

ORIGINAL ARTICLE

Pain, disability, and lifestyle: Patients with complex regional pain syndrome compared to chronic musculoskeletal pain—A retrospective analysis

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Abstract

Background: Complex regional pain syndrome (CRPS) is an orphan disease occurring as a complication after trauma. Due to its acute onset and the typical clinical presentation of the inflammatory and autonomous signs, it is an eye-catching chronic pain disease affecting also young and working people. In social media and the internet, high pain severity and the unfavourable prognosis are often empathized.

Methods: Here, we compared epidemiological, pain and lifestyle factors of 223 CPRS patients from the “ncRNAPain” cohort with 255 patients with chronic musculoskeletal pain (MSK). MSK patients were recruited at the beginning of a multimodal pain therapy programme. We searched for factors predicting pain intensity.

Results: Both chronic pain diseases affected women in middle age. Patients with MSK were more obese, drank more alcohol, and were less educated (Pearson chi-square Test or Mann–Whitney/U-Test). Both groups smoked more than healthy people in the OECD (Organization for Economic Cooperation and Development). Mann–Whitney/U-Test confirmed that CRPS patients did not have more severe pain and did not suffer more from pain-related disability than patients with MSK. CRPS patients also had less psychiatric comorbidities. Multiple linear regression analysis revealed that group assignment, depressive characteristics, body mass index, average alcohol consumption and smoking predicted higher pain ratings, while disease duration, anxiety symptoms or gender had no influence on pain intensity.

Conclusion: In summary, our study supports a more optimistic view on pain in CRPS patients in comparison to MSK and identifies lifestyle factors that might contribute to the pathophysiology like smoking and drinking. Important next steps are the identification of CRPS patients at risk for chronification or—vice versa—with protective factors for pain resolution.

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Significance: This study compares complex regional pain syndrome (CRPS) and chronic musculoskeletal pain and questions previously reported pain, disability and lifestyle factors associated with CRPS.

1 | INTRODUCTION

Complex regional pain syndrome (CRPS) develops as a rare complication of bone fractures or soft tissue injuries of extremities. The diagnosis is made clinically according to the Budapest criteria: patients suffer from excessive pain “disproportionate to the preceding trauma,” sensory alterations (hyperalgesia, allodynia), autonomic changes such as oedema, temperature differences, skin colour changes, sweating, and motor and trophic changes (Dietz et al., 2019). In contrast to other chronic pain syndromes, CRPS starts acutely and has clear and often very impressive clinical signs.

CRPS is estimated to occur at a rate of 5.5 per 100,000 person years in North America (Elsharydah et al., 2017). After injury of their extremities, 5.5–26.2 of 100,000 patients develop CRPS (Birklein & Dimova, 2017; de Mos et al., 2007; Sandroni et al., 2003). Women are affected 2–3-times more often and most patients are between 50–70 years old (Castillo-Guzmán et al., 2015).

We previously conducted a study funded by the EU “ncRNAPain” and prospectively collected data from CRPS patients recruited from outpatient pain clinics in Würzburg and Mainz (Dietz et al., 2019; Dimova et al., 2020). In this large ncRNAPain cohort, lifestyle factors and demographics, as well as pain and comorbidities, have not been evaluated yet. In general, risk factors for disabling chronic pain in Germany are obesity, low income, and depression (Hauser et al., 2015). Patients with chronic musculoskeletal pain (MSK) likelier suffer from obesity or unemployment and have a lower education level than CRPS patients (Cruz et al., 2020; Mather et al., 2019). Psychiatric comorbidities like depression and anxiety have been described in CRPS and chronic pain patients (Ott & Maihofner, 2018; Park et al., 2020; Reis et al., 2019). In CRPS in a US national inpatient database, higher median education, drug abuse, headache and depression were associated with a higher risk of CRPS (Elsharydah et al., 2017). Specifically, patients with obesity, hypothyroidism and diabetes were at lower risk to develop CRPS (Elsharydah et al., 2017). Pain in CRPS communicated in the lay press as the “worst pain condition” (Mayoh, 2017; Thompson, 2019). However, a comparison with other pain diseases has not been addressed so far.

Here, we used our large cohort of CRPS patients to challenge previous epidemiological and lifestyle factors as well as pain and comorbidities and to compare CRPS

to a patient group with typical chronic MSK pain. These data could help to identify the putative risk factors that could be approached (e.g. smoking) or channel patients to preventive measurements (Hsu et al., 2002; Mekhail et al., 2020).

2 | STUDY DESIGN AND METHODS

2.1 | Description of the two cohorts

ncRNAPain CRPS cohort: Data from 333 patients was reviewed, already summarized in a table by the ncRNAPain study group. 110 (29.6%) were excluded because of age < 18 and >80 years ($N = 2$), incomplete data ($N = 20$) and follow-up visits of the same patient ($N = 88$). In the end, we included 223 CRPS patients, 80% were CRPS type I, in this study (Figure 1).

MSK cohort: 2034 data sets from medical files from patients treated in the Center for Interdisciplinary Pain Medicine (ZiS) at University Hospital Würzburg from January 2018 to August 2020 were reviewed. We then focused on the patients admitted for a multimodal interdisciplinary day pain therapy ($N = 334$). After excluding patients with other pain diseases as their main diagnosis, like fibromyalgia, CRPS, chronic neuropathic pain and headache ($N = 48$), as well as age > 80 years ($N = 28$) or missing data ($N = 3$), 255 could be included in our study. “Missing data” were files with more than three unavailable items (Figure 1).

From both groups, information from the patient (doctor’s assessment and discharge letters, German pain questionnaire) and ncRNAPain study files were gathered regarding gender, age, height/weight/BMI, pain intensity, von Korff Score, pain duration, smoking, alcohol consumption, comorbidities (allergies, depression and anxiety characteristics), graduation, qualification, and occupation level. To estimate depressive symptoms, the ncRNAPain patients had to fill the Beck Depression Inventory 2, German version (BDI-II; range 0–63; 0 and 13 minimal depression, 14–19 mild depression, 20–28 moderate depression, and 29–63 severe depression). Anxiety characteristics in the ncRNAPain cohort were measured by the State-Trait Anxiety Inventory, German Version, (trait anxiety subscale STAI-T, range 20–80). For the STAI-T, a value ≤ 39 was defined as normal (Dietz et al., 2019). The severity of chronic pain was evaluated in both cohorts by

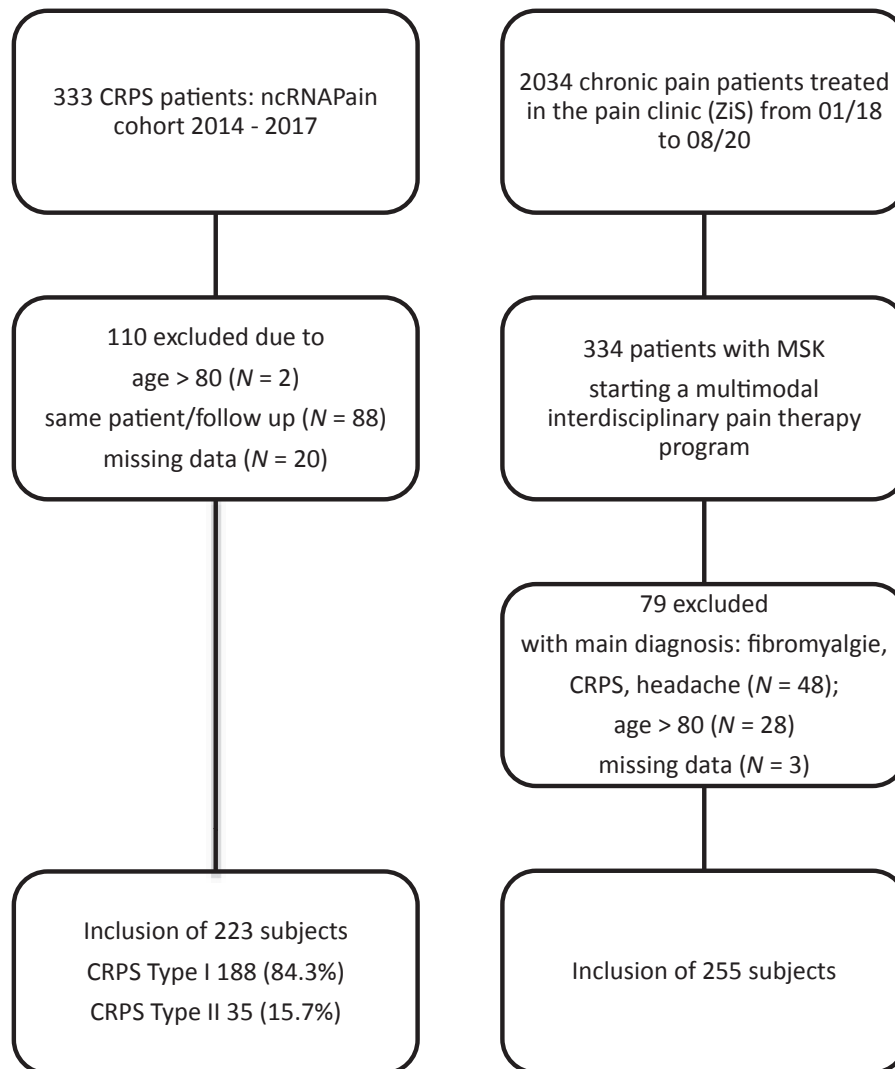


FIGURE 1 Flow chart of the analysis. CRPS, complex regional pain syndrome group; MSK, musculoskeletal group

the von Korff Score, measuring pain intensity and pain disability. It allows differentiating persons with high pain scores who are not disabled from persons with comparable pain who are significantly disabled. Von Korff Score is divided into a four level categorical variable (Grade 0 no pain; Grade 1-low disability + low intensity; Grade 2-low disability-high intensity; Grade 3-high disability- moderately limiting; Grade 4-high disability-severely limiting) (Von Korff et al., 1992, 2020).

The MSK patients completed the German pain questionnaire (Deutscher Schmerzfragebogen, DSF, of the Deutsche Schmerzgesellschaft). A part of this questionnaire is the DASS, a 21-item self-reported questionnaire that measures depression, anxiety, and tension/stress. Each scale contains seven items, with a range from 0 to 3 (severity/frequency). The scores for depression, anxiety, and stress are added up (maximal score in each category 21). The cutoff values for stress are ≥ 10 , for depression ≥ 10 , and for anxiety ≥ 6 (Scherf-Clavel et al.,

2020). Psychotherapists evaluated all MSK pain patients and verified the questionnaire's results. All data were obtained at the beginning of the therapy/study.

2.2 | Statistics

Data were collected and listed in Excel 2016 and SPSS 26 tables. Using SPSS 26 for all statistical tests to analyse group differences, Pearson chi-square test for nominal data (gender, depression, anxiety, allergies, tobacco, alcohol consumption, occupation), Mann-Whitney/U-Test for ordinal and metric data (graduation, qualification, age, weight, BMI, height, pain intensity, pain duration in years) were performed, as the cohorts were not normally distributed. Figures and tables were created with Graph pad prism 9, Excel 2016 and Word 2016. The significance level was set at 5%, p -values < 0.05 were significant, multiple linear regression was calculated.

3 | RESULTS

3.1 | Epidemiology and lifestyle

In both cohorts, CRPS and MSK patients, there was a female preponderance (Table 1). This was even more pronounced in the CRPS group (about $\frac{3}{4}$ females in CRPS vs. $\frac{2}{3}$ females in MSK). Both groups had an age peak in the 6th decade, with CRPS patients being slightly younger.

Patients in the MSK group were slightly heavier than the CRPS patients; their height was similar. The BMI in both groups indicated that one-third of the CRPS patients were overweight (BMI 25.0–29.9) vs. one-fourth in the MSK group. Twice the number of patients with MSK were obese (BMI > 30.0) compared to CRPS patients.

The highest level of graduation was comparable in both groups but patients in the CRPS group had a slightly higher qualification level. CRPS patients tended to be on sick leave. Patients with MSK were often unemployed or on a disability pension.

Alcohol consumption was significantly higher (15.0%) in the MSK group using dichotomous answers, as well as in the subcategories based on frequency (Table 1). Tobacco use did not differ between both groups.

3.2 | Pain and comorbidities

Current pain intensity, mean pain and max pain on the day of admission (musculoskeletal) or the study inclusion were all significantly lower in the CRPS group by 1.7 points at the NRS scale (Figure 2). No clinically relevant differences (>2.0 points) were found between males and females in both groups.

Many MSK patients suffered from more than one painful region: most often back pain followed by joint pain. A small proportion also had headaches and pain at several regions of the body, but did not meet the criteria for fibromyalgia. Fewer CRPS patients suffered from pain in other body regions.

Pain duration was nearly nine times longer in patients with MSK compared to CRPS patients: $\frac{3}{4}$ in the CRPS group had a disease duration less than one year versus $\frac{1}{8}$ in the MSK cohort (Figure 3).

To identify possible predictors of the pain intensity (current, average, maximum) we conducted a multiple regression analysis including eight factors: group assignment, pain duration in years, gender, depressive characteristics, anxiety symptoms, BMI, average alcohol consumption and smoking. The R^2 for current pain was 0.28 (adjusted $R^2 = 0.27$), for average pain 0.25 (adjusted 0.23), for maximum pain 0.21 (adjusted 0.19), indicative

for a high goodness of fit (Cohen, 1988). Group assignment, depressive characteristics, BMI, average alcohol consumption and smoking (the latter only for current pain) predicted a higher pain intensity (Table 2).

Almost $\frac{2}{3}$ of the MSK pain patients had a von Korff Score Grade 4 compared to $\frac{1}{2}$ of the CRPS group, indicating a high pain severity (Table 1, Figure 4).

Patients with MSK pain suffered more from psychiatric comorbidities than CRPS patients: depressiveness was 2.5-times and anxiousness 3.1-times more prevalent (Table 1).

4 | DISCUSSION

In this study, we investigated epidemiologic factors, pain characteristics and comorbidities in two large cohorts (CRPS and MSK pain patients), to identify differences and possible risk factors for these diseases. In general, CRPS and MSK pain patients were quite similar in age, sex, and body weight. In addition, we could falsify several assumptions regarding CRPS: patients with CRPS had moderate (and not very strong) pain, were psychologically reasonably well and did not smoke or drink more alcohol.

We confirmed that female gender and middle age predominate in chronic pain—independent of an acute start of pain like in CRPS or a slow process of pain chronification as in MSK (Elsharydah et al., 2017; Larsson et al., 2012; Santos et al., 2020; Scholz-Odermatt et al., 2019). Obesity was more prevalent in the MSK group: It is a known risk factor for chronic pain (Hauser et al., 2015; Lier et al., 2016; Suri et al., 2017) and weight loss improves the pain condition (Bout-Tabaku et al., 2019).

In contrast to previous investigations, we did not identify more smokers in the CRPS group compared to the MSK group (Goh et al., 2017; Hsu et al., 2002). However, both groups smoked more frequently compared to the normal population (18% smokers of all adults in OECD countries) although in general smoking rates decreased by five percent over the last decade. People with a higher education smoke less (Ämter, 2019). Since CRPS patients are higher educated, one would have expected less smokers in the CRPS group. Tobacco consumption is associated with a higher risk for chronic pain and a poorer prognosis in CRPS (Cimmino et al., 2011; Goh et al., 2017; Kirsch Micheletti et al., 2019).

More MSK pain patients consumed alcohol. Globally, 47% of the population are currently drinking (Manthey et al., 2019)—similar to the CRPS group. The literature is inconclusive about alcohol intake and chronic pain. On one hand, alcohol consumption is not increased in pain patients (Ferreira et al., 2013; Kirsch Micheletti et al., 2019). On the other hand, moderate drinking is seen as a protective factor for chronic back pain (Suri et al., 2017).

TABLE 1 Epidemiological data

Variables	MSK (N = 255)	CRPS (N = 223)—type I/II 188 (84.3%)/35 (15.7%)
Gender (%)***		
Female/male	160 (62.7)/95 (37.3)	173 (77.6)/50 (22.4)
Age**		
Mean (range)	54.6 (20–80)	50.9 (18–77)
Weight in kg**		
Mean (range)	82.7 (43.0–144.2)	76.9 (35.0–160.0) ^b
Body mass index**		
Mean (range)	28.7 (18.2–51.2)	26.8 (16.4–45.9) ^b
Body mass index class kg/m ² (%)***		^b
Underweight < 18.5/normal weight 18.5–24.9/ overweight 25.0–29.9/Adipositas I° 30.0–34.9	2 (0.8)/84 (32.9)/66 (25.9)/58 (22.7)	6 (2.7)/92 (41.8)/78 (37.5)/26 (11.8) 11 (5.0)/7 (3.2)
Adipositas II° 35.0–39.9/Adipositas III° ≥40.0	34 (13.3)/11 (4.3)	
Height in m		
Mean (range)	1.7 (1.3–2.0)	1.7 (1.5–1.9) ^b
Depressive characteristics (%)***		
Yes/no/unclear	157 (61.6)/98 (38.4)/0	61 (27.5)/159 (71.6)/2 (0.9) ^a
Anxiety characteristics (%)***		
Yes/no/unclear	56 (22.0)/199 (78.0)/0	18 (8.1)/203 (91.4)/1 (0.5) ^a
Allergies (%)***		
Yes/no/unclear	136 (53.3)/119 (46.7)/0	82 (36.9)/140 (63.1)/0 ^a
Back pain (%)***		
Yes/no/unclear	198 (77.6)/57 (22.4)/0	59 (26.6)/163 (73.4)/0 ^a
Joint pain (%)***		
Yes/no/unclear	141 (55.3)/114 (44.7)/0	35 (15.8)/187 (84.2)/0 ^a
Headache (%)		
Yes/no/unclear	48 (18.8)/207 (81.2)/0	40 (18.0)/180 (81.1)/2 (0.9) ^a
Multilocular pain (%)		
Yes/no/unclear	10 (3.9)/245 (96.1)/0	10 (4.5)/212 (95.5)/0 ^a
Tobacco (%)		
Yes/no	76 (29.8)/179 (70.2)	42 (31.8)/90 (68.2) ^f
Alcohol consumption (%)***		
Yes/no/no information	148 (58.0)/106 (41.6)/1 (0.4)	96 (43.0)/119 (53.4)/8 (3.6)
Average alcohol consumption (%)***		
Every day/4–6 week/1–3/week/1–3/ month/<1/ month/no/no information	25 (9.8)/8 (3.1)/25 (9.8)/43 (16.9)/ 47 (18.4)/106 (41.6)/1 (0.4)	34 (15.2)/4 (1.8)/21 (9.4)/32 (14.3)/6 (2.7)/118 (52.9)/8 (3.6)
Graduation (%)		
At school/lower sec. school/intermediate sec. school/baccalaureate/without/other	0/116 (45.5)/72 (28.2)/61 (23.9)/6 (2.4)/0	^c 1 (0.5)/87 (39.7)/83 (37.9)/41 (18.7)/3 (1.4)/4 (1.8)
Qualification (%)		
At school/apprenticeship or college/foreman/ university/without/other	3 (1.2)/196 (76.9)/3 (1.2)/37 (14.5)/16 (6.3)/0	^e 7 (4.1)/107 (63.3)/4 (2.4)/33 (19.5)/11 (6.5)/7 (4.1)
Occupation (%)***		

(Continues)

TABLE 1 (Continued)

Variables	MSK (N = 255)	CRPS (N = 223)—type I/II 188 (84.3%)/35 (15.7%)
Fulltime/part time/mini-job/at home/ unemployed/in education	51 (20.0)/32 (12.5)/8 (3.1)/5 (2.0)/29 (11.4)/7 (2.7)	^d 43 (19.9)/14 (6.5)/0/4 (1.9)/4 (1.9)/0 101 (46.8)/34 (15.7)/16 (7.4)
On sick leave > 6 weeks/ongoing pension procedures or retired/retired because of pain	50 (19.6)/70 (27.5)/3 (1.2)	
Pain duration in years ^{***}		
Mean (range)	9.3 (0–50.0) ^c	1.3 (0–15.8) ^d

Note: Significance * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, chi-square-test, Mann-Whitney-U-test as appropriate, lacking sample's normal distribution.

Abbreviations: CRPS, complex regional pain syndrome group; MSK, musculoskeletal pain group.

^aOne value missing.

^bThree values missing.

^cFour values missing.

^dSeven values missing.

^eFifty-four values missing.

^fOne hundred seven values missing.

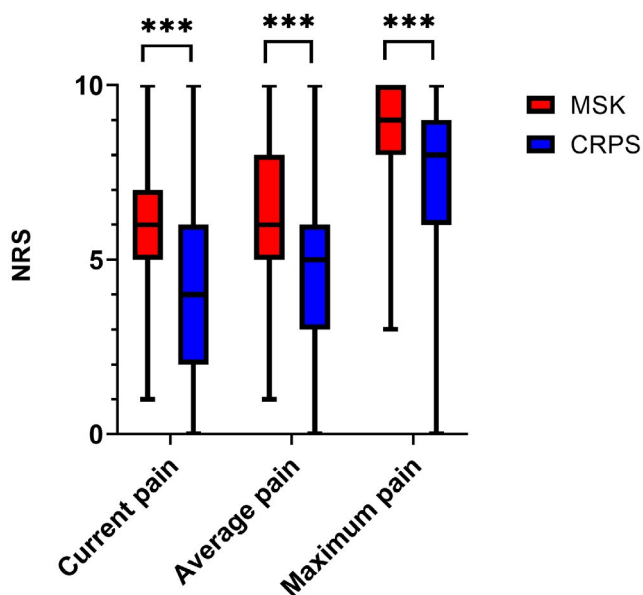


FIGURE 2 Lower pain intensity in CRPS patients. Boxplots display pain intensity with median, 25% and 75% percentile and range. Current pain was measured at the beginning of therapy (MSK: $N = 251$ —4 missing) or study inclusion (CRPS: $N = 221$ —2 missing), average and maximum pain in the three months before. Non-parametric Mann-Whitney/U-Test, no normal distribution. Significance *** $p < 0.001$. CRPS, complex regional pain syndrome group; MSK, musculoskeletal group; NRS, numeric rating scale

Alcohol seems not to be a contributing factor in CRPS patients.

In our study, CRPS patients were higher qualified with a similar graduation level—in line with the literature (Elsharydah et al., 2017; Mather et al., 2019; Scholz-Odermatt et al., 2019). Low education is a risk factor for MSK pain (Cimmino et al., 2011). Many of the CRPS

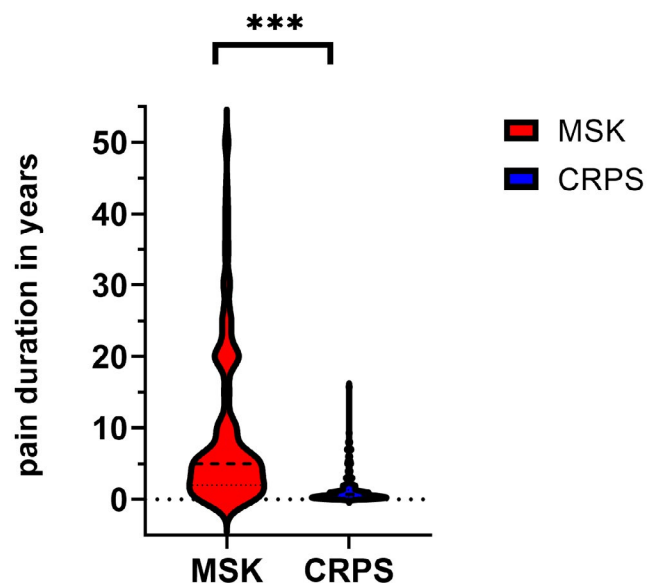


FIGURE 3 Shorter pain duration in patients with CRPS. Violin plots depict pain duration in years in MSK vs. CRPS (9.3 vs. 1.3). Dashed line shows Mean. MSK: $N = 251$ —4 missing; CRPS: $N = 216$ —7 missing. Non-parametric Mann-Whitney/U-Test, no normal distribution. Significance *** $p < 0.001$. CRPS, complex regional pain syndrome group; MSK, musculoskeletal group

patients were on sick leave, while MSK pain patients faced more unemployment and disability pension. This might be due to the longer disease duration.

In contrast to lay press and literature, CRPS patients in our cohort reported lower current, mean, maximal NRS-scores and pain disability compared to the MSK group (Thompson, 2019). Does pain duration explain this finding? Although intuitive, data are sparse. Bendayan et al. followed acute pain individuals from onset to chronification over two years. In the beginning, pain intensity was

TABLE 2 Probable risk factors for pain intensity

Variable	Current pain			Average pain			Maximum pain		
	Not standardized	Std. Err.	Standardized	Not standardized	Std. Err.	Standardized	Not standardized	Std. Err.	Standardized
Constant	7.494***	0.987		6.571***	0.898		9.522***	0.839	
Group	-1.940***	0.272	-0.370***	-1.430***	0.247	-0.307***	-1.283***	0.231	-0.303***
Pain duration in years	0.009	0.012	0.037	0.007	0.011	0.032	0.006	0.011	0.029
Gender	-0.454	0.238	-0.087	-0.325	0.216	-0.070	-0.106	0.203	-0.025
Depression characteristics	-0.637**	0.244	-0.129**	-0.593**	0.222	-0.135**	-0.495*	0.207	-0.124*
Anxiety characteristics	-0.254	0.322	-0.038	-0.184	0.293	-0.031	-0.338	0.275	-0.063
Body mass index	0.073***	0.018	0.183***	0.076***	0.017	0.214***	0.043**	0.015	0.131**
Smoking	-0.252*	0.118	-0.097*	-0.160	0.107	-0.069	-0.129	0.100	-0.062
Alcohol consumption	0.175*	0.070	0.114*	0.198**	0.064	0.144**	0.162**	0.060	0.130**
R ²	0.283			0.249			0.208		
Corr. R ²	0.267			0.232			0.191		
F (df = 8; 364)	17.979			15.057			11.891		

Note: Multiple linear regression for all subjects. Regression coefficients (standardized and not standardized) and standard error (Std. Err.) of constants and variables. Coefficient of determination (R²), corrected coefficient of determination (Corr. R²). F-Statistics. Significance * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

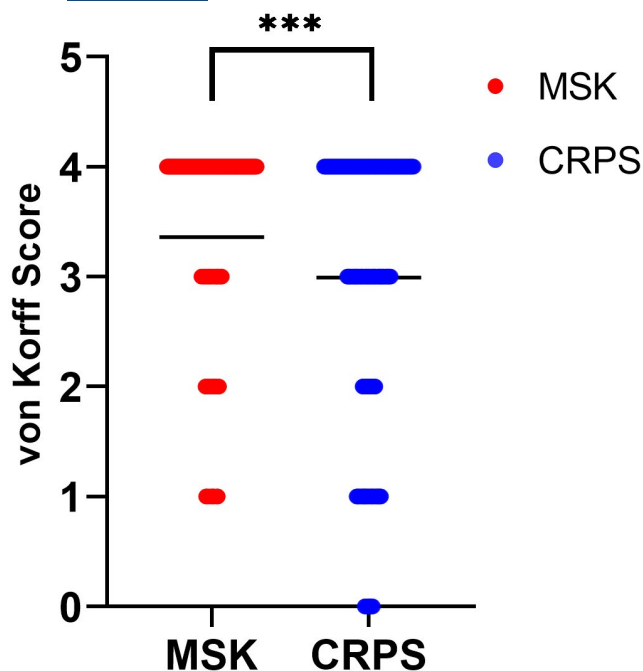


FIGURE 4 Lower pain-related disability in CRPS patients in von Korff Score Grade 1–4. Interleaved scatterplots show the pain-related disability by von Korff Score (Grade 1–4). Solid lines depict the Mean. MSK: $N = 255$; CRPS: $N = 223$. Non-parametric Mann–Whitney/U-Test, no normal distribution. Significance $***p < 0.001$. CRPS, complex regional pain syndrome group; MSK, musculoskeletal group

higher. It decreased within three months with no further change for up to two years (Bendayan et al., 2017). Furthermore, we found only a very low correlation between pain duration and intensity in all patients. No clinically significant differences were observed between women and men as described before (Meyer-Frießem et al., 2020).

Anxiety and depression are relevant comorbidities in chronic pain diseases (Hauser et al., 2015; Lentz et al., 2019; Park et al., 2020). The diagnosis was based on questionnaires in CRPS patients, questionnaires and clinical diagnosis in MSK pain patients. One-fourth of CRPS patients reported depressive and 8 out of 100 anxious symptoms similar to previous studies (Bean et al., 2014, 2015). But CRPS patients were much less affected compared to MSK pain patients. Disease duration might explain this again, but bias due to different diagnostic procedures cannot be excluded. Psychiatric comorbidities, especially depression, may predict poor outcomes of CRPS in longitudinal studies; their treatment might be a therapeutic approach to prevent chronification and aggravation.

Our study has limitations due to its retrospective cross-sectional character for the chronic MSK patients. All patients were seen in tertiary pain centres at a University Hospital—so patients in both groups are often severely affected. While the CRPS patients were mostly seen at the

beginning of the disease, MSK patients usually suffered from more severe symptoms and disability, which justified the need for multimodal pain therapy. Apart from this limitation, both groups are represented in this setting. Second, we did not include a detailed pain medication history in the data acquisition. So this might have influenced the reported pain intensity but also disease burden. However, Gallizzi et al. (2015) found at best a low correlation between prescribed pain medication and pain intensity. Another limitation is the large difference in the disease duration. Although we wanted to show that this is an important distinguishing criterion of the two diseases, this might lead to selection bias. We characterized the two groups and emphasized the differences, but the study design did not allow to identify valid risk factors for the two pain disorders due to the lack of a control group. Furthermore, we do not know how e.g. lifestyle factors, besides smoking and alcohol consumption, and comorbidities compare to the normal population.

5 | CONCLUSION

Pain intensity, pain duration, pain-related disability, psychiatric comorbidities, and socioeconomic factors (sick leave, unemployment, and disability pension) were different between CRPS patients and MSK patients which can partly be considered as therapeutic targets. In contrast, more smokers in both diseases could stimulate research on the pathophysiology of pain and ingredients of cigarettes. In our cohort alcohol consumption, smoking, BMI, depression, and group assignment could predict higher pain intensity levels. Furthermore, we could not support the evidence that CRPS has the highest pain intensity and pain-related disability and promote a more optimistic view of CRPS.

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CONFLICT OF INTEREST

G. Kindl, K. Teichmüller, F. Escolano-Lozano have no conflict of interests. H.L. Rittner and F. Birklein received EU funds for ncRNAPain Study.

AUTHOR CONTRIBUTION

GK conducted the data analysis and wrote the first draft of the paper. FEL recruited patients and collected data. KT helped with the statistical analysis. HR and FB

designed the study and helped with the data analysis and writing the paper. All authors critically revised the manuscript.

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