Fatigue in primary care: Longitudinal associations with pain

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ABSTRACT

So far, most studies on the association between pain and fatigue have used cross-sectional data. We analysed the possibilities for a temporal relationship between pain and fatigue in a cohort study of patients presenting with fatigue in primary care. Of 856 recruited patients, 642 (75%) completed postal questionnaires after the consultation, and at one, four, eight and 12 months follow-up, with completion rates ranging from 82% to 88%. Pain was measured using the Short-Form health survey (SF-36) and fatigue using the severity scale of the Checklist Individual Strength (CIS). Longitudinal associations were analysed using generalised estimated equations (GEE). We used three different models assessing possible relationships between the symptoms in time, either in the same intervals or with a time-lag, suggesting either a synchronous or temporal association. The regression coefficients were strongest in the model assessing synchronous change, indicating that a one-point improvement in pain was associated with a 0.25 improvement in fatigue in the same time interval (adjusted for potential confounding). Baseline duration of fatigue and expectations of its future course significantly modified the association in this model, with stronger associations between changes in pain and fatigue found in patients with a shorter duration of fatigue or more positive expectations. The models using a time lag showed a significant but inverse association between changes in pain and subsequent changes in fatigue. The results indicate that changes in pain and fatigue are directly related in time, rather than showing temporal associations

1. INTRODUCTION

Fatigue and pain often co-occur and are both frequently presented nonspecific symptoms in primary care. Having multiple symptoms may increasingly add to limitations in functioning [37], which can be an important reason to consult the GP. Although the association between pain and fatigue has been reported in both community studies and secondary care populations with chronic fatigue syndrome (CFS), fibromyalgia, rheumatoid arthritis or cancer, no longitudinal studies have been performed in primary care populations.

Most studies that have been performed on the overlap between pain and fatigue have used cross-sectional data [3], [15], [22], [33] and [40]. However, in a prospective cohort study among employees, a higher pain score predicted worse fatigue outcome after 1 year [13]. We found a similar association between baseline pain and fatigue outcome among primary care patients [25]. Furthermore, in subgroups of these patients

showing different trajectories of fatigue severity (chronic fatigue, recurrent fatigue, fast or slow recovery), levels of pain showed similar patterns in time [26].

Longitudinal analysis is needed in order to assess whether fatigue and pain are consistently associated in time within patients: are changes in pain over time associated with (subsequent) changes in fatigue? Similar risk factors for fatigue and pain and the finding of similar patterns in time suggest a proportionate relationship; this would yield a synchronous association between changes in fatigue and pain. Alternatively, fatigue may be a consequence of experiencing episodes of pain. A third possibility is that pain may be more easily experienced when feeling fatigued possibly because of a lowered pain threshold, which may be associated with processes of neuroimmunological dysregulation [21]. The finding that many pain-related diagnoses were made in our cohort of patients presenting with fatigue in the year after the consultation for fatigue might indicate towards this third possibility.

Several factors, including sleep problems, level of distress, patients' expectations regarding the course of fatigue, and duration of fatigue at presentation, might confound or modify the associations between fatigue and pain. Pain has been suggested to exacerbate sleep difficulties [24], and sleep problems have been suggested to be (part of) the cause of fatigue in pain patients [8], while conversely, sleep problems have been found to predict the onset of chronic widespread pain [12]. Increased levels of distress and negative expectations have been associated with an unfavourable outcome of both pain and fatigue [6], [19], [26], [27] and [35], and could therefore account for or modify the association between these symptoms. Finally, baseline duration of fatigue could confound or modify the association between fatigue and pain, as patients experiencing chronic fatigue at baseline may also have chronic pain.

Our aim was to investigate the longitudinal association between fatigue and pain in patients presenting with fatigue in primary care, taking into account different possibilities for a temporal relationship:

(1) Changes in fatigue and pain show a synchronous association; (2) changes in pain are associated with subsequent changes in fatigue; (3) changes in fatigue are associated with subsequent changes in pain. We also explored the influence of sleep, distress, negative expectations and baseline duration of fatigue on the longitudinal association between pain and fatigue.

2. METHODS

2.1. Participants

We conducted an observational cohort study among adult patients presenting with a main symptom of fatigue in 147 practices across the Netherlands. We approached all general practitioners in several geographical areas, including rural and urban practices, and both solo practitioners as well as group practices. Additionally, as part of their specialty training, GP trainees from the VU University were instructed to invite patients to the study. From June 2004 to January 2006, 111 GPs and 57 trainees recruited patients with a new episode of fatigue. This implied that the patient had visited the GP neither for the same episode of fatigue nor for a different episode within the past 6 months. Patients who were receiving or had received chemotherapy or radiotherapy within 3 months before the consultation, and women who were pregnant or less than 3 months postpartum, were excluded. Eligible patients were informed about the study by the GP and invited to participate. If interested, they were sent an information letter and the baseline questionnaire. Patients were enrolled when they returned a signed consent form. Participants completed postal questionnaires shortly after the consultation (baseline), and at 1, 4, 8 and 12 months after baseline.

2.1.1. Outcomes

Both fatigue and pain were measured at baseline and at each moment of follow-up. Pain was measured with the Short-Form health survey (SF-36), a widely used questionnaire for perceived health and functioning [1] and [38]. The pain scale consists of two items, both relating to the past 4 weeks. One item measures severity of pain on a 6-point Likert scale ('no pain' to 'very severe pain'). The other item measures the extent to which pain caused impairment in usual daily activities on a 5-point Likert scale ('not at all' to 'very much'). Standardised final scores range from 0 to 100, with higher scores indicating less pain. Fatigue was measured with the Checklist Individual Strength (CIS), which has been validated in several fatigued populations [4] and [39]. The CIS is a 20-item questionnaire, scored on a 7-point Likert scale. The severity scale consists of 8 items, with a score range between 8 and 56. Questions relate to fatigue in the past 2 weeks. In order to facilitate interpretation and comparison of the regression

coefficients, the fatigue subscale was also standardised to a scale ranging from 0 to 100 to yield similar final scales for pain and fatigue. Higher scores indicate more fatigue.

2.1.2. Potential confounders or effect modifiers

Apart from gender and age, we took account of four factors that could explain or modify the association between fatigue and pain. Levels of distress, sleep problems, duration of fatigue at baseline and expectations of a chronic course of fatigue were considered as potential confounders or effect modifiers of the association between changes in fatigue and pain, more or less directly influencing the association between both symptoms in either direction. Although sleep problems, distress and perceptions regarding symptoms may vary over time, only baseline values were available for these variables. Therefore all covariates in our models were time-independent.

Sleep problems were measured with a subscale from the SCL-90 Checklist, containing three items scored on a 5-point Likert scale (range 3–15) [2]. Distress was measured with the Four-Dimensional Symptom Questionnaire (4DSQ), which has been validated in primary care populations [34]. The 4DSQ measures psychological distress, depression, anxiety and symptoms possibly indicating somatisation. The distress scale contains 16 items, resulting in a standardised score range between 0 and 32. Some examples of items are ‘Did you become emotional easily in the past week?’ and ‘Did you feel that you could no longer cope with things in the past week?’ Duration of fatigue at baseline was measured in number of months, and dichotomised at 6 months for analysis. Expectations regarding the course of fatigue were measured with the Illness Perception Questionnaire-Revised (IPQ-R); this scale comprises six items scored on a 5-point Likert scale, with a score range between 5 and 30 [23].

2.2. Statistical analysis

Descriptive statistics were used to present baseline characteristics and mean scores for pain and fatigue over the 12 months follow-up period. Mean scores were calculated for the whole population and for 4 subgroups that were pre-defined according to different patterns of fatigue in terms of severity. These groups had either high (>34) or low (⩽34) scores on the CIS at all time points during follow-up (chronic course, fast recovery); low scores from 4 months onwards (slow recovery) or a recurrence of high scores after initial improvement [25].

We used Generalised Estimating Equations (GEE) with robust standard errors (SPSS 15.0) to model pain and fatigue over time. In order to gain a more complete picture of the longitudinal association between fatigue and pain, we used three models to assess this association (see Fig. 1). In the first model, we investigated whether a change in fatigue over time was associated with a change in pain during the same time period (model of change). As the analysis requires a distinction between predictor and outcome variables, this first model had two versions, either using change in fatigue or using change in pain as outcome variable. The second model addressed the question whether changes in fatigue would likely be a consequence of previous changes in pain. In this model, we studied the association between changes in pain in the first three measurement intervals during follow-up, with changes in fatigue in the subsequent intervals. The third model was a reverse of the second model, assessing the associations of changes in fatigue with subsequent changes in pain.

[FIGURE 1]

GEE enables correction for dependency of observations within individuals over time, by choosing a ‘working’ correlation structure. In the analyses of all models we used an independent working correlation structure, which implies that within-person correlations between all measurements are equal to zero. This seemed to be the best option given the fact that adjustments were made for within-subject correlations by modelling of changes over time rather than absolute values at different time points [36]. GEE is assumed to be robust against the choice of an incorrect correlation structure [41].

To explore the confounding effects of age, gender, baseline levels of pain and fatigue, sleep problems, distress, baseline duration of fatigue and perception of the course, we added these factors (individually) to each model and studied changes in the estimated regression coefficients (crude versus adjusted) for the association between pain and fatigue. Next, to explore to what extent sleep problems, baseline levels of distress, duration of fatigue and negative expectations regarding the course of fatigue modified the association between changes in pain and in fatigue, we added interaction terms to the model and checked direction and significance ($p < 0.10$) of the interaction term.

3. RESULTS

3.1. Population characteristics

Of 856 patients who were invited to participate, 642 (75%) gave informed consent and completed the baseline questionnaire. Participants in the study were on average 5 years older ($p < 0.01$) and more often female (73% vs. 65%; $p < 0.05$). Baseline characteristics are presented in Table 1. Completion rates during follow-up ranged from 82% to 88%. Completers were on average 8 years older ($p < 0.001$) compared to participants who were lost to follow-up. A majority of patients (58%) reported chronic fatigue (at least 6 months) at baseline.

[TABLE 1]

The course of fatigue and pain over time in the total population gradually improved during the 1-year follow-up (Table 2). The percentage of participants showing severe fatigue (original score > 34) dropped from 90% at baseline to 45% after 1 year (data not shown). [Fig. 2] and [Fig. 3] show mean changes in pain and fatigue over time in the pre-defined subgroups with different trajectories of fatigue. The results show similar patterns over time for both symptoms, although mean changes in fatigue are larger than changes in pain.

[TABLE 2.]

[FIGURE 2 AND FIGURE 3]

3.2. Model of change

The results of the GEE analysis, showing associations between fatigue and pain on an individual level, are presented in Table 3. The results of the first model, representing the association between changes in fatigue and pain over the same time intervals, showed a significant relation between changes in both symptoms ($p < 0.001$), in both directions, with similar strength. Since the improvement of symptoms has an inverse direction on the scales of the CIS and SF36, the negative regression coefficients indicate that improvements in pain are associated with improvements in fatigue, and vice versa. The regression coefficients thus indicate that one point improvement in pain score corresponds with a 0.25 reduction, i.e. improvement in fatigue score, and a one-point increase in fatigue score corresponds with a 0.20 decrease, i.e. deterioration in pain score. In both models of change, the association was not confounded by baseline levels of pain or fatigue, age, gender, or any of the other four potential confounders. In the model using change in fatigue as outcome, a significant interaction was observed with negative expectations of the course of fatigue ($p = 0.04$) and baseline duration of fatigue ($p = 0.02$), but not for sleep problems ($p = 0.83$) or level of distress ($p = 0.99$). These interactions indicate that for patients with chronic fatigue and patients with more negative perceptions, the association between changes in fatigue and pain is weaker than for patients with fatigue of shorter duration or with better expectations. In the inverse model of change, using change in pain as outcome, no interactions were observed.

[TABLE 3.]

3.3. Models with time-lag

The second model, assessing the longitudinal relation between changes in pain and subsequent changes in fatigue, also showed a significant relationship ($p < 0.01$). The positive regression coefficient indicates that an increase (i.e. improvement) in pain score was associated with a subsequent increase (i.e. deterioration) in fatigue score. Assessment of potential confounders and effect modification did not significantly change this association. The outcome of the third model, assessing the relation between changes in fatigue and subsequent changes in pain, did not show a significant association (Table 3).

4. DISCUSSION

4.1. Main results

In this study we used three different models to analyse the longitudinal relationship between pain and fatigue in fatigued patients. The results suggest that the association is strongest in the model reflecting synchronous change in both symptoms. Adding a time-lag to the models resulted in an inversion of the regression coefficient in the model in which changes in pain predict subsequent changes in fatigue.

Contrary to our hypotheses, this result suggests an inverse relationship between changes in symptoms with a decrease in pain followed by an increase in fatigue (or vice versa). Several explanations may account for this finding. Given the strong association between fatigue and pain within time intervals, fluctuations in symptom scores between intervals would result in decreases in pain being followed by subsequent increases in both pain and fatigue, and vice versa. Indeed we found negative correlations between subsequent changes of either symptom in all subgroups of patients showing different course of fatigue over time [25], indicating that an increase in pain (or fatigue) was followed by a decrease in pain (or fatigue) and vice versa. This results in an inverse relationship between both symptoms when a time lag is included in the model. Additional analyses confirmed our findings by showing that average pain scores within intervals were positively associated with average fatigue scores in the next interval. Thus, the results do not seem to support the hypotheses suggesting that changes in fatigue could be a consequence of changes in pain or vice versa. Rather, they seem to strengthen our first hypothesis, indicating that symptoms of fatigue and pain are more closely related in time.

4.2. Effect modification

In a previous analysis [26], we showed that expectations of fatigue lasting a long time consistently predicted poor fatigue outcome in two prognostic models focusing on either chronic fatigue or fast recovery. In one of the models, pain also contributed to a chronic outcome of fatigue. Other studies have also shown the predictive value of expectations [6], co-existing pain [13] and also fatigue duration [32]. Several studies among pain patients have shown that negative expectations regarding pain recovery contributed to a poor outcome in terms of pain or return to work [9], [14] and [17]. Therefore, these symptom perceptions are likely to worsen outcome of both (associated) symptoms; thus we expected that negative expectations or chronic fatigue would strengthen the association between the two symptoms.

These factors did not confound the association between pain and fatigue, but surprisingly, in patients with chronic fatigue at baseline or negative expectations the association between changes in fatigue and pain was weaker compared to patients with fatigue of short duration or more positive expectations. A possible explanation of this unexpected finding is that patients with negative perceptions and/or chronic fatigue are likely to have more symptoms, including co-occurring pain, and may show little change over time given the persistence of their symptoms. Furthermore, unhelpful health perceptions and additional problems, in particular symptoms of depression or anxiety, may more strongly influence the course or impact of fatigue in these patients than co-existing pain. Previous research has shown that depression or anxiety can mediate associations between pain and fatigue, but this has mainly been investigated in patients diagnosed with rheumatoid arthritis [19] and [30] or a functional syndrome [11] for whom these health problems may be longstanding and more severe. Our study did not include a thorough assessment of mental health problems, but only measured symptoms of anxiety and depression. These findings merit further investigation especially in primary care populations presenting with fatigue.

Illness perceptions have been measured in a wide range of patients with specific diseases or symptoms. We only measured perceptions regarding fatigue and did not include expectations of pain outcome. However, patient perceptions are also more generally associated with health or (coping with) symptoms [5], [7] and [10], and considering the association between pain and fatigue, it could be worthwhile to use more general rather than symptom-specific perceptions in future studies. Prior to this analysis, we assumed that expectations regarding fatigue could have a similar effect on pain as well, but these expectations did not modify the association in the model using change in pain as outcome. Although this may indicate a symptom-specific rather than a general effect, this result could also be related to the fact that fatigue was more of a problem in our population than pain, resulting in smaller changes in pain compared to fatigue outcome.

We selected a limited number of factors that might influence the association between pain and fatigue. However, other factors might be important in the co-occurrence of both symptoms. Self-efficacy did not predict outcome in our prognostic analysis [26], but is related to expectations of the course of symptoms

and has been associated with reporting both pain and fatigue [7], [18] and [31], and multiple symptoms in general [37]. Chronic disease may also explain or modify the relationship between fatigue and pain. However, data on comorbidity and new diagnoses in this cohort show that very few patients had or received a diagnosis that is clearly indicative of severe pain, such as rheumatoid arthritis or cancer. Moreover, patients can experience fatigue and pain in a wide range of severity regardless of diagnosis, and in many cases these symptoms remain medically unexplained.

4.3. Strengths and limitations

To our knowledge no previous studies have analysed the longitudinal relationship between pain and fatigue in patients consulting the GP for fatigue. We studied these symptoms in a large cohort with five repeated measurements within one year. The advantage of longitudinal analysis is that the individual development of both fatigue and pain in time can be investigated. Our results add epidemiological evidence to a direct association between pain and fatigue over time in individual patients.

A limitation of this study concerns the analysis of potentially confounding and modifying factors. Follow-up data on these factors were not available, while some of these factors, namely, sleep problems, distress and perceptions are in fact also time dependent. Taking account of these factors seems to be important considering suggested (psycho) physiological mechanisms. Processes of both neuroimmunological dysregulation, resulting in central sensitisation, and neuroendocrine disturbance may play a role in the occurrence of pain and fatigue symptoms in patients with CFS, chronic widespread pain and fibromyalgia [20], [21], [28] and [29]. Dysfunction of neuroendocrine processes has also been associated with disturbed sleep and distress [20], [28] and [29]. Therefore, a repeated measurement of sleep and distress may reveal a confounding or modifying effect of these factors in the co-occurrence of fatigue and pain. To gain a better insight in the nature of the association between these symptoms, further longitudinal studies should take into account the time-dependent nature of potential modifying factors.

To answer our study question on the association between symptom change in both fatigue and pain, using equal time periods for the analysis would have been preferable. However, the main objective of our cohort study was to study the course of fatigue over time, and the timing of measurements was specifically chosen to optimally measure changes in fatigue following consultation. Although there is little knowledge on time patterns in biological processes relevant to fatigue, we expected most change in the first months, and therefore an additional assessment at 1 month was added. The difference between one or several months, however, may not be so critical when looking at temporal changes in multiple symptoms. Our hypothesis considered the *order* of changes in fatigue and pain in general, and the longitudinal analysis takes this into account, for the three different periods of time.

In contrast to fatigue, we did not have information on the duration of pain at baseline. Similar to the influence of fatigue duration on the relationship between fatigue and pain, the duration of pain could affect the occurrence of changes in fatigue as well. Furthermore, we used different scales for measuring fatigue and pain; since our study focused on patients with fatigue, our measurement of pain was less elaborate. The pain scale we used is well validated and has frequently been used; however, it consists of only two questions, with a limited number of response options, consequently leaving little room for detecting small changes. To gain more insight into longitudinal associations between both symptoms, it could be useful to use similar scales rating the severity (and impact) of symptoms. Our research question may also yield further insight when studied in a population of patients with both fatigue and pain as a main symptom. Nevertheless, we were able to show a longitudinal association between changes in pain and fatigue in patients presenting with fatigue, confirming the importance of co-occurring symptoms in patients with fatigue.

4.4. Study implications

Experiencing multiple symptoms has been associated with poor functioning and psychological symptoms [16] and [37]. Increasingly severe and limiting pain or fatigue has been shown to be increasingly associated with co-occurring fatigue or pain, and people reporting both symptoms more often experience anxiety or depression [7] and [11]. Our study shows that changes in pain and fatigue are directly associated in time. Future research, including qualitative studies, should further address which factors contribute to the longitudinal association of these common symptoms.

CONFLICT OF INTEREST

The authors state that there were no financial or other relationships that may represent any conflict of interest.

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TABLES AND FIGURES

Fig. 1. Schematic representation of the models used to analyse the longitudinal association between fatigue and pain.

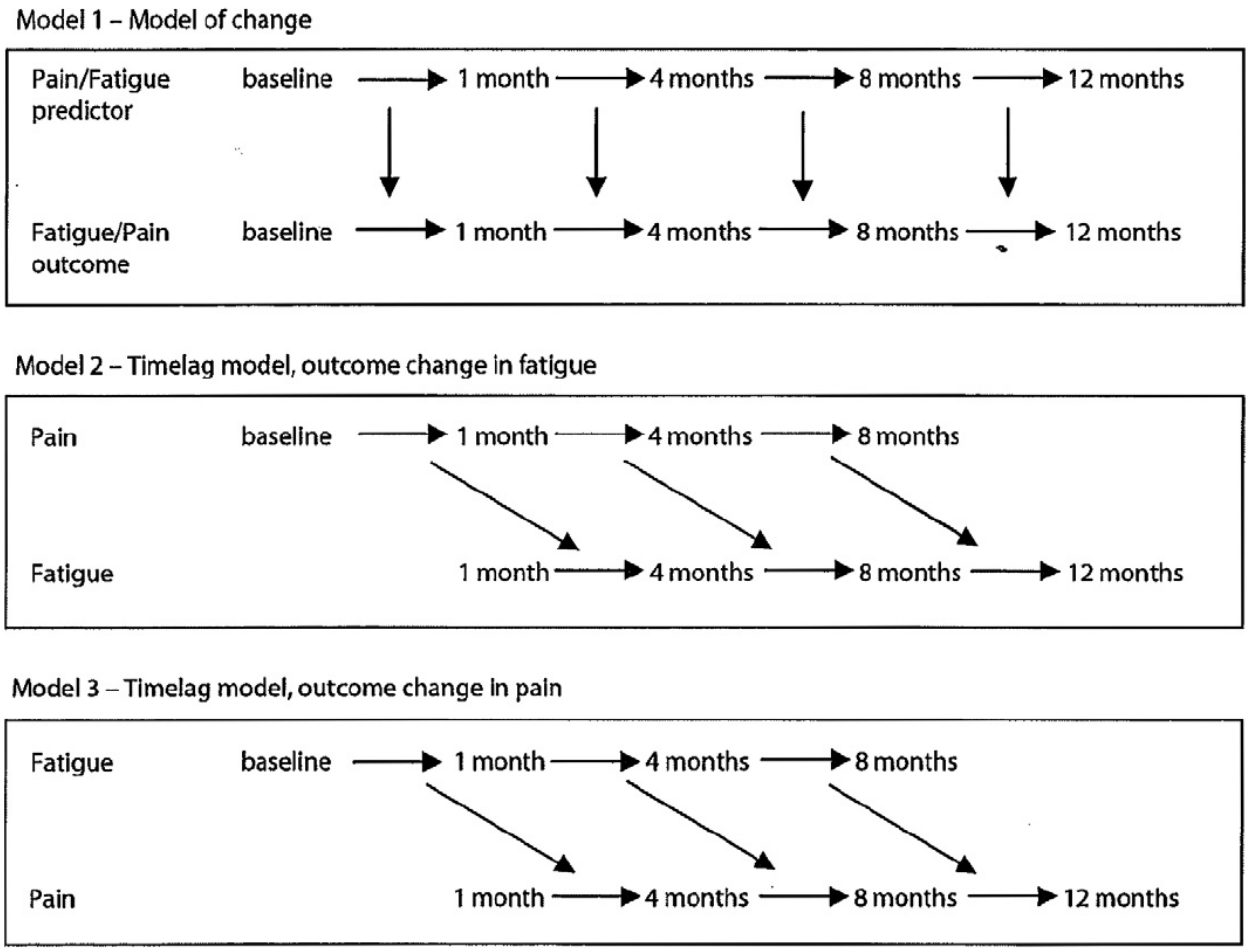


Table 1
Patient characteristics at baseline.

Patient characteristics	Number of patients (%) or mean (SD)
Age	41.8 (16.3)
Gender (female)	467 (73)
Married or living together	411 (64)
Care for children	242 (38)
Paid work	492 (77)
Educational level	
Primary	40 (6)
Secondary	483 (75)
College/university	118 (18)
Duration of fatigue	
<3 months	142 (23)
3–6 months	115 (19)
6–12 months	114 (18)
⩾1 year	252 (40)
Distress (4DSQ; range 0–32)	
Baseline; 1 year	13 (7.4); 8.7 (7.0)
Sleep (SCL90; range 3–15)	
Baseline; 1 year	7.0 (3.1); 6.4 (2.7)
Expecting a chronic course of fatigue (IPQ-R; range 5–30)	17 (4.5)

4DSQ = Four-dimensional symptom questionnaire; SCL90 = Symptom Checklist90; IPQ-R = Illness Perception Questionnaire-Revised.

Fig. 2. Standardised fatigue score in subgroups defined by fatigue severity over time (higher scores indicate more fatigue).

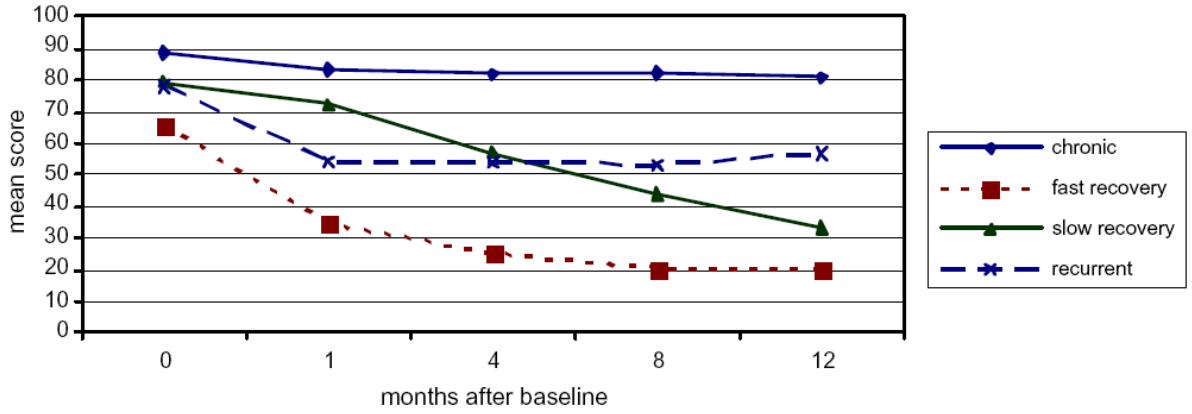
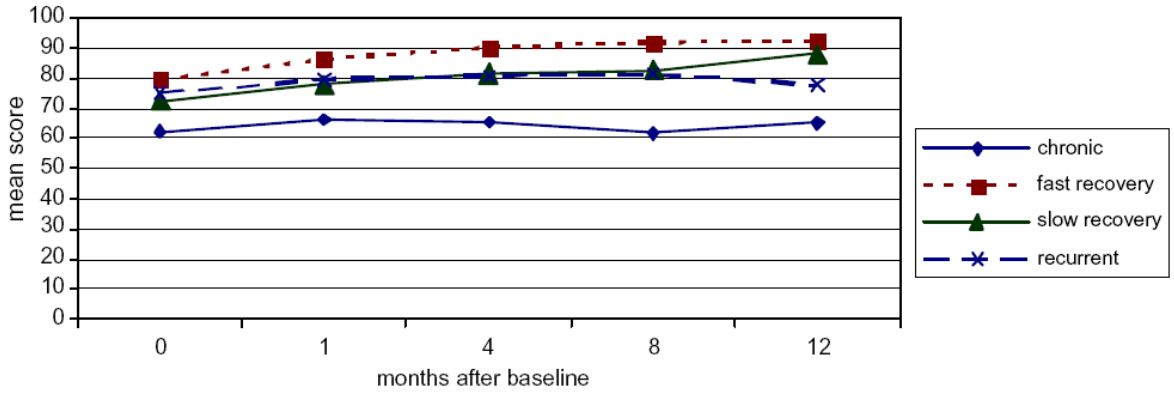


Fig. 3. Pain score in subgroups defined by fatigue severity over time (higher scores indicate less pain).



Nijrolder, I., Windt, D.A.W.M. van der, Twisk, J.W., Horst, H.E. van der. Fatigue in primary care: longitudinal associations with pain. Pain: 2010, 150(2), 351-357

Table 2
Scores of pain and fatigue over time.

	Baseline	1 Month	4 Months	8 Months	12 Months
Fatigue	79 (17)	63 (23)	57 (26)	53 (28)	50 (28)
CIS severity scale, standardised scores; mean (SD)	*n* = 641	*n* = 560	*n* = 560	*n* = 521	*n* = 565
Pain	72 (24)	77 (24)	78 (24)	78 (25)	79 (24)
SF36; mean (SD)	*n* = 642	*n* = 561	*n* = 560	*n* = 522	*n* = 566

CIS = Checklist Individual Strength; SF36 = Short-Form Health Survey 36. Note: higher scores on the fatigue scale indicate *more* fatigue, while higher scores on the pain scale indicate *less* pain.

Table 3
Longitudinal associations between fatigue and pain.

	Crude model		Adjusted for baseline pain and fatigue		Adjusted model*	
	B (95%CI)	*P*-value	B (95%CI)	*P*-value	B (95%CI)	*P*-value
Model of change, outcome: change in fatigue						
Predictor: change in Pain	−0.27 (−0.31; −0.18)	<0.001	−0.26 (−0.33; 0.19)	<0.001	−0.25 (−0.31; −0.18)	<0.001
Model of change, outcome: change in pain						
Predictor: change in Fatigue	−0.20 (−0.25; −0.15)	<0.001	−0.21 (−0.26; 0.16)	<0.001	−0.20 (−0.25; −0.15)	<0.001
Time lag model, outcome: change in fatigue						
Predictor: change in Pain	0.12 (0.04; 0.19)	0.002	0.12 (0.04; 0.16)	0.002	0.12 (0.05; 0.20)	0.002
Time lag model, outcome: change in pain						
Predictor: change in Fatigue	0.05 (−0.01; 0.11)	0.091	0.05 (−0.01; 0.11)	0.091	0.06 (0.02; 0.12)	0.083

Note: Higher scores on the fatigue scale indicate *more* fatigue, while higher scores on the pain scale indicate *less* pain.
* Model adjusted for age, gender, baseline levels of pain, fatigue, sleep, distress and expectations of a chronic course of fatigue.