Postprint Version	1.0
Journal website	http://dx.doi.org/10.1016/j.ejpain.2009.05.010
Pubmed link	http://www.ncbi.nlm.nih.gov/pubmed/19540139
DOI	10.1016/j.ejpain.2009.05.010

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Co-occurrence and associations of pain and fatigue in a community sample of Dutch adults

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ABSTRACT

Widespread pain and chronic fatigue are common in the general population. Previous research has demonstrated co-occurrence of syndromes that are associated with pain and fatigue (fibromyalgia and chronic fatigue syndrome), but there is limited existing data on the co-occurrence of these symptoms in general. This study investigates the co-occurrence of pain and fatigue, and characterises people with these symptoms individually, and in combination. A postal questionnaire was sent to a random sample of 4741 community dwelling Dutch adults registered with five general practices. There were 2447 participants (adjusted response = 53.5%). Persistent fatigue was reported by 60% of the 451 subjects with chronic widespread pain. Chronic widespread pain was reported by 33% of the 809 responders with persistent fatigue. Anxiety and depression were more common in subjects who reported both symptoms than those who reported either one or neither. Participants who had chronic disease, high body mass index, low activity levels or did not perceive ability to influence health had higher adjusted odds of reporting both symptoms (but not one alone) than subjects not having these characteristics. Pain and fatigue occur more often than would be expected by chance and there are a number of reasons for this. Clinicians should be aware that co-occurrence of the symptoms is common, especially in people who have high BMI or chronic disease, and that people with both symptoms are often anxious or depressed. Further work should address longitudinal associations of pain and fatigue.

1. INTRODUCTION

Numerous studies have demonstrated that chronic widespread pain ([Croft et al., 1993], [Hunt et al., 1999] and [White and Thompson, 2003]) and fatigue ([Pawlikowska et al., 1994], [Lawrie and Pelosi, 1995], [Skapinakis et al., 2000] and [Reyes et al., 2003]) are common symptoms in the general population. These symptoms have a varying degree of severity, being most severe in their associated syndromes of fibromyalgia (Wolfe et al., 1990) and chronic fatigue syndrome ([Fukuda et al., 1994] and [Reeves et al., 2003]).

Individuals with fibromyalgia are often more tired than those without ([Hudson et al., 1992] and [Buchwald and Garrity, 1994]). Conversely people with chronic fatigue syndrome more often have fibromyalgia than people who do not have this condition (Jason et al., 2000). Co-occurrence of the more general symptoms of pain and fatigue is less well investigated. Some authors have reported higher levels of

fatigue in subjects with pain ([Croft et al., 1993] and [Wolfe et al., 1995]), or that pain was more common in fatigued individuals ([Wessely et al., 1997] and [Njoku et al., 2007]), but a recent review could not identify studies reporting in more detail on the overlap of pain and fatigue in the community (Creavin, 2008). This is important as both symptoms influence quality of life ([Schweitzer et al., 1995] and [Aaron et al., 2002]), are associated with increased healthcare usage ([Hamilton et al., 2001] and [Kadam et al., 2005]), and psychological distress ([Wessely et al., 1997] and [Benjamin et al., 2000]). Having both symptoms may be more detrimental than one symptom alone.

Previous work has identified that pain is more often reported by individuals who are older ([Wolfe et al., 1995] and [Papageorgiou et al., 2002]) or female ([Croft et al., 1993] and [White and Thompson, 2003]). Additionally, subjects with widespread pain have higher levels of anxiety or depression ([Wolfe et al., 1995], [Hunt et al., 1999] and [Schochat and Raspe, 2003]). Similar associations of age, gender, anxiety, and depression, have been demonstrated with fatigue ([Skapinakis et al., 2000], [Hickie et al., 2002], [Bierl et al., 2004] and [Evengard et al., 2005]). Given this evidence, it is likely that these factors are also strongly associated with both symptoms in combination, although this has not been explored in depth. Less evidence exists for an association of pain or fatigue with lifestyle factors, such as high body mass index (BMI, [Kato et al., 2006] and [Schur et al., 2007], low activity levels ([Kroenke et al., 1988] and [Schur et al., 2007]), (co-morbid) chronic disease (Kenter et al., 2003) or self-efficacy ([Barry et al., 2003] and [Turner et al., 2005]). BMI, activity levels, chronic disease and illness perceptions are of interest because they are potentially modifiable, and while this is an epidemiological study, if an association exists, further work might explore a role for an intervention to modify these factors.

This paper aims to investigate the frequency with which pain and fatigue co-occur. Additionally, the association of BMI, activity levels, chronic disease and illness perceptions with reporting both symptoms will be explored.

2. METHODS

The sample for this analysis was participants in a large cross-sectional study conducted in the Netherlands (Van der Windt et al., 2008). A random sample of 4741 adults aged 18 years and over (approximately, 20% of the sampling frame) was taken from the registration lists of five General Practices. Individuals who did not speak Dutch and a small number of patients with severe psychiatric disorders or serious or life-threatening conditions (who were unfit to complete a questionnaire, or for whom the questionnaire would be too much of a burden) were excluded by General Practitioners (GPs).

2.1. Data collection

An information letter and self-completion postal survey was sent to the study sample. Non-responders were sent a reminder card two weeks after the initial questionnaire, on which they could indicate reasons for non-response. A further letter, with a new copy of the questionnaire, was sent after four weeks. The medical ethics review board of the VU University medical centre granted ethical approval.

2.2. Measures

The questionnaire asked about the presence of symptoms including fatigue and musculoskeletal pain lasting at least 24 h in the past month ([Pope et al., 1997], [Papageorgiou et al., 2002] and [Thomas et al., 2004]) and about GP consultation for these symptoms (*yes* or *no*) in the past 3 months. Pain was classified as being in the following locations: hand or wrist, elbow or arm, shoulder, neck, back, hip or knee, ankle or foot. In addition, responders were asked to indicate when the symptoms started (response options: *less than* 1 *month ago*, 1–3 *months ago*, 3–6 *months ago, more than* 6 *months ago*), how frequently the symptoms were experienced in the past 3 months and how often they caused limitations of work or daily activities (three response options: *sometimes – about once per month, often – about* 5 *days per month,* (*nearly*) *always – more than half of all days*). BMI was calculated using responders self reported height and weight. The survey had additional questions concerning age, sex, presence of a chronic disease (self-reported asthma, heart disease, diabetes, cancer, arthritis, fibromyalgia, any), and the frequency of physical activity (*How often in the past* 3 *months did you exercise or carry out heavy physical work* (*in leisure time*) *lasting long enough to get sweaty*, response options: *less than once per month, about once per month, about two to three times per month, about one to two times per week, three or more times per week*), which was analysed as less than weekly vs. weekly or more). The Hospital Anxiety and Depression Scale (Zigmund and Snaith, 1983) was used, with subscale scores of 8–10 for "possible" and more than 10 for "probable" anxiety or depression, as recommended by the instrument developers. Personal control was assessed using one item of

the illness perception questionnaire (*I believe I can influence my health*, five response options including *don't know*: *fully agree to fully disagree*) (Moss-Morris et al., 2002).

2.3. Definitions

Table 1 presents the empirical definitions of pain and fatigue. All responders to the survey were categorised into one of four mutually exclusive pain categories. The definition for chronic widespread pain approximated the American College of Rheumatology definition (Wolfe et al., 1990), but subjects did not need to have pain in contralateral limbs, as this information was unavailable for the empirical analysis. Subjects who had pain lasting more than 3 months in each of upper limb (any of hand/wrist, elbow/arm, shoulder) and lower limb (any of hip/knee, ankle/foot) and axial pain (either neck or back) were classified as having chronic widespread pain.

[TABLE 1.]

Subjects with chronic widespread pain were further classified into those who were limited by their pain in two of the three anatomical sites on at least 5 days per month (classified as having limiting widespread pain, CWP+L) and those who were not limited by their pain to this extent (classified as having non-limiting widespread pain, CWP−L). Subjects who did not meet the criteria for CWP but reported pain in at least one of the seven locations (hand/wrist, elbow/arm, shoulder, neck, back, hip/knee, ankle/foot) lasting at least 3 months were classified as having chronic regional pain (CP) ([IASP, 1986] and [Macfarlane et al., 2008]). Subjects not meeting these criteria were classified as having no chronic pain. Subjects were included in only one group, which means for example, that although participants with CWP+L met criteria for CWP−L and CP, they were analysed separately.

Additionally, all subjects were classified into one of three mutually exclusive fatigue groups. Many definitions exist in the literature, both for chronic fatigue, and chronic fatigue syndrome; this paper focuses on chronic fatigue. Chronic fatigue is often defined as fatigue that lasts more than 6 months, but this is not always the case ([David et al., 1990] and [Skapinakis et al., 2003]). In this study, to aid comparisons between chronic fatigue and chronic pain, chronic fatigue was defined as fatigue that lasted for 3 months or more. Subjects who reported fatigue in the last month and also fatigue lasting 3 months or more and occurring on at least 5 days per month were classified as having persistent fatigue (PF−L). Subjects who were additionally limited by their fatigue on at least 5 days per month were classified as having limiting persistent fatigue (PF+L). All subjects not meeting these criteria were classified as having no persistent fatigue.

For analysis of the co-occurrence of the symptoms, subjects were again classified into one of four mutually exclusive groups but for this part of the analysis the limiting effect of the symptoms was not considered. Subjects with both CWP and persistent fatigue were classified as having both symptoms. Subjects with CWP but not fatigue were classed as having CWP only, subjects with persistent fatigue but not CWP as having fatigue only, and all others as having neither symptom.

2.4. Analysis

Cross-tabulations were used to examine the proportion of subjects with pain (chronic regional, CWP with and without limitations of daily life) who reported fatigue and the proportion with fatigue (with and without limitations) who reported pain. Results were further stratified by age and gender.

When examining differences in demographics between the subjects with different symptoms (neither, pain, fatigue, both), chi square tests were used to test statistical significance of findings across subgroups for categorical variables and ANOVA was used to test the null hypothesis that the mean for BMI and age was equal in all groups. Post hoc analyses using Bonferroni adjustment (dividing the significance level of $\alpha = 0.05$ by the number of tests) was used to test which between-subgroup differences were statistically significant.

Odds ratios (ORs) with 95% confidence intervals (95% CI) were produced using logistic regression to examine the association of reporting both symptoms with BMI (<25 kg/m^2 vs. ≥ 25 kg/m^2), activity levels (weekly vs. less than weekly), chronic disease and perceived ability to influence health (perceives ability vs. don't know vs. does not). Odds ratios were subsequently adjusted for age, gender, anxiety and depression. SPSS 14.0 was used for all statistical analyses.

3. RESULTS

Completed questionnaires were returned by 2447 individuals, a further 171 blank questionnaires were sent back as a result of incorrect address or deceased addressee. The adjusted response rate was therefore 53.5%. Demographics of the responders have been presented previously (Van der Windt et al., 2008). In brief, 58% of responders were female and the mean (standard deviation) age was 49.9 (16.1) years. Approximately half of responders were overweight or obese, 8% perceived that they could not influence their health, 31% had a chronic disease and 50% exercised less than weekly. Analysis of non-response suggested that non-responders were more likely to be male and aged slightly younger than responders (Van der Windt et al., 2008).

Chronic regional pain was reported by 966 (39%) of all 2447 responders. A further 451 individuals (18%) reported chronic widespread pain, of whom 332 (14% of all responders) were limited by their symptoms.

The prevalence of non-limiting persistent fatigue was 17% (n = 404), and a further 405 responders (17%) reported limiting persistent fatigue.

3.1. Co-occurrence of symptoms

Persistent fatigue was more common with increasingly severe pain, being reported by 18% of subjects with no chronic pain, 37% with chronic regional pain, 47% of those with CWP not limiting daily activities (CWP−L) and 64% of subjects with CWP that did limit daily activities (CWP+L).

Pain was more common in fatigued individuals than those without fatigue. Chronic regional pain was reported by 37% of subjects with no fatigue, 48% of those with persistent fatigue not limiting daily activities (PF−L) and 42% with persistent fatigue that did limit daily activities (PF+L). Similarly, CWP−L was reported by 4% of persons with no fatigue, 7% with PF−L and 6% with PF+L. The association was most marked for CWP+L; this degree of pain was reported by 7% of subjects with no fatigue, 18% with PF−L and 34% with PF+L.

When stratified by gender the results showed a similar pattern in men and women with fatigue occurring more often in women with pain than men. Chronic regional pain was reported by 49% of fatigued men and 43% of fatigued women, and CWP was reported by a further 30% of fatigued men and 34% of fatigued women. In both genders, persistent fatigue was reported more often by those with CWP (55% of males, 62% of females) than those with chronic regional pain (31% of males, 41% of females) (see Fig. 1).

[FIGURE 1]

When stratified by age approximately 45% of fatigued individuals in each age group reported chronic regional pain. In contrast CWP was reported by 22% of the fatigued young persons (<40 years), 36% of the fatigued middle aged (40–60 years) and 44% of the fatigued older persons (>60 years). Fatigue was reported more often by young persons with pain (45% of those with chronic regional pain and 71% with CWP) than middle aged (37% of those with chronic regional pain and 59% with CWP) or older people (31% with chronic regional pain and 53% with CWP) (see Fig. 2).

[FIGURE 2]

Table 2 shows the characteristics of subjects with either, neither or both CWP and persistent fatigue based on unadjusted analysis. ANOVA demonstrated statistically significant differences in mean age across the groups, with the fatigue only group having the lowest mean age and the pain only group having the highest mean age. Post hoc analysis with Bonferroni correction showed that there were statistically significant differences between the group with no symptoms and those with either pain or fatigue, and between those with pain only and those with fatigue only, but not for other comparisons (data not shown). Mean BMI was lowest in those with neither pain nor fatigue and highest in those with pain only, and post hoc analysis demonstrated a statistical difference between subjects with neither symptom and subjects with pain only or both, and those with fatigue only and those with pain only or both.

[TABLE 2.]

Chi square tests demonstrated statistically significant findings for all other characteristics (demographic variables, self-reported chronic disease and psychological factors), with the exception of cancer. For several comparisons (gender, overweight/obese, unemployment, one-person households, weekly exercise, heart disease, arthritis, and psychological factors) there was a trend for the group with both symptoms to be a more extreme version of the groups with one symptom (e.g. 17% of subjects with both symptoms were

probable cases of depression, compared to 8% of those with CWP, 12% with fatigue and 3% with neither symptom). The proportion of subjects who reported caring for others was similar in the group with both symptoms (35%) and those with neither symptom (36%), lowest in the group with pain only (27%) and highest in the group with fatigue only (45%); the proportion with young children showed a similar trend (18%, 18%, 11%, 28%, respectively). The proportion of responders with only a primary level of education was higher in both the group with pain only (42%) and the group with both symptoms (35%) than either responders with fatigue only or neither symptom (both 25%). Subjects with either both symptoms, or fatigue only, more often smoked every day (26%, 22%) than those with pain only (19%), or neither symptom (18%), but were less often consumers of more than 10 units of alcohol per week. For comparisons of asthma and diabetes subjects in the three groups with symptoms were consistently different to subjects in the group with neither symptom.

Table 3 shows the crude and adjusted odds ratios for the association of reporting both symptoms (rather than neither) with BMI, activity levels, perceived ability to influence health and chronic disease. After adjusting for confounders (age, gender, anxiety and depression), odds of reporting both symptoms (rather than neither) were statistically significantly higher in subjects with higher BMI compared to normal or low (OR 1.7, 95% CI: 1.2, 2.3), being active less than weekly compared to being active weekly (OR 1.5, 95% CI: 1.1, 2.1), having any chronic disease (OR 3.9. 95% CI: 2.9, 5.4), and with the perception of not being able to influence health (OR 3.2, 95% CI: 2.0, 5.1). Reporting both pain and fatigue had strong associations with some specific chronic conditions: heart disease (OR 2.6, 95% CI 1.6, 4.5); diabetes (OR 2.3, 95% CI 1.3, 4.0); arthritis (OR 5.0, 95% CI 3.2, 7.9); fibromyalgia (OR 13, 95% CI 4.6, 38.4); and cancer, although this association was not statistically significant (OR 2.2, 95% CI: 0.95, 5.27).

[TABLE 3].

4. DISCUSSION

4.1. Main findings

Previous work has shown co-occurrence of strictly defined syndromes associated with pain and fatigue, but to our knowledge this study is the first to quantify the co-occurrence of pain and fatigue as symptoms in the general population. Our results demonstrate that the co-occurrence of pain and fatigue is consistently high regardless of age or sex.

Fatigue was reported by 64% of subjects with limiting widespread pain, compared to 18% of subjects with no chronic pain. In people with limiting fatigue, 34% also had limiting widespread pain, compared to 7% of non-fatigued individuals. Some of the findings may be due to the underlying prevalence of the symptoms alone, that is, the symptoms may have occurred together by chance, and this can be calculated by multiplying the prevalence of one symptom by the other. In this study nearly two times as many women and three and a half times as many men with CWP+L reported limiting fatigue as would be expected given the underlying prevalence of the symptoms, and this finding was consistent across all age groups (data not shown, but available from authors). Increased odds of reporting both symptoms were found in subjects with higher BMI, being less active than weekly, having certain chronic diseases (heart disease, diabetes, arthritis) and with the perception of not being able to influence health.

4.2. Possible explanations for the co-occurrence of pain and fatigue

In a cross-sectional study it is impossible to determine the direction of causality, if any exists. It is likely that there is more than one explanation for the co-occurrence of pain and fatigue, and indeed the extent to which any one mechanism mediates the co-occurrence in an individual may vary over time. Some chronic diseases can cause both pain and fatigue, such as cancer ([Wagner and Cella, 2004] and [Van den Beuken-van Everdingen et al., 2007]), multiple sclerosis ([O'Connor et al., 2007] and [Putzki et al., 2008]), and arthritis ([Wolfe et al., 1996], [La Montagna et al., 1997], [Peat et al., 2001] and [Grotle et al., 2008]). Although only 25% of subjects with both symptoms reported such a condition (i.e. cancer or arthritis), any underlying painful chronic condition may account for some of the empirical findings, as fatigue is a common feature of chronic pain (Zautra et al., 2007). A second explanation is that the symptoms are linked as a result of drug side effects, such as opioid analgesics (Ytterberg et al., 1998), agents for neuropathic pain (Kusturica et al., 2002) or inhibitors of angiotensin converting enzyme (Join Formulary Committee, 2008). A third reason for symptom co-reporting is that both pain and fatigue are associated with anxiety or

depression. Mental health problems are more common in people with widespread pain (Benjamin et al., 2000), fatigue has been reported to be common in people with depression ([Kumar et al., 2004] and [Shiels et al., 2004]) and depressed people more often have high levels of pain (Bair et al., 2003). The odds ratios were attenuated after adjustment for anxiety and depression and residual confounding is possible. It is possible that other psychological factors may explain part of the apparent relationship between self-reported chronic disease and reporting of both symptoms. Processes of somatisation may increase attention to bodily symptoms, and strengthen the attribution of such sensations to physical illness. This could, for example, increase the reporting of fatigue, pain, non-cardiac chest pain, and possibly self-reported heart disease. Fourthly, it is possible that pain and fatigue *per se* might be directly pathologically linked, and this might be mediated through central sensitisation, resulting from neuroendocrine disturbance (McBeth et al., 2007), which has been proposed as a pathological mechanism responsible for part of both fibromyalgia (Yunus, 2007) and chronic fatigue syndrome (Meeus and Nijs, 2007). Finally, the symptoms may be reported in parallel but not causally linked.

4.3. Limitations of the study

The data in this study was based on self-report. We have used components of validated questionnaires to provide data on psychological factors (anxiety, depression and illness perceptions) and have provided full details of questions that were not part of a previously used questionnaire. The assessment of symptoms can only be based on self-report, and we selected questions that have been used in other community-based surveys (e.g. [Pope et al., 1997] and [Papageorgiou et al., 2002]). However, this issue should be considered when interpreting the estimates for the prevalence of chronic disease, and the associations of the symptoms with the chronic diseases. Other investigators have reported similar figures for the prevalence of asthma (5%, c.f. 8% Dalstra et al., 2005 and 5% ([Mohangoo et al., 2006] and [Uijen et al., 2008])), diabetes (5%, c.f. 3% Dalstra et al., 2005 and 6.8% (Bindraban et al., 2008)), heart disease (7%, c.f. 3.4% Dalstra et al., 2005)), cancer (2%, c.f. 1.5% Dalstra et al., 2005)), arthritis (7%, c.f. 5% Dalstra et al., 2005)) and fibromyalgia (1% c.f. 2%, Wolfe et al., 1995). Our estimates for the prevalence of symptoms are supported by comparison with the existing literature (discussed below).

4.4. Comparison to existing literature

The estimated prevalence of chronic widespread pain in this study (18%) is higher than other estimates (e.g. 11% in Croft et al., 1993; 13% in Hunt et al., 1999). One reason for this might be because the American College of Rheumatology (ACR) definition of chronic widespread pain (Wolfe et al., 1990) was only approximated in this study. In our definition, subjects did not need to have pain in contralateral limbs, as this information was unavailable for the empirical analysis.

The prevalence of persistent fatigue was also higher than other population based estimates (e.g. 18% in Pawlikowska et al., 1994; 14% in Lawrie and Pelosi, 1995). This could be because the current study used a temporal element of 3 months, as opposed to the more commonly used 6 months duration. However, this seems unlikely because the prevalence of frequent fatigue lasting 3 months or more (33%) was very similar to the prevalence of fatigue lasting 6 months or more (30%) (Creavin, 2008). Existing literature reveals remarkable consistency in the prevalence of fatigue, even when large differences in the definition exist, for example, Skapinakis et al. (2003) reported that the prevalence of fatigue lasting 1 month or more was 15%, which is similar to the figure of 11.5% reported by David et al. (1990) for fatigue lasting 3 months or more, and the 11.3% reported by Wessely et al. (1996) for fatigue lasting 6 months or more. The definition of persistent fatigue was less restrictive than previous definitions of fatigue, most notably that for chronic fatigue syndrome (Fukuda et al., 1994), and therefore we suggest that other differences in definition (or selective non-response, discussed below) may explain the higher estimates reported here.

The degree of symptom co-occurrence is supported by the work of others who have demonstrated that fatigue is more common in people with chronic widespread pain than those without pain (Croft et al., 1993) and that there is more pain in people with more severe fatigue than less severe fatigue (Njoku et al., 2007).

4.5. Response rate and generalizability of findings

The response rate for the survey was less than desired, despite following measures which have been suggested to increase response (Edwards et al., 2002). Other community studies investigating the prevalence of pain or fatigue have also reported response rates below 65% (Pawlikowska et al., 1994: 48.3% (64% after adjustments); Picavet and Schouten, 2003: 46.9%; Huibers et al., 2004: 45%). We used several methods to estimate the potential influence of non-response on our findings in particular regarding estimates of the prevalence of symptoms. Compared to the Dutch population (Statistics Netherlands, 2008)

the study sample was largely similar with comparable levels of chronic disease, but had a higher proportion of females, older people, one-person households and unemployed people. Selective non-response of healthy individuals may have resulted in an overestimation of the prevalence of chronic widespread pain and persistent fatigue, assuming that non-responders were more likely to be without these symptoms. In this study, 29% of non-responding subjects who gave a reason for non-participation indicated that they had no health problems. Analyses of response to subsequent mailings showed that there might be some selective non-response of persons with more anxiety or depression, but the number and severity of symptoms were similar in early and late responders (Van der Windt et al., 2008). In a sensitivity analysis, if all non-responders were free of CWP and persistent fatigue then in a sample of 4741 people, chronic widespread pain would be found in 451 and persistent fatigue would be found in 809, giving prevalences of 10% and 17%, respectively, close to previously reported estimates ([Croft et al., 1993], [Pawlikowska et al., 1994], [Lawrie and Pelosi, 1995] and [Hunt et al., 1999]).

4.6. Implications and further work

It is likely that more than one explanation connects the symptoms and further work could investigate the extent to which each of these mechanisms mediate the co-occurrence of the symptoms. It would also be helpful to investigate the interactions between pain and fatigue over time, particularly to determine in which people the symptoms progress to functional syndromes, and how this progression occurs. This may help in the early identification of individuals with poor outcome, and may help to develop more successful, targeted interventions for pain and fatigue. It will be important to carry out such research in community-based or primary care populations if the aim is to prevent chronic symptoms and related disability, rather than to focus on management of chronic functional syndromes.

The finding that perceived ability to influence health was strongly associated with reporting both symptoms also deserves further investigation. Personal control or self efficacy has previously been found to be associated with a poorer outcome for fatigue (Ray et al., 1997), and greater pain-related disability (Asghari and Nicholas, 2001) and may have additional associations with depressive symptoms, employment status and pain distribution (Rahman et al., 2004). Patients who have additional symptoms, (i.e. both pain and fatigue rather than one symptom alone), may have greater disease severity, either perceived or actual, and this may affect their self efficacy. The perception of being unable to influence health may be related to an increased tendency to report symptoms (making co-occurrence more likely to be reported), or be a valid perception that results from severe and disabling symptoms. Additionally, perceived ability to influence health may be partly responsible for the other associations that were noted, as perceptions have previously been shown to be associated with being physically active (Gillis, 1993), which in turn is known to be related to BMI (Murphy et al., 2007) and therefore diabetes (Manson et al., 1992), heart disease (Manson et al., 1999), and arthritis (Sahyoun et al., 1999).

Pain and fatigue are very common symptoms in the general population and are often limiting in nature. Co-reporting of the symptoms is common, and happens more often than expected by chance, especially in those with more severe symptoms. Reporting both symptoms is associated with high BMI, low levels of activity and not perceiving the ability to influence health. Additional associations exist with chronic disease, anxiety, and depression. Clinicians should be aware that pain and fatigue often co-occur, particularly in people with high BMI and chronic disease, and should be alert for anxiety and depression in patients who report both symptoms.

ACKNOWLEDGEMENTS

Dr. George Peat provided some advice on the statistical analysis. The authors thank the doctors, staff and patients of the participating general practices.

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TABLES AND FIGURES

Table 1: Empirical definitions of pain and fatigue.

Definition	
Chronic regional pain	Pain in the last month and also pain lasting at least 3 months in at least one of seven locations
Non-limiting chronic widespread pain (CWP−L)	Pain in the last month and also pain lasting at least 3 months in each of upper limb, lower limb and axial pain
Limiting chronic widespread pain (CWP+L)	As CWP−L and additionally limited by their pain in two of the three anatomical sites on at least 5 days per month
Non limiting persistent fatigue (PF)	Fatigue in the last month and also fatigue lasting 3 months or more and occurring on at least 5 days per month
Limiting persistent fatigue (PF+L)	As PF and additionally limited by their fatigue on at least 5 days per month

Fig. 1. Co-occurrence of pain and fatigue stratified by gender.

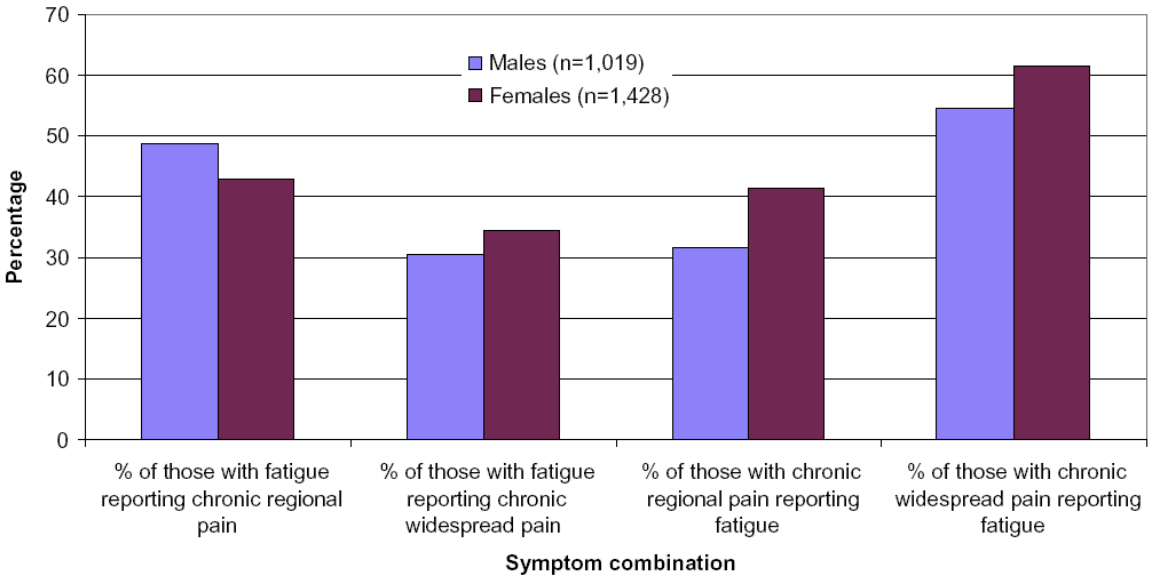

Fig. 2. Co-occurrence of pain and fatigue in different age groups.

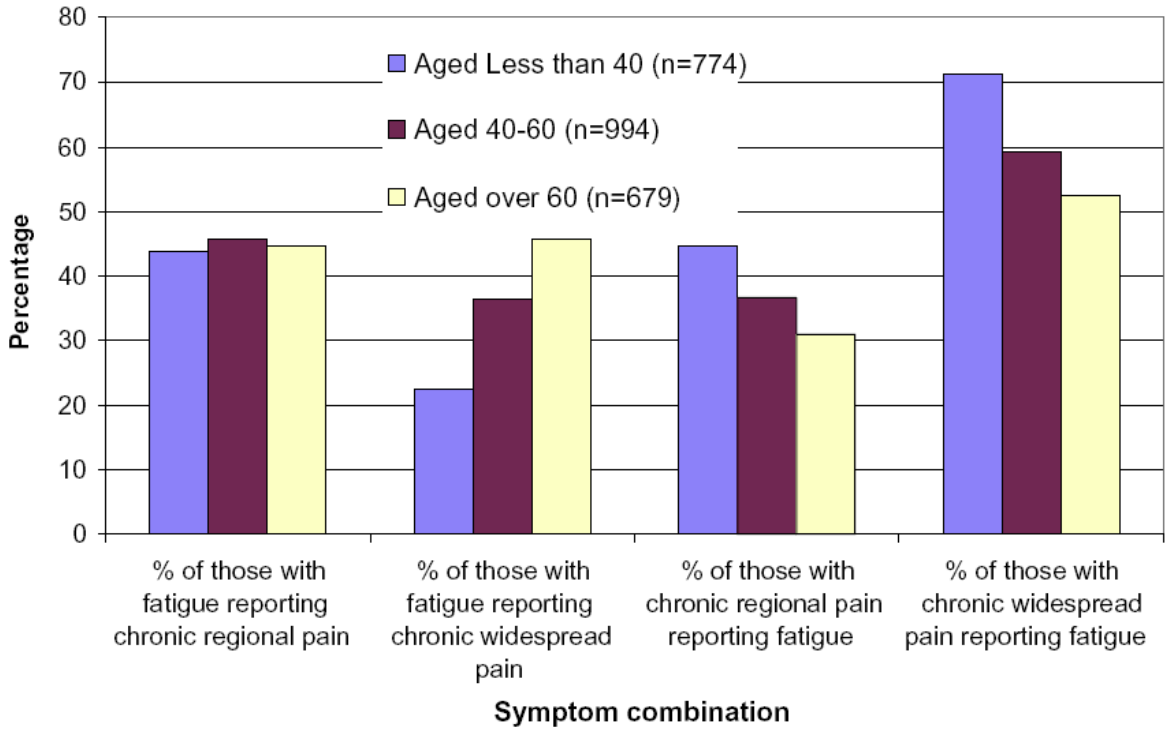

Table 2: Characteristics of responders with pain and fatigue, alone and in combination (n = 2447a), figures are % (n), unless indicated otherwise.

	Neither (n = 1455)	**Fatigue only (n = 541)**	**Pain only (n = 183)**	**Pain and fatigue (n = 268)**	**Pb**
Female	51.8 (753)	67.5 (365)	65.0 (119)	71.3 (191)	<0.001
Mean age (SD)	49.9 (16.4)	46.9 (16.1)	56.0 (13.6)	52.2 (14.8)	<0.001
Mean BMI (SD)	25.4 (4.2)	25.6 (6.1)	27.1 (14.6)	27.0 (5.0)	<0.001
Overweight or obese					
(BMI ≥ 25)	48.5 (682)	47.1 (245)	55.1 (97)	62.8 (162)	<0.001
Unemployedc	6.3 (92)	15.0 (80)	15.4 (28)	31.9 (85)	<0.001
One person household	18.6 (270)	17.7 (96)	23.0 (42)	25.4 (68)	<0.001
Care for others	35.6 (518)	45.2 (244)	26.8 (49)	35.0 (93)	<0.001
Children aged <5 years old	18.2 (204)	28.1 (114)	10.6 (15)	17.6 (30)	<0.001
Education: primary only	25.1 (363)	24.8 (134)	41.8 (76)	35.0 (93)	<0.001
Education: college or	38.3 (555)	39.4 (213)	25.3 (46)	22.2 (59)	<0.001

	Neither (n = 1455)	**Fatigue only (n = 541)**	**Pain only (n = 183)**	**Pain and fatigue (n = 268)**	**Pb**
university					
Exercise weekly	53.7 (782)	45.8 (248)	50.3 (92)	39.2 (105)	<0.001
Smoke everyday	17.9 (260)	22.4 (121)	19.2 (35)	25.6 (68)	0.036
>10 units alcohol per week	16.3 (236)	11.8 (63)	20.3 (37)	11.7 (31)	<0.001
Self-reported chronic disease					
Asthma	4.1 (59)	8.3 (45)	7.7 (14)	7.5 (20)	0.001
Heart disease	4.8 (70)	9.8 (53)	7.1 (13)	12.3 (33)	<0.001
Diabetes	3.7 (54)	6.5 (35)	8.7 (16)	8.6 (23)	<0.001
Cancer	1.7 (25)	2.4 (13)	1.6 (3)	3.4 (9)	0.316
Rheumatoid Arthritis or osteoarthritis	4.6 (67)	5.0 (27)	20.2 (37)	21.3 (57)	<0.001
Fibromyalgia	0.4 (6)	0.2 (1)	3.8 (7)	6.3 (17)	<0.001
No chronic disease	76.2 (1104)	66.9 (362)	51.9 (95)	42.2 (113)	<0.001
Psychological factors					
Illness perception: can influence health (largely/fully disagree)	5.9 (85)	8.4 (45)	9.9 (18)	17.5 (46)	<0.001
Anxiety, probable (HADS > 10)	3.8 (54)	16.4 (88)	10.0 (18)	27.2 (72)	<0.001
Depression, probable (HADS > 10)	2.6 (37)	11.7 (63)	8.3 (15)	17.3 (46)	<0.001

a Figures are subject to missing data (<5% per variable) and are given as percentage of column total.
b ANOVA for continuous variables (age and BMI), Chi squared for categorical variables (all others).
c Unemployed: figure given include both “unemployed” and receiving “disability benefit”.

Table 3: Odds ratios (and 95% confidence intervals) for the association of BMI, activity, illness perception and chronic disease with reporting both pain and fatigue (n = 268a) compared to neither symptom (n = 1455a).

Factor		**R^2**	**Crude OR (95% CI)**	**Adjusted[b] OR (95% CI)**
BMI	≥25 vs. <25	0.02	1.79 (1.37, 2.36)	1.67 (1.22, 2.28)
Activity	Less than weekly vs. at least weekly	0.02	1.80 (1.38, 2.35)	1.52 (1.13, 2.05)
Illness perception	Do not know vs. agree	0.08	3.14 (2.30, 4.29)	2.13 (1.49, 3.05)
	Disagree vs. agree	0.08	4.52 (3.03, 6.74)	3.23 (2.03, 5.13)
Chronic disease	Asthma	0.01	1.90 (1.13, 3.22)	1.49 (0.82, 2.70)
	Heart disease	0.02	2.77 (1.79, 4.28)	2.64 (1.56, 4.46)
	Diabetes	0.01	2.43 (1.46, 4.03)	2.26 (1.27, 4.01)
	Cancer	0.00	1.98 (0.91, 4.29)	2.24 (0.95, 5.27)
	Arthritis (rheumatoid or osteoarthritis)	0.07	5.57 (3.80, 8.16)	5.04 (3.21, 7.92)
	Fibromyalgia	0.04	16.29 (6.36, 41.71)	13.22 (4.56, 38.36)
	Any chronic disease	0.11	4.39 (3.35, 5.76)	3.93 (2.87, 5.40)

[a] Maximum group size. Subject to missing data.
[b] Adjusted for age, sex, anxiety and depression.