

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

Velzen, G.A.J. van

#### Citation

Velzen, G. A. J. van. (2022, November 16). Sex, quality of life and brain function in complex regional pain syndrome. Retrieved from https://hdl.handle.net/1887/3486306

Version: Publisher's Version

Licence agreement concerning inclusion of doctoral

License: thesis in the Institutional Repository of the University

of Leiden

Downloaded from: <a href="https://hdl.handle.net/1887/3486306">https://hdl.handle.net/1887/3486306</a>

**Note:** To cite this publication please use the final published version (if applicable).

# Health-related quality of life in 975 patients with complex regional pain syndrome type 1

Gijsbrecht A.J. van Velzen, MD<sup>1,2</sup>; Roberto S.G.M. Perez, PhD<sup>2,3,4</sup>; Miriam A. van Gestel, PhD<sup>2,5</sup>; Frank J.P.M. Huygen, MD, PhD<sup>2,6</sup>; Maarten van Kleef, MD, PhD<sup>2,7</sup>; Frank van Eijs, MD, PhD<sup>2,8</sup>; Albert Dahan, MD, PhD<sup>2,9</sup>; Jacobus J. van Hilten, MD, PhD<sup>1,2</sup>; Johan Marinus, PhD<sup>1,2</sup>.

Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands;
Knowledge consortium TREND, Leiden, The Netherlands;
Department of Anaesthesiology, VU University Medical Centre, Amsterdam, The Netherlands;
Institute for Extramural Medicine (EMGO), Amsterdam, The Netherlands;
Department of Medical Statistics and BioInformatics, Leiden University Medical Centre,
Leiden, The Netherlands;
Department of Anaesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands;
Department of Anaesthesiology, Maastricht University Medical Center, Maastricht, The
Netherlands;
Department of Anaesthesiology, Sint Elisabeth Hospital, Tilburg, The Netherlands;
Department of Anaesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

#### **ABSTRACT**

There are limited data available on health-related quality of life (OoL) in patients with complex regional pain syndrome (CRPS). In the present study we examined QoL in 975 CRPS patients attending 6 different clinics in the Netherlands, OoL was assessed using the MOS 36-Item Short-Form Health Survey (SF-36) with the Mental Health Summary Score (MHS) and the Physical Health Summary Score (PHS) as dependent variables. The influences of gender, type of affected limb, disease duration, pain scores, CRPS severity and set of diagnostic criteria used were investigated. We found the lowest scores of OoL in the physical domains of the SF-36, with lower-limb CRPS patients reporting poorer results than patients with an affected upper limb. Influence of gender on OoL was not observed, and correlations of OoL with disease duration and the CRPS severity score were weak. Pain correlated moderately with OoL. In addition, patients fulfilling stricter diagnostic criteria (ie, the Budapest criteria) had lower QoL scores than patients fulfilling less strict criteria (ie, the Orlando criteria). We conclude that loss of QoL in CRPS patients is due mainly to reduced physical health. A comparison with data available from the literature shows that CRPS patients generally report poorer QoL than patients with other chronic pain conditions, particularly in the physical domains. Pain correlated moderately with OoL and therefore deserves ongoing attention by physicians. Finally, patients meeting the diagnostic Budapest criteria have lower OoL scores than patients meeting the Orlando criteria, highlighting the impact of different sets of criteria on population characteristics.

#### **INTRODUCTION**

Complex regional pain syndrome (CRPS) is a condition that may have a profound effect on daily life, often invaliding patients for many years<sup>67,68</sup>. Typically, CRPS develops after a trauma to 1 of the limbs, but occasionally progresses to other limbs<sup>69-71</sup>. In the acute phase, patients report intense pains accompanied by autonomic, trophic and motor disturbances of the affected limb<sup>1</sup>. A considerable number of patients develop a chronic course in which autonomic signs are usually less pronounced and pain, along with sensory and motor disturbances predominates<sup>13</sup>. The incidence ranges from 5.5 to 26.2 per 100,000 person-years<sup>4,72</sup>, with the highest incidence rates occurring between 61 and 70 years and with females being affected 3 to 4 times more often than men<sup>4</sup>.

Although, in recent years, considerable progress has been made in the understanding of the pathophysiology of CRPS<sup>1</sup>, this has not translated into an effective therapy from which all patients benefit; a large group of patients experience incomplete recovery and are confronted with long-term disability and partial or complete inability to resume their former jobs<sup>10,73</sup>.

It is self-evident that such disease consequences may have grave impact on the lives of CRPS patients. Indeed, previous studies on quality of life (QoL) of CRPS patients reported high levels of disability, continuing pain and motor disturbances. However, these studies were usually performed in small samples<sup>11–14</sup> or involved patients in trials who had to meet certain eligibility criteria, which affected the generalizability of the findings<sup>14,15</sup>. In the present study we therefore analysed the QoL data of almost a 1000 Dutch patients collected over the past 10 years in 5 major CRPS clinics. Specifically, we studied the influence of gender, type of involved extremity (upper or lower), disease duration and pain on perceived QoL.

In addition we studied the influence of diagnostic criteria on QoL, as the profile of signs and symptoms differs according to the diagnostic criteria the patient fulfils<sup>74</sup>, whereas QoL may vary with perceived complaints. Lastly, we included the CRPS severity score, a recently developed severity index that counts the number of the patient's signs and symptoms, to study the relationship between the number of occurring signs and symptoms and perceived OoL <sup>75</sup>.

#### **METHODS**

#### Participants

Patients were recruited from 5 pain clinics and one department of neurology of university hospitals participating in TREND (short for Trauma RElated Neuronal Dysfunction, a

Dutch knowledge consortium that integrates research on CRPS; www.trendconsortium.nl). All patients were 18 years or older; fulfilled either the diagnostic criteria for CRPS adopted at the 1993 consensus conference ('Orlando criteria') <sup>7</sup>, the Budapest clinical (Bdp-c) or the Budapest research (Bdp-r) criteria <sup>75</sup>; and did not have any other conditions that could account for the signs and symptoms encountered. Exclusion was made at the presence of dementia, cognitive impairment or any other kind of inability to understand and to complete self-assessment questionnaires.

#### Assessment methods and measurement instruments

Methods of examining patients were standardised across centres by the use of a universally applied measurement protocol and 3-monthly plenary training sessions. Signs and symptoms were recorded on a standard score sheet. Patients also completed a set of questionnaires. All data were stored in a NEN-7511 certified, central web-based data management system (ProMISe©). Written informed consent was obtained from all participants, procedures were in accordance with the Declaration of Helsinki, and the protocol was approved by the medical ethical committees of all participating centres.

We classified patients in 3 groups to examine the influence of the involved limb on QoL; 1 upper limb affected, 1 lower limb affected and more than 1 limb affected. To evaluate the influence of diagnostic criteria on perceived QoL, we allocated patients to the most strict criterion they met (Orlando < Bdp-c < Bdp-r).

The Dutch version of the Medical Outcomes Study Short Form 36 (SF-36) was used as outcome measure of QoL in this study<sup>76</sup>. This generic questionnaire consists of 8 health domains: 1) limitations in *Physical Functioning*; 2) limitations in usual role activities due to physical problems (*Role Physical*); 3) *Bodily Pain*; 4) *General Health* perceptions; 5) *Vitality*; 6) limitations in *Social Functioning* due to physical problems; 7) limitations in usual role activities due to emotional problems (*Role Emotional*) and 8) general *Mental Health*. For the main analysis, the Physical Health sum Score (PHS) (mean of domains 1-4) and the Mental Health sum Score (MHS) (mean of domains 5-8) were used. Scores are presented as percentages (0-100), with higher scores indicating better QoL.

Pain was quantified using the pain rating index of the McGill Pain Questionnaire<sup>77</sup> and the Numeric Rating Scale. The McGill Pain Questionnaire consists of 20 categories of 3 or 4 rank ordered words that evaluate different aspects of pain (range 0-63; higher scores indicating more pain). For the Numeric Rating Scale score, we asked patients to rate the average pain intensity of the previous week on a scale from 0 to 10, with 10 reflecting the worst pain imaginable.

As an indicator of severity of CRPS, we used the CRPS Severity Score, a checklist consisting of 17 CRPS associated signs and symptoms<sup>75</sup>.

The following questionnaires were not used in the primary analyses of this study, but were included to provide a broader perspective on the mental and physical health of patients: The Hospital Anxiety and Depression Scale<sup>78</sup>; the Radboud Skills Questionnaire<sup>79</sup>; and the Questionnaires on Walking and Rising<sup>80,81</sup>. The Hospital Anxiety and Depression Scale measures the presence and severity of mood disorders (range 0-42, with higher scores indicating more severe anxiety or depression); in the present study, the mean Anxiety and Depression scores of this questionnaire were used. The Radboud Skills Questionnaire measures the difficulty that patients with an affected upper limb perceive when performing manual activities of daily life (range 1-5, with higher scores indicating worse functioning). The Questionnaires on Walking and Rising measures limitations in walking and rising in patients with an affected lower limb (range, 0-30; summary score of 'walking inside', 'walking outside' and 'rising', with higher scores indicating worse functioning; because of the different number of items in these three scales, all scores were first transformed to a 0-10 scale and next summed).

#### Statistics

All statistical analyses were performed with IBM<sup>©</sup> SPSS<sup>©</sup> Statistics version 20 (IBM Corporation). Normality of the data was checked by inspecting histograms of frequency distributions, normal probability plots, residual scatter plots and the Kolmogorov-Smirnov test. Data were considered statistically significant when P values were less than .05 and corrected for multiple comparisons (Bonferroni) when multiple analyses were performed within the same research question.

For the difference in QoL scores between sexes the independent t-test was used, and an Analysis of Variance (ANOVA) was carried out to examine the influence of type of limb or CRPS criteria on QoL. The Pearson correlation coefficient was calculated to examine the correlation between QoL and age, disease duration, symptom severity or pain. Coefficients of 0.70 or higher were classified as strong, those 0.30–0.69 as moderate and those less than 0.30 as weak  $^{82}$ . Data are presented as mean scores  $\pm$  standard deviations (SD).

### **RESULTS**

#### Study participants

A total of 975 patients (age:  $46.8\pm14.3$  years; 817 female) were included in the analysis, of whom 374 (38.4%) had an affected upper limb and 408 (41.8%) had an affected lower limb (Table 1). In 193 (19.8%) patients more than one limb was affected: 28 (2.8%) patients had

2 affected upper limbs, 25 (2.6%) had 2 affected lower limbs, and the remaining 140 (14.4%) had a combination of an affected upper and lower limb (n=53; 5.4%) or more than 2 affected limbs (n=87; 8.9%). Mean disease duration was  $4.73\pm6.64$  years. All 975 patients fulfilled the Orlando criteria, while 697 (71.5%) met the Bdp-c and 447 (45.8%) the Bdp-r criteria.

Table 1

| Table 1   |                  |  |  |
|---|------------------|--|--|
| Demographic and clinical characteristics of study patients. |                  |  |  |
| N (% females)   | 975 (83.9)       |  |  |
| Mean (SD) age, years  | 46.8 (14.3)      |  |  |
| Mean (SD) age at onset, years                               | 42.1 (15.6)      |  |  |
| Median (IQR) disease duration, years                        | 1.8 (0.4-6.7)    |  |  |
| Employed / unemployed / retired / missing %                 | 51 / 28 / 9 / 12 |  |  |
| N 1 arm / 1 leg / >1 limb                                   | 374 / 408 / 193  |  |  |
| Fulfilling only Orlando criteria (%)                        | 975 (100)        |  |  |
| Fulfilling Bdp-c criteria (%)                               | 697 (71.5)       |  |  |
| Fulfilling Bdp-r criteria (%)                               | 447 (45.8)       |  |  |
| CRPS Severity Score, median (IQR)                           | 11.0 (8-13)      |  |  |
| Hospital Anxiety and Depression Scale, mean (SD)            |                  |  |  |
| Anxiety   | 6.17 (3.8)       |  |  |
| Depression  | 4.93 (3.8)       |  |  |
| McGill Pain Questionnaire, mean (SD)                        | 25.50 (11.7)     |  |  |
| Walking and Rising Questionnaire, mean (SD)                 | 18.73 (7.7)      |  |  |
| Radboud Skills Questionnaire SQ, mean (SD)                  | 3.05 (0.9)       |  |  |
| SF-36   |                  |  |  |
| Physical Health Summary score, mean (SD)                    | 34.9 (18.0)      |  |  |
| Physical Functioning, mean (SD)                             | 41.4 (26.1)      |  |  |
| Role Physical, mean (SD)                                    | 18.1 (30.7)      |  |  |
| Bodily Pain, mean (SD)                                      | 27.5 (20.5)      |  |  |
| General Health, mean (SD)                                   | 52.1 (21.7)      |  |  |
| Mental Health Summary score, mean (SD)                      | 58.4 (21.1)      |  |  |
| Vitality, mean (SD)   | 47.3 (19.9)      |  |  |
| Social Functioning, mean (SD)                               | 58.9 (26.8)      |  |  |
| Role Emotional, mean (SD)                                   | 60.2 (44.3)      |  |  |
| Mental Health, mean (SD)                                    | 67.1 (18.4)      |  |  |
|   |                  |  |  |

Bdp-c = Budapest clinical criteria; Bdp-r = Budapest research criteria; IQR = interquartile range; SD = standard deviation; SF-36 = MOS 36-Item Short-Form Healthy Survey.

The results of the Numeric Rating Scale, McGill Pain Questionnaire, Hospital Anxiety and Depression Scale, CRPS severity score, Radboud Skills Questionnaire and questionnaires on Walking and Rising are listed in table 1.

#### General results of the SF-36

The SF-36 scores were substantially lower in the physical domains, in particular, in *Role Physical* and *Bodily Pain* sections, in comparison to the mental domains (Table 1).

#### QoL and gender differences

No difference in gender was found for the PHS (t(973)=0.728, p=.47), the MHS (t(973)=-.43, p=.67), or for any of the subdomains, although a trend was seen for *Vitality* (t(965)=2.81, p=.005) which just did not survive the correction for multiple comparisons (Table 2).

Table 2 SF-36 scores according to gender

| GE 26 1 :                 | 24.1         | - I          | 1 (: 40.005)         |
|---------------------------|--------------|--------------|----------------------|
| SF-36 domains             | Male         | Female       | p-value (sig.<0.005) |
| Physical functioning      | 45.88 (26.2) | 40.49 (25.8) | .018                 |
| Role physical             | 16.34 (30.5) | 18.48 (30.8) | .429                 |
| Bodily pain               | 28.27 (22.2) | 27.36 (20.2) | .608                 |
| General health            | 52.45 (22.0) | 52.00 (21.6) | .815                 |
| Physical health sum score | 35.86 (17.1) | 34.71 (18.2) | .467                 |
| Vitality                  | 51.38 (21.0) | 46.50 (19.6) | .005                 |
| Social functioning        | 59.89 (25.6) | 58.79 (27.0) | .639                 |
| Role emotional            | 54.08 (45.0) | 61.44 (44.1) | .059                 |
| Mental health             | 65.21 (19.3) | 67.44 (18.2) | .165                 |
| Mental health sum score   | 57.72 (20.9) | 58.51 (21.1) | .669                 |

SF-36 = MOS 36-Item Short-Form Healthy Survey. Numbers represent means (standard deviations); Domains were considered statistically different when p-value < 0.005 (Bonferroni corrected 0.05).

#### QoL and affected limb

Although no difference in MHS score was found between patients with 1 affected upper limb, 1 affected lower limb, or more than 1 affected limb (F(2,972)=1.84, p=.042) (Bonferronicorrected p-value, p<.017), analysis of the constituting domain scores indicated differences in *Vitality* (with patients with multiple affected limbs reporting lower scores than both other groups) and *Social Functioning* (with patients with an affected upper limb reporting higher scores than both other groups), but not in *Role Emotional* or *Mental Health* (table 3).

For the PHS a significant difference between the groups was found (F(2,972)=36.86, p<.001). Post-hoc analysis showed worse scores for patients with an affected lower limb in comparison to patients with an affected upper limb, with the lowest scores being found for

patients who had more than 1 affected limb. In addition, significant differences were foundfor all physical domain scores except *Role Physical*, with patients who had multiple affected limbs reporting lower scores than patients with 1 affected upper limb, but not than those with 1 affected lower limb

**Table 3** SF-36 scores of patients classified according to type of affected limbs.

|                           | 1                           | 0 71                        |                           |                 |
|---------------------------|-----------------------------|-----------------------------|---------------------------|-----------------|
|                           | 1                           | 2                           | 3                         | Omnibus p value |
| SF-36 domains             | 1 upper limb                | 1 lower limb                | >1 limb                   |                 |
| Physical functioning      | 57.85 (21.5) <sup>2,3</sup> | 32.55 (22.6) 1              | 28.23 (24.5) 1            | <.001           |
| Role physical             | 16.62 (29.1)                | 20.12 (32.0)                | 16.88 (31.2)              | .237            |
| Bodily pain               | 29.62 (22.2) <sup>3</sup>   | 27.44 (19.4)                | 23.55 (19.0) 1            | .004            |
| General health            | 56.35 (21.4) <sup>3</sup>   | 53.06 (20.9)                | 41.70 (20.4) 1            | <.001           |
| Physical health sum score | 40.33 (17.4) 2,3            | 33.36 (17.2) <sup>1,3</sup> | 27.62 (17.7) 1,2          | <.001           |
| Vitality                  | 50.26 (20.4) <sup>3</sup>   | 47.20 (19.3) <sup>3</sup>   | 41.75 (19.2) 1,2          | <.001           |
| Social functioning        | 65.39 (25.2) <sup>2,3</sup> | 54.98 (26.7) <sup>1</sup>   | 54.97 (27.8) <sup>1</sup> | <.001           |
| Role emotional            | 59.67 (44.0)                | 59.11 (44.6)                | 63.70 (44.2)              | .477            |
| Mental health             | 66.88 (18.5)                | 66.41 (18.4)                | 68.89 (18.2)              | .293            |
| Mental health sum score   | 60.53 (21.5)                | 56.93 (20.5)                | 57.30 (21.4)              | .042            |

SF-36 = MOS 36-Item Short-Form Healthy Survey. Numbers represent means (standard deviations); Domains were considered statistically different when p-value <.005 (Bonferroni corrected .05) Numbers in superscript indicating significant differences with other groups (p<0.017) for the same domain.

No significant differences in MHS or PHS were found between patients with 1 or 2 affected upper or lower limbs (all four P-values > .06).

#### QoL, disease duration and age

Correlations between of disease duration and age and with the various summary and domain scores were all weak (table 4). When we divided the patients in 3 approximately equal age-groups, namely  $\leq 40.0$ , 40.1-55.0,  $\geq 55.1$  years, it was apparent that the oldest CRPS patients had the highest PHS scores ( $32.73\pm16.53$ ,  $33.99\pm17.62$ ,  $38.33\pm19.47$ , respectively) (F(2,974)=8.24, p<.001) and the highest MHS scores ( $57.17\pm20.24$ ,  $56.68\pm21.77$ ,  $61.80\pm20.74$ , respectively) (F(2,974)=5.56, p=.004). Post-hoc analysis showed that only *Bodily Pain* (from the PHS) and *Vitality* (from the MHS) were significantly related to age.

#### QoL and pain

Correlations with the Numeric Rating Scale or McGill Pain Questionnaire were generally higher for the physical domain scores than for the mental domain scores, with the physical domain scores mostly showing moderate correlations with pain ratings. The highest correlations were found with the *Bodily Pain* scale (table 4).

**Table 4** Matrix showing correlations between OoL and other variables

| SF-36 domains             | Age      | Disease<br>duration | NRS       | MPQ       | Severity score |
|---------------------------|----------|---------------------|-----------|-----------|----------------|
| Physical functioning.     | 0.085    | -0.185 **           | -0.374 ** | -0.365 ** | -0.109 *       |
| Role physical             | 0.029    | 0.094 *             | -0.275 ** | -0.273 ** | -0.136 **      |
| Bodily pain               | 0.118 ** | 0.025               | -0.600 ** | -0.472 ** | -0.161 **      |
| General health            | 0.085    | -0.238 **           | -0.296 ** | -0.293 ** | -0.039         |
| Physical health sum score | 0.111*   | -0.095*             | -0.514**  | -0.472 ** | -0.158**       |
| Vitality                  | 0.205 ** | -0.122 **           | -0.305 ** | -0.392 ** | -0.086         |
| Social functioning        | 0.090    | -0.036              | -0.320 ** | -0.419 ** | -0.060         |
| Role emotional            | -0.014   | 0.116 **            | -0.157 ** | -0.188 ** | -0.021         |
| Mental health             | 0.049    | 0.055               | -0.204 ** | -0.275 ** | -0.026         |
| Mental health sum score   | 0.080    | 0.032               | -0.302 ** | -0.382 ** | -0.056         |

MPQ = McGill pain questionnaire; NRS = numeric rating scale; Qol = quality of life; SF-36 = MOS 36-Item Short-Form Health Survey, Pearson's correlation was considered significant when  $\star r = P < .005$ ,  $\star r = P < 0.001$ 

**Table 5** SF-36 scores of patients classified according to strictest criteria they fulfilled

|                           | 1                           | 0                         | ,                         |         |
|---------------------------|-----------------------------|---------------------------|---------------------------|---------|
|                           | 1                           | 2                         | 3                         | Omnibus |
| SF-36 domains             | Orlando                     | Bdp-c                     | Bdp-r                     | p value |
| Physical functioning      | 47.94 (26.2) <sup>3</sup>   | 42.36 (25.3) <sup>3</sup> | 36.75 (25.5) 12           | <.001   |
| Role physical             | 26.01 (35.9) <sup>2,3</sup> | 16.70 (29.7) <sup>1</sup> | 14.09 (26.8) 1            | <.001   |
| Bodily pain               | 34.96 (22.9) <sup>2,3</sup> | 25.97 (19.6) <sup>1</sup> | 23.72 (18.1) <sup>1</sup> | <.001   |
| General health            | 56.28 (22.2) <sup>3</sup>   | 51.74 (21.4)              | 49.66 (21.2) 1            | <.001   |
| Physical health sum score | 41.37 (20.3) 2,3            | 34.48 (17.7) 1            | 31.11 (15.4) 1            | <.001   |
| Vitality                  | 51.87 (20.1) <sup>2,3</sup> | 46.25 (19.7) 1            | 45.05 (19.5) <sup>1</sup> | <.001   |
| Social functioning        | 65.53 (27.3) <sup>2,3</sup> | 58.24 (26.5) 1            | 55.30 (26.0) 1            | <.001   |
| Role emotional            | 67.04 (42.3) <sup>2</sup>   | 55.74 (44.8) 1            | 58.54 (44.8)              | .009    |
| Mental health             | 68.47 (18.1)                | 66.51 (19.1)              | 66.55 (18.7)              | .337    |
| Mental health sum score   | 63.21 (20.9) 2,3            | 56.61 (21.3) 1            | 56.38 (20.6) 1            | <.001   |

SF-36 = MOS 36-Item Short-Form Healthy Survey. Numbers represent means (standard deviations); Domains were considered statistically different when p-value <.005 (Bonferroni corrected 0.05) Numbers in superscript indicating significant differences with other groups (p<0.017) for the same domain.

#### QoL and symptom severity

The CRPS severity score for patients affected in one limb significantly correlated with the PHS (r=-0.16, p<.001) but not with the MHS (r=-0.06, p=0.13) (table 4). Post-hoc analysis showed that the strongest correlations were found for *Physical Functioning*, *Role Physical* and *Bodily Pain*. However, when the patient group was divided in subgroups based on the set of CRPS criteria they fulfilled, correlations were no longer significant.

#### OoL and CRPS criteria

Table 5 shows the data of the MHS and PHS for patients meeting the different sets of diagnostic criteria. A significant difference between the groups emerged for MHS (F(2,972)=10.4, p<.001) and PHS (F(2,972)=29.6, p<.001), with the post-hoc analysis showing a significantly higher MHS and PHS for the Orlando group than the Bdp-c or Bdp-r group, while no difference was found between both Budapest groups.

#### **DISCUSSION**

This study examined QoL in a large group of almost a 1000 Dutch patients with CRPS. We observed the following: 1) QoL in CRPS patients was mostly determined by the loss of physical capabilities, and less so by mental complaints; 2) no gender differences in QoL of patients with CRPS; were found 3) CRPS patients with an affected lower limb have worse PHS scores than patients with an affected upper limb; 4) pain intensity is moderately associated with both the PHS and MHS of the SF-36 in CRPS; 5) correlations between QoL and symptom severity were weak for the PHS, and absent for the MHS; and 6) patients meeting the Budapest diagnostic criteria have worse QoL as compared to patients meeting the Orlando criteria, underscoring the impact of different sets of criteria on sample characteristics.

#### QoL, type of affected limb, and physical functioning

Although, in CRPS patients, both PHS and MHS are lower than in the general population<sup>83</sup>, our findings indicate that patients are burdened mainly by the physical consequences of CRPS.

PHS was lower in patients with an affected lower limb as compared to patients with an affected upper limb, which was largely due to the lower scores in the *Physical Functioning* domain. This finding is likely explained by a bias of this domain towards lower limb functions: 9 out of 10 *Physical Functioning* items apply to lower limb function, whereas only 4 of 10 apply to upper limb function. Nevertheless, as illustrated by the scores of the Radboud Skills Questionnaire and questionnaires on Walking and Rising, CRPS is associated with severe disability, which corresponds with findings of others showing that a large proportion of CRPS patients experience partial or complete inability to resume their former job 10,73.

Clear explanations for the poor physical functioning of CRPS patients cannot be inferred from this study and are still a major question mark in CRPS research. The small but significant negative correlation between disease duration and *Physical Functioning* shows at least that long-term CRPS may have a negative effect on physical function. A role for kinesiophobia, often hypothesised to have a strong negative influence on physical function in CRPS, could

not be confirmed in recent studies<sup>8485</sup>; instead a negative association of functional limitations with perceived harmfulness of activities and "resting" as a pain coping strategy was found. This seems to point out that patient's attitude and behaviour towards pain is a very important aspect in the physical impairments they experience. In line with these findings, new therapies for CRPS patients are being developed focussing on improvement of physical function rather than pain reduction<sup>84,86</sup>. The question, however, remains why precisely CRPS patients show these low *Physical Functioning* and *Role Physical* scores, which are lower than scores in other musculoskeletal or neuropathic pain conditions, such as rheumatoid arthritis<sup>82</sup>, neuralgic amyotrophy patients<sup>87</sup>, and lower limb amputees with or without phantom limb pain<sup>82,88,89</sup>. Only fibromyalgia patients exhibit worse scores in many domains<sup>90</sup>, however, in contrast to fibromyalgia, in which the condition also greatly affects mental health<sup>90</sup>, QoL of CRPS patients is best explained by the impact of the condition on physical health. This is further substantiated by the fact that the Hospital Anxiety and Depression Scale scores in this cohort were considerably better than in a large group of fibromyalgia patients<sup>91</sup>.

In previous studies, it has often been assumed that physical complaints experienced by CRPS patients start off initially with an aberrant host response to tissue damage that triggers a cascade of reactions leading to peripheral and central sensitization, which may have profound and prolonged influence on pain and function, although the precise mechanisms are not clear<sup>52</sup>. In addition, CRPS is associated with central changes in sensorimotor cortical networks<sup>40</sup>, which may further add to functional limitations.

#### QoL and gender

We found no difference in QoL between males and female CRPS patients. This is in contrast with the somewhat worse scores found for women in the general Dutch population<sup>92</sup> and with the results of many studies on QoL in the chronically ill (see Sprangers et al<sup>93</sup> for a review on QoL in a range of different chronic patient groups). The pain scores of men and women were also similar, which again is quite remarkable if one considers that women generally have less efficient pain inhibitory controls than men<sup>73</sup>. Hypothetically this might indicate that once men are afflicted with CRPS, the characteristics of CRPS have the same impact on QoL as in females.

#### QoL and age

In this study, younger CRPS patients exhibited lower QoL scores than older CRPS patients. Given that we found no difference in the CRPS severity score between age groups:  $\leq$ 40 years (10.6 $\pm$ 3.57), 40.1–55.0 years (10.6 $\pm$ 3.52) and  $\geq$ 55.1 years (10.1 $\pm$ 3.45), p=.24, one may speculate that this could be due to the more demanding societal activities with which younger people tend to be confronted (e.g. work, family duties), which can be severely hindered by CRPS. However, conclusions drawn from these results must be interpreted with

caution, given the cross-sectional nature of this study and the facts that absolute differences were small and correlations between the SF-36 domains and age were weak.

#### QoL and pain

Pain scores correlated moderately with the PHS and MHS. Although one might have expected these correlations to be stronger, it is known that pain intensity is a moderate predictor of disabilitie<sup>3</sup> and that pain reduction per se does not necessarily result in a significant increase in *Physical Functioning*<sup>94</sup>, the domain with 1 of the lowest scores in our patient group. In our data, the correlation between the Numeric Rating Scale or McGill Pain Questionnaire and *Physical Functioning* or *Role Physical* was not strong.

#### OoL and CRPS criteria and severity

It is again noteworthy that of all patients who fulfil the Orlando criteria, only two thirds fulfilled the Bdp-c criteria whereas less than one-half met the Bdp-r criteria. It is obvious that criteria matter. The main difference between the Orlando criteria (the former IASP criteria) and the Bdp-c and Bdp-r criteria is, besides the inclusion of signs, the addition of motor symptoms and signs to the Budapest criteria. Therefore it is not surprising that patients who fulfilled the Budapest criteria had lower QoL scores and, in particular, lower PHS scores, than patients who fulfilled the Orlando criteria.

CRPS severity measured with the number of signs and symptoms showed only weak correlation with the PHS. These correlations were lower than those in a study that found significant correlations between all SF-36 domains (except *General Health*) and the CRPS severity score<sup>75</sup>. We have no clear explanation for this difference, especially as scores on the PHS domains were remarkably similar to those in our study. Still, the reported correlations in that paper were generally weak as well. This once more underlines that relations between impairments and disabilities are not as direct and strong as one might expect. The physical consequences of having a complex pain *syndrome* are apparently much more complicated than can be inferred from a simple summation of the associated signs and symptoms.

#### Limitations

Several aspects should be taken into account when interpreting the results of this study. First, the institutes that participated in this study are nearly all specialised academic centres, and generalization of the results is therefore limited. However, due to the complexity of the diagnosis and treatment of the condition, CRPS patients are generally referred to specialised clinics, which, in the case of The Netherlands, are often academic centres, which makes selection towards more severely affected cases in the present study less likely. Nevertheless, an earlier study in The Netherlands reported that about 25% of patients are not seen by a medical specialist but only by their general practitioner<sup>4</sup>, and therefore selection bias cannot

be ruled out completely. In addition, different specialists were involved in the collection of information on signs and symptoms, and although measures to reduce variability in assessment were imposed, this may have led to some residual inaccuracy.

To summarize, this is, to our knowledge, the largest report on QoL in patients with CRPS. The study shows that CRPS patients generally report a poorer QoL than patients with other chronic pain conditions, particularly in the physical domains. Gender and the type of affected limb do not influence QoL. In contrast, the diagnostic criteria used do matter: patients fulfilling stricter criteria (i.e., the Budapest criteria) had lower QoL scores than patient's fulfilling the Orlando criteria. Finally, pain scores correlated moderately with QoL, underscoring the need for further studies aimed at improving pain management in CRPS.

#### Acknowledgements

This study was performed within TREND (www.trendconsortium.nl) and supported by a grant from the Netherlands' Ministry of Economic Affairs [grant number BSIK03016].

The authors report no conflicts of interest that pertain to the subject of this study.