Sex, quality of life and brain function in complex regional pain syndrome

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Chapter ٣

Sex matters in complex regional pain syndrome

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ABSTRACT

Background

Complex Regional Pain Syndrome (CRPS) is much more prevalent in women than men but potential differences in clinical phenotype have not been thoroughly explored to date. Differences in the clinical presentation between sexes may point at new avenues for a more tailored management approach of CRPS. We therefore explored if in CRPS the patient's sex is associated with differences in clinical and psychological characteristics.

Methods

In this cross-sectional study of 698 CRPS patients (599 females) fulfilling the Budapest clinical or research criteria, CRPS signs and symptoms, CRPS severity, pain (average pain intensity in the previous week and McGill pain rating index), pain coping (Pain Coping Inventory), physical limitations (Radboud Skills Questionnaire (upper limb), Walking and Rising questionnaire (lower limb)), anxiety and depression (Hospital Anxiety and Depression scale) and kinesiophobia (Tampa scale for kinesiophobia) were evaluated.

Results

Male CRPS patients used more often extreme words to describe the affective qualities of pain, used more passive pain coping strategies, and were more likely to suffer from depression and kinesiophobia.

Conclusion

Sex-related differences are present in CRPS, but the effect is generally small and mainly concerns psychological functioning. A greater awareness of sex-specific factors in the management of CRPS may contribute to achieving better outcomes.

INTRODUCTION

Complex Regional Pain Syndrome (CRPS) patients suffer from intense pain with sensory, autonomic, motor and trophic changes of the affected limb, resulting in profound loss of quality of life (this thesis, chapter 2). Typically the syndrome is preceded by tissue damage of the affected limb[1]. Previous research efforts suggest that CRPS is a multifactorial disorder that is associated with an aberrant host response to tissue injury[1]. The various involvement of perturbed biological pathways underlying aberrant inflammation, vasomotor dysfunction, and maladaptive neuroplasticity likely account for the clinical heterogeneity of CRPS[1]. Clinical heterogeneity is also encountered in studies directed at the development of therapeutic approaches for this condition, pointing to the existence of distinct subgroups that exhibit a varying response to treatment. Given the complex nature of CRPS, future treatment strategies likely will benefit from the identification of unique factors associated with treatment response in particular patients, enabling a more personalized approach. Although the syndrome is clearly much more common in females of all ages, affecting 2 to 4 times as many females as males, it is unclear if sex is associated with differences in the clinical presentation of CRPS[4]. Findings in the general population indicate that in experimentally-induced pain, women have lower pain thresholds and experience greater temporal summation of pain to brief, repeated, or dynamic stimuli than men; however, women also show greater adaptation to sustained stimuli then men[95]. In addition, women report higher prevalence and severity of pain in daily life, experience a higher severity of mood disturbance and seek more social support when suffering pain[16,96–99]. Knowledge of sex-related factors in the clinical presentation of CRPS patients could potentially reveal new avenues for a more tailored approach to management.

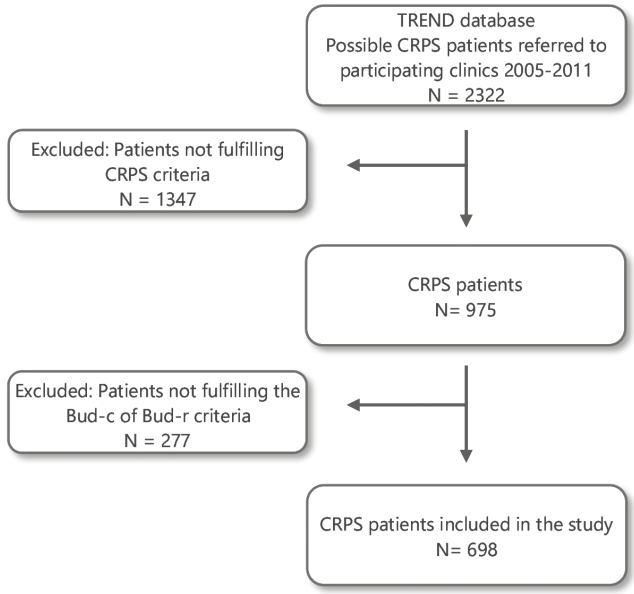
We therefore evaluated the clinical presentation of men and women with CRPS in a large cohort of almost 700 CRPS patients recruited in academic and regional hospitals in the Netherlands and used the term *"sex"* to denote the different groups. Specifically, we examined potential sex-related differences in signs and symptoms, pain coping, self-reported physical disability, anxiety, depression, and kinesiophobia.

METHODS

Participants

Patients were recruited between January 2005 and December 2011 from five pain clinics and one department of neurology of academic and regional hospitals in the Netherlands participating in TREND (short for Trauma RElated Neuronal Dysfunction, a Dutch knowledge consortium on CRPS). The included patients were all 18 years or older and fulfilled gener-

ally accepted CRPS criteria, specifically the 'Budapest clinical' (Bdp-c) or the 'Budapest research'(Bdp-r) criteria (figure 1). We excluded patients if they had other conditions that could account for the signs and symptoms encountered, dementia, cognitive impairment or any other condition that could affect the ability to understand and complete self-assessment questionnaires. We use the term *"sex"* instead of "*gender"* to denote the different groups since we identify the patients based on their biological sexes, not "*gender"* which encompasses social and cultural values.



Figuur 1: Flow-chart of inclusion. Bdp-c, Budapest clinical; Bdp-r, Budapest research; CRPS, complex regional pain syndrome; TREND, Trauma RElated neuronal dysfunction

Assessment methods and measurement instruments

The protocol was approved by the medical ethical committees of all participating centres in accordance with the Declaration of Helsinki. All participants gave written informed consent. We standardised methods of examination across centres and recorded signs and symptoms on a standard score sheet. All data were stored in a NEN-7511 certified, central web-based data management system (ProMISe©).

CRPS signs and symptoms

We examined 22 distinctive CRPS signs (observed during examination) and symptoms (reported by patients); specifically: allodynia (pain to normally innocuous stimuli) to light touch, to deep joint pressure and to movements; hyper- and hypoesthesia; hyper- and hypoalgesia; skin colour changes; temperature asymmetry; oedema; hyper- and hypohydrosis;

trophic changes of hairs, nails and skin; muscle atrophy; decreased range of motion; paresis; abnormal postures; tremors; myoclonic jerks and bradykinesia.

CRPS severity score

We calculated the CRPS severity score (CCS)[75], a measure designed to reflect the presence and severity of CRPS. The CCS is based on the presence or absence of 9 signs (hyperpathia/hyperalgesia to pinprick; hyperpathia/hyperalgesia to light touch [brush], cold, warm, vibration, or deep manual joint pressure; temperature asymmetry; skin colour changes; oedema; sweating asymmetry; trophic/dystrophic changes; motor changes; and decreased active range of motion) and eight symptoms (hyperpathia/allodynia (all types); bilateral temperature asymmetry; skin colour changes; oedema; sweating asymmetry; trophic/dystrophic changes (hair, nails, or skin); motor changes (e.g. weakness, tremor, dystonia); and decreased active range of motion. Range 0-17.

Pain

We used 2 measurement instruments to evaluate pain. First, the numeric Rating Scale (NRS) which is the average pain intensity of the previous week on a scale from 0 to 10, with 10 reflecting the worst pain imaginable. Second, the McGill Pain Rating Index to quantify pain (range 0-63; higher scores reflect more pain)[77,100]. The Pain Rating Index is a sum score calculated over ranked words that express three qualities of pain, namely *sensory* qualities (such as temporal, spatial, pressure, thermal qualities), *affective* qualities (tension, fear, autonomic changes) and *evaluative* qualities (subjective intensity of pain).

Pain coping

Patients completed the Pain Coping Inventory (PCI) questionnaire to assess pain coping strategies[101,102]. The questionnaire comprises 6 pain coping dimensions, grouped into "active" (Pain transformation, Distraction, Reducing demands; range 12-48) and "passive" domains (Retreating, Worrying, Resting; range 21-84); higher scores in these dimensions indicate more use of the corresponding strategy.

Self-reported physical disability

To assess physical limitations in daily life, patients completed the Radboud Skills Questionnaire (RASQ)[79,103] if arms were affected and the Walking and Rising questionnaire (WRQ)[81,104] if legs were affected. The primary outcome of the RASQ is a summary score of 6 domains: personal care (e.g. personal hygiene), domestic activities (e.g. housekeeping), recreational activities (e.g. sports), social activities (e.g., going on outings), work (i.e., performing occupation) and other (e.g., using personal computer). Mean domain and total scores are calculated and range from 1 to 5, with higher scores reflecting worse functioning. For the WRQ we used the summary score of the following three domains: walking inside, walking

outside and rising; because of the different number of items for these 3 domains, subscale scores were first standardized to a 0-10 scale before adding up (total range 0-30; higher scores indicating worse walking ability).For regression analyses (see *statistics* section), we used the physical health sum score (PHS) of the MOS 36-Item Short-Form Health Survey (SF36)[76,92], which measures limitations in physical function.We used this scale because it addresses physical disability of the whole body in contrast to the RASQ and WRQ, which only measure limitations in upper and lower extremity function.

Anxiety and depression

To measure anxiety and depression, we used the Anxiety and Depression subscales of the Hospital Anxiety and Depression scale (HADS-A and HADS-D, respectively)[105,106].

Kinesiophobia

Kinesiophobia was measured using the Dutch version of the Tampa Scale for Kinesiophobia (TSK)[107], a questionnaire consisting of 17 questions addressing patient's belief that activities that increase pain cause further harm (range 17-68, higher scores indicating more kinesiophobia).

Statistics

We analysed all data using IBM® SPSS® statistics software version 23. First, we calculated group (sex) differences in all measures. In categorical data (dichotomous variables CRPS signs and symptoms; HADS-A and D) sex differences were calculated using Chi-square tests with exact significance values in conjunction with odds ratios as a measure of effect size. In continuous data, T-tests were used in conjunction with Hedges' *g* as a measure of effect size (Hedges'*g* due to unequal sample sizes of males and females; .20=small, .50=medium, .80=large effect)[108]. In addition, if the previous analyses resulted in differences in continuous measures, the analysis was followed up with a multiple regression analysis to control for the potential influence of confounders. Independent variables were added to the model using a simultaneous forced entry method ("ENTER" method), which is used when a hierarchical order of the independent variables is not a-priori known or considered relevant.We selected the following independent variables based on previous literature or on our assumption of possible interaction of the concerned variable with sex: "sex"; "age" at time of inclusion; "disease duration";"McGill pain rating index";"CRPS severity score";"affected limbs" (upper limb(s), lower limb(s) or a combination of upper and lower limbs, imputed as 2 dummy variables in linear regression); and the "sum score physical health SF36 (PHS)". Missing values in the independent variables of the regression analysis were replaced by means if less than 5% of the independent variables were missing. Data were considered statistically significant if p-values were <.05. To control for false discovery rate, we used the Benjamini-Hochberg procedure[109] with an alpha of <.05 within the following different domains: CRPS

signs and symptoms, pain scores (NRS and McGill pain rating index), CCS, self-reported disability (WRQ, RASQ) and psychological variables (active and passive PCI, HADSA&D and kinesiophobia). Data in the text are presented as mean scores ± standard deviations.

RESULTS

Six-hundred-ninety-eight patients (age: 46.1±14.2 years; 599 (86%) female) were included in the analysis, of which 267 (38.3%) with an affected upper limb, 278 (39.8%) with an affected lower limb and 153 (21.9%) with more than one limb affected. Mean disease duration at time of inclusion in male patients was 4.7±6.9 years and 5.2±7.1 years in female patients. All 698 patients fulfilled the Bdp-c criteria, of which 448 (64.2%) also the Bdp-r criteria. Six-hundred-eighty-six patients (589 female) completed the McGill pain questionnaire, 565 patients (481 female) the NRS, 385 patient (335 female) the RASQ, 401 patients (349 female) the WRQ, 609 (522 female) the PCI, 684 patients (587 female) the HADS and 679 patients (582 female) the TSK. In the regression analyses, missing independent variables were replaced by means, which occurred in no more than 2% (disease duration 99%, CRPS severity score 99%, McGill pain rating index 98% complete data). Baseline results are listed in table 1.

CRPS signs and symptoms

No sex difference was found in CRPS signs and symptoms.(see supplementary data for the results of the uncorrected data).

CRPS severity score

The CRPS severity score was not significantly different between sexes (females: 11.8±2.7, males: 11.5±3.0): t(686)= -1.112, p=.266.

Pain

The average pain in the previous week as measured by the NRS was similar for female and male patients (females: 6.5±1.8, males: 6.3±2.0), t(-.563)= -.816, p=.390. In contrast, the McGill pain rating index was slightly higher for male CRPS patients than for female CRPS patients (females: 27.0±11.5, males: 29.4±12.0), t(684)=2.011, p=.045, g_{Hedges}= .22 (uncorrected results). This result which was entirely driven by the difference in affective quality of pain: male patients more often used extreme words to describe the affective qualities of pain (females 4.6±3.4, males 5.9±3.6, t(684)=3.56, p<.001). *Sensory* qualities (females 15.4±7.0, males 16.2±7.3, t(684)=.99, p=.32) and evaluative qualities (females 7.3±2.9, males 6.8±2.9, t(684)=1.45, p=.15) were not significantly different.

Table 1 Demographic and clinical variables

		Male	Female
Number of included patients (%)	698	99 (14.2)	599 (85.8)
Mean (SD) age, years	46.1 (14.2)	49.0 (12.9)	45.7 (14.4)
Mean (SD) age at onset, years	41.1 (15.4)	44.0 (13.5)	40.6 (15.7)
Median (IQR) disease duration, years	2.0 (0.5-7.1)	1.6 (0.4-6.1)	2.1 (0.5-7.2)
N 1 arm / 1 leg / >1 limb	267/278/153	40/42/17	227/236/136
Fulfilling Bdp-r criteria (%)	448 (64.2)	60 (60.1)	388 (64.8)
CRPS Severity Score, median (IQR)	12 (10-14)	11.5 (3.0)	11.8 (2.7)
McGill Pain Rating Index, mean (SD)	27.2 (11.6)	29.4 (12.0)	26.9 (11.4)
Sensory qualities	15.6 (7.0)	16.2(7.3)	15.5(6.9)
Affective qualities	4.8 (3.4)	5.9 (3.6)	4.6 (3.4)
Evaluative qualities	6.9 (2.9)	7.3 (2.9)	6.8 (2.9)
Numeric rating scale (NRS)	6.5 (1.8)	6.3 (2.0)	6.5 (1.8)
Pain Coping Inventory, active, mean (SD)	28.5 (5.2)	27.7 (5.6)	28.7 (5.1)
Pain Coping Inventory, passive, mean (SD)	42.1 (9.1)	44.2 (10.4)	41.7 (8.9)
RAdboud Skills Questionnaire, mean (SD)	3.2 (0.9)	3.1 (0.9)	3.3 (0.9)
Walking and Rising Questionnaire, mean (SD)	19.9 (7.4)	18.9 (7.5)	20.0 (7.4)
Hospital Anxiety and Depression Scale- depression subscale, mean (SD)	5.1 (3.9)	6.1 (4.3)	4.9 (3.8)
Dichotomous (cutoff ≥ 8) (%)	164 (23.5)	32 (32.3)	132 (22.0)
Hospital Anxiety and Depression Scale- anxiety subscale, mean (SD),	6.3 (3.8)	6.7 (4.0)	6.2 (3.7)
Dichotomous (cutoff ≥ 8) (%)	212 (30.4)	32 (32.3)	184 (30.7)
Tampa Scale of Kinesiophobia, mean (SD)	38.1 (8.2)	40.6 (7.8)	37.7 (8.2)
MOS 36-Item Short-Form Health Survey, Physical health Sum Score, mean (SD)	32.3 (16.3)	33.9 (15.9)	32.1 (16.4)

Bdp-c = Budapest clinical criteria; Bdp-r = Budapest research criteria; CRPS = complex regional pain syndrome; IQR = interquartile range; SD = standard deviation.

Pain coping

Male patients reported a higher use of *passive* pain coping mechanisms than female patients (females: 41.7±8.9, males: 44.2±10.4), t(607)=2.37, p=.018, g_{Hedges}= .15. Controlling for the potential effects of the confounders *age, disease duration, CRPS severity score, pain, physical health and affected limb*, the contribution of "sex" to the model remained significant, albeit small; β_{st-sex}= -.077, p=.024 [table 2].

No difference in *active* pain coping mechanisms were found (females: 28.7±5.1, males: 27.7±5.6) t(607)=-1.66, p=.097).

Table 2 Linear regression model Pain Coping Inventory

Variables	B(SE)	β_{st}	Sig.
Constant	48.488 (2.298)		
Sex	-1.882 (.832)	-.077	.024
Age	-.002 (.021)	-.004	.907
Disease duration	.000 (.046)	-.000	.997
CRPS severity score	-.079 (.106)	-.025	.457
McGill Pain rating index	.141 (.029)	.190	.000
Physical health sum score	-.195 (.020)	-.371	.000
Affected limbs A	-1.553 (.652)	-.090	.017
Affect limbs B	-3.804 (.945)	-.167	.000

R^2 (variance explained by the model) = .226; Sex: male>female; Sig. = significance ($p<.05$); Affected limbs A = dummy variable affected lower limb(s) v.s. affected upper limb(s); Affected limbs B = dummy variable affected lower limb(s) and upper limb(s) v.s. affected upper limb(s). β_{st} = standardized β; CRPS = complex regional pain syndrome; SE = standard error.

Self-reported physical disability

We found no group differences in the RASQ (females: 3.3±.9, males:3.1±.9) t(383)=-.999, p=.318 or WRQ (females: 20.0±7.4, males: 18.9±7.5) t(399)=-1.001, p=.317.

Anxiety and depression

No difference in anxiety scores (HADS-A) was found between the groups: (females 6.1±3.1, males 6.6±4.1) t(680)=-.294, p=.769.

Male CRPS patients had higher depression scores (HADS-D) than female patients: (females 4.9±3.8, males 6.1±4.3) t(682)=2.677, p=.008. The adjusted effect of sex in the logistic regression model remained significant (β_{st} sex = -.078, p=.024) [table 3].

Kinesiophobia

Male patients had higher scores of kinesiophobia than female patients (female 37.7±8.2, males 40.6±7.8) t(677) = 2.94, p=.001, g_{Hedges}= .36). The effect of sex in the regression model controlling for the potential influence of confounders remained significant ($\beta_{st\text{-}sex}$ = -.113, p=.002) [table 4].

DISCUSSION

We studied sex differences in 698 CRPS patients and found that male patients used more often extreme words to describe the affective qualities of pain, used slightly more often passive pain coping strategies, and were more likely to suffer from depression and kinesiophobia.

Table 3 Regression model HADS-D

Variables	B(SE)	β_{st}	Sig.
Constant	9.139 (1.061)		
Sex	-1.054 (.384)	-.096	.006
Age	.001 (.01)	-.005	.881
Disease duration	-.021 (.021)	-.037	.332
CRPS severity score	-.040 (.049)	-.029	.410
McGill Pain rating index	.033 (.013)	.098	.015
Physical health sum score	-.091 (.009)	-.384	.000
Affected limbs A	-.800 (.301)	-.103	.008
Affect limbs B	-1.459 (.436)	-.142	.001

R^2 (variance explained by the model) = .186; Sex: male>female; Sig. = significance ($p<.05$); Affected limbs A = dummy variable affected lower limb(s) v.s. affected upper limb(s); Affected limbs B = dummy variable affected lower limb(s) and upper limb(s) v.s. affected upper limb(s). βst = standardized β; CRPS = complex regional pain syndrome; SE = standard error.

Table 4 Linear regression model Tampa Scale of Kinesiophobia

Variables	B(SE)	β_{st}	Sig.
Constant	41.692 (2.324)		
Sex	-2.621 (.842)	-.113	.002
Age	.048 (.022)	.084	.026
Disease duration	-.004 (.046)	-.003	.933
CRPS severity score	.024 (.107)	.008	.825
McGill Pain rating index	.066 (.029)	.094	.024
Physical health sum score	-.140 (.020)	-.283	.000
Affected limbs A	-1.441 (.659)	-.088	.029
Affect limbs B	-2.846 (.956)	-.132	.003

R^2 (variance explained by the model)=.120; Sex: male>female; Sig. = significance ($p<.05$); Affected limbs A = dummy variable affected lower limb(s) v.s. affected upper limb(s); Affected limbs B = dummy variable affected lower limb(s) and upper limb(s) v.s. affected upper limb(s). βst = standardized β; CRPS = complex regional pain syndrome; SE = standard error.

The NRS, which depicts the average pain in the previous week, was similar for female and male patients. In contrast, pain evaluated with the McGill pain rating index was somewhat higher in male patients. Although surprising considering the overwhelming evidence for the opposite in the general- and pain population, the result appeared mainly driven by the questions concerning the affective qualities of pain; male patients more often used extreme words to describe the affective qualities of pain whereas sensory and evaluative qualities of pain were not significantly different between the groups. Therefore, although pain intensity was not significantly higher, male CRPS patients might have suffered more from the pain

than female patients, an effect that is potentially mediated by the higher levels of passive pain coping, depression and kinesiophobia found in male CRPS patients.

Male CRPS patients reported more passive pain coping strategies than female patients. Passive pain coping strategies are associated with decreased physical functioning and increased psychological distress[110]. Indeed, in our sample, passive pain coping was negatively correlated with physical health (depicted by the SF-36 Physical health Sum Score, table 1) and positively correlated with the RASQ and WRQ (Pearson's r=-.39, r=.3.0 and 2.5 respectively; all p<.001). In CRPS patients with an affected lower limb, "resting" as a passive pain coping mechanism had the largest effect on difficulties in rising and walking[85]. This effect was even larger in comparison to pain or CRPS severity[85]. In addition, CRPS patients using active, instead of passive pain coping strategies do better in overall functioning, physical functioning, mood, and the ability to cope with pain and pain flare-ups[111]. Female pain patients generally use a wider range of coping mechanisms than male patients, seek more social support and are more prone to pain-related catastrophizing[112]. In contrast, male patients use less coping strategies, more avoidance, seek less social support, are more likely to use alcohol and more passive coping strategies when they perceive their pain as threatening[113]. In addition, male patients show lower levels of daily activities than female patients reporting the same pain severity[99]. Physicians may therefore consider assessing a patients' resilience by inquiring about social ties and community support, use of sedatives and avoidance behaviour, especially when managing male patients.

Of note is that we found no difference in anxiety scores between the sexes. In the general population females report higher anxiety scores and are at greater risk of anxiety disorders than men. Furthermore, in chronic (musculoskeletal) pain patients, anxiety has been found associated with pain in male, but not in female patients [96]. In contrast, in our sample, an equally weak, positive correlation between pain and anxiety was found in both groups (Pearson's r=.21; with p=.04 in males and p<.001 in females). The presence of anxiety in CRPS patients is conceivable considering its influence on quality of life (this thesis, chapter 2), physical health, and clinical signs such as higher levels of pain, allodynia, motor disturbances, oedema, skin colour and temperature changes, independent of the sex. Possibly the comparatively high overall level of anxiety in this condition (>30% were classified as 'anxious'), while mean group levels are close to the applied cut-off value) outweighs the potential contribution of sex on these features.

Surprisingly, male CRPS patients were more likely to suffer from depression. This contradicts the common notion that females, both in the general and chronic pain populations, are twice as likely to suffer from depression than males[114]. Moreover, in one much smaller study in CRPS patients (n=24), female CRPS patients scored higher in depression[115]. For both sexes,

the association between CRPS and depression has been documented before [for review see[116]] and in one study previous-day-pain was a significant predictor of next day's negative and depressed mood[117]. However, there is evidence suggesting that in male patients with chronic pain, depression is associated with impairment of activity, and less so with pain[118]. Against this background it is relevant to take into account that CRPS is strongly associated with reduced physical health (this thesis, chapter 2), which may result in male patients being more depressed than female patients. Indeed, in our study we found a weaker negative correlation between physical health and depression in female as compared to male patients (Pearson's r=-.25 and r=-.37, respectively; both p<.001).

Male CRPS patients also had higher scores of kinesiophobia than female patients. This finding is in line with those of previous studies in chronic musculoskeletal pain patients[107,119], although, to the best of our knowledge, a clear explanation for these findings is lacking. Kinesiophobia is common in CRPS and may contribute to functional limitations[120]1), although this association was not found by others[85]. In addition, in patients with pain-related fear, therapies that focussed on physical exposure instead of pain reduction resulted in better physical performance[84,121]. This underlines the necessity of incorporating kinesiophobia assessment in the management of CRPS. Our data suggest that this might even be more important in male than female CRPS patients.

We found no significant differences in CRPS signs or symptoms. However, potential differences in signs and symptoms were much more difficult to detect, given that patients had to meet Budapest criteria to be included in the study. Concerning the results of the noncorrected data, subsequent research could focus on a potential difference in allodynia to deep joint pressure, since this sign was the most promising of all distinguishing female from male patients.

The strengths of this study are the large sample size and the use of - and regular training in - standardized assessments of CRPS signs and symptoms in the participating clinics. However, some main limitations need to be mentioned; one is the cross-sectional study design which makes it impossible to draw conclusions on causality. The second limitation is that this study was executed in patients who were treated in specialised academic centres and referral bias can therefore not be ruled out, although it should be noted that, in particular at the time the data for this study were collected, most CRPS patients in the Netherlands were referred to specialised clinics such as those in which the present data were collected. It is further of note that we have little reason to assume that any potential referral bias would have affected the relationship between sex and the variables that were identified. Third, all patients were recruited only in the Netherlands. It may be worthwhile to explore if they also hold for other regions.

To summarize, male CRPS patients seem to experience a slightly higher psychological burden than female CRPS patients in the absence of significant differences in clinical presentation. Of note is that, except for depression, the effect sizes were generally small and that variables other than sex often accounted for more of the variance in the investigated outcomes. Although results of cross-sectional studies cannot be causally interpreted, they may nevertheless provide clues that may be relevant to follow up. A greater awareness of sex-specific factors in the management of CRPS may contribute to achieving better outcomes.

Acknowledgement

We commemorate prof. dr. Roberto Perez. A very enthusiastic, talented and kind colleague who passed away last year at the age of 49. Roberto was a true pioneer of CRPS research and a dedicated member of the TREND consortium. We here acknowledge Roberto's important contribution to the design and data collection of this study.

SUPPLEMENTARY DATA

CRPS signs

	Male Nr (total)	Female Nr (total)	Chi-square (degrees of freedom)
Allodynia to light touch	47 (95)	271 (579)	$X^2(1)=.23$, p=.658
Allodynia to deep joint pressure	47 (86)	360 (534)	$X^2(1)=5.35$, p=.027
Allodynia to movements	59 (88)	348 (534)	$X^2(1)=.18$, p=.809
Hyperesthesia	43 (94)	257 (581)	$X^2(1)=.08$, p=.823
Hyopesthesia	35 (85)	233 (540)	$X^2(1)=.12$, p=.814
Hyperalgesia	58 (94)	372 (578)	$X^2(1)=.25$, p=.644
Hypoalgesia	26 (86)	168 (538)	$X^2(1)=.03$, p=.901
Skin colour changes	62 (96)	366 (578)	$X^2(1)=.06$, p=.820
Temperature asymmetry	57 (96)	369 (579)	$X^2(1)=.67$, p=.426
Edema	52 (96)	308 (580)	$X^2(1)=.04$, p=.912
Hyperhydrosis	21 (94)	114 (576)	$X^2(1)=.33$, p=.580
Hypohydrosis	5 (88)	26 (534)	$X^2(1)=.11$, p=.790
Trophic changes hair	27 (92)	136 (554)	$X^2(1)=.96$, p=.364
Trophic changes nails	22 (92)	158 (552)	$X^2(1)=.87$, p=.382
Trophic changes skin	30 (91)	155 (555)	$X^2(1)=.97$, p=.381
Muscle atrophy	31 (91)	157 (564)	$X^2(1)=1.49$, p=.261
Decreased range of motion	71 (92)	454 (571)	$X^2(1)=.62$, p=.678
Paresis	53 (87)	343 (548)	$X^2(1)=.09$, p=.812
Abnormal postures	18 (89)	119 (555)	$X^2(1)=.07$, p=.889
Tremors	13 (88)	64 (555)	$X^2(1)=.76$, p=.480
Myoclonic jerks	8 (86)	27 (542)	$X^2(1)=2.63$, p=.125
Bradykinesia	50 (80)	317 (518)	$X^2(1)=.05$, p=.902

Results are uncorrected for multiple comparison. Allodynia = pain to normally innocuous stimuli; Hyper- and hypoesthesia = increased/decreased sensitivity to touch; Hyper- and hypoalgesia = increased/decreased pain sensation; Bradykinesia = slowing of movements

CRPS symptoms

	Male Nr (total)	Female Nr (total)	Chi-square (degrees of freedom)
Allodynia to light touch	53 (95)	361 (579)	$X^2(1)=1.48$, p=.255
Allodynia to deep joint pressure	43 (86)	297 (534)	$X^2(1)=.94$, p=.352
Allodynia to movements	55 (88)	352 (534)	$X^2(1)=.39$, p=.547
Hyperesthesia	41 (94)	288 (581)	$X^2(1)=1.15$, p=.317
Hyopesthesia	29 (85)	210 (540)	$X^2(1)=.71$, p=.405
Hyperalgesia	55 (94)	361 (578)	$X^2(1)=.53$, p=.493
Hypoalgesia	21 (86)	113 (538)	$X^2(1)=.51$, p=.481
Skin colour changes	85 (96)	514 (578)	$X^2(1)=.01$, p=1.00
Temperature asymmetry	87 (96)	553 (579)	$X^2(1)=.23$, p=.686
Edema	83 (96)	488 (580)	$X^2(1)=.34$, p=.649
Hyperhydrosis	62 (94)	323 (576)	$X^2(1)=3.22$, p=.091
Hypohydrosis	9 (88)	56 (534)	$X^2(1)=.01$, p=1.000
Trophic changes hair	36 (92)	235 (554)	$X^2(1)=.35$, p=.571
Trophic changes nails	47 (92)	317 (552)	$X^2(1)=1.29$, p=.307
Trophic changes skin	33 (91)	211 (555)	$X^2(1)=.10$, p=.816
Muscle atrophy	31 (91)	181 (564)	$X^2(1)=.14$, p=.718
Decreased range of motion	69 (92)	455 (571)	$X^2(1)=1.05$, p=.334
Paresis	66 (87)	411 (548)	$X^2(1)=.03$, p=..895
Abnormal postures	43 (89)	295 (555)	$X^2(1)=.72$, p=.425
Tremors	37 (88)	191 (555)	$X^2(1)=1.93$, p=.187
Myoclonic jerks	8 (86)	27 (542)	$X^2(1)=2.63$, p=.125
Bradykinesia	50 (80)	317 (518)	$X^2(1)=.05$, p=.902

Allodynia = pain to normally innocuous stimuli; Hyper- and hypoesthesia = increased/decreased sensitivity to touch; Hyper- and hypoalgesia = increased/decreased pain sensation; Bradykinesia = slowing of movements