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ORIGINAL REPORT

GENERALIZED PAIN IS ASSOCIATED WITH MORE NEGATIVE CONSEQUENCES THAN LOCAL OR REGIONAL PAIN: A STUDY OF CHRONIC WHIPLASH-ASSOCIATED DISORDERS

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Objective: **The main aims of this study were: (*i*) to determine, for chronic whiplash-associated disorders, whether widespread pain has more severe consequences for other symptoms and different aspects of perceived health than does local/regional pain; (*ii*) to investigate whether pain, depression, and symptoms not directly related to pain are intercorrelated and to what extent these symptoms correlate with catastrophizing according to the Coping Strategy Questionnaire.**

Design: **Descriptive cross-sectional study.**

Patients: **A total of 275 consecutive chronic pain patients with whiplash-associated disorders who were referred to a university hospital.**

Methods: **Background history, Beck Depression Inventory, Coping Strategy Questionnaire, Life Satisfaction Checklist, the SF-36 Health Survey and EuroQol were used to collect data.**

Results: **Spreading of pain was associated with negative consequences with respect to pain intensity and prevalence of other symptoms, life satisfaction/quality and general health. The subjects differ with respect to the presence of symptoms not directly related to pain. A minor part of the variation in Back Depression Inventory was explained by direct aspects of pain, indicating that, to some extent, generalization of pain is related to catastrophizing thoughts.**

Conclusion: **Widespread pain was associated with negative consequences with respect to pain intensity, prevalence of other symptoms including depressive symptoms, some aspects of coping, life satisfaction and general health.**

Key words: neck, whiplash, generalized pain, neuroplasticity, depression, catastrophizing.

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INTRODUCTION

Sudden changes in acceleration or deceleration due to impact (i.e. whiplash trauma) can affect the neck and, under certain circumstances, can cause acute stiffness and neck-shoulder pain (acute whiplash-associated disorder, WAD). Back pain, paraesthesiae, weakness in the arms, dysphagia, visual and auditory disturbances, tinnitus, and vertigo may sometimes be present in the acute phase. The majority of subjects with acute WAD will be cured within 3 months of the trauma (1), but for a minority the acute neck pain may develop into chronic pain.

Although different patho-anatomical disturbances have been reported (2), there is no consensus in the literature concerning peripheral patho-anatomical alterations in the chronic stage. It is unclear whether the central nervous system (CNS) can preserve pain experiences without a nociceptive input from the periphery in the chronic stage. Neurobiological networks in the brain process nociceptive input. This processing interacts with psychological factors and dependent on the environmental situation. The neurobiological systems of nociception and pain are plastic; i.e. when submitted to significant nociception, the function may change in different ways (for example, wind-up, classic central sensitization, long-term potentiation, changed cortical representation and changed descending mechanisms) (3, 4). The total sensitivity and gain of the pain system will be determined in combination with the influences of psychological factors and the environmental context. In addition, pain interacts with motor control, immunological and endocrinological systems. In most cases plastic changes, such as peripheral and central sensitization, diminish as a response to the recovery of the affected tissue. Hence a complex pattern of factors determines the multifaceted perception of pain and pain behaviours in a specific situation. The central and peripheral pain systems as well as the tissues could be seen as an integrated system, and the role of either of these parts could vary individually in chronic pain. Pharmacological challenges of chronic WAD indicate that heterogeneous conditions with different pain mechanisms are activated (5). It is a clinical experience that some patients with chronic WAD also develop widespread pain. Fibromyalgia has been discussed as a possible negative consequence of trauma to the neck. In a controlled study, it was reported that fibromyalgia was significantly more frequent following neck injury (22%) than following lower extremity fracture (1%) (6). In a study of female home-care personnel, pain in the neck and shoulders was associated more often with pain in areas other than the lower back (7). In a general population sample, the total number of areas on a pain drawing increased with increased pain in the neck-shoulder area (8). Pain in several anatomical regions appears to be a risk factor

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for chronic pain (for references see (9)). Studies of other groups of patients with chronic widespread pain (not due to trauma) report high levels of disability and low quality of life compared with those with chronic local or regional pain (7, 9, 10).

Passive coping, including catastrophizing, is strongly associated with depression, slowed recovery, chronic pain, disability and poor outcome (11–14). Such associations generally persist when controlling for depression (13, 14). In a longitudinal study of WAD, the catastrophizing item of the Coping Strategy Questionnaire (CSQ) contributed significantly to emotional distress (15). The role of *active* coping strategies for health and disability is not clear (11–13).

A high prevalence of depression is found in individuals with chronic pain and is reported to be associated with higher levels of pain and disability (for references see (16)). Depressed patients appear to be more prone to use passive strategies than non-depressive patients (17). We reported recently that aspects of health and health-related quality of life in chronic WAD correlate with degree of depression, number of not directly pain-related symptoms, and catastrophizing, followed by pain intensities (11). Even though a low proportion of patients scored a more serious depressive state, depression was important for low well-beeing. Chronic widespread pain is associated with increased frequency of different physical and psychological symptoms (18, 19).

A recent review of conservative treatments for WAD concluded that there was a lack of clinical evidence with respect to treatment of patients with chronic WAD (20). One possible interpretation is that the complexity and heterogeneity of WAD makes optimal interventions difficult. A more differentiated and deeper understanding of the complexity of WAD might be needed in order to develop more effective treatments and rehabilitation programmes.

Aims

The present cross-sectional study of consecutive patients with WAD referred to a pain and rehabilitation centre at a university hospital aimed to answer the following questions:

- Does chronic WAD with widespread pain have more severe consequences with respect to other symptoms, coping strategies, and different aspects of perceived health than chronic WAD with local/regional pain?
- Do pain, depression, and symptoms that are not directly pain-related intercorrelate, and to what extent do these symptoms correlate with catastrophizing?

METHODS

Subjects

A total of 275 subjects were recruited for this cross-sectional study from consecutive patients seeking care at the Pain and Rehabilitation Centre of the University Hospital, Linköping, Sweden. Patients fulfilling the criteria of WAD were included in the study. Diagnoses of chronic WAD were established from the patients' case histories and clinical examinations. Radiological evaluation (X-ray, magnetic resonance imaging) was performed only when there was a suspicion of skeletal damage or disc herniation.

Methods

Each patient received a questionnaire shortly before examination at the centre. The questionnaire was completed at home and delivered to the physician at the visit to the centre. The questionnaire contained the following items and instruments:

- Age, gender, and anthropometrical data.
- Number of days sick leave during the previous 12 months, number of months out of work, degree of sick leave (0%, 25%, 50%, 75% or 100%), degree of disability pension (0%, 25%, 50%, 75% or 100%) and number of visits to physician recent 6 months.
- Pain intensity ratings at 11 pre-defined anatomical regions (11). For the rating of pain intensity, a visual analogue scale (VAS) was used; the scale was 100 mm long with defined end-points ("no pain" and "worst pain imaginable") but without marks in between (results in cm). All the questions regarding pain concerned the previous 7 days.
- Number of the above pre-defined anatomical regions associated with pain (Pain Regions Index (PRI) with possible range: 0–11).
- Presence of other pain-related symptoms: pain radiating to the arm(s), pain radiating to the leg(s), headache, perception of heavy head and pain in the throat. For each of these symptoms, the patients chose from the following alternatives: 0 = "no, never", 1 = "no, seldom", 2 = "yes, occasionally", and 3 = "yes, often". In the analyses and tables these symptoms were dichotomized (0–2 vs 3).
- The Beck Depression Inventory (BDI) (21) evaluates 21 symptoms of depression into a scale ranging from 0 to 63. A score of less than 10 indicates no or minimal depression, 10–18 indicates mild to moderate depression, 19–29 indicates moderate to severe depression, and 30 or more indicates severe depression. For psychiatric patients, a screening cut-off point of 12/13 is suitable, whereas 9/10 is appropriate in screening medical patients (used in the present study).
- A total of 31 different symptoms – not directly pain-related – were registered: sleeping difficulties, tachycardia, bowel problems, gastritis, fatigue-tiredness, weak voice, nausea, anxiety, difficulty with changes in light intensity, concentration problems, hoarseness, difficulty with swallowing, difficulty with urinating, vertigo, numbness in hands, changed perception hands, blurred vision, defecation problems, sound sensitivity, changes in alcohol sensitivity, light sensitivity, feeling of fullness of ear, irritable, memory problems, diminished field of vision, low mood, changed perception of touch in the legs, difficulty with control of legs, fatigue in the legs, twitches in the legs, and difficulty walking down stairs. For each symptom the patients chose from the following alternatives: 0 = "no, never", 1 = "no, seldom", 2 = "yes, occasionally", and 3 = "yes, often". In the analyses and tables, these symptoms were dichotomized (0–2 vs 3).
- An index that counted the number of the above symptoms that were not directly pain-related (in the dichotomized form) was also computed (Non Pain Symptoms Index (NPSI); possible range 0–31).
- The CSQ (22) is often used to measure how patients cope with pain and includes 8 types of coping strategies with the aim of describing this. These coping strategies are diverting attention, re-interpreting pain sensation, coping self-statements, ignoring pain sensations, praying and hoping, catastrophizing, increased behavioural activities, and pain behaviour. Each strategy is evaluated according to its frequency of use, ranging from "never" (0) to "always" (6) with a maximum score of 36. Two additional questions concern the perception of control and possibility of minimizing pain (not used in the present study). The Swedish version of the CSQ was used in the present study.
- The instrument Life Satisfaction Questionnaire (LiSat-11) (23) consisted of estimations of life satisfaction in general as well as 10 specific domains to be estimated: satisfaction with vocational situation, financial situation, leisure situation, contact with friends and acquaintances, sexual life, activities of daily living (ADL), family life, and partnership. Two additional variables were added to this list: satisfaction with physical and psychological health. Each item has 6 possible answers: 1 = "very dissatisfying", 2 = "dissatisfying",

3 = "fairly dissatisfying", 4 = "fairly satisfying", 5 = "satisfying", and 6 = "very satisfying".

- SF-36 Health Survey (Swedish version) is an instrument that intends to give a representation of multi-dimensional health concepts and measurements of the full range of health states, including levels of well-being and personal evaluations of health (24). The instrument comprises 36 questions covering 8 items or dimensions: physical functioning, role limitations due to physical pain, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Each item score is coded, summed and transformed to a standardized scale calculated from a specific score algorithm (ranging from 0 to 100 with 2 end-points identified as "worst" and "best" possible health state). The transformed score has been used in this study.
- The EuroQol instrument (25) captures a patient's perceived state of health. A state of health is defined as combinations of 5 dimensions and 3 levels of choice (no problems, some problems, or severe problems) for each dimension: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This descriptive system covers the first part of the instrument. The answers are coded (1–3). The codings are transformed by a table or by using an algorithm to score the findings (EQ-5D). A second part concerns a self-estimation of today's health according to a 100-point scale, a "thermometer" (EQ-VAS) with defined end-points (high value indicates good health and low value indicates bad health). Thus the 2 parts comprise different aspects related to health as quality of life. In this study the total score (EQ-5D) and the self-estimation scale (EQ-VAS) are reported.

Statistics

SPSS (version 12.0) and SIMCA-P (version 10.2) software were used for statistical evaluations. Results are generally given as mean values with 1 standard deviation (1 SD). Kruskal-Wallis and Mann-Whitney tests were used to test differences between groups (i.e. as *post hoc* tests). χ^2 test was used to analyse whether groups had different distributions. Spearman's rho was used to test bivariate correlations.

Principal component analysis (PCA) using SIMCA-P was used to extract and display systematic variation in a data matrix and is a multivariate correlation analysis. A component consists of a vector of numerical values between –1 and 1, referred to as loadings and obtained significant components are uncorrelated. Variables that have high loadings (with a positive or negative sign) on the same component are inter-correlated. Items with high loadings (ignoring the sign) are considered to be of great or moderate importance for the component under consideration.

Partial least squares or projection to latent structures (PLS) were used to regress one or several Y-variables using several other variables (X-variables) (26). The variable influence on projection (VIP) parameter gives information about the relevance of each X- and Y-variable pooled over all dimensions. Thus the VIP parameter gives information about the relevance of each X variable, both for the X- and Y-model parts. X- variables with a VIP ≥ 1.0 are most influential for the model**.** The PLS regression coefficients may be re-expressed as a regression model and express the influence of each X-variable on Y in each single component. In the present study, the variable of importance for explaining Y was primarily identified by a VIP value ≥ 1.0 and secondarily by the regression coefficient in relation to Y. Multiple linear regression (MLR) could have been an alternative method for the prediction, but it assumes that the regressors (X-variables) are independent and only 1 Y-variable at a time can be predicted. If multi-collinearity (high correlations) occurs among the X-variables, the calculated regression coefficients become unstable and their interpretability breaks down (26). PLS and PCA also have the advantages that they do not require interval-scale measurements are not sensitive to violations of multivariate normality (27).

Two concepts are further used to describe the results: R^2 and Q^2. R^2 describes goodness of fit (the fraction of sum of squares of all the variables explained by a principal component). Q^2 describes goodness of prediction (the fraction of the total variation of the variables that can be predicted by a principal component using cross-validation methods) (26). Outliers were identified using the 2 powerful methods available in SIMCA-P: score plots in combination with Hotelling's T^2 (identifies strong outliers) and distance to model in X-space (identifies moderate outliers).

In all statistical analysis, $p \leq 0.05$ was regarded as significant.

RESULTS

This article is the second report from our cohort of patients with chronic WAD. Mean values for the different variables and indices were published previously (11) (Table I).

Formation of 3 subgroups based on number of regions with pain (PRI)

The WAD cohort was divided into 3 subgroups based on PRI (group 1: 0–3 regions ($n = 45$; 17%); group 2: 4–7 regions

Table IA–C. *Groups based on Pain Regions Index (group 1 = 0–3 anatomical regions engaged (n = 45); group 2 = 4–7 anatomical regions engaged (n = 152) and group 3 = 8–11 anatomical regions engaged (n = 74)) (above the dotted line). The left-hand columns show given mean values and standard deviation (SD) for all subjects taken together; note that the mean values for the group as a whole has been published earlier in the first report from this cohort (11). The 3 groups have been compared with respect to (Table IA) background data, (Table IB) symptoms and (Table IC) coping strategies and health related to quality of life issues (LiSat-11, SF36 and EuroQol).*

A

Variables	Group 1 Mean (SD)	Group 2 Mean (SD)	Group 3 Mean (SD)	*p*-value
Number of pain regions	2.4 (0.8)	5.5 (1.1)	9.0 (1.1)	< 0.001
Background data				
Age (years)	38.2 (12.4)	38.2 (11.7)	38.3 (11.1)	ns
Gender (% women)	62.8	62.5	71.8	ns
Weight (kg)	72.9 (15.0)	74.0 (16.0)	70.4 (14.0)	ns
Length (cm)	172.8 (9.1)	173.2 (9.2)	168.6 (8.6)	0.001
Months since in occupation	10.6 (10.1)	24.1 (39.2)	16.2 15.1)	ns
Days sick leave last 12 months	165 (146)	200 (143)	238 (139)	ns
Degree of sick leave (%)	59 (44)	60 (46)	56 (47)	ns
Degree of disability pension (%)	8 (27)	17 (37)	30 (43)	0.002
Visits to physicians (*n*)	3.2 (2.3)	3.7 (2.5)	4.3 (3.0)	ns

p-values are given if significant.

(n = 152; 56%); and group 3: 8–11 regions (n = 74; 27%) (Table IA). Very similar results with respect to the different consequences reported below were obtained when cluster analysis was made (not presented).

Background data. Somewhat (non-significant) higher proportions of women were found in the group with highest PRI (group 3; Table IA). There was a significant difference in degree of disability pension between groups (highest prevalence in group 3).

Pain symptoms. Pain intensity in the head, the neck and shoulders, and the lower back differed significantly between the 3 groups (Table IB). The frequencies of radiation to arms and legs were highest in group 3 and lowest in group 1. No significant differences were found for the other pain-related symptoms displayed in Table IB.

Not directly pain-related symptoms including depression. In the whole cohort, the proportion with a score ≥ 10 on the BDI (i.e. at least mild to moderate depression) was 55.9% and with

Table IB. *Groups based on Pain Regions Index contd.*

Variables	Group 1 Mean (SD)	Group 2 Mean (SD)	Group 3 Mean (SD)	p-value
Number of pain regions	2.4 (0.8)	5.5 (1.1)	9.0 (1.1)	< 0.001
Pain symptoms				
Pain intensity – Head	5.4 (2.1)	5.7 (2.1)	6.5 (2.1)	0.009
Pain intensity – Neck	5.4 (1.8)	6.1 (2.1)	6.9 (1.8)	< 0.001
Pain intensity – Shoulders	4.5 (1.9)	5.3 (2.2)	6.2 (2.2)	0.004
Pain intensity – Hands	3.5 (2.9)	4.4 (2.5)	4.9 (2.6)	ns
Pain intensity – Upper Back	4.4 (1.3)	5.1 (2.3)	5.8 (2.5)	ns
Pain intensity – Lower back	4.3 (1.1)	4.4 (2.6)	5.6 (2.6)	0.010
Pain radiation arm*	0.2 (0.4)	0.4 (0.5)	0.7 (0.5)	< 0.001
Pain radiation leg*	0.0 (0.0)	0.2 (0.4)	0.4 (0.5)	< 0.001
Headache*	0.55 (0.50)	0.62 (0.49)	0.64 (0.48)	ns
Perception of heavy head*	0.46 (0.50)	0.53 (0.50)	0.56 (0.50)	ns
Pain in the throat*	0.02 (0.15)	0.05 (0.22)	0.07 (0.26)	ns
Non-pain symptoms				
BDI	8.7 (4.8)	14.4 (8.0)	17.0 (9.8)	< 0.001
NPSI	3.4 (3.6)	5.2 (4.5)	5.9 (4.6)	0.027
Sleeping difficulties*	0.30 (0.46)	0.54 (0.50)	0.49 (0.50)	0.020
Tachycardia*	0.02 (0.16)	0.04 (0.20)	0.03 (0.17)	ns
Bowel problems*	0.07 (0.26)	0.16 (0.37)	0.10 (0.30)	ns
Gastritis*	0.07 (0.26)	0.15 (0.36)	0.15 (0.36)	ns
Fatigue-tiredness*	0.49 (0.51)	0.67 (0.47)	0.75 (0.43)	0.014
Weak voice*	0.03 (0.16)	0.04 (0.19)	0.03 (0.17)	ns
Nausea*	0.14 (0.35)	0.14 (0.35)	0.13 (0.33)	ns
Anxiety*	0.10 (0.30)	0.10 (0.30)	0.11 (0.32)	ns
Difficulty with changes in light intensity*	0.17 (0.38)	0.25 (0.44)	0.14 (0.35)	ns
Concentration problems*	0.35 (0.48)	0.39 (0.49)	0.40 (0.49)	ns
Hoarseness*	0.05 (0.22)	0.05 (0.22)	0.03 (0.17)	ns
Difficulty with swallowing*	0.02 (0.15)	0.04 (0.20)	0.08 (0.28)	ns
Difficulty with urinating*	0.05 (0.22)	0.03 (0.18)	0.09 (0.28)	ns
Vertigo*	0.28 (0.45)	0.34 (0.48)	0.29 (0.46)	ns
Numbness in hands*	0.41 (0.50)	0.42 (0.50)	0.36 (0.48)	ns
Changed perception hands*	0.33 (0.48)	0.29 (0.46)	0.30 (0.46)	ns
Blurred vision*	0.12 (0.33)	0.13 (0.34)	0.12 (0.33)	ns
Defecation problems*	0.07 (0.26)	0.09 (0.29)	0.04 (0.20)	ns
Sound sensitivity*	0.15 (0.36)	0.23 (0.43)	0.26 (0.44)	ns
Changes in alcohol sensitivity*	0.08 (0.28)	0.12 (0.33)	0.15 (0.36)	ns
Light sensitivity*	0.14 (0.35)	0.21 (0.41)	0.15 (0.36)	ns
Feeling of fullness of ear*	0.09 (0.29)	0.10 (0.31)	0.22 (0.42)	ns
Irritable*	0.28 (0.45)	0.40 (0.49)	0.51 (0.50)	ns
Memory problem*	0.28 (0.45)	0.33 (0.47)	0.44 (0.50)	0.043
Diminished field of vision*	0.05 (0.23)	0.10 (0.30)	0.05 (0.21)	ns
Low mood*	0.10 (0.30)	0.24 (0.43)	0.24 (0.43)	ns
Changed perception of touch in the legs*	0.12 (0.33)	0.14 (0.35)	0.10 (0.30)	ns
Difficulty with control of legs*	0.02 (0.16)	0.08 (0.28)	0.04 (0.20)	ns
Fatigue in legs*	0.05 (0.23)	0.12 (0.32)	0.14 (0.35)	ns
Twitches in the legs*	0.00 (0.00)	0.05 (0.21)	0.01 (0.12)	ns
Difficulty walking down stairs*	0.13 (0.34)	0.14 (0.35)	0.10 (0.30)	ns

*Yes, often: 1, and other alternatives: 0. BDI: Beck Depression Inventory; NPSI: Non Pain Symptoms Index (ns denotes no significant difference).

≥ 19 on BDI (i.e. at least moderate to severe depression) was 23.6%. The BDI differed between the 3 groups ($p < 0.001$) (Table IB). The proportion of subjects with a score ≥ 10 on the BDI was 36.4% in group 1, 68.7% in group 2, and 78.1% in group 3. Corresponding figures for a score ≥ 19 on BDI were 2.3%, 24.7% and 34.2% respectively.

The NPSI differed significantly between the 3 groups ($p = 0.027$); group 1 had the lowest number of symptoms (Table IB). The individual items that differed between the 3 groups were sleeping difficulties ($p = 0.020$), fatigue-tiredness ($p = 0.014$), and memory problems ($p = 0.043$) (Table IB).

Coping Strategy Questionnaire (CSQ). Significant differences were found for 2 of the subscales of CSQ (Table IC). Group 3 with high PRI showed highest values both for the catastrophizing ($p = 0.013$) and the reinterpret pain sensation ($p = 0.023$) subscales and group 1 (low PRI) had the lowest values (Table IC).

Aspects of life satisfaction and generic health. Eight out of 11 scales of the LiSat-11 showed significant differences between the 3 groups; no significant differences were found for the subscales vocational situation, sexual life, and partnership relations (Table IC). According to SF-36, all scales except "Role physical" differed between the 3 groups even though a similar trend was found for the other scales (Table IC). EQ-5D ($p < 0.001$) and EQ-VAS ($p < 0.001$) differed between the 3 groups; i.e. group 1 had the best situation and group 3 the worst situation (Table IC).

Conclusions with respect to the first aim. Widespread pain in chronic WAD was associated with more negative consequences with respect to pain intensity, prevalence of other symptoms (including depressive symptoms), some aspects of coping, life satisfaction/quality, and general health than was local or regional pain in chronic WAD.

Correlations between symptoms and with catastrophizing

Correlations between symptoms. According to the univariate analyses, PRI correlated weakly but significantly with BDI (rho = 0.298, $p < 0.001$) and NPI (rho = 0.174, $p = 0.022$). No significant correlations existed between BDI and NPSI (rho = 0.128, $p = 0.098$).

Table IC. *Groups based on Pain Regions Index contd.*

Variables	Group 1 Mean (SD)	Group 2 Mean (SD)	Group 3 Mean (SD)	*p*-value
Number of pain regions	2.4 (0.8)	5.5 (1.1)	9.0 (1.1)	< 0.001
Coping Strategy Questionnaire				
Diverting attention	10.3 (7.1)	12.1 (7.5)	13.3 (7.1)	ns
Reinterpret pain sensations	4.4 (6.0)	6.3 (6.9)	7.9 (7.3)	0.023
Coping self-statement	16.6 (8.2)	16.1 (7.9)	15.7 (7.2)	ns
Ignoring pain sensations	12.6 (7.7)	12.9 (7.7)	13.8 (6.9)	ns
Praying or hoping	11.0 (6.8)	12.7 (8.0)	13.4 (7.5)	ns
Catastrophizing	11.2 (7.9)	13.8 (7.8)	15.7 (7.6)	0.013
Increased behavioural activities	14.0 (7.8)	12.8 (6.8)	14.1 (6.5)	ns
Scales of LiSat-11				
Life as a whole	4.5 (1.2)	3.7 (1.3)	3.4 (1.4)	< 0.001
Vocational situation	3.4 (1.7)	3.0 (1.7)	2.6 (1.7)	ns
Financial situation	4.2 (0.8)	3.6 (1.5)	3.3 (1.5)	0.007
Leisure	4.1 (1.3)	3.3 (1.5)	2.9 (1.4)	< 0.001
Contacts with friends	4.9 (1.4)	4.2 (1.4)	3.6 (1.5)	< 0.001
Sexual life	4.0 (1.3)	3.7 (1.7)	3.3 (1.7)	ns
ADL	5.5 (1.2)	4.9 (1.2)	4.0 (1.4)	< 0.001
Family life	5.3 (0.8)	4.7 (1.3)	4.6 (1.3)	0.010
Partnership relations	4.6 (1.5)	4.5 (1.6)	4.2 (1.6)	ns
Physical health	3.3 (1.5)	2.6 (1.3)	2.0 (1.2)	< 0.001
Psychological health	4.4 (1.1)	3.7 (1.4)	3.6 (1.2)	0.003
SF36				
Physical functioning	70.1 (16.3)	59.8 (24.6)	45.9 (23.9)	< 0.001
Role physical	19.4 (33.7)	10.8 (26.1)	8.7 (24.2)	ns
Bodily pain	32.5 (16.5)	23.8 (14.2)	21.1 (14.8)	0.004
General health	59.2 (18.2)	44.5 (19.2)	34.0 (20.1)	< 0.001
Vitality	43.0 (20.8)	28.7 (19.2)	22.8 (16.8)	< 0.001
Social functioning	72.1 (25.6)	56.9 (29.5)	45.6 (23.9)	< 0.001
Role emotional	67.5 (42.0)	47.4 (45.9)	52.2 (45.9)	0.026
Mental health	72.7 (18.7)	59.4 (22.2)	58.4 (18.5)	< 0.001
EuroQol				
EQ-5D	0.4 (0.3)	0.3 (0.3)	0.2 (0.3)	< 0.001
EQ-VAS	54.8 (17.5)	39.7 (18.9)	34.8 (20.8)	< 0.001

ADL: activities of daily living; LiSat: Life Satisfaction Checklist; SF36: Short-Form 36-Item Health Survey; EQ: EuroQol.

To understand the multivariate correlation pattern of the different symptoms and related indices (i.e. the variables displayed in Table IB together with sex), a PCA was made. The significant model obtained ($R^2 = 0.24$, $Q^2 = 0.15$) consisted of 2 components (Table II). According to the first component (p1), NPSI and some of the different non-pain symptoms (difficulty with changes in light intensity, concentration problems, fatigue-tiredness, sound sensitivity, and light sensitivity) intercorrelated. Because NPSI and the different not directly pain-related symptoms loaded on the first component explaining most of the variation in the data matrix, it can be concluded that subjects differ relatively prominently with respect to the presence of such symptoms. It can be argued that NPSI and the different not directly pain-related symptoms must correlate; however, when omitting the NPSI from the analysis, the same principal pattern was found (not shown).

Table II. *Principal component analysis of the different symptoms and indices related to symptoms. A 2-component (p1 and p2) model was obtained ($R^2 = 0.24$). Loadings of importance for each component are in bold type. The bottom row shows the variation (R^2) of each component.*

Variables	*p[1]*	*p[2]*
Sex	0.01	0.04
Pain intensity – head	–0.04	**–0.33**
Pain intensity – neck	–0.04	**–0.37**
Pain intensity – shoulders	–0.02	**–0.37**
Pain intensity – hands	0.00	**–0.35**
Pain intensity – upper back	–0.06	**–0.33**
Pain intensity – lower back	–0.05	**–0.34**
Pain radiation arm	–0.02	**–0.23**
Pain radiation leg	–0.07	**–0.19**
PRI	–0.05	**–0.22**
BDI	–0.03	**–0.17**
NPSI	**–0.35**	0.01
Headache	–0.14	0.03
Sleeping difficulties	–0.16	–0.01
Tachycardia	–0.11	0.00
Bowel problems	–0.06	–0.02
Gastritis	–0.10	0.01
Fatigue/tiredness	**–0.22**	–0.07
Perception of heavy head	**–0.21**	0.00
Weak voice	–0.06	0.07
Nausea	–0.10	0.08
Anxiety	–0.08	–0.05
Difficulty with changes in light intensity	**–0.23**	0.04
Concentration problems	**–0.23**	–0.01
Hoarseness	–0.14	0.06
Pain in the throat	–0.11	0.06
Difficulty with swallowing	–0.10	0.03
Difficulty with urinating	–0.12	0.05
Vertigo	–0.19	0.04
Numbness in hands	–0.19	0.05
Changed perception hands	–0.19	0.08
Blurred vision	–0.15	0.05
Defecation problems	–0.08	0.01
Sound sensitivity	**–0.22**	–0.02
Changes in alcohol sensitivity	–0.18	0.00
Light sensitivity	–0.22	–0.01
Feeling of fullness of ear	–0.16	0.00
Irritable	–0.19	–0.07
Memory problem	–0.22	–0.01
Diminished field of vision	–0.17	0.02
Low mood	–0.18	–0.06
Changed perception of touch in the legs	–0.15	0.14
Difficulty with control of legs	–0.12	0.09
Fatigue in legs	–0.12	0.00
Twitches in the legs	–0.09	0.05
Difficulty walking down stairs	–0.12	0.11
R^2	0.15	0.09

PRI: Pain Regions Index; BDI: Beck Depression Inventory; NPSI: Non Pain Symptoms Index.

Pain intensity variables, BDI, PRI, and radiation of pain to the arm/arms showed high loadings on the second component (p2) and were thus positively intercorrelated and not correlated with NPSI and its items. To further confirm that BDI showed the strongest correlation with pain symptoms, a PLS regression of BDI (logarithm due to skewness) was made (6 multivariate outliers were excluded). The significant regression ($R^2 = 0.16$; $Q^2 = 0.05$; details not shown) showed that BDI correlated positively with the pain symptoms (i.e. PRI and pain intensities in different anatomical regions) and not with other not directly pain-related symptoms. However, the great majority (84%) of variation in BDI is explained by unknown factors/aspects other than the symptoms investigated in the present study.

The relationships between different symptoms and catastrophizing. When the catastrophizing subscale of CSQ was regressed ($R^2 = 0.31$; $Q^2 = 0.22$), the following symptoms were most important (in descending order): BDI (VIP = 3.25), pain intensity of upper back (VIP = 2.70), pain intensity of hands (VIP = 2.47), pain intensity of lower back (VIP = 2.34), pain intensity of neck (VIP = 2.15), pain intensity of head (VIP = 1.66), pain intensity of shoulders (VIP = 1.63) and PRI (VIP = 1.23).

Conclusions with respect to the second aim. NPSI and the not directly pain-related symptoms correlated in the multivariate context, but these variables did not correlate with the pain intensity variables, PRI and BDI. The latter group of symptoms showed the strongest correlations with catastrophizing.

DISCUSSION

The following are the major results relevant to the two aims of this study:

First aim

Widespread pain in chronic WAD is associated with negative consequences with respect to pain intensity, prevalence of other symptoms (including depressive symptoms), some aspects of coping, life satisfaction and general health (Table I).

Second aim

In the more total multivariate context, NPSI (and its items) did not correlate with the pain intensity variables, PRI and BDI (Table II) or with catastrophizing. Even though BDI and these pain variables intercorrelated, the correlation was weak

or moderate since only a minor part (16%) of the variation in BDI was explained by these aspects of pain. The latter group of symptoms (i.e. BDI, PRI, and pain intensities) showed the strongest intercorrelation with catastrophizing.

Comparisons between subgroups based on PRI

Subgrouping based on PRI. A relatively prominent proportion (27%) of the cohort of patients with chronic WAD definitely had widespread pain (i.e. they belonged to subgroup 3 with 8–11 pre-defined anatomical regions with pain; Table IA). Although different definitions have been used in the literature, most population-based studies of the prevalence of widespread pain report figures between 5% and 10% (for a brief review see (7)). The figure from the present study, based on a selection of subjects with WAD, is considerably higher and seems reasonable since the most severe cases are referred to specialist departments at university hospitals.

Several authors report data indicating that pain from the neck-shoulder region is associated with higher risk for widespread pain than pain from other anatomical regions (6–8). At present it is not known whether WAD *per se* is associated with an over-representation of widespread pain in comparison with other local or regional pain conditions. A study comparing chronic WAD and idiopathic neck pain presented data indicating increased risk for widespread hypersensitivity to mechanical pressure and thermal stimuli in chronic WAD (28). Other studies have presented data showing that chronic WAD is associated with widespread sensory changes (for references see (29)), which might be a necessary step towards development of the perception of widespread pain.

Background data and possible selection effects. The background data showed few significant differences between the 3 subgroups (Table IA). The significantly higher degree of disability pension appears reasonable when taking the total situation (symptoms, coping, health, and life satisfaction) for this subgroup into consideration. No significant gender difference existed between the 3 subgroups, although the prevalence of women tended to be highest in subgroup 3. Earlier we have reported from this cohort that there was no significant gender difference in PRI (11). Whether these findings with respect to gender are representative for chronic WAD in the population or only for patients referred to a specialist clinic are unknown. Population-based studies of chronic widespread pain report higher prevalences of widespread pain in women than in men (30, 31). For the diagnosis fibromyalgia, which is a subgroup of chronic widespread pain, consistently higher prevalences have been found in women than in men in both population-based and clinically-based studies (32). From the present study, it can also be noted that gender does not influence the correlation pattern of symptoms according to the multivariate analysis (Table II), since gender did not load high on any of the 2 significant components.

However, our results concerning the consequences might be biased due to the higher proportions of women and disability pension in the subgroup with highest PRI. Another factor that might bias our results is the selection of the most complicated patients for referral to the university hospital. Hence the present results, that widespread pain is associated with more negative consequences, need to be confirmed in community-based studies of chronic WAD.

Aspects of health and life satisfaction. Patients with chronic WAD rate their satisfaction with life as a whole (physical and psychological health) lower than healthy controls (33). A prominent majority of the different items and scales concerning life satisfaction and health (i.e. LiSAT-11, SF-36 and EuroQol) in the present study showed significant differences between the 3 subgroups, with the most unfavourable situation for the widespread pain group. In occupationally active home-care personnel, widespread pain was associated with low health and high disability (7). Also, other studies show that widespread pain is associated with poor outcome of recovery and disability (9, 10, 29). Although the unfavourable situation for the subgroup with the highest PRI might be due to the spread of pain factors, such as the higher proportions of women and/or disability pension in subgroup 3, this might have biased our results.

Pain intensities. Widespread pain was associated with significantly higher pain intensities for several, but not all, anatomical regions (Tables I and II), which agrees with the results of Ektor-Andersen et al. (8). Consistent with this, Lundberg & Gerdle (7) reported in the epidemiological study of female home-care personnel that subjects with a high number of tender points and widespread pain also had higher pain intensities. One possible interpretation that has to be confirmed in prospective studies is that high pain intensities not only increase the risk for chronic pain conditions but also for spreading pain.

Catastrophizing. In our first study from the present cohort of patients with chronic WAD, we identified different subgroups based on their coping strategies (11); the subgroup with lowest degree of catastrophizing generally had the best situation with respect to pain intensities, number of other symptoms, and aspects of health and life satisfaction. Moreover, aspects of pain, depression, and catastrophizing in a complex way were important when regressing aspects of health and life satisfaction. A recent prospective study of recovery reported that depression and passive coping strategies interacted (13) and the authors highlighted the importance of assessment of both coping behaviours and depressive symptomatology. Few differences existed in the present study with respect to coping strategies and only the "reinterpreting pain sensations" and "catastrophizing" scales of CSQ differed significantly between the 3 subgroups based on PRI and with highest values in the widespread pain group (Table I). Catastrophizing thoughts could be correlated with maintaining chronic pain (4). The use of passive strategies such as catastrophizing has been found to be strongly associated with poor outcome (12–14). Prospective studies indicate that the role of coping strategies increases with the duration of WAD (34, 35). This, together with observations that catastrophizing can decrease after cognitive behavioural treatment, indicates that the coping style is not a stable individual characteristic but a more dynamic process (13, 14).

According to the PLS regression, the catastrophizing subscale of CSQ showed strongest correlations with BDI, followed by different specific pain intensities and PRI. Our result, with a positive correlation between catastrophizing and depression, agrees with studies of different pain conditions including rheumatoid arthritis and fibromyalgia (14, 36). Edwards et al. (14) concluded that catastrophizing exerts its harmful effects by multiple mechanisms: from maladaptive influences on the social environment to direct amplification of the processing of pain by the CNS. A further contribution of our study is that we found that some of the variance of catastrophizing was correlated with the spreading of pain in WAD. Edwards et al. (14), in a literature review, reported similar observations from studies of patients with fibromyalgia and scleroderma. Although our result indicates that spreading of pain is related to catastrophizing, the direction of causality cannot be determined in the present cross-sectional study.

Not directly pain-related symptoms. BDI and NPSI increased with the number of anatomical regions with pain (PRI) according to the subgroup analysis (Table IB). This agrees with reports that widespread pain is associated with other symptoms including depression (19, 29). One possible interpretation is that high PRI, high pain intensities and increased prevalence of other symptoms including depression is due to a more severe trauma and/or part of a post-traumatic stress syndrome. However, several neurophysiological studies have reported signs of central sensitization in chronic WAD (for references see (37)) and the results of pharmacological challenges of chronic WAD demonstrate a heterogeneity in pain mechanisms (5). Hence the increase in prevalence of symptoms might be because a subgroup of patients with WAD developed central sensitization. The development of sensitization and widespread generalized pain appears to occur independently of psychological variables (28, 29), but is associated with a higher prevalence of psychological symptoms (29).

It has been argued that chronic pain is associated with hyper-vigilance to body signals and thereby more symptoms are reported. Sterner et al. (33) reported that patients with chronic WAD had a significantly higher prevalence of different symptoms than healthy controls, but they also noted that the chronic WAD group did not exhibit a homogenous increase in all types of symptoms. For individual not directly pain-related items (cf. Table IB), only sleeping difficulties, fatigue-tiredness, and memory problems showed significant differences between the 3 subgroups and with the worst situation in the widespread pain group (subgroup 3). An alternative is that the increased prevalences of these symptoms just reflects secondary psychological consequences of having chronic pain in a large part of the body. These symptoms can result from cognitive difficulties. It has also been debated whether such symptoms reflect undetected brain injuries due to trauma in WAD, but no convincing studies show brain damage in patients with WAD (37).

Inter-relationships between different types of symptoms

BDI did not – in the more complete multivariate context – correlate with the non-pain symptoms including the cognitive/neuropsychological symptoms identified in the first component (Table II). Because NPSI and its items were not correlated with pain intensities, widespread pain, and BDI (i.e. loading on different components in Table II), it could be concluded that high pain intensity and widespread pain does not necessarily reflect a *general* hyper-vigilance for body sensations and thereby more symptoms. It can be argued that our results do not consider that the psychometric properties of NPSI (and the items constituting it) are unknown and more studies are needed to confirm our result in this part.

When regressing BDI, we found that widespread pain (PRI) was the most important regressor followed by pain intensity variables of different anatomical regions. Most other studies have identified that chronic pain is associated with increased prevalence of depression and/or depressive mood; for reference see (16). In contrast to these results, Sullivan et al. (36) found no correlation between pain and BDI. However, only a small part of the variation was explained (16%) in our regression of BDI, and thus the correlation between BDI and aspects of pain were only weak or moderate, although significant.

Sterner et al. (33) suggested that cognitive/neuropsychological symptoms were consequences of high pain intensity rather than pain *per se*. We are unable to confirm such a direct relationship between pain intensity and cognitive/neuropsychological symptoms in the present within-group analysis of chronic WAD, since these 2 groups of symptoms loaded on different components in the PCA (Table II). Moreover, the present cohort of subjects with chronic WAD differ quite notably with respect to the presence of cognitive/neuropsychological symptoms since they loaded on the first component of the PCA (Table II).

CONCLUSION

According to the present cross-sectional study, widespread pain in chronic WAD is associated with negative consequences with respect to pain intensity, prevalence of other symptoms (including depressive symptoms), some aspects of coping, life satisfaction/quality and general health. Our results indicate that, in different ways, the subgroup with widespread pain had a more fragile life situation than those with more local or regional WAD. Based on our results, we argue that a preventive perspective might be urgent and that clinical rehabilitation requires a broad assessment of the spread of pain, cognitive, and neuropsychological symptoms, and depressivity and catastrophizing thoughts or strategies. Prospective studies – investigating, for example, the effect of early enhanced pain-relieving efforts for local/regional pain in WAD to prevent pain generalization and negative consequences – are important.

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