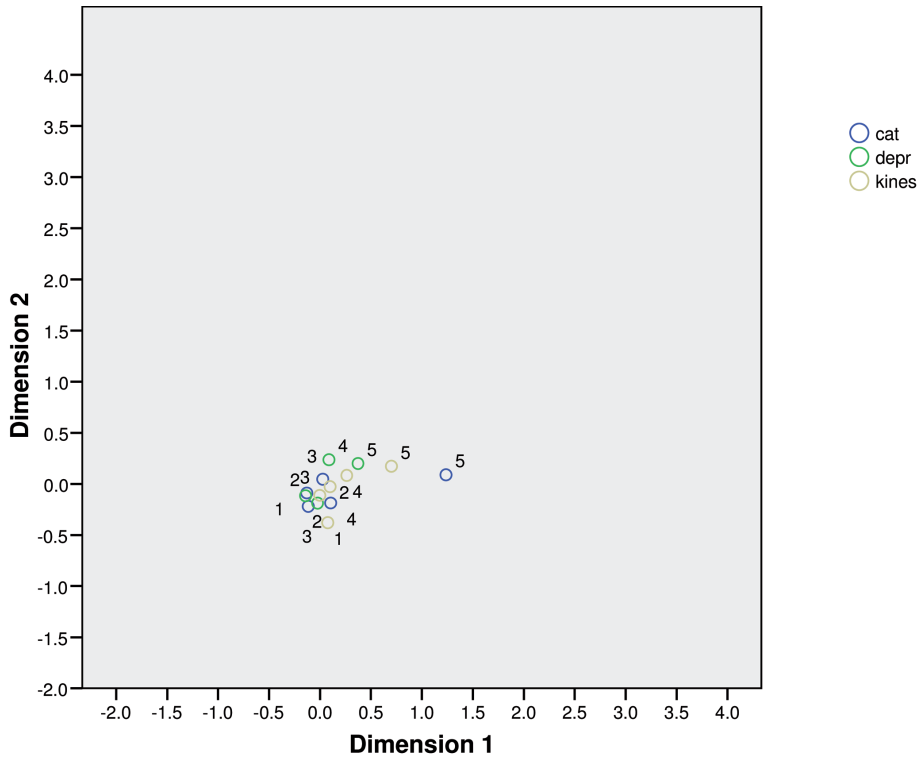

Figure 6.4. The (dis)similarities of the category points (in terms of z-scores) represent the psychological variables on the two-dimensional solution of the (non)change of symptoms.
cat = catastrophizing, depr = depression, kines = kinesiophobia

DISCUSSION

Catastrophizing seems to play a role in the maintenance of CRPS1 symptoms. Patients in the highest quintile of catastrophizing appeared to suffer for a longer period of time from disuse-related CRPS symptoms. The mean score of the patients in the highest quintile of catastrophizing was high, but the number of patients with a high score was relatively low (9 patients, 6.7%). For kinesiophobia, the clinical relevance of the results is unclear. Depression seems to play no role in the maintenance of disuse-related symptoms.

Other studies have emphasized the importance of identifying possible psychosocially inciting risk factors for chronic pain[32,51]. Klenerman[22] stated that a chain of reactions of catastrophizing and avoidance can lead to disuse, disability, and depression, and probably to chronic pain, creating a vicious circle.

Because only one patient in the current study suffered from substantial

kinesiophobia, the FAM does not appear to be directly applicable to patients with CRPS1. According to our knowledge, only one study investigated the FAM in patients with CRPS1, assessing the effectiveness of graded activity in patients with CRPS1. The authors concluded that graded exposure in vivo resulted in a reduction of pain-related fear, pain intensity, and disability in patients with CRPS1. This result could be explained without the FAM: because catastrophizing may lead to disuse-related symptoms, graded activity may lead to improvement. Leaving kinesiophobia out of the model results in a simpler model without loss of significant information.

There is neurological evidence for the association between catastrophizing and CRPS1. Klaver and de Wilde[52] reported that the perigenual area and the insula are activated in patients with chronic pain. Catastrophizing thoughts about pain correlate positively with the activity of the perigenual area and the insula.

Because catastrophizing is an important predictor of the course of CRPS1, leading to prolonged existence of disuse-related symptoms, cognitive interventions, graded activity, and physical therapy could be important components of treatment for patients with CRPS1 to prevent chronification of this syndrome. Physiotherapy (activation/mobilization) is supposed to have a positive effect on the course of CRPS1 because pain is reduced and active mobility is improved[53, 54], even in progressed CRPS1[55]. According to Guo et al.[18] physical therapy is a cornerstone of CRPS1 treatment. However, no controlled clinical trial data supporting its efficacy are available. Patients are advised to mobilize their extremity, without avoiding pain completely; the symptoms of CRPS1 have to return to the level of symptoms present at exercise initiation two hours after the exercise is completed. This approach also prevents a patient from developing a tendency to disuse.

A possible explanation for the finding that patients with an affected hand maintain CRPS symptoms more often than patients with an affected wrist, ankle, or foot might be that patients with a hand fracture were in a plaster cast for a longer period of time.

Results of this study must be interpreted with caution. The participants at T3 (one year after trauma) are a subgroup of participants at T2 because at T3 only patients exhibiting at least 4 of 4 IASP diagnostic criteria at T2 were included. Furthermore, the number of patients included in this study was limited.

CONCLUSIONS

Catastrophizing is an important factor in the maintenance of CRPS1 symptoms for a subgroup of patients.
We recommend that further research on the course of CRPS1 should focus on (psychological) factors that contribute to the chronification of this invalidating syndrome.

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CHAPTER 7

Skin surface temperature to differentiate between Complex Regional Pain Syndrome type 1 fracture patients and fracture patients with and without symptoms

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Accepted for publication by Anesthesia & Analgesia

ABSTRACT

Objective To assess the validity of skin surface temperature recordings, based on various calculation methods applied to the thermographic data, to diagnose acute Complex Regional Pain Syndrome type 1 (CRPS1) fracture patients.

Methods Thermographic recordings of the palmar/plantar side and dorsal side of both hands or feet were made on CRPS1 patients and in control fracture patients with/without and without complaints similar to CRPS1 (total in the 3 subgroups = 120) just after removal of plaster. Various calculation methods applied to the thermographic data were compared using ROC analysis to obtain indicators of diagnostic value.

Results There were no significant differences in demographic data and characteristics between the three subgroups. The most pronounced differences between the three subgroups were vasomotor signs in the CRPS1 patients. The involved side in CRPS1 patients was more often warmer compared with the non-involved extremity. The difference in temperature between the involved site and the non-involved extremity in CRPS1 patients significantly differed from the difference in temperature between the contralateral extremities of the two control groups. The largest temperature difference between extremities was found in CRPS1 patients. The difference in temperature recordings comparing the palmar/plantar and dorsal recording was not significant in any of the groups. The sensitivity and specificity varied considerably between the various calculation methods used to calculate temperature difference between extremities. The highest level of sensitivity was 71% and the highest specificity was 64%, the highest positive predictive value reached a value of 35% and the highest negative predictive 84%, with a moderate $0.60 \geq AUC \leq 0.65$.

Conclusion The validity of skin surface temperature recordings under resting conditions to discriminate between acute CRPS1 fracture patients and control fracture patients with/without complaints is limited and only useful as a supplementary diagnostic tool.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a complication after surgery or trauma, although spontaneous development has also been described. CRPS is characterised by signs and symptoms of inflammation and central sensitisation. The diagnosis can be made using several different criteria sets, of which the most popular are the International Association of the study of Pain (IASP) and the Bruehl criteria sets[1]. There are two types of CPRS; type 1 without an obvious detectable nerve lesion (CRPS1) and type 2 with an obvious detectable nerve lesion (CRPS2).

The IASP criteria have a high sensitivity but a lower specificity, whereas the Bruehl criteria have a high specificity but a lower sensitivity. The IASP criteria are useful in the clinical setting, whereas the Bruehl criteria appear to be more useful for research purposes[2]. New IASP criteria are under discussion[3] and attempts have been made to obtain a less subjective diagnosis by using diagnostic tools such as 3-phase bone scan, X-ray, MRI, fMRI, and temperature measurement devices[4]. Due to the limited validity of clinical diagnoses, it may be difficult to differentiate CRPS1 from other related diseases. It is assumed that a false-positive diagnosis for CRPS1 is overexpressed, especially in patients with unclear complaints of symptoms such as pain[2].

Temperature is one of the parameters used in the diagnosis of CRPS1. Surface temperature of an extremity reflects the result of a complex combination of centrally regulated and locally affected thermoregulatory systems. We previously described a calculation method to examine the difference between videothermographic pictures of CRPS1 patients and healthy controls[5]. To date, only a few studies have reported on the diagnostic value of temperature differences at the early onset of CRPS1 using thermography. In 1998 Birklein et al. described the temperature development in CRPS1 after a fracture compared to healthy subjects using different sympathetic stress factors[6]; Gradl et al. reported on 158 fracture patients of whom 18 developed CRPS[7]; and Schurmann et al. investigated differences in sympathetic control of 50 CRPS1 patients compared with 50 normal fracture patients and 50 controls (no fracture); a high sensitivity and specificity was found[8]. However, none of the above-described methods has been accepted as a gold standard. Thus factors that still need to be studied further are the sensitivity, specificity, positive predictive value and negative predictive value. All this can be explored by comparing patients who develop CRPS1 after a fracture, the CRPS1 patients, to patients who develop signs and symptoms after a fracture similar to CRPS1 , the control patients with complaints . A third control group is added comprised out of patients after fracture who have no symptoms or signs of CRPS1, controls without complaints. Furthermore, to derive indices on diagnostic value, ROC curves to calculate the diagnostic value should be used. Several other factors related to thermographic recordings and analysing methods also warrant further study. On average, thermographic recordings consist of

2,300 pixels each representing a temperature on one extremity, thus calculation methods that compare the whole temperature profile of both hands should be considered. In addition, none of the earlier studies made a comparison between the palmar/plantar side and the dorsal side. The present study focuses on the validity of static skin surface temperature recording, applying different mathematical methods, to diagnose (acute) CRPS1 patients. The term 'static thermography' refers to a thermographic recording of an extremity without application of any disturbing factors on temperature regulation of that extremity.

METHODS

This study was approved by the Medical Ethics Committee of the Erasmus MC (MEC no 198.780/2001/24). All participants provided written informed consent.

Patients with various types of fractures were first seen in the emergency room (ER) at three hospitals, the Erasmus MC, the Medical Center Rijnmond-Zuid location south, and the Medical center Rijnmond-Zuid location Clara (Figure 7.1).

All patients were treated with a plaster cast during 6 (IQR 4-8) weeks, depending on the type of fracture. A questionnaire on the symptoms of CRPS1 was filled out by the plaster specialist on average 2 (IQR 0-5) days after removal of the plaster. Excluded were patients younger than 18 years and patients with demonstrable nerve damage in the fractured limb following CRPS type II. In addition, patients unable to fill in a Dutch-language questionnaire were also excluded. A questionnaire on the symptoms of CRPS1 was filled out by means of a short interview that addressed the anamnesis part of symptoms of CRPS1 proposed by Bruehl et al. and by the International Association for the Study of Pain (IASP)[1]. CRPS1 was considered to be present when patients had continuing pain, hyperesthesia, temperature asymmetry and/or skin color asymmetry, edema and/or sweating asymmetry, motor and/or trophic changes. When patients met 4 out of 5 of the Bruehl criteria and/or 4 out of 4 of the IASP criteria they were referred to an anaesthesiologist (FJPM) who has a wide experience with CRPS1 patients; this physican made a comprehensive physical examination after which only the Bruehl criteria were noted for each patient. This resulted in three groups: 1) 24 fracture patients fulfilling the Bruehl criteria designated as the 'CRPS1 patients', 2) 84 fracture patients with various complaints but not fulfilling the Bruehl criteria designated as 'Control patients with complaints', and 3) 12 randomly selected (normal healing) fracture patients without any visible signs/complaints designated as 'control patients without symptoms'. To be sure that patients with pain but without CRPS1 did not developed CRPS1 after their first visit, a second visit was planned 8 weeks later. After the first consultation with the physician, videothermographic images were recorded following a standard pro-

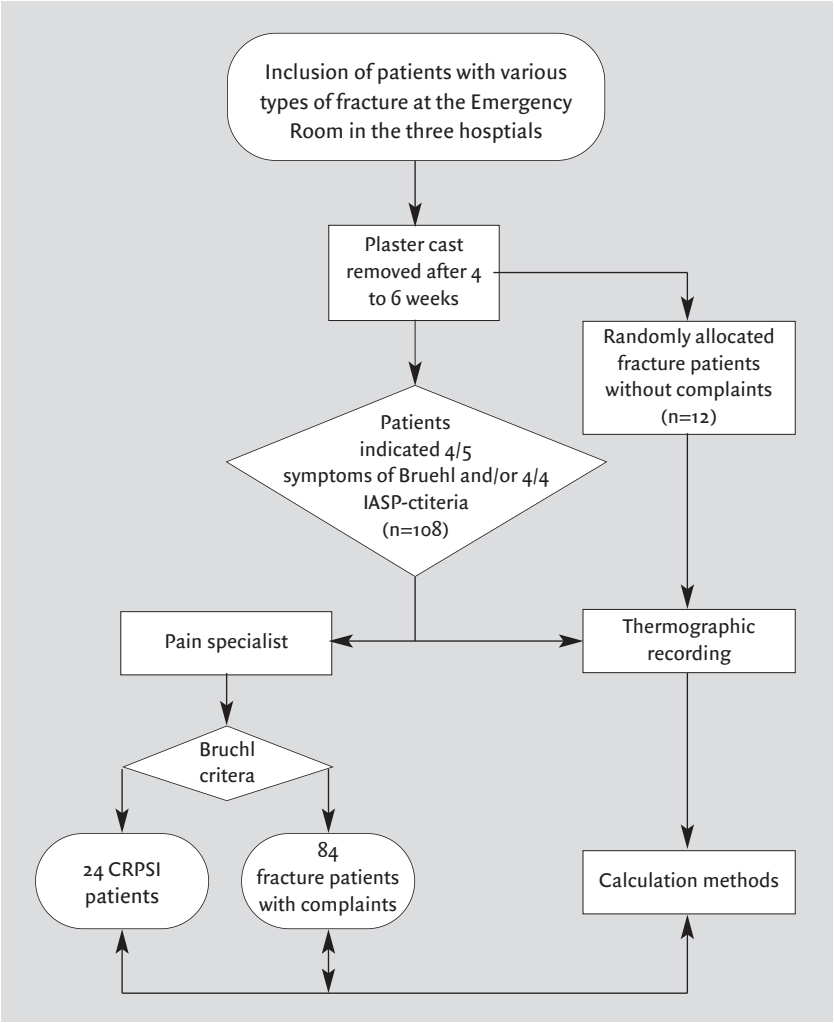

Figure 7.1. Flowchart of the inclusion procedure of patients in the present study

tocol. The physician was blinded for the thermographic recording and the technician who performed the recordings was blinded for the diagnosis by the physician. Before the recording, patients were acclimatised in a room with a mean temperature of 23°C (range 22.5°C –23.5°C) and a relative humidity of 50% (range 45%-55%) during 15 minutes. Patients were placed in a chair in an upright position.
Measurements of the involved (fracture) and non-involved (not fractured) extremity were performed on the palmar/plantar side and the dorsal side. The hands where placed in a plexiglas frame. The frame has positioning points between digit 1 and digit 2, and between digit 3 and digit 4, which allows to record comparable parts of the extremity in different patients.

Based on average temperature of the palmar/plantar side, >+0.3ºC was considered as warmer and <–0.3ºC was as considered colder.
The foot temperature was recorded using a support below the ankle which enables recording of the plantar aspect of the foot; the dorsal aspect was recorded by placing the feet on the ground. To establish whether the temperature difference also spread outside of the fractured area, a thermographic recording depicting the front of the leg from the knee down to the ankle was recorded in the same upright position.

Skin temperature of both extremities was registered with a computer-assisted infrared thermograph (ThermaCAM SC2000, Flir Systems, Berchem, Belgium). This infrared thermographic camera has a resolution of 320x240 pixels. Each temperature value measured in the picture is represented by one pixel; this gives a total of 76,800 temperature values recorded in one image. The thermographic images were stored on a hard disk (ThermaCAM Researcher 2001 HS, Berchem, Belgium) awaiting further analysis.

The distance between the camera and the hand being measured was adjusted to 68 cm; thereby the resolving capacity on the hand is 0.8x0.8 mm^2. The distance between the camera and the feet was adjusted to 90 cm to accommodate the whole foot; thereby the resolving capacity on the feet was 1.2x1.2 mm^2.

To obtain only those pixels that represent the hand or feet, the data are filtered by a threshold. On average one hand is represented by 23,500 pixels and a foot by 12,000 pixels.

Calculation methods

Most of the commonly used methods calculate differences in mean skin surface temperature between the involved (fractured) and the non-involved (not fractured) extremity. However, these methods take into account the total surface extremity, or only an arbitrary region of interest such as the fingertips/toes. We developed inhouse software using Matlab to facilitate these and newly developed calculation methods as described below.

Absolute difference in mean hand or foot temperature

The difference between average hand/foot temperature was calculated for both the palmar/plantar side and dorsal side using the following formula:

$$\Delta \overline{T}_{absolute\ extremity} = \left| \overline{T}_{involved} - \overline{T}_{non\_involved} \right| \qquad \text{Equation 7.1}$$

Absolute difference in mean fingertip temperature
A square was placed around each finger and toe tip of the extremity. The zeros in the square, indicating background, were filtered out.

$$\overline{\Delta T_{absolute\ tips}} = \frac{\sum_{tip=1}^{5} \left| \overline{T}_{involved_{up}} - \overline{T}_{non\_involved_{up}} \right|}{5} \qquad \text{Equation 7.2}$$

Absolute static temperature difference between wrist/ankle and fingertip/toe tip
For the hands, 5 points at the wrist (base), 5 points at the knuckle of each finger, and 5 points at the tip of each finger were defined using software. On each hand or foot, 5 lines were automatically drawn by computer over the hand/foot, as shown in Figure 7.2a and Figure 7.2b.

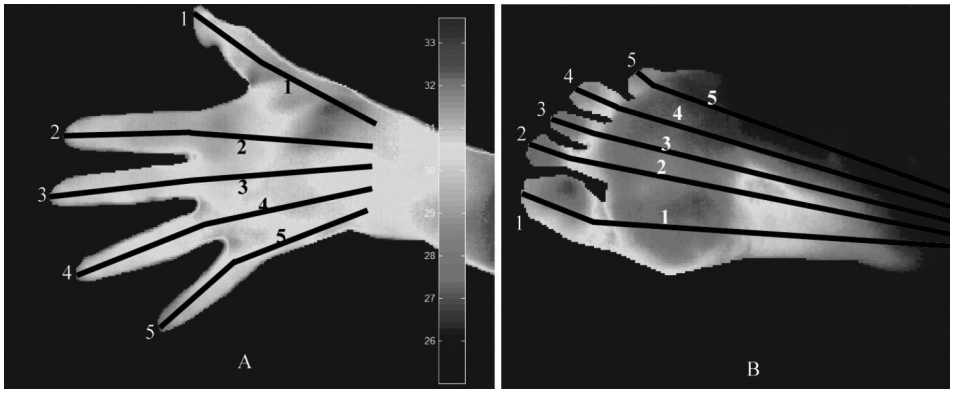

Figure 7.2. Examples of thermographic recordings of a) hand, and b) foot. The numbers 1 to 5 at the finger toe tips indicate the location used to calculate the mean finger and mean toe tip temperature. The numbers 1 to 5 on the lines indicate the lines drawn by software over the hand/feet and fingers/toes.

Hereafter a line was fitted through the temperature points that lay on the five lines. The slope, calculated by the fit, of each line was used to calculate the temperature increase/decrease across each of the fingers. The increase/decrease of each finger on the involved was subtracted from the increase/decrease of the corresponding fingers on the non-involved site. This result was summed to indicate a total difference in temperature increase/decrease between the extremities. The same procedure was applied for the calculation of foot temperatures. For this five points were defined at the ankle (base), 5 points at the base of each toe, and 5 points at the tip of each toe (Figure 2b). The aim of this calculation is to give an indication of the difference in vasomotor tone between the involved and non-involved side. A large decrease in temperature between wrist compared to finger tips or ankle compared to toe tip indicates a high vasomotor tone resulting in low blood flow through fingers and toes, whereas a small decrease in temperature indicates a low vasomotor tone.

Asymmetry factor

This calculation method determines the asymmetry factor (correlation) between the temperature histogram of the involved and non-involved extremity, based on the method described by Huygen et al.[9]. The asymmetry factor describes the degree of dissimilarity (expressed in correlation coefficient) between the temperature data obtained from the involved hand/foot compared with that from the non-involved hand/foot. A score of 1 indicates a similar temperature distribution between involved and non-involved side; a lower score indicates less similarity. This method intends to take into account all aspects of the whole temperature profile in comparing hands.

Euclidian distance

This Euclidian distance is a measure of the distance between the temperature histograms of the involved and non-involved side[10].

$$D\,(Involved, Non\_involved = \sqrt{\sum_{i=1}^{i=max(i)} (Involved(i) - Non\_involved\,(i))^2} \qquad \text{Equation 7.3}$$

D	=	Distance between histograms
Involved, Non-involved	=	Frequency value of a class
i	=	Bin class number

The class width was set to 0.1°C. This calculation effectively calculates the degree of similarity in the shape of the temperature histogram of the involved and non-involved site. The above-described calculations were used to measure the similarity of the palmar/plantar side and the dorsal side between the involved and non-involved extremity.

Total temperature difference between fingers and toes

For the hands, 5 points at the wrist (base), 5 points at the knuckle of each finger, and 5 points at the tip of each finger were defined using software. On each hand or foot, 5 lines were automatically drawn by computer over the hand/foot, as shown in Figure 2a and Figure 2b. The temperature profile of each line on the involved hand/foot was compared with non-involved hand/foot using cross-covariance (mean-removed cross-correlation). The total difference was calculated by summing the maximum cross-correlation found on each finger, with a maximum shift of 20 pixels. This measurement intends to take into account the irregularity in temperature that is found in most CRPS1 patients. This irregularity expresses itself in so called hot spots and cold spots; this method is able to compare local disturbance on temperature that can be a result of, for example, a local inflammation.

Statistical analyses

Data analyses were performed with SPSS 14.0. One-way analysis of variance (ANOVA) was used to calculate any significant differences in age and weeks after trauma between CRPS1 patients, control patients with complaints, and control patients without symptoms. Cross-tabs Chi-square was used to test whether the signs showed a significant difference between CRPS1 patients and control patients with complaints.

One-way analysis of variance (ANOVA) (Bonferroni test correction) was used to test whether the outcomes of the calculation methods used on the thermographic data showed a significant difference between CRPS1 patients, control patients with complaints, and control patients without symptoms.

The ROC is used to calculated the diagnostic value. The ROC is a graph, which is a very good indicator of the discriminating power of a diagnostic method. The coordinates of the graph are defined by calculating the sensitivity and specificity at different values of the diagnostic test (in this article the various methods to calculate the temperature difference between extremities), so called 'cut-off points'. This results in a graph of the true positive rate (sensitivity) against the false positive rate (specificity) for the different possible 'cut-off points' in a given diagnostic test. The most valid diagnostic cut-off value was chosen at the highest combination of sensitivity and specificity. The area under the ROC is a measure of the accuracy of the diagnostic test at hand, expressed in area under the curve (AUC). The accuracy is measured by a five point system: excellent (AUC of 1-0.9), good (AUC of 0.9-0.8), fair (AUC 0.8-0.7) poor (AUC of 0.7-0.6), fail (AUC of 0.6-0.5) (Metz 1978; Parker et al. 2003). More insight into the diagnostic value of thermography is gained when the positive and negative predictive values are also calculated. The positive predictive value is the proportion of patients with positive test results who are correctly diagnosed. The negative predictive value is the proportion of patients with negative test results who are correctly diagnosed. In all tests a p value <0.05 was considered to be statistically significant.

RESULTS

Demographic data and characteristics of the study population are given in Table 7.1. No significant difference was found in the incidence of CRPS1 patients among the three participating hospitals. Control patients with symptoms were significantly older compared with the other two groups. There was no significant difference between the three groups in the number of weeks after trauma, or in the location of the fracture. In CRPS1 patients the involved side was more often warmer than colder (18 versus 6) compared with the non-involved side.

Table 7.1. Data on demographics of patients included in this study

	CPRS1 patients (n=24)	Control patients with complaints (n=84)	Control patients without complaints (n=12)
Erasmus MC hospital (n=49)	9	36	4
Medical Center Rijnmond-Zuid location South (n=53)	11	35	7
Medical Center Rijnmond-Zuid location Clara (n=18)	4	13	1
Mean Age(Y) (SD)	56 (15.4)	54 (16)	42 (17.7)*
Male/Female	7/17	20/64	7/5
Average weeks after trauma (SD)	16 (11.4)	16 (11.0)	> 16 (15.0)
Location fracture upper limb (n=61)	8 Left/4 Right (n=12)	32 Left/13 Right (n=45)	0 Left/ 4 Right (n=4)
Location fracture lower limb (n=59)	9 Left /3 Right (n=12)	20 Left/19 Right (n=39)	3 Left/ 5 Right (n=8)
Involved side warmer[1]	18	42	7
Involved same temperature	0	1	1
Involved side colder	6	41	4

* Significant difference between age of CRPS1 fracture group compared to control fracture group

1 Based on average temperature palmar/plantar side, > +0.3ºC was considered warmer, < –0.3 ºC was considered colder

Data on symptoms according to the Bruehl criteria are given in Table 7.2. By definition, control patients without complaints had no symptoms/ nor signs. Although CRPS1 patients had a slightly higher pain score (5.9) than the control patients with complaints (4.8), the difference was not significant (p=0.104). Because CRPS1 patients were included according to the Bruehl criteria a 100% score in each category on each symptom was mandatory. The control patients with complaints also showed relatively high percentages on all symptoms, except for vasomotor signs. A marked increase was found comparing sensory and vasomotor signs of the CRPS1 patients to the controls with complaints, whereas changes in sudomotor/ edema and motor/trophic signs were more alike.

Table 7.2. Data on symptoms and signs of CRPS1 patients and controls with symptoms

	Pain VAS median (range) (0-10)	Sensory category (%)			Vasomotor category (%)			Sudomotor/edema category (%)			Motor/trophic category (%)		
		Yes	No	Missing	Yes	No	Missing	Yes	No	Missing	Yes	No	Missing
Symptoms (reported by patient)													
CRPS1 patients (n=24)	5.9 (4.-7.0)	Per definition : 100%											
Control patients with complaints (n=84)	4.8 (2.8-7.0)	73	27	0	55	44	1	76	24	0	72	26	2
Signs (determined by pain specialist)													
CRPS1 patients (n=24)	n.a.	38*	62*	0	92*	8*	0	83*	17*	0	79*	21*	0
Controls patients with complaints (n=84)	n.a.	12	87	1	35	64	1	41	58	1	37	62	1

* Displayed symptom group significantly different between CRPS1 patients and control patients with symptoms

n.a. = not available

Table 7.3 presents data on differences in skin surface temperature between the involved and non-involved side as calculated by the various mathematical methods for each of the three groups. There is an overall significant difference comparing all three groups for all measurements except absolute static temperature difference between wrist/ankle and fingertips/toe tips. The difference between CRPS1 patients and control patients with complaints is significant for Euclidian distance and total of difference between fingers/toes. There was a significant difference found between CRPS1 patients and control patients without complaints in the absolute difference in mean hand/foot temperature, in asymmetry factor, in Euclidian distance. The difference in temperature between involved and non-involved side (as indicated by the various calculation methods) shows a tendency to decrease; the largest difference in temperature was found in CRPS1 patients compared to the two other groups.

Table 7.3. Data of various calculations on temperature difference between the CRPS1

		Absolute difference mean hand or foot temperature (°C)	Absolute difference mean finger/toe tiptemperature (°C)
CRPS1 patients (n=24)[1]		1.0 (0.85)	1.4 (1.46)
Control patients with complaints1 (n=84)[1]		0.7 (0.56)	0.9 (1.00)
Control patients without complaints[1] (n=12)		0.27 (0.16)	0.5 (0.30)
			Overall
Whole group	SS	4.6	11.5
	df	2	2
	MS	2.3	5.7
	F	6	5.4
	P	0.003*	0.006*
			Differences between
Difference between CRPS1 patients and control patients with complaints		0.3 (p=0.089)	0.5 (p=0.18)
Difference between CRPS1 patients and control patients without		0.7* (p=0.003)	1.0* (p=0.027)
Difference between control patients with complaints and control patients without complaints		0.3 (p=0.089)	0.4 (p=0.55)

1 Data are mean (SD)
2 Bonferonni correction
* $p < 0.05$

The differences in temperature between the palmar/plantar side and dorsal side are small and not significant; therefore only the palmar side of hands and feet are presented in Tables 7.3 and 7.4. Indicators which reflect the diagnostic value (such as sensitivity and specificity) are presented in Table 7.4.

fracture patients, control patients with symptoms and control patients without symptoms

Absolute static temperature difference between wrist/ankle and fingertips/toe tips (ºC)	Asymmetry factor	Euclidian distance	Total of difference between fingers/toes
4.3 (4.71)	0.39 (0.38)	2176 (1301)	13287 (4334)
4.0 (4.4)	0.60 (0.32)	1506 (692)	12918 (4095)
2.8 (2.0)	0.83 (0.41)	1549 (912)	12535 (4573)
differences			
40.8	0.98	8169794	1.7E008
2	2	2	2
20.4	0.49	4084897	5.5E08
1.08	4.9	5.19	8.9
0.343	0.008*	0.007*	0.000*
the three different groups²			
–0.4 (p=1.000)	–0.21 (p=0.102)	_670* (p=0.006)	369* (p=0.038)
1.6 (p=0.960)	–0.46* (p=0.007)	–626* (p=0.009)	751 (p=1.000)
2 (p=0.46)	–0.2343 (p=0.102)	43 (p=1.000)	382 (p=0.169)

Table 7.4. Data on receiver operative curve (ROC) analysis on temperature difference comparing CRPS1 patients to control patients with symptoms

		Absolute difference mean hand or foot temperature	Absolute difference mean finger/toe temperature	Absolute temperature difference between wrist/ankle and fingertips/ toe tips	Asymmtry factor	Euclidian distance	Total of variation between fingers and toes
CRPS1 patients compared to control patients with complaints	Cut-off point	>0.99(°C)	>0.7(°C)	>2.0(°C)	<0.61	>1293	>10925
	Sensitivity[1](%)	48 (27-69)	67 (45-84)	63 (40-81)	63 (41-81)	71 (49-87)	64 (41-81)
	Specificity[1](%)	64 (52-76)	57 (45-69)	41 (30-53)	61 (49-72)	36 (44-58)	43 (31-55)
	Positive predictive value (%)[2]	31	34	25	35	31	28
	Negative predictive value (%)[2]	78	84	78	83	82	78
	AUC[3]	0.60	0.60*	0.60	0.63*	0.65*	0.60

1 Percentage (95% C.I.)
2 Based on the incidence of the studied population, this was 25%
3 Area under the curve (AUC), each had a 95% and a C.I. of 0.50 to 0.70
* $p < 0.05$

The positive predictive value, negative predictive value and AUC are similar for all calculation methods, whereas the sensitivity and specificity differ. The absolute difference in mean hand/foot temperature was a weak predictor of CRPS1 patients, whereas average fingertip temperature, asymmetry factor, Euclidian distance and total difference in temperature between fingers and toes proved to have stronger diagnostic value.

CONCLUSION/DISCUSSION

Significant differences between CRPS1 patients, control patients with complaints, and control patients without complaints were found as reflected by the various mathematical methods used to calculate temperature differences. ROC analysis of the diagnostic value of thermography calculated a moderate discriminating power, as indicated by an AUC of ≤ 0.7. Furthermore, not every mathematical method showed a significant difference between the three subgroups. The control patients with complaints showed overlap with CRPS1 patients in both symptoms and signs. Moreover, there is a large overlap between symptoms; most prominent in CRPS1 fracture patients were the displayed vasomotor symptoms, indicating that vasomotor signs belong to the most prominent signs at early onset of CRPS1; this has also been reported by others[1,6,8,11-15]. The differ-

ence in temperature between the involved and non-involved side (as indicated by the various calculation methods) shows a tendency to decrease, the highest difference expressed by the CRPS1 patients and the lowest difference observed in control patients without complaints; this phenomenon was also found in studies by Schurmann et al. and Bruehl et al.[8,11,13].

Studies on the use of thermography to discriminate between CRPS1 patients and non-CRPS1 patients lack consistency regarding the calculation methods used on the thermographic data (e.g. whole-hand calculations, spots, and fingertips), the statistical analyses used, as well as the description of and inclusion criteria applied. Birklein et al. was unable to calculate specificity and negative/positive predictive values because they did not include patients with symptoms similar to CRPS1[6]. Gradl et al. used an arbitrary fixed cut-off value of >1.5°C for fingertip/hand temperature difference and found that thermography had a low sensitivity and specificity; moreover, they did not report on positive/negative predictive values nor did they use ROC analysis to derive indices on diagnostic value at other cut-off values[12]. Shurmann et al. used only fingertip temperature to calculate the difference between the involved/non-involved extremity and did not compare other calculation methods on thermographic data[13]. There is some overlap of the absolute mean temperature difference between the involved/non-involved extremity found in CRPS patients between the present study and values reported in the literature. ROC analysis results in a range of cut-off values with an associated sensitivity and specificity. In this study we found a difference of > 0.99°C on absolute mean temperature difference between extremities to be the optimum cut-off value as indicated by ROC analysis, whereas Bruehl et al. found a difference of >0.82°C to be optimum[11]. Furthermore, in the present study a mean asymmetry factor of 0.39 was found for patients and 0.83 for control patients without complaints. In our previous study a mean asymmetry of 0.45 was found for CRPS1 patients and 0.91 for healthy controls[9]. In the literature sensitivity is reported to range from 58-93% and specificity from 86-89%[8,12,16]; none of these latter studies reported on AUC. In our study the highest sensitivity was 71% and the highest specificity 64% with a moderate AUC of >0.63. In this study the cut-off value was chosen that resulted in the highest combination of sensitivity and specificity. Different cut-off value could also have been considered however, because of the low AUC as calculated by the ROC, a different cut-off value will only alter the sensitivity at the cost of specificity. In conclusion, a different cut-off does not improve the diagnostic capabilities as a whole. The positive and negative predictive values can be calculated using the calculated sensitivity and specificity combined with the incidence of the studied population. In this study, fracture patients with a high risk of CRPS1 were included, therefore in the analysis the incidence of the studied population was used. Only Gulevich et al. reported on positive predictive value (90%) and negative predictive value (94%)[16]. In our study, the highest positive predictive value was 35% and the highest negative predictive value was 84%. The reason

for the high level of positive predictive value found in the study of Gulevich et al. compared to this study could be due to the sympathetic stress methods used in that study.

Although we were only interested in the diagnostic value of temperature recordings at the very early stage after the onset of CRPS1, one of the limitations of this study is a lack of follow up. Data obtained after 6, 12 and 18 weeks could emphasize the difference between CRPS1 patients and slow recovering control patients with complaints. None of the patients with pain but without CRPS1 developed CRPS1 according to the second follow-up visit 8 weeks later.

One could argue the temperature difference in CRPS1 patients already could have spread outside the fractured area thus increasing the difference between the CRPS1 group and the control fracture group. However, the difference between the involved and non-involved leg was not significant in any of the three groups, nor was this difference significant between the three groups.

The validity of thermographic recording to discriminate between CRPS1 fracture patients and control patients with complaints, at the early onset of CRPS1 is limited, therefore thermography should be considered as an additive diagnostic tool. When an abnormal pattern of temperature is identified and confirmed using the cut-off values as indicated in the results of this study a follow-up of these patients is advisable. In that case the best performing mathematical methods that are able to evaluate all the collected thermographic data are the asymmetry factor, the Euclidian distance and total of variation between fingers and toes. There is no preference of recording on palmar/plantar or dorsal side other than for pragmatically reasons.

Some studies have shown an increase in temperature difference after methods in which the sympathetic system is provoked[15,17]. Further research should focus on this aspect and investigate there effect on the temperature difference between extremities and their effect on the various indicators for diagnostic purposes.

ACKNOWLEDGMENTS

This study was performed within TREND (Trauma Related Neuronal Dysfunction), a knowledge consortium that integrates research on Complex Regional Pain Syndrome type 1. The project is supported by a Dutch Government grant (BSIK03016). The authors thank Prof. Rianne de Wit for her assistance in the setup of this study and Laraine Visser-Isles (Dept. of Anesthesiology) for assistance with the English language.

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CHAPTER 8

Conclusion and general discussion

Patients with the Complex Regional Pain Syndrome (CRPS1) are often stigmatized because of the idea that their disease is related to psychological vulnerability. The relationship between psychological factors and CRPS1 is much debated in the literature, as yet with no definitive conclusion. The main research question of this thesis addresses this problem: is there an association between psychological factors and the development and/or maintenance of CRPS1? Figure 1 provides a summary of the different aspects of CRPS1 investigated in this thesis.

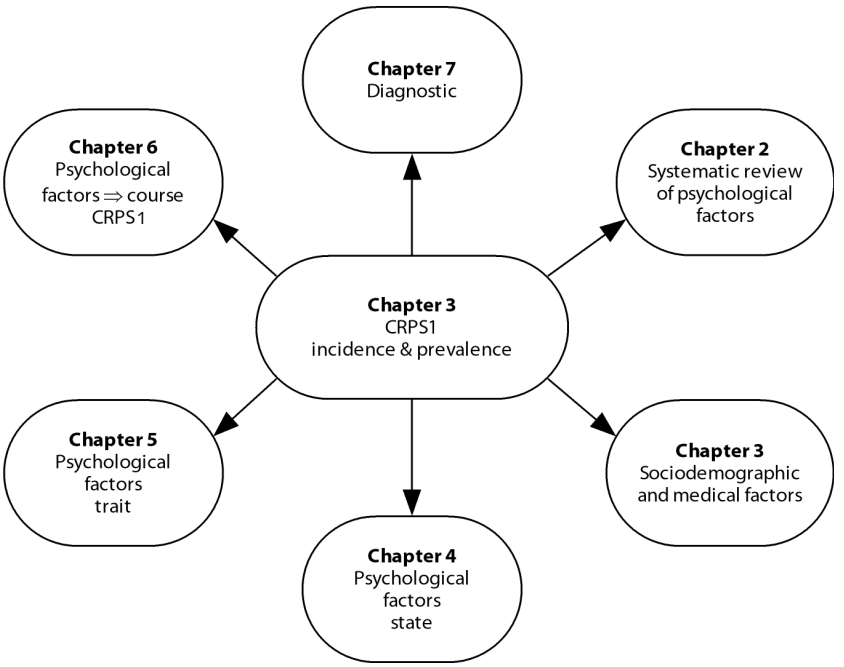

Figure 8.1. Aspects of CRPS1 and the corresponding chapters of this thesis

The purpose of this final chapter is to summarize and integrate the conclusions of the previous chapters and to discuss the implications. Furthermore, it contains proposals for future research on CRPS1.

Psychological stigma of patients with CRPS1

To answer the main research question, we performed a systematic review and a prospective multicenter cohort study including 596 patients with a single fracture. In the systematic review of the available literature (chapter 2), we summarized data from 31 studies. Furthermore, we weighted the methodological quality of the studies. Psychological factors included in the review were state-like (e.g., depression, anxiety) and trait-like (e.g., neuroticism, hostility). For both categories, the studies with the highest

methodological quality showed that there is no association between psychological factors and CRPS1. However, because most studies were retrospective or cohort studies, more prospective data are needed to corroborate this finding. Therefore, we studied the association between psychological factors and the onset of CRPS1 using such a prospective design (chapter 4). It appeared that, after controlling for possible confounded items within the subscales of the Symptom-Checklist-90 (SCL-90), none of the investigated psychological factors contributed to the prediction of the development of CRPS1. In another study, the possibility of the existence of a "CRPS personality" was investigated (chapter 5). Patients completed the Dutch Personality Inventory, and in a clinical interview the heightened scores on the SCL-90 were weighted. A DSM-IV classification was made when appropriate. The conclusion of this study was that a specific CRPS1 personality does not exist, a finding in accordance with the results of several other studies reporting no differences in personality characteristics between patients with CRPS1 and other patient groups[1-5]. The general conclusion of these studies supports the findings of our systematic review that psychological factors are not related to the onset of CRPS1. These findings suggest that the stigma of an association between CRPS1 and psychological vulnerability is unjustified.

Several factors might have led to the idea that psychological factors are important in the development of CRPS1. First, much remains to be discovered about the cause of CRPS1. Most physicians are trained mainly with a somatic focus in treating patients, and because the pathophysiology of CRPS1 is still not well understood, physicians may tend to conclude that CRPS1 is a psychological problem. It has been found that doctors use the label "psychogenic pain" when patients do not respond to medical or surgical treatment or when patients display behavior that the doctors find difficult to cope with[6]. These issues might also be present in (some) patients with CRPS1; many patients with CRPS1 visit several different doctors. Patients thus are medicalized and may become experts on CRPS1, a factor that doctors may find difficult to manage. Furthermore, patients are told that CRPS1 will disappear spontaneously, but at the same time, x-rays are made, medication is prescribed, and even in extreme cases, extremities are amputated. These ambiguous signs by the physician might lead to further medicalizing.

Concerning the maintenance of CRPS1, we stated in our systematic review that no definite conclusion can be drawn about the association between psychological factors and the maintenance of CRPS1 (chapter 2). We also performed a study on the association between psychological factors and the course of disuse-related CRPS1 symptoms (chapter 6). Based on those results, we concluded that disuse-related CRPS1 symptoms are likely to exist for a longer period in patients with the highest score on catastrophizing.

Uniformity of diagnosis

Large, prospective studies on the incidence of CRPS1 in an at-risk population are lacking. In the prospective study described in this thesis (chapter 3), 42 out of 596 patients with a fracture (7.0%) developed CRPS1 according to the Bruehl criteria[7], 21.3% according to the criteria of Veldman[8], and 48.5% according to the criteria of the IASP[9]. The differences between the incidence rates of CRPS1 reported in the literature can mainly be explained by the lack of uniformity of diagnostic criteria and an unclear or absent description in some articles of the criteria used. This variability hinders comparisons between studies and enhancement of knowledge about the pathophysiology of CRPS1, and as a consequence, also limits the treatment options. The most frequently used criteria in the Netherlands are the criteria of Veldman[8], the IASP-criteria[9], and the criteria of Bruehl[7]. The main differences among these criteria are the type and number of symptoms included and consequently their respective sensitivity and specificity. The IASP and Veldman criteria are anamnestic and therefore more lenient than objective criteria, with low specificity and high sensitivity (IASP sensitivity: 0.98, specificity: 0.36)[7]. However, the criteria of Bruehl can be divided into symptoms reported by the patient and signs assessed by the physician. The criteria of Bruehl have a high specificity (0.94) but a low sensitivity (0.70)[7]. A disadvantage of the criteria of Bruehl is that time-dependent signs, such as when the swelling is most prominent during the evening, cannot be assessed by the physician at the time of diagnosis. Perez et al.[10] stated that patients with CRPS1 should not be diagnosed according to a specific set of criteria but instead by means of subgroups within this population. We recommend development of objective criteria for subgroups in which the time-dependency of the symptoms is taken into account. For example, the Budapest criteria[11], which are the Bruehl criteria extended with allodynia to deep somatic pressure and to joint movement, could be extended with a 24-hour objective measurement of the symptoms.

A limitation of the studies described in this thesis is the restricted number of patients who developed CRPS1. However, this is one of the largest prospective studies on the association between psychological factors and CRPS1. Furthermore, a general limitation of studies on CRPS1, including the current study, is the lack of a gold standard for diagnosing CRPS1. We used the criteria of Bruehl[7], with a high specificity but a lower sensitivity, which could mean masking of CRPS1 in the control group of patients.

To improve the diagnostics of patients with CRPS1, the additional value of videothermographic data to diagnose CRPS1 was studied (chapter 7). The findings indicated that the validity of skin surface temperature recordings under resting conditions to discriminate between acute CRPS1 fracture patients and control fracture patients with/without complaints is limited and only useful as a supplementary diagnostic tool. More research should be performed on the diagnostic methods for CRPS1. Furthermore,

when patients are diagnosed with CRPS1, the time-dependent presentation of CRPS1 symptoms should also be taken into account.

Recommendations for clinical care and further research

Based on the results of the studies described in this thesis, there is no evidence for the idea that there is a psychological cause of CRPS1. Concerning clinical care of patients with CRPS1, investments should be made in making physicians aware that a "CRPS personality" does not exist and that a distinction should be made between the causes and consequences of a disease. Furthermore, because catastrophizing is important in the course of CRPS1, standard care should include some cognitive–psychological elements. A trained nurse can be well equipped to support patients in this way. Furthermore, patients should be informed about the effects of disuse on the course of CRPS1, and they should be advised about the amount of physical activity during the recovery from the trauma.

Further research should focus on the role of psychological factors in the chronification of CRPS1. Furthermore, we concluded that none of the CRPS1 patients were free of symptoms at one year after trauma; further research should study this outcome with a longer follow-up period. Further investigations should be, contrary to many earlier studies, high-quality studies, with a sufficient number of patients with CRPS1 and a prospective design. Also, the inclusion criteria should be well defined and recorded to compare the results of the different studies.

Further research should focus on the pathophysiology of CRPS1 and possible risk factors described in this thesis, namely a fracture of the ankle, musculoskeletal comorbidities, rheumatoid arthritis, and a dislocation of the fracture. The fact that CRPS1 patients reported musculoskeletal comorbidities and rheumatoid arthritis more often may guide research into the pathophysiology. Studies on the pathophysiology of CRPS1 and the prevention of chronification of this syndrome are recommended. CRPS1 is an invalidating pain syndrome with a negative effect on the quality of life of these patients[12] and their ability to contribute to society[13].

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SUMMARY

As described in **chapter 1**, Complex Regional Pain Syndrome (CRPS) usually develops after a small trauma (such as an injury or fracture) or after surgery; however, spontaneous development of CRPS has also been reported. CRPS type 1 (CRPS1) arises without an obvious detectable nerve lesion, whereas type 2 (CRPS2) manifests with an obvious detectable lesion. Commonly reported features of this syndrome are continuing pain, as well as disturbances of the sensory, vasomotor, sudomotor, motor and trophic systems. CRPS is an invalidating pain syndrome. Unfortunately, because there is no gold standard to diagnose CRPS1,the results of studies on CRPS can be diverse and difficult to compare. Besides the somatically oriented explanations for CRPS1, it has been suggested that 'psychological peculiar' patients have an increased risk for developing CRPS1; others, however, deny this influence. The purpose of this thesis was to investigate the association between psychological factors and CRPS1.

C**hapter 2** presents a review of the literature on psychological factors and CRPS1; this review included 31 articles. Of the few prospective studies, none of them reported a relationship between depression, anxiety, neuroticism, anger and CRPS1. The retrospective studies tended to yield contradictory results regarding psychological problems in patients with CRPS1. In the majority of studies no differences were found between patients with CRPS1 and other patient groups. However, a few studies reported more distress or higher levels of distress in patients with CRPS1 compared to the control groups. The studies with a higher methodological quality also indicated no relationship between psychological factors and CRPS1. Only life events seemed to be associated with CRPS1, in the sense that patients who experienced more life events seemed to have a higher chance of developing CRPS1. Of the 31 reviewed studies, 24 (77%) had a poor to moderate methodological quality. It was concluded that additional studies, with a higher methodological quality and more participants, should be performed to further explore the association between psychological factors and the onset and course of CRPS1.

The study in **chapter 3** investigated the incidence of CRPS1 in patients with a single fracture of the hand, wrist, ankle or foot and evaluated possible associations between demographic and/or medical factors and CRPS1. The study population included 596 patients from three hospitals. The participants completed a questionnaire on symptoms of CRPS1 at plaster removal (T1), at 3 months (T2) and at one year (T3) after trauma. At baseline (T0) and at T2 patients also completed a questionnaire on demographic and medical variables. CRPS1 was diagnosed according to the criteria of Bruehl, the criteria of the International Association for the Study of Pain (IASP) and the criteria of Veldman. Of the participants at baseline, 48.3% developed CRPS1 according to the IASP criteria, 21.3% according to the criteria of Veldman and 7.0% when the Bruehl criteria were applied. Risk factors for CRPS1 were an intra-articular fracture, rheumatoid arthri-

tis, fracture of the ankle, musculoskeletal comorbidities, and a dislocated fracture. Fracture of the ankle and dislocation of the fracture contributed significantly to the development of CRPS1. At T3, none of the CRPS1-patients was free of symptoms. Furthermore, at both To and T2, patients with CRPS1 reported a lower quality of life on the physical composite score compared with patients without CRPS1.

The study in **chapter 4** investigated a probable association between psychological factors and CRPS1. At baseline (i.e. within 2 weeks after trauma) patients with a fracture of the hand, wrist, ankle or foot were included and asked to fill in the Symptom Checklist-90 (SCL-90) as well as a questionnaire on demographic and medical variables. Furthermore, at plaster removal (T1) and at 3 months after trauma (T2), the participants completed a questionnaire on the symptoms of CRPS1. A diagnosis of CRPS1 was made by an anesthesiologist based on the Bruehl criteria. The psychological factors analysed were: agoraphobia, depression, somatization, insufficiency, sensitivity, insomnia and life events. When measuring psychological factors in patients with CRPS1, confounding might occur; as stated by Bruehl and Chung, patients with CRPS1 might score higher on the agoraphobia subscale because of protective behaviour concerning their affected extremity, not because they are in fact agoraphobic. Other subscales of the SCL-90 (somatization, insomnia, and insufficiency) might be affected in the same way. After correction for these possibly confounding items, none of the psychological factors significantly contributed to the prediction of the development of CRPS1. The scores on the SCL-90 subscales fall within the range of the general population and are, in most cases, average or below average when compared with a reference group of pain patients or with patients with psychiatric poblems. In conclusion, there is no empirical evidence to diagnose patients with CRPS1 as being psychologically different from the general population.

The study in **chapter 5** investigated the association between personality factors and the development of CRPS1. For this, the subscale scores of the Dutch Personality Inventory (DPI) of patients with CRPS1 were compared with the DPI scores of the reference groups. At baseline (To) and at T2 (3 months after trauma) the participants were asked to fill in the SCL-90. Patients with a high score (as defined by the questionnaire) on the SCL-90 completed the DPI and were invited for a (semi) structured clinical interview. Discontentedness and dominance appeared to be predictive of CRPS1, although patients with CRPS1 as a group did not score differently on the DPI from the normal population. Based on these results there seems to be no empirical evidence to diagnose CRPS1 patients as being psychologically different from the normal population.

As mentioned in chapter 2, there is a lack of studies on the relation between psychological factors and the course of CRPS1.

In **chapter 6,** we studied the relation between psychological factors and the course of disuse-related symptoms. At T2, patients completed the SCL-90, the Tampa Scale of Kinesiophobia (TSK) and the Pain Coping and Cognition List (PCCL) to measure depression, kinesiophobia and catastrophizing, respectively. The course of CRPS-symptoms between T2 and T3 which could be related to disuse was explored, namely: temperature asymmetry, color asymmetry, (between the affected and the unaffected side), restricted range of motion, loss of strength, changes in hair growth, changes in nail growth, and thinner skin. Patients with the highest score on catastrophizing suffered from temperature asymmetry, color asymmetry, loss of range of motion, and loss of strength at both T2 and T3.

All studies on CRPS1 are limited because of the lack of a gold standard to diagnose CRPS1. In **chapter 7**, the validity of skin surface temperature recordings by videothermograph to diagnose CRPS1 was explored. Just after plaster removal, thermographic recordings of the palmar/plantar side and dorsal side of both the affected and the unaffected hands/feet were made in CRPS1 fracture patients as well as in control fracture patients both with and without complaints similar to CRPS1. Various calculation methods applied to the thermographic data were compared. We concluded that the validity of skin surface temperature recordings (under resting conditions) to discriminate between acute CRPS1 fracture patients and control fracture patients with/without complaints is limited and useful only as a supplementary diagnostic tool.

Finally, in **chapter 8**, the main findings of this thesis are presented and discussed, and recommendations are made for further research.

Based on the results of the studies described in this thesis we conclude that there is no evidence for a psychological cause of CRPS1. Catastrophizing is, however, an important factor in the maintenance of symptoms related to CRPS1.

SAMENVATTING

Zoals beschreven in **hoofdstuk 1**, het Complex Regionaal Pijn Syndroom type 1 (CRPS1) ontstaat meestal na een trauma zoals een fractuur of na een chirurgische ingreep. Spontaan ontstaan van CRPS1 is ook beschreven. Symptomen van CRPS1 zijn: continue pijn, en sensorische, vasomotorische, sudomotorische, motorische en trofische stoornissen. Naast CRPS type 1 bestaat er ook een type 2. Bij CRPS type 2 is er sprake van een aantoonbaar zenuwletsel, terwijl dat bij CRPS type 1 niet het geval is. CRPS1 is een invaliderende ziekte. Er is geen gouden standaard om CRPS1 te diagnosticeren, waardoor de studies naar CRPS1 soms zeer verschillende resultaten laten zien en daardoor lastig te interpreteren zijn. Naast de somatische verklaringen van CRPS1 bestaat er ook het idee dat patiënten die 'psychologisch bijzonder' zijn een verhoogd risico hebben om CRPS1 te krijgen, hoewel anderen dit tegenspreken. Het doel van dit proefschrift was om de associatie tussen psychologische factoren en CRPS1 te onderzoeken.

Hoofdstuk 2 is een review van de literatuur met betrekking tot psychologische factoren en CRPS1, waarin 31 artikelen staan beschreven. Het kleine aantal prospectieve studies lieten geen relatie zien tussen depressie, angst, neuroticisme, woede en CRPS1. De resultaten van de retrospectieve studies spreken elkaar tegen aangaande de rol van psychologische factoren en CRPS1; de meeste studies rapporteerden geen verschil tussen patiënten met CRPS1 en andere patiëntengroepen, maar een aantal concludeerden dat patiënten met CRPS1 ernstigere of meer psychologische problemen hebben dan andere patiënten. Opvallend is dat de studies met de hoogste methodologische kwaliteit geen relatie vonden tussen psychologische factoren en CRPS1. De enige factor die mogelijk geassocieerd is met CRPS1 is life events, waarbij patiënten die meer levensgebeurtenissen hebben meegemaakt een grotere kans hebben om CRPS1 te ontwikkelen. De meeste studies in dit review hadden slechts een zwakke of matige methodologische kwaliteit (N = 24: 77%). De conclusie was dat meer studies met een hoge methodologische kwaliteit zouden moeten worden uitgevoerd om definitieve conclusies te kunnen trekken. Daarnaast zou ook de invloed van psychologische factoren op het beloop van CRPS1 onderzocht moeten worden.

Het doel van de studie in **hoofdstuk 3** was het beschrijven van de incidentie en het beloop van CRPS1 in patiënten met een enkelvoudige fractuur van de pols, hand, voet of enkel. Ook is de associatie tussen zowel demografische als medische factoren en het ontstaan van CRPS1 onderzocht. Patiënten werden geïncludeerd in 3 Rotterdamse ziekenhuizen (n = 596). De deelnemers vulden een vragenlijst bestaande uit aan CRPS1 gerelateerde symptomen in direct na gipsafname (T1), 3 maanden na het trauma (T2) en 12 maanden na het trauma (T3). Op baseline (T0) en op T2 vulden patiënten ook vragenlijsten in m.b.t. demografische factoren en hun medisch functioneren. De diagnose CRPS1 werd gesteld aan de hand

van de Bruehl criteria door een anesthesioloog die gespecialiseerd is in CRPS1. Daarnaast werden ook ook criteria van de International Association for the Study of Pain (IASP) en de Veldman criteria toegepast. Van de deelnemers op baseline ontwikkelden 48.3% CRPS1 volgens de IASP criteria, 21.3% volgens de criteria van Veldman en 7.0% wanneer de criteria van Bruehl werden gehanteerd. Risicofactoren voor het ontwikkelen van CRPS1 zijn: een intra-articulaire fractuur, reuma, een enkelfractuur, skeletspieren-gerelateerde comorbiditeiten en een gedisloceerde fractuur. Een enkelfractuur en een gedisloceerde fractuur dragen significant bij aan de voorspelling van CRPS1. Geen enkele CRPS1-patient was klachtenvrij 12 maanden na het trauma en de kwaliteit van leven van patiënten met CRPS1 is lager op de somatische subschaal (op zowel T2 als T3) vergeleken met de patiënten zonder CRPS1.

Hoofdstuk 4 beschrijft een studie naar de samenhang tussen psychologische factoren en CRPS1 naast de verklaarde variantie van medische factoren in het ontstaan van dit syndroom. Deelnemers vulden op baseline de SCL-90 in. De volgende psychologische factoren werden meegenomen in de analyse: agorafobie, depressie, somatiseren, insufficiëntie, sensitiviteit, slaapproblemen en life events. Patiënten met CRPS1 werden gediagnosticeerd volgens de criteria van Bruehl. Wanneer psychologische factoren worden gemeten bij patiënten met CRPS1 zou er sprake kunnen zijn van confounding, zoals geopperd door Bruehl & Chung; patiënten met CRPS1 hebben mogelijk een hoge score op de agorafobie-subschaal niet vanwege het feit dat ze agorafobisch zijn, maar omdat ze hun aangedane ledemaat beschermen omdat ze bang zijn dat iemand ertegenaan zou stoten. De subschalen somatische klachten, slaapproblemen en insufficientie van denken en handelen zouden ook op deze manier beïnvloed kunnen zijn. Na correctie van deze mogelijk vertekende items droeg geen enkele psychologische factor significant bij aan de voorspelling van CRPS1. Verder vallen de scores op de SCL-90 van patiënten met CRPS1 binnen de range van de algemene bevolking en de meeste patiënten met CRPS1 hebben een gemiddelde of beneden gemiddelde score op de subschalen van de SCL-90 in vergelijking met de normgroepen pijnpatiënten en psychiatrische patiënten. Op basis van deze resultaten hebben we geconcludeerd dat er geen empirisch bewijs is voor het stigmatiseren van patiënten met CRPS1 als 'psychologisch bijzonder.'

Het doel van de studie in **hoofdstuk 5** was het onderzoeken van de associatie tussen persoonlijkheid en het ontstaan van CRPS1. Patiënten met een hoge of zeer hoge score op de SCL-90 (gedefinieerd door de vragenlijst) vulden de Nederlandse Persoonlijkheidsvragenlijst (NPV) in en werden uitgenodigd voor een semi-gestructureerd interview. Ontevredenheid en dominantie droegen significant bij aan de voorspelling van CRPS1, hoewel de groep CRPS1-patienten als geheel geen afwijkende score hadden ten opzichte van de algemene bevolking. Deze resultaten lieten zien dat er

geen bewijs is voor de theorie dat CRPS1-patienten psychologisch gezien afwijken van de algemene bevolking.

In **hoofdstuk 6** staat een studie beschreven naar de relatie tussen psychologische factoren en het instandhouden van CRPS1-symptomen. Drie maanden na het trauma (T2) vulden de deelnemers de volgende vragenlijsten in: SCL-90 (om depressie te meten), de Tampa-schaal voor Kinesiofobie (TSK) en de Pijn Coping en Cognitielijst (om catastroferen te meten). Het beloop van de volgende disuse-gerelateerde symptomen tussen T2 en T3 werd meegenomen in de analyse: temperatuurverschil, kleurverschil, bewegingsbeperking, krachtsverlies, verandering in haargroei, verandering in nagelgroei, en dunnere huid. De meerderheid van patiënten met de hoogste score op catastroferen rapporteerden de volgende symptomen op zowel T2 als T3: temperatuurverschil, kleurverschil, bewegingsbeperking en krachtsverlies.

Een beperking van alle studies naar CRPS1 is het gebrek aan een gouden standaard om patiënten met CRPS1 te diagnosticeren. In **hoofdstuk 7** is de waarde van het maken van videothermografische opnamen in de diagnostiek van CRPS1 onderzocht. Patiënten met CRPS1 na een fractuur werden vergeleken met patiënten met een fractuur zonder CRPS1 (met of zonder klachten). Direct na gipsafname werden videothermografische opnamen gemaakt van de palmaire/plantaire zijde van de aangedane en niet-aangedane handen/voeten. Verschillende rekenmethoden werden toegepast op de videothermografische data. De conclusie was dat statische videothermografische opnamen slechts van beperkte diagnostische waarde zijn om een onderscheid te maken tussen patiënten met CRPS1 en patiënten zonder CRPS1 met of zonder klachten.

Gebaseerd op de resultaten van de verschillende studies in dit proefschrift kan worden geconcludeerd dat er geen bewijs is voor het idee dat CRPS1 een psychologische oorzaak heeft. Catastroferen is een belangrijke factor in de overgang van acute naar chronische CRPS1.

DANKWOORD

Ik ben veel mensen dank verschuldigd die een waardevolle bijdrage hebben geleverd aan de totstandkoming van dit proefschrift.

Allereerst mijn promotor, prof.dr. J. Klein: beste Jan, bedankt voor de prettige samenwerking; dat je deur altijd openstond voor overleg heb ik zeer gewaardeerd.

Dr. F. Huygen, beste Frank, bedankt voor het leggen van de basis voor dit onderzoek, het overbrengen van veel medische kennis en het consulteren van de vele patiënten die in dit onderzoek hebben geparticipeerd.

Dr. A. Van 't Spijker, beste Adriaan; bedankt voor de prettige samenwerking; je persoonlijke betrokkenheid waardeer ik zeer en je enthousiasme en nieuwsgierigheid werken aanstekelijk. We hebben 'robuust' werk afgeleverd!

Prof.dr. R. de Wit: beste Rianne, ik wil je bedanken voor de mogelijkheid om dit belangrijke onderzoek uit te voeren in de stimulerende werkomgeving die het Pijnkenniscentrum voor mij was. Je kritische blik heeft de kwaliteit van ons onderzoek verbeterd en ik heb er veel van geleerd.

Prof.dr. J. Passchier: beste Jan, bedankt voor je bijdrage als co-auteur en het beoordelen van mijn manuscript. Ik werk met veel plezier op jouw afdeling. Andere leden van de kleine commissie: prof.dr. P. Patka en prof.dr. H. Stam, hartelijk dank voor het beoordelen van mijn manuscript. Tevens wil ik prof.dr. Geertzen en prof.dr. M. van Kleef bedanken voor hun bereidheid zitting te nemen in de grote commissie.

In totaal hebben 596 patiënten aan ons onderzoek deelgenomen. Ik wil hen allen hartelijk bedanken voor het invullen van de lange vragenlijsten en in sommige gevallen het brengen van een extra bezoek aan het Erasmus MC.

De stichting Erasmus Fonds Pijnbestrijding en het Pijnkenniscentrum van het Erasmus MC wil ik bedanken voor de financiële ondersteuning van het onderzoek.

Ook ben ik veel dank verschuldigd aan de gipsverbandmeesters van het Erasmus MC (Rene, Max, Diane, Petra en Robert) en het Medisch Centrum Rijnmond Zuid locaties Zuider en Clara (Carla, Astrid, Bert, Tineke, Jan, Walter, Beatrix en Conny). Ondanks de hoge werkdruk hebben jullie veel patiënten voor ons onderzoek weten te includeren, waarvoor mijn dank.

Dr. D.L. Stronks, beste Dirk: het filosoferen over methodologie, statistiek en oosterse wijsheden heb ik zeer gewaardeerd. Je hebt een waardevolle bijdrage geleverd aan de inhoud van de artikelen.

Hugo, bedankt voor je statistische bijdrage aan hoofdstuk 6; je uitdrukking 'we pakken het meteen even op' gaf mij vertrouwen in het eindresultaat.

Inmiddels is het Pijnkenniscentrum als afdeling verleden tijd, maar de goede herinneringen blijven, mede door mijn collega's uit die tijd: Rhodee, Anneke, Dirk, Nanda, Thea, Wendy, Tilly, Albertina, Michael en Yvonne: ik wens jullie allemaal alle goeds voor de toekomst.

Een deel van de patiënten werd voor diagnostiek doorverwezen naar het Pijnbehandelcentrum, waar ze werden ingepland en opgevangen door het secretariaat: Anita, Margo, Corinne, Petra en Marion: bedankt daarvoor!

Sjoerd, jouw kennis van techniek, je enthousiasme en je kritische blik hebben mijn proefschrift in meerdere opzichten verbeterd. Ik weet dat we ook zonder Pijn vrienden zullen blijven.

Bij het includeren en interviewen van honderden patiënten op meerdere locaties was de hulp van studenten onmisbaar, dus wil ik hen graag bedanken; Alexandra, Shenaida, Aarti, Marijana, Barbara, Elsbeth, Jelle, Aarnoud, Brisa, Ameeta, Fatma, Astrid, Maartje, Meike en David: Ik heb een leuke tijd met jullie gehad en veel van jullie geleerd (jullie hopelijk ook van mij).

Ik ga iedere dag met veel plezier naar mijn werkplek op de afdeling Medische Psychologie en Psychotherapie van het Erasmus MC, mede dankzij de leuke collega's die ik daar heb getroffen. Specifiek wil ik graag mijn kamergenoten Laura en Eveline bedanken voor hun steun en gezelligheid. Silvia, ik heb met veel plezier met jou samengewerkt en ik wens je veel geluk in de Verenigde Staten.

Mijn vriend(inn)en zijn een onmisbaar deel van mijn leven: hartelijk bedankt voor jullie steun en interesse.

Mijn ouders wonen 'ver' weg, maar bij twee families in het westen voel ik me absoluut ook thuis: mijn 'adoptiegezin' bestaande uit Ilse, Yannick en Mylah en de familie Daalmeijer; ik waardeerde julllie affectieve en gastronomische ondersteuning zeer.

(Schoon)familie: zoals wij thuis vaak zeggen: die kies je niet. Maar ik heb het goed getroffen! Bedankt voor jullie getoonde belangstelling.

Mijn ouders: Coos en Myra, bedankt voor het feit dat ik altijd op jullie terug kan vallen.

Mijn paranimfen: Femke en Job. Femke, ik deel al veel leuke herinneringen met jou, ook op het gebied van onderzoek doen, met als hoogtepunten onze boeiende stage in de VS en jouw promotie. Een vriendschap voor het leven! Job, ik ben erg trots op het feit dat je op deze dag als grote broer naast me wilt staan. Je bent iemand op wie ik altijd kan rekenen en dat is een zeer prettig idee.

Vincent, beloofd is beloofd: vanaf nu zal de verhouding tussen werk en vrije tijd anders worden. Heel erg bedankt voor je geduld, steun en je relativerende Twentse nuchterheid.

Annemerle

CURRICULUM VITAE

Annemerle Beerthuizen was born on 17th December 1978, in Nijmegen, the Netherlands. She completed her secondary education in 1997 at the OSG Erasmus in Almelo. From 1997 to 2002 she studied Human Movement Sciences at the Faculty of Health Sciences of the Maastricht University. Her internship took place at the laboratory of cognition and action of the Department of Psychology, Penn State University, State College, USA; the main focus of her study was the frame of reference in arm movements was studied. She graduated in 2002 and in February of that year began her PhD studies at the Department of Anesthesiology (Pain Knowledge Center) and the Department of Psychology & Psychotherapy of the Erasmus MC in Rotterdam. For these studies the author investigated the role of psychological factors in the Complex Regional Pain Syndrome (CRPS), as presented in this thesis. From August 2006 she has been working as a post-doc conducting a nationwide intervention study on the quality of life of patients with hepatitis C, and as a lecturer in communication skills and professional behaviour.