Chronic Widespread Pain in Patients with Rheumatoid Arthritis and the Relation Between Pain and Disease Activity Measures over the First 5 Years

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ABSTRACT. ***Objective.*** To study the prevalence of chronic widespread pain (ChWP), chronic regional pain (ChRP), and fibromyalgia in patients with early rheumatoid arthritis (RA) followed for 5 years after inclusion, and to study the effect of pain on measures of disease activity and function.

Methods. A questionnaire was sent to 1910 patients participating in the Better Anti-Rheumatic Pharmacotherapy study. The responders (73%) were divided into 3 groups according to the reported pain duration and distribution — patients having no chronic pain (NChP), ChWP, and ChRP. Outcome measures were the 28-joint Disease Activity Score (DAS28), the Health Assessment Questionnaire (HAQ), and C-reactive protein (CRP).

Results. Thirty-four percent of respondents reported ChWP, 46% ChRP, and 20% NChP. Patients reporting ChWP were more often women and had more pain and tender joints at inclusion. From 6 months to 5 years of followup, mean DAS28, visual analog scale (VAS) pain, VAS global health, and HAQ were significantly higher in the ChWP group than in the other groups. However, all groups showed a similar pattern in swollen joint count, erythrocyte sedimentation rate (ESR), and CRP. From 12 months the ChWP group was treated with prednisolone to a greater extent than the ChRP group, and it had a rate of treatment with disease-modifying antirheumatic drugs similar to that of the ChRP group.

Conclusion. ChWP is a common feature in RA, more associated with high values for variables related to pain such as the DAS28 and HAQ than to indicators of ongoing inflammation such as swollen joint count, ESR, and CRP. Patients with ChWP should be identified so that adequate treatment also of the noninflammatory pain may be instituted. (First Release Nov 1 2013; J Rheumatol 2013;40:1977–85; doi:10.3899/jrheum.130493)

Key Indexing Terms:
CHRONIC WIDESPREAD PAIN RHEUMATOID ARTHRITIS PAIN
DISEASE ACTIVITY MEASURES CLINICAL ASSESSMENT

Rheumatoid arthritis (RA) affects about 0.5 to 1% of the adult population[1]. Pain is a central feature in RA, with a great influence on self-reported health and physical function[2]. Pain is also a common problem in the general population[3,4].

Chronic pain is not only a symptom of the rheumatic disease, but could also be a disease in itself, where the biomedical disorder is only part of the explanation in a broader biopsychosocial context. This is especially the case when pain is perceived from several regions of the body, as in chronic widespread pain (ChWP). Fibromyalgia (FM) is a subgroup of ChWP, characterized also by a generalized allodynia, fatigue, and other somatic symptoms[5,6]. The prevalence of ChWP and FM in the population is about 10% and 2%, respectively[3,7]. In patients with RA, the prevalence of FM has been reported to be 10-fold higher[8]. ChWP and FM are also reported to be more common in women[3,9].

Measures such as the 28-joint Disease Activity Score (DAS28) and the Health Assessment Questionnaire (HAQ) may be influenced by pain. There have been studies evaluating DAS28 and HAQ in patients with RA and concomitant FM (RAF). These studies reported an elevated disease activity according to DAS28 and a decreased physical function according to HAQ in patients with RAF compared to RA patients without RAF[8,10]. A further study found that women had higher DAS28 and HAQ compared to men despite a similar degree of joint destruction[11]. In a study to determine whether DAS28 is applicable to all patients with RA, Leeb and coworkers found that DAS28 is dependent on the patient's sex and pain perception[12].

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The first aim of our present investigation was to study the prevalence of ChWP, chronic regional pain (ChRP), and FM in patients with RA. The second aim was to study the effect of pain on outcome as measured by DAS28, HAQ, and C-reactive protein (CRP) over a 5-year period.

MATERIALS AND METHODS

Patients. Our study included 1910 eligible patients from the Better Anti-Rheumatic Pharmacotherapy (BARFOT) study, who in 2010, 5–18 years after disease onset, answered a questionnaire concerning lifestyle factors, pain, fatigue, comorbidity, HAQ, EuroQol EQ-5D, and treatment (Figure 1). BARFOT is a longitudinal, multicenter observational study that started in 1992 of patients with early RA. Patients have been consecutively included after being diagnosed with RA according to the American College of Rheumatology 1987 criteria[13], provided that they had a disease duration of 1 year or less. After baseline evaluation, regular followup assessments according to the study protocol will be conducted at 3 and 6 months, and at 1, 2, 5, 8, and 15 years.

Of the 1910 who received the questionnaire, 1386 patients responded, giving a response rate of 73%. The nonresponders were slightly older (mean 56 vs 55 yrs, p = 0.036), and had at inclusion higher DAS28 (mean 5.4 vs 5.2, p = 0.022), worse global health (mean 48 vs 45, p = 0.036), and more swollen joints (mean 11.0 vs 10.3, p = 0.023). More patients had antinuclear antibody (32% vs 23%, p = 0.003) and fewer had rheumatoid factor (RF; 57% vs 62%, p = 0.013). There were no significant differences in sex, visual analog scale (VAS) pain, erythrocyte sedimentation rate (ESR), CRP, HAQ, tender joints, or smoking habits at inclusion.

The patients were divided into 3 groups according to pain duration and distribution reported in the questionnaire. Those with pain < 3 months were regarded as having no chronic pain (NChP group). Patients who had experienced pain > 3 months during the past year in both the left and right side of the body, both above and below the waist, and along the axial skeleton (i.e., in the cervical spine, the anterior chest, the thoracic spine, or the lower back) were the ChWP group, including the FM subgroup[6]. The data on FM diagnosis is patient-reported. The third group, the ChRP group, comprises patients with chronic pain in at least 1 region for > 3 months during the past year, but not fulfilling the criteria for ChWP.

Clinical disease assessments. Disease activity was measured by the composite index DAS28, consisting of 4 components: a VAS for global health (VAS GH), ESR, and number of tender and swollen joints, calculated on 28 joints[14]. Remission was defined as DAS28 < 2.6[15]. Disability was assessed using the Swedish version of the Stanford HAQ and pain was evaluated by a VAS for pain[16]. ESR and CRP were analyzed by routine methods at each clinic. RF was measured by an agglutination test where a titer of > 1/20 was considered positive.

Questionnaire. The questionnaire assessed lifestyle factors, pain, a 28-joint score (according to DAS28), comorbidity, and HAQ, but in our study the focus was on the patients' assessment of pain, joint score, fatigue, and HAQ. The questionnaire also included the Euroqol EQ-5D, a 5-part questionnaire measuring health-related quality of life, where 1 is best and 0 worst[17,18].

Pain distribution was described on a pain manikin[3]. The manikin consisted of these regions: chest, neck, thoracic spine, lumbar and sacral spine, shoulder and upper arm, elbow and forearm, hand and wrist, buttock, hip and thigh, knee, lower leg and foot at both left and right side. Patient-reported tender and swollen joints were assessed according to a 28-joint score. The questionnaire also contained a numeric rating scale (NRS) for pain (NRS pain), fatigue (NRS fatigue), and global health (NRS GH) as 11-point Likert scales from 0 (no pain/fatigue/GH) to 100 (worst pain/fatigue/health), where each step is 10 points.

Statistical methods. Statistical analyses were performed using SPSS Statistics 18 software. All significance testing was 2-tailed and conducted at the 0.05 significance level. To test differences between groups, the chi-squared test was used for proportions and the Kruskal-Wallis test with posthoc analysis or the Mann-Whitney U test for continuous variables, because some of the variables were not normally distributed. Correlations were performed by the Spearman's test. A multiple logistic regression analysis was performed to assess whether VAS pain > 46 (baseline mean value) was an independent factor for reporting NChP or ChWP in the questionnaire.

The analysis was controlled for age, sex, disease duration, RF, smoking habits, DAS28, and HAQ > 1 (mean value) at inclusion.

Both VAS scales (from the clinical followup) and NRS scales (from the questionnaire) were used. Studies comparing different methods of pain measurement show good correlation between VAS and NRS[19].

Approval and consent. Ethical approval was obtained from the Regional Ethical Review Board at Lund University, Lund, Sweden, at study start (LU 2009/670). Our study followed the guidelines from the Helsinki Declaration. Written consent from the participants was obtained. The patient database is located at Spenshult Hospital for Rheumatic Diseases. All handling of the database is according to ISO 9001.

RESULTS

Prevalence of reported pain. The mean (SD) disease duration from inclusion to questionnaire was 9.1 (3.7) years. Thirty-four percent of the patients reported ChWP, 46% ChRP, and 20% no NChP. Patient-reported prevalence of FM was 4%.

Demographic and clinical characteristics at inclusion. Table 1 shows demographic and clinical characteristics at inclusion of all patients and also split by pain groups (NChP,

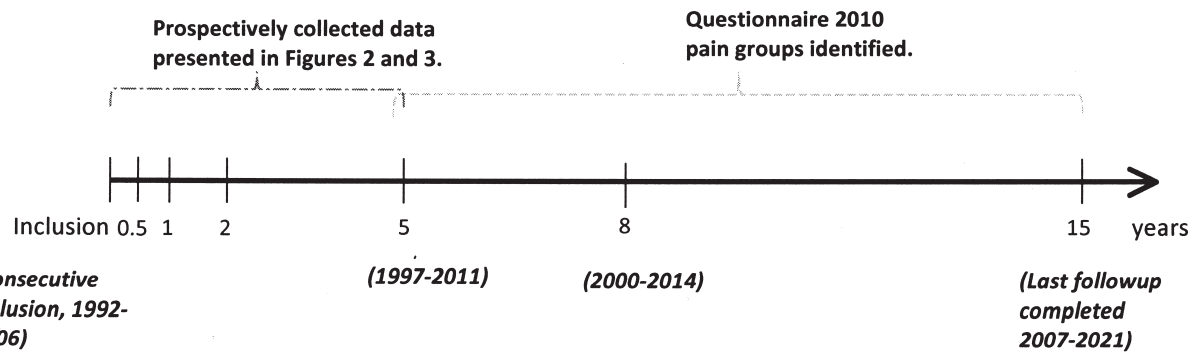

Figure 1. Study timeline from start to last followup after 15 years.

Table 1. Disease characteristics at inclusion in the different pain groups. Data are mean (SD) unless otherwise indicated.

	NChP, n = 274	ChRP, n = 647	ChWP, n = 465	All, n = 1386	p*
Age, yrs	54.1 (15.9)	55.4 (14.0)	54.9 (13.2)	55.0 (14.2)	0.6
Disease duration (mos)	5.9 (3.2)	6.0 (3.0)	6.3 (3.2)	6.1 (3.1)	0.1
Women (%)	60	67	79	70	< 0.001
Ever smoker (%)	50	58	60	57	0.047
RF positive (%)	57	65	62	62	0.06
DAS28 (0–10)	5.00 (1.29)	5.23 (1.26)	5.33 (1.19)	5.22 (1.25)	0.008
HAQ (0–3)	0.80 (0.58)	0.96 (0.58)	1.14 (0.62)	0.99 (0.61)	< 0.001
VAS pain (0–100 mm)	37.2 (23.7)	46.2 (23.6)	51.9 (22.7)	46.3 (23.9)	< 0.001
VAS GH (0–100 mm)	37.1 (25.3)	44.6 (25.3)	50.3 (24.3)	45.0 (25.4)	< 0.001
No. swollen joints	10.6 (5.9)	10.4 (5.7)	9.9 (5.7)	10.3 (5.7)	0.3
No. tender joints	7.2 (6.0)	7.8 (6.0)	9.2 (6.4)	8.2 (6.2)	< 0.001
CRP (mg/l)	28.4 (27.6)	33.5 (38.5)	28.8 (36.1)	30.9 (35.9)	0.004
ESR (mm/h)	33.9 (23.1)	36.5 (24.7)	32.0 (23.9)	34.5 (24.2)	0.008

* P values denote the overall significance of differences between groups calculated by the Kruskal-Wallis test or by the chi-squared test. NChP: no chronic pain or pain < 3 months during the past 12 months; ChRP: chronic regional pain, pain in at least 1 region for > 3 months in the past year, not fulfilling the criteria for ChWP; ChWP: chronic widespread pain, pain > 3 months during the past year in both left and right side of the body, both above and below the waist and along the spine; RF: rheumatoid factor; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; GH: global health; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

ChRP, and ChWP) as reported at followup. At inclusion the mean (SD) age was 55 (14) years, the DAS28 was 5.22 (1.25), and the HAQ was 0.99 (0.61). Seventy percent of patients were women and 57% were ever smokers. Sixty-two percent of the patients were RF-positive.

The patients reporting ChWP were more often women than the patients reporting ChRP and NChP ($p < 0.001$) and had more pain and tender joints, while the number of swollen joints was similar. The patients in the NChP group were less frequently current or previous (ever) smokers at baseline compared to the patients in the ChRP and ChWP groups ($p = 0.047$), respectively.

Treatment. There were no significant differences between the groups in disease-modifying antirheumatic drug (DMARD) treatment at inclusion, nor at 6 or 12 months. At 24 and 60 months there were more untreated patients in the NChP group: 20% and 30% compared to 14% and 19% in the ChRP group, and 16% and 21% in the ChWP group, respectively. There were more patients (11%) treated with DMARD other than methotrexate and sulfasalazine in the ChWP group, compared to 6% in the NChP group and 8% in the ChRP group, at the 24-month followup. In terms of cumulative DMARD use from inclusion to time for questionnaire, the ChRP and ChWP groups had used significantly more different DMARD than the NChP group (Table 2). There were no significant differences in prednisolone treatment between groups at inclusion, nor at 6 months. At 12 months, fewer patients in the NChP group and more patients in the ChWP group were treated with prednisolone (27% vs 36%, $p = 0.026$). At 24 months there were more patients treated with prednisolone in the ChWP group ($p = 0.014$) than in the other groups. At 60 months, more patients in the ChWP group were treated with prednisolone; the NChP group had fewer patients treated with prednisolone ($p = 0.028$).

Correlations of pain with disease-related variables. VAS pain and VAS GH correlated significantly at inclusion ($r = 0.6$) and at all followup visits ($r = 0.8$, $p < 0.001$). This was the case also for VAS pain and HAQ ($r = 0.5$ at inclusion, 6 and 12 months, and $r = 0.6$ at 24 and 60 months, $p < 0.001$) and for VAS pain and tender joints ($r = 0.3$ at inclusion and $r = 0.5$ at all the other followup periods, $p < 0.001$). In contrast, the correlations between VAS pain and swollen joints, ESR, and CRP were medium ($r = 0.3$, $p < 0.001$) and small ($r = 0.2$, $p < 0.001$, and $r = 0.2$, $p < 0.001$), respectively.

Chronic widespread pain and disease symptoms reported in the questionnaire. In the followup questionnaire, the patients in the ChWP group reported more pain, worse global health, more fatigue, more swollen and tender joints, and worse HAQ and EQ-5D compared to the patients in the other groups ($p < 0.001$). This group of patients scored worse in NRS fatigue and in EQ-5D compared with the groups not fulfilling the ChWP criteria and/or reporting < 7 painful regions — NRS fatigue mean (SD), 61.3 (23.1) vs 35.4 (26.6), $p < 0.001$, and EQ-5D mean (SD) 0.56 (0.27) vs 0.76 (0.19), $p < 0.001$ (Table 2).

ChWP and the development of disease-related variables over time. The clinical variables developed similarly over time, decreasing after 6 months from a high baseline value. Then in most cases, the curve leveled out, with no or only minor further change.

When the variables were split by pain group, 2 different patterns of development emerged over time. At baseline the ChWP group had higher values for pain, DAS28, VAS

Table 2. Patient assessments from questionnaire in the different pain groups. Data are mean (SD) unless otherwise indicated.

	NChP, n = 274	ChRP, n = 647	ChWP, n = 465	All, n = 1386	p*
Disease duration from inclusion to questionnaire, yrs	8.8 (3.9)	9.0 (3.5)	9.3 (3.8)	9.1 (3.7)	0.1
NRS pain†	8.2 (14.2)	34.9 (22.5)	50.5 (21.9)	35.3 (25.6)	< 0.001
NRS GH†	10.3 (14.6)	30.3 (20.7)	46.7 (22.6)	31.7 (24.1)	< 0.001
NRS fatigue†	20.7 (22.5)	38.6 (26.2)	56.9 (24.4)	41.5 (28.2)	< 0.001
No. swollen joints (28)	0.9 (2.6)	3.0 (4.6)	6.2 (6.6)	3.7 (5.5)	< 0.001
No. tender joints (28)	1.1 (2.8)	4.8 (5.4)	10.0 (7.5)	5.8 (6.7)	< 0.001
HAQ	0.16 (0.31)	0.54 (0.56)	0.95 (0.60)	0.60 (0.60)	< 0.001
EQ-5D	0.89 (0.14)	0.73 (0.19)	0.61 (0.25)	0.72 (0.23)	< 0.001
No. DMARD used**	2.3 (1.6)	2.8 (1.8)	3.0 (1.8)	2.8 (1.8)	< 0.001
No. painful regions	0 (0)	3.4 (2.0)	8.3 (3.3)	4.4 (3.9)	< 0.001
Painful regions ≥ 7 (%)	0	8	68	26	< 0.001

* Kruskal-Wallis test. ** Cumulative number of DMARD used since diagnosis; † 0–100 (no pain/fatigue/GH to worst pain/fatigue/GH). NChP: no chronic pain or pain < 3 months during the past 12 months; ChRP: chronic regional pain, pain in at least 1 region for > 3 months in the past year, not fulfilling the criteria for ChWP; ChWP: chronic widespread pain, pain > 3 months during the past year in both left and right side of the body, both above and below the waist and along the spine; HAQ: Health Assessment Questionnaire; GH: global health; NRS: numeric rating scale; DMARD: disease-modifying antirheumatic drugs.

global, tender joint count, and HAQ than did the NChP group, and higher HAQ, VAS pain, and VAS GH than did the ChRP group. The decrease at 6 months was less pronounced in the ChWP group, and subsequently the curves leveled out in a parallel way, with the ChWP group continuously at a significantly higher level than the other groups. Thus, the ChWP group had significantly higher values than both the other groups from 6 months to 5 years (Figure 2A-E).

However, the graphs for swollen joint count, ESR, and CRP showed a different pattern. At baseline, the ChWP group did not have the highest values and its decrease at 6 months was similar to that in the ChRP group. These groups then remained on a similar level, significantly higher than that of the NChP group (Figure 3A-C).

ChWP, disease activity, and remission. The mean DAS28 level in the ChWP group remained consistently above the lower limit for low disease activity (DAS28 ≤ 3.2), and in the ChRP group, the mean DAS28 was always above the limit for remission (DAS28 < 2.6; Figure 3A).

At 5-year followup, 30% of the patients in the ChWP groups were in remission versus 70% of the patients in the NChP group and 47% in the ChRP group ($p < 0.001$).

Prediction of ChWP. Pain VAS above the average (46) at inclusion was an independent predictor of reported ChWP 9 years later (OR 2.2, 95% CI 1.5–3.3, $p < 0.001$), controlled for age at inclusion, sex, disease duration, RF, smoking habits, DAS28, HAQ > 1 (mean), and CRP. Other independent predictors were female sex (OR 2.4, 95% CI 1.6–3.7, $p < 0.001$), ever smoker (OR 1.6, 95% CI 1.1–2.4, $p = 0.014$), and a HAQ score above 1 at inclusion (OR 1.9, 95% CI 1.3–3.0, $p = 0.003$; Table 3).

DISCUSSION

Our study focused on chronic pain and its relation to disease activity and function in patients with RA. A followup questionnaire with a mean followup time of 9 years revealed a high prevalence of ChWP, which was more related to pain at disease onset and to several other pain-related variables than to direct indicators of inflammation.

Of the patients with RA, 34% reported ChWP and 46% ChRP. In studies of the general population the prevalence of ChWP varies between 11% and 14% and the prevalence of ChRP has been found to be 24%. Studies of the prevalence of ChWP and ChRP in patients with RA are scarce. Reported prevalence of ChWP in patients with RA varies between 17% and 20%, which is somewhat lower than the prevalence we found. This difference is probably due to different methods of diagnosing ChWP between the studies[8,20].

Four percent of the patients had FM, somewhat more than the 1–3% reported in the general population[3,7,21], but much less than previously reported (17% to 25% in studies of patients with RA[22,23]). The low rate of patients with FM in our study could be because the diagnosis was patient-reported, not clinically based. However, when the new clinical FM criteria, which do not require a tender point examination[5] were applied, 23% of the patients reported ChWP and 7 or more painful regions for > 3 months. This group of patients had fatigue and impaired quality of life in line with what has been described in patients with FM[24,25] and could probably be patients with RAF.

There is evidence that the local pain typical of RA might progress to a more widespread chronic pain despite adequate treatment of the inflammation[22]. If so, this could explain the increased prevalence of FM in patients with RA. The mechanism behind this spread of symptoms is not fully understood, but one explanation could be central sensitization of the central nervous system[26,27]. There are also studies showing proinflammatory cytokines, e.g., inter-

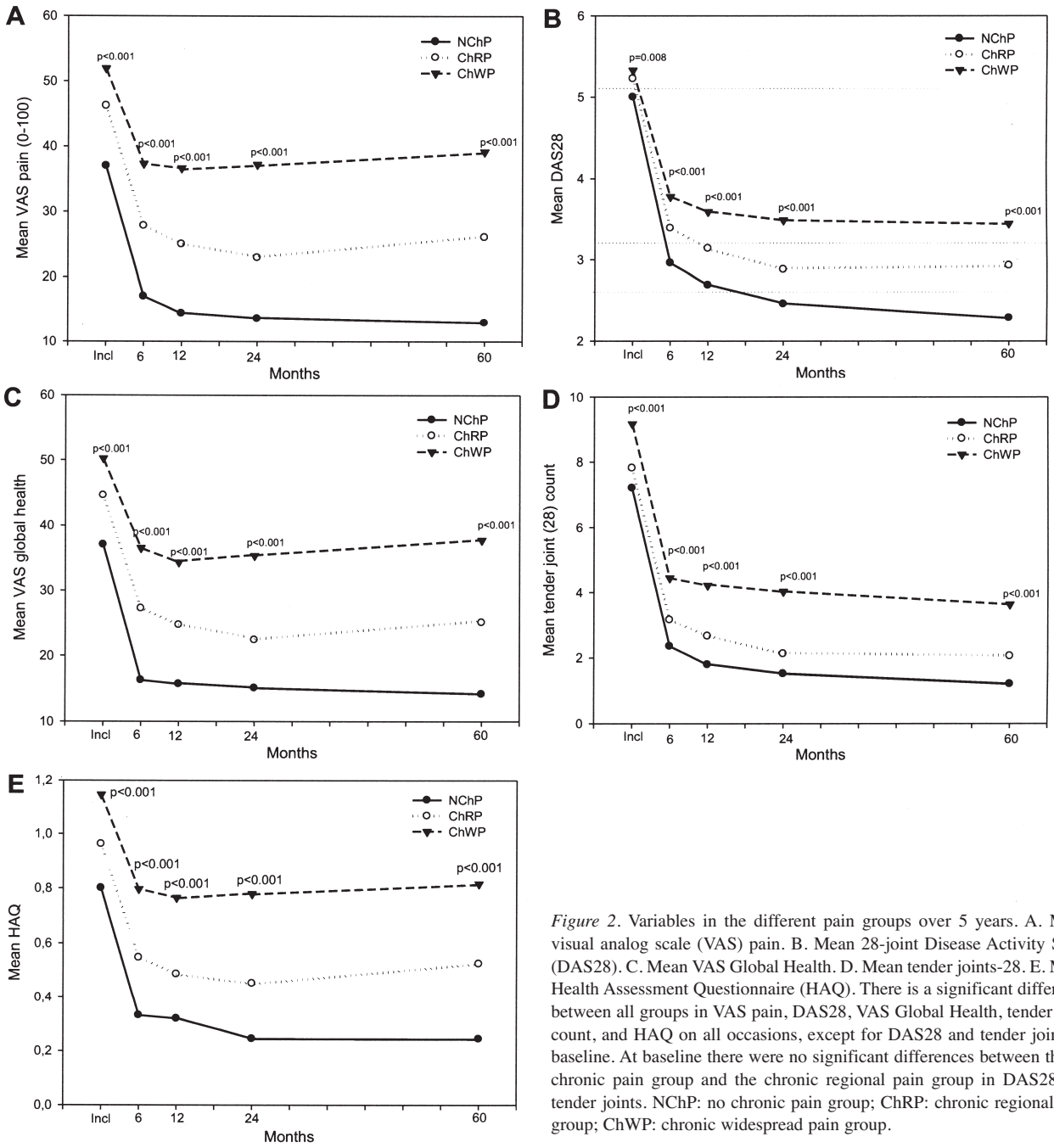

Figure 2. Variables in the different pain groups over 5 years. A. Mean visual analog scale (VAS) pain. B. Mean 28-joint Disease Activity Scale (DAS28). C. Mean VAS Global Health. D. Mean tender joints-28. E. Mean Health Assessment Questionnaire (HAQ). There is a significant difference between all groups in VAS pain, DAS28, VAS Global Health, tender joint count, and HAQ on all occasions, except for DAS28 and tender joints at baseline. At baseline there were no significant differences between the no chronic pain group and the chronic regional pain group in DAS28 and tender joints. NChP: no chronic pain group; ChRP: chronic regional pain group; ChWP: chronic widespread pain group.

leukin 8, being involved in the evolution and maintenance of chronic pain[28].

ChWP was more closely associated with pain-related variables such as HAQ, VAS GH, and VAS pain than with variables more closely linked to the inflammatory process. Inflammation assessed by ESR, CRP, and number of swollen joints decreased in all pain groups as did the number of swollen joints, indicating suppression of the inflammatory process.

The patients reporting ChWP invariably had the highest DAS28, with a mean level above 3.2 at all timepoints. Further, this group had the lowest rate of patients in remission at 5-year followup. There is a study reporting that only 1 out of 32 patients with RAF had a DAS28 below 3.2 and that no patient was in remission according to the European League Against Rheumatism criteria[10], a finding similar to the results in our study in patients reporting ChWP.

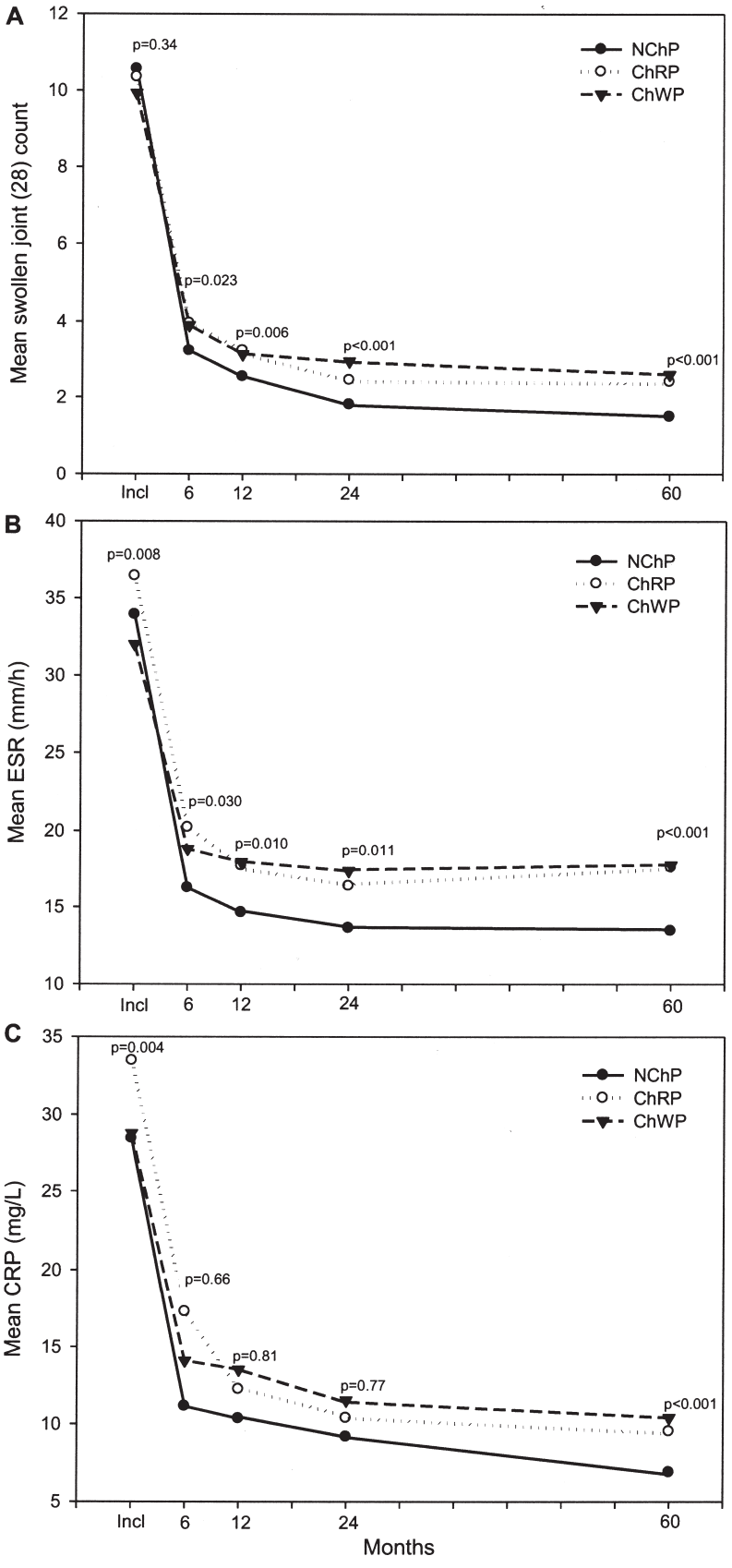

Figure 3. Mean swollen joints-28 (A), erythrocyte sedimentation rate (ESR; B), and C-reactive protein (CRP; C) during 60 months in the different pain groups. There was no difference in swollen joint-28 between groups at baseline. At followup the no chronic pain (NChP) group had a significantly lower count than the other groups. There was no difference between chronic regional pain (ChRP) and chronic widespread pain (ChWP) at any timepoint. At baseline the ChRP group had significantly higher mean ESR than the ChWP group. At followup the NChP group had lower mean ESR than the other groups at all timepoints. There were no differences between the ChRP and ChWP group. The ChWP group had lower mean CRP than both the other groups at baseline. At the 5-year followup, the NChP group had lower mean CRP than the other groups. There was no significant difference between the ChRP and ChWP group.

Table 3. Patients scoring VAS pain more than mean 46.3 at inclusion had an increased risk of reporting chronic widespread pain (ChWP) vs no chronic pain (NChP) 9 years after inclusion, controlled for sex and baseline age, disease duration, RF, smoking habits, DAS28, HAQ > 1, and CRP.

	OR (95% CI)	p
Vas pain > 46.3	2.2 (1.5–3.3)	< 0.001
Female	2.4 (1.6–3.7)	< 0.001
Age	1.0 (0.99–1.01)	0.46
Ever smoker	1.6 (1.1–2.4)	0.014
DAS28	1.0 (0.8–1.2)	0.99
HAQ > 1	1.9 (1.3–3.0)	0.003
CRP	1.0 (0.99–1.004)	0.46
RF positivity	1.1 (0.8–1.7)	0.53

RF: rheumatoid factor; VAS: visual analog scale; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein.

Because GH, one of the components of DAS28, is influenced by pain, the levels of DAS28 may be increased also by noninflammatory pain secondary to FM or some other noninflammatory, pain-generating musculoskeletal disorder[12]. Further, the significantly higher number of tender joints in the ChWP group may be caused by noninflammatory joint tenderness, which may further increase DAS28. Thus, an underestimation of patients in remission may occur with a possible unwanted effect of overtreatment with antiinflammatory drugs.

Pain, however, seemed to be less well-treated, even though the ChWP group got as much DMARD and glucocorticoid treatment as the ChRP group. Other studies have reported analogous findings[2,10]. Thus, patients with RAF were treated with prednisolone more frequently than RA patients without FM. The inflammation seems then to be as well-treated in the ChWP group as in the other groups. Therefore, the greater pain, higher HAQ, and more tender joints reported by the patients in the ChWP group could have causes other than inflammation, and thus may call for alternative treatment.

Early identification of patients with pain not responding to antirheumatic treatment should be encouraged. For this group of patients, early multidisciplinary team treatment and patient education and/or cognitive behavioral therapy should be considered, in addition to individualized drug pain treatment.

There were more women in the ChWP group than in the ChRP and NChP groups. This disparity is known from studies of ChWP[3] and FM[9]. There are many possible explanations for why men and women differ in how they experience and grade their pain, from biological differences (possible link between gonadal hormones and pain response) to different pain perception and learned behaviors[29,30,31]. In accordance with our data, a sex difference in remission rate in patients with RA at the 2-year and 5-year followup visits has been reported[11]. Of interest, in addition to a lower remission rate, women also had more pain and higher HAQ scores compared with men. This suggests a more severe RA in women. However, a study finds similar degrees of radiographic joint destruction in women and men despite worse scores for DAS28 and HAQ in women[11]. The sex discrepancy in DAS28 and HAQ could exist because these measures are dependent on pain.

There were more ever smokers in the ChWP group compared to the ChRP and NChP groups, but the statistical evidence was weak and inconclusive. However, there are other studies reporting that patients with ChWP or FM were smokers to a greater extent than patients without ChWP or FM[21,32,33]. The prevalence of ever smokers in the general population (16-84 yrs) in Sweden in 2010 was 42%, according to the Swedish National Institute of Public Health, somewhat lower than the rate of ever smokers in our study (57%).

A metaanalysis shows that the rate of ever smokers among patients with RA was 51%, which is in the magnitude of this study. The high rate of smokers in RA patients is well known and smoking is a risk factor for developing RA[34].

It is interesting to note that the patients who reported ChWP at followup had higher levels of pain already at inclusion. This could indicate that subjects with RA having or developing ChWP might be identified early in the disease course. This would allow additional treatment, to possibly prevent or reduce pain development. In a study of the general population by Bergman, *et al*, the strongest predictor for persistence of pain at the 3-year followup visit was an increased number of painful regions at baseline[35]. Female sex, ever smoking and a HAQ score above 1 were also independent baseline predictors of future reporting of ChWP, while this was not the case for CRP or DAS28.

The strength of our study is the prospectively collected data in a large cohort of early RA. A limitation is the wide range of disease duration at the time of the questionnaire. Another limitation is that the pain distribution is only assessed once and thereby is unknown at inclusion, which means that the patients might have had ChWP already at inclusion. Widespread osteoarthritis (OA) would conceivably be a source of ChWP and could confound the assessment of the rheumatoid disease activity. However, the presence of OA is not documented in the BARFOT cohort. Thus, radiographs of knees and hips, which should be joints of interest when studying OA, are not assessed in the BARFOT study. With regard to hand OA, the impression from the followup radiographs is that hand OA is not common enough to influence the main results of our study.

Selection bias may occur when the response rate is limited. However, a response rate of 73% to a questionnaire of this kind appears to be satisfactory and is similar to what is reported from studies by others[36,37,38]. Although there was some evidence suggesting higher disease activity

among nonresponders, this was contradicted by the absence of differences in sex, VAS pain, ESR, CRP, HAQ, or tender joint count. Thus, no convincing evidence of selection bias was established.

In the questionnaires, the patients themselves assessed tender and swollen joints. This might give rise to bias because the agreement between patient and physician ratings of swollen joints has been shown to be low[36] but could be improved by training[39], which of course was not possible in our study.

ChWP was common in this longterm study of patients with early RA and was associated with pain-related variables such as DAS28, tender joint count, VAS GH, and HAQ. In contrast, variables more closely related to inflammation such as swollen joint count and acute phase reactants such as ESR and CRP were less distinctly associated with ChWP. Nevertheless, the ChWP group received more antirheumatic treatment, possibly because of overestimation of their true disease activity. Coexistence of ChWP in patients with RA should be identified so that the patients may get adequate treatment not only of the rheumatic disease but also of the noninflammatory pain disorder.

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REFERENCES

1. Symmons DP. Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome. Best Pract Res Clin Rheumatol 2002;16:707-22.
2. Taylor P, Manger B, Alvaro-Gracia J, Johnstone R, Gomez-Reino J, Eberhardt E, et al. Patient perceptions concerning pain management in the treatment of rheumatoid arthritis. J Int Med Res 2010;38:1213-24.
3. Bergman S, Herrstrom P, Hogstrom K, Petersson IF, Svensson B, Jacobsson LT. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. J Rheumatol 2001;28:1369-77.
4. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333.
5. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 2011;38:1113-22.
6. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
7. Lindell L, Bergman S, Petersson IF, Jacobsson LT, Herrstrom P. Prevalence of fibromyalgia and chronic widespread pain. Scand J Prim Health Care 2000;18:149-53.
8. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize RA patients with fibromyalgia. J Rheumatol 2004;31:695-700.
9. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
10. Ranzolin A, Brenol JC, Bredemeier M, Guarienti J, Rizzatti M, Feldman D, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:794-800.
11. Ahlmen M, Svensson B, Albertsson K, Forslind K, Hafstrom I. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Ann Rheum Dis 2010;69:230-3.
12. Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B. Disease activity score-28 values differ considerably depending on patient's pain perception and sex. J Rheumatol 2007;34:2382-7.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
14. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
15. Landewe R, van der Heijde D, van der Linden S, Boers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65:637-41.
16. Ekdahl C, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Use of a Swedish version of the Stanford Health Assessment Questionnaire. Scand J Rheumatol 1988;17:263-71.
17. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199-208.
18. Brooks RG, Jendteg S, Lindgren B, Persson U, Bjork S. EuroQol: health-related quality of life measurement. Results of the Swedish questionnaire exercise. Health Policy 1991;18:37-48.
19. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage 2011;41:1073-93.
20. Wolfe F, Hauser W, Hassett AL, Katz RS, Walitt BT. The development of fibromyalgia - I: examination of rates and predictors in patients with rheumatoid arthritis (RA). Pain 2010;152:291-9.
21. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21:403-25.
22. Atzeni F, Cazzola M, Benucci M, Di Franco M, Salaffi F, Sarzi-Puttini P. Chronic widespread pain in the spectrum of rheumatological diseases. Best Pract Res Clin Rheumatol 2011;25:165-71.
23. Toms J, Soukup T, Bradna P, Hrncir Z. Disease activity composite indices in patients with rheumatoid arthritis and concomitant fibromyalgia. J Rheumatol 2010;37:468.
24. Farrar JT, Young JP Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.
25. Wolfe F, Michaud K, Li T, Katz RS. EQ-5D and SF-36 quality of life measures in systemic lupus erythematosus: comparisons with rheumatoid arthritis, noninflammatory rheumatic disorders, and fibromyalgia. J Rheumatol 2010;37:296-304.
26. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10:895-926.

27. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther 2011;13:211.
28. Kadetoff D, Lampa J, Westman M, Andersson M, Kosek E. Evidence of central inflammation in fibromyalgia-increased cerebrospinal fluid interleukin-8 levels. J Neuroimmunol 2012;242:33-8.
29. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10:447-85.
30. Johansson EE. Story och bevis om smärta och genus. "Prinsessan på ärten" - en myt om kvinnlighet tränger till vetenskap? [Swedish]. Story and evidence about pain and gender. "The Princess on the Pea"—a myth about femininity penetrating to sciences? Lakartidningen 2004;101:3774, 3776, 3778-9.
31. Robinson ME, Riley JL 3rd, Myers CD, Papas RK, Wise EA, Waxenberg LB, et al. Gender role expectations of pain: relationship to sex differences in pain. J Pain 2001;2:251-7.
32. Mitchell MD, Mannino DM, Steinke DT, Kryscio RJ, Bush HM, Crofford LJ. Association of smoking and chronic pain syndromes in Kentucky women. J Pain 2011;12:892-9.
33. Vandenkerkhof EG, Macdonald HM, Jones GT, Power C, Macfarlane GJ. Diet, lifestyle and chronic widespread pain: results from the 1958 British Birth Cohort Study. Pain Res Manag 2011;16:87-92.
34. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum 1996;39:732-5.
35. Bergman S, Herrstrom P, Jacobsson LT, Petersson IF. Chronic widespread pain: a three year followup of pain distribution and risk factors. J Rheumatol 2002;29:818-25.
36. Barton JL, Criswell LA, Kaiser R, Chen Y-H, Schillinger D. Systematic review and metaanalysis of patient self-report versus trained assessor joint counts in rheumatoid arthritis. J Rheumatol 2009;36:2635–41.
37. Hagen KB, Kvien TK, Bjørndal A. Musculoskeletal pain and quality of life in patients with noninflammatory joint pain compared to rheumatoid arthritis: a population survey. J Rheumatol 1997;24:1703-9.
38. Haglund E, Bergman S, Petersson IF, Jacobsson LT, Strömbeck B, Bremander A. Differences in physical activity patterns in patients with spondylarthritis. Arthritis Care Res 2012;64:1886-94.
39. Levy G, Cheetham C, Cheatwood A, Burchette R. Validation of patient-reported joint counts in rheumatoid arthritis and the role of training. J Rheumatol 2007;34:1261-5.