

Musculoskeletal pain is associated with a long-term increased risk of cancer and cardiovascular-related mortality

J. McBeth¹, D. P. Symmons¹, A. J. Silman^{1,2}, T. Allison³, R. Webb⁴, T. Brammah⁵ and G. J. Macfarlane⁶

Objectives. To test the hypothesis that individuals with regional and widespread pain disorders have an increased risk of mortality.

Methods. We conducted a prospective cohort study of 4515 adults. Subjects were an age- and sex-stratified sample who had participated in a population study of pain occurrence during 1996. Based on those reports subjects were classified as having no pain, regional pain or widespread pain. All subjects were identified on the National Health Service Central Register and followed up until April 2005, a total of 8.2 yrs, at which time information was obtained on vital status, and if applicable, date and cause of death. The relationship between pain status and subsequent death is expressed as mortality rate ratios with 95% CIs, adjusted for age, gender, ethnicity and practice.

Results. A total of 35.2% reported regional pain and 16.9% satisfied criteria for widespread pain. In comparison with those without pain, there was a 20% and 30% increased risk of dying over the follow-up period among subjects with regional and widespread pain, respectively. The specific causes of death in excess were cancer and cardiovascular disease. In addition, the mortality risk from both cancer and cardiovascular deaths was found to increase as the number of pain sites that subjects reported increased.

Conclusions. This study supports a previous observation that persons with regional and widespread pain are at an increased risk of cancer death. Possible mechanisms should be explored.

KEY WORDS: Pain, Musculoskeletal, Mortality, Cancer, Cardiovascular, Epidemiology, Population-based study, Prospective, Mechanisms.

Introduction

Pain that is widespread throughout the body is the cardinal symptom of fibromyalgia [1]. Although the aetiology of this syndrome is unclear a number of factors including trauma [2], genetic factors [3–5] and psychological factors [6] have been implicated in symptom onset. In the short term following onset, the majority of cases of chronic widespread pain [7] and fibromyalgia [8] tend to persist and are associated with a loss of function and high levels of disability [9]. The long-term health consequences of having chronic widespread pain is however unclear.

We have previously demonstrated that subjects who reported widespread pain in a population-based survey [10] had an increased risk of mortality compared with those reporting no pain over the following 9 yrs. Although deaths from external causes (suicides and accidents) were increased in those with widespread pain, these deaths were rare and the excess mortality was almost entirely explained by deaths from cancer. Similar relationships, albeit slightly attenuated, were observed for those subjects reporting regional pain symptoms. A further analysis of the same data set revealed that widespread pain was associated with both cancer onset (incidence) and subsequent reduced survival [11]. The strongest relationship was with breast and prostate cancer, with smaller effects for gastrointestinal and lung cancer. These relationships persisted after adjustment for age, gender, social class and smoking. Although intriguing, this was

the first report of such a relationship and subsequent analyses of data relating to chronic pain in general [12] or ‘widespread’ pain [13, 14] have been equivocal. These discrepancies may be explained by differences in the cohorts studied or uncontrolled confounding effects. The observation requires replication in a separate population-based cohort before investigating mechanisms that potentially link regional and widespread pain and mortality. A cohort study conducted in 1996 in the North West of England afforded a unique opportunity to do so.

The aim of the current study was to determine whether our initial observation of a higher rate of cancer mortality among subjects with regional and widespread pain would be confirmed in a new general population sample.

Methods

Study design

The study was a population-based cross-sectional study of pain and has been described in detail elsewhere [15, 16]. In brief, subjects aged 16 yrs and over were recruited from three general practices in North West England. The Tameside and Glossop Research Ethics Committee approved the original study. The follow-up study was approved by the North West Multi-centre Research Ethics Committee and the University of Manchester Committee on the Ethics of Research. The Office for National Statistics approved the provision and use of death registration data. An age- (16–44, 45–64, 65–74 and 75+ yrs) and sex-stratified random sample of 750 subjects from each stratum was identified from the combined practice lists. Of those, 86 subjects were excluded from the original sample selected as they had recently died or were terminally ill and were replaced with the next eligible patient on the list. Each of the remaining subjects was mailed a postal questionnaire between January and November 1996 with non-responders being sent a reminder postcard 2 weeks after the mailing of the initial questionnaire and a further copy of the questionnaire 2 weeks later. A total of 4515 subjects returned the questionnaire, giving a response rate of 78.5% after removing from the denominator those subjects who had moved and were unlikely to have received the study questionnaire ($N = 228$). Younger subjects and men were more likely not to participate.

¹Arthritis Research Campaign (ARC) Epidemiology Unit, Epidemiology Research Group, Research School of Translational Medicine, University of Manchester, Manchester, ²ARC House, Chesterfield, ³National Primary Care Research and Development Centre, ⁴Psychiatry and Health Methodology Research Groups, School of Community Based Medicine, University of Manchester, Manchester, ⁵Tameside General Hospital, Ashton-Under-Lyne and ⁶Aberdeen Pain Research Collaboration (Epidemiology Group), Department of Public Health, University of Aberdeen, School of Medicine, Aberdeen, UK.

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Correspondence to: J. McBeth, Arthritis Research Campaign (ARC) Epidemiology Unit, Epidemiology Research Group, Research School of Translational Medicine, Stopford Building, University of Manchester, Manchester, M13 9PT, UK. E-mail: john.mcbeth@manchester.ac.uk

Study questionnaire

The study questionnaire gathered demographic information: age, gender and ethnicity. In the questionnaire, subjects were asked whether they had experienced any pain in the past month that had lasted for 1 week or longer. Those who answered 'yes' were asked to indicate the site of their pain on a blank body manikin. Subjects' reports were scored using a 10-section coding schedule with each section being scored 0 'pain not present' or 1 'pain present'.

Deprivation

Postcodes were available for each person who returned a health survey. Each subject was assigned a Townsend score (a measure of material deprivation) based on their postcode [17]. The Townsend score includes four variables, derived from the Census: unemployment (percentage of economically active residents [aged 16+ yrs] who are unemployed), overcrowding (percentage of private households with more than one person per room), non-home ownership (percentage of private households that are not owner occupied) and lack of car ownership (percentage of private households that do not own a car). The score is calculated by summing the standardized scores for each variable (the unemployment and overcrowding percentages must first be transformed using the natural log function). Scores >0 indicate higher levels of deprivation, and negative values indicate less deprived areas.

Classification of pain status

On the basis of their pain reports, subjects were classified into one of three groups: those reporting 'no pain'; those reporting pain which did not satisfy criteria for widespread pain were classified as having 'regional pain'; and those reporting pain that satisfied the AHC criteria for widespread pain used in their classification of fibromyalgia [1]. To satisfy these criteria subjects must have reported pain on the left and right hand sides of the body, above and below the waist, and pain in the axial skeleton. In addition, we were interested to examine the relationship between increasing number of pain sites reported by subjects and the risk of mortality. To do so we summed the total number of sites in which subjects had reported pain constructing a 'pain total score' variable with scores ranging from 0 to 10.

Subject follow-up and ascertainment of vital status

All subjects were followed up until either death or 30 April 2005, a total of 8 yrs of follow-up for those still alive. Demographic details of all subjects were sent to the National Health Services Central Register, which holds information on all subjects who have registered with a general practitioner. In the United Kingdom, 95% of subjects are registered with a general practitioner. All subjects in the current study were successfully identified and were 'flagged' enabling them to be tracked over time. The NHS register is linked to official records that allow vital status and, if dead, cause of death to be determined. Underlying cause of death was coded using the International Classification of Diseases (ICD) 10th revision [18].

Statistical analysis

The number of person-years at risk of dying was calculated from the date of subjects returning their baseline questionnaire to either the end of the follow-up period (30 April 2005) or if the person had died, the date of death. The mortality rates in the 'no pain', 'regional pain' and 'widespread pain' groups were then calculated. We then calculated standardized mortality ratios (SMRs), i.e. the ratio of observed to expected number of deaths, standardized to the population of North West England. SMRs were calculated

TABLE 1. Characteristics of study population

	No pain (n=1993)	Regional pain (n=1590)	P*	Widespread pain (n=761)	P**
Age, mean (SD), yrs	56.0 (19.9)	62.5 (17.3)	0.00	64.7 (15.4)	0.00
Gender, female, n (%)	951 (47.7)	825 (51.9)	0.01	456 (59.9)	0.00
Practice, n (%)					
1	715 (46.9)	545 (35.8)	0.08	264 (17.3)	0.01
2	602 (42.6)	536 (37.9)		275 (19.5)	
3	676 (48.1)	509 (36.2)		222 (15.8)	
Ethnic group, n (%) ^a					
White	1889 (95.7)	1514 (96.4)	0.75	719 (95.5)	0.76
Afro-Caribbean	38 (1.9)	30 (1.9)		15 (2.0)	
Indian	21 (1.1)	12 (0.8)		10 (1.3)	
Pakistani	6 (0.3)	2 (0.1)		2 (0.3)	
Bangladesh	9 (0.5)	5 (0.3)		6 (0.8)	
Chinese	4 (0.2)	2 (0.1)		0 (0.0)	
Other	7 (0.4)	5 (0.3)		1 (0.1)	

^aExcludes subjects with missing data. *Regional pain compared with no pain, P-value by chi-squared test. **Widespread pain compared with no pain, P-value by chi-squared test.

for the whole study population and separately by pain status at baseline. The number of expected deaths was obtained by multiplying the numbers of person-years at risk by the age, gender and calendar year-specific mortality rates for the North West England population obtained from the Office for National Statistics. For each SMR, a 95% CI was calculated assuming that the number of deaths followed a Poisson distribution. The relationship between pain status and subsequent all-cause mortality was quantified using a Cox proportional hazards model. Similar analyses were conducted to examine the relationship with cause-specific mortality. For all analyses the 'no pain' group was classified as the referent group. To explore the relationship between the number of pain sites reported and mortality the total pain score variable described above was entered as a continuous variable. To take account of the unequal probability stratified sampling design, age-sex stratum-specific sampling probability weights were applied to each subject and 'weighted' Cox proportional hazards models were fitted [19]. All models were adjusted for the potential confounding effects of age, gender, practice, Townsend score (in quartiles) and ethnicity (as defined in Table 1). Our results are presented as mortality rate ratios (MRRs) with 95% CI. None of the estimated models violated the assumption of proportionality over time.

Role of the funding source

The study sponsors did not influence the study design, collection, analysis and interpretation of data, nor the writing of the report and decision to submit the article for publication.

Results

Of the 4515 subjects who completed the baseline survey, 2331 (51.6%) were females. Pain status was not available for 171 (3.8%). Of the remaining subjects, 1993 (44.1%) reported no pain, 1590 (35.2%) had regional pain and 761 (16.9%) were classified as having widespread pain (Table 1). Compared with those reporting no pain, subjects with widespread pain were more likely to be females (47.7% and 59.9%, respectively, $P=0.00$) and older (mean age: 56.0 and 64.7, respectively; $P=0.00$). The majority of subjects were white ($n=4270$, 95.9%) and there were no statistically significant differences in ethnicity between pain groups.

Overall, 4344 subjects contributed 30440 person-years of follow-up to the study. Follow-up ranged from 0.4 to 8.3 yrs. As shown in Table 2, those subjects who initially reported no pain

TABLE 2. Pain status and subsequent all-cause mortality risk

Pain status	Number in group	Person-years of follow-up	Number of deaths	Rate ^a	Crude		Adjusted			
					MRR	(95% CI) ^b	MRR ^b	(95% CI) ^b	MRR ^c	(95% CI) ^b
No pain	1993	14 308	389	27.2	Referent	–	Referent	–	Referent	–
Regional pain	1590	10 954	411	37.5	1.9	1.6, 2.3	1.2	1.02, 1.4	1.2	1.01, 1.4
Widespread pain	761	5178	217	41.9	2.4	1.9, 2.9	1.3	1.1, 1.5	1.3	1.1, 1.5

^aPer 1000 person-years. ^bAdjusted for age, sex, practice and ethnic group. ^cPlus adjustment for Townsend score.

TABLE 3. Pain status and subsequent mortality risk: specific cause of death

Cause of death	ICD-10 rubric	Number of deaths	Crude				Adjusted			
			Regional pain		Widespread pain		Regional pain		Widespread pain	
			MRR	95% CI	MRR	95% CI	MRR ^a	95% CI	MRR ^a	95% CI
All cancers	C00-D48	228	2.1	1.5, 3.1	3.0	1.9, 4.5	1.3	0.98, 1.8	1.8	1.3, 2.6
Cardiovascular disease	I00-I99	478	2.1	1.6, 2.6	2.7	2.0, 3.6	1.1	0.93, 1.6	1.3	0.99, 1.6
Respiratory disease	J00-J99	174	1.4	0.9, 2.0	1.8	1.1, 2.7	0.8	0.6, 1.1	1.0	0.7, 1.6
All external causes	V01-Y09	12	1.4	0.4, 4.9	1.3	0.2, 7.3	0.8	0.2, 3.1	0.6	0.1, 3.8
Other	– ^b	126	1.8	1.1, 2.8	1.6	0.9, 2.9	1.0	0.7, 1.4	0.8	0.5, 1.4

^aAdjusted for age, sex, Townsend score, practice and ethnic group. Subjects with no pain are the referent group for all analyses. ^bAll other codes excluding those listed above.

had the lowest mortality rate (27.2/1000 person-years), followed by those with regional pain (37.5/1000 person-years) while those with widespread pain had the highest mortality rate (41.9/1000 person-years).

The overall rate of mortality in our study population was similar to that of the North West of England (SMR = 1.05; 95% CI 0.99, 1.12). When we examined the standardized rate stratified by pain status we found a similar mortality experience among those subjects reporting no pain (SMR = 1.03; 95% CI 0.96, 1.10). However, reporting regional pain (SMR = 1.10; 95% CI 0.95, 1.27) or widespread pain (SMR = 1.14; 95% CI 0.99, 1.30) was associated with an elevated all-cause mortality risk.

After adjusting for the effects of age, gender, Townsend score and ethnicity, the weighted analysis showed that subjects with regional pain were 20% and those with widespread pain 30% more likely to die over the 8-yr follow-up period when compared with those with no pain. When we examined the relationship between pain status at baseline and subsequent cause-specific mortality (Table 3) regional pain was associated with an elevated mortality risk from cancer (MRR = 1.3; 95% CI 0.98, 1.8) but not cardiovascular disease (MRR = 1.1; 95% CI 0.93, 1.6). Subjects with widespread pain had an elevated risk of deaths from cancer (MRR = 1.8; 95% CI 1.3, 2.6) and cardiovascular disease (MRR = 1.3; 95% CI 0.99, 1.6), although the latter relationship was not statistically significant. We hypothesized that these relationships were explained by pain arising from comorbid disease at the time of questionnaire completion. However, when we excluded those subjects who had died during the first year of follow-up the relationship with widespread pain remained unchanged for both cancer and cardiovascular deaths. The small number of deaths attributable to specific cancer sites prohibited a more detailed analysis. Pain status was not associated with deaths from any other cause. We then examined the relationship between the total pain score and cause-specific mortality. An increasing number of pain sites was associated with both cancer (MRR = 1.06; 95% CI 1.01, 1.1) and cardiovascular (MRR = 1.02; 95% CI 0.99, 1.1) deaths.

Discussion

We have previously reported an increased mortality rate in subjects who reported regional and widespread pain in a community-based study of pain [11]. In that report, the excess mortality was almost entirely due to deaths from cancer. We have replicated those findings in a large population in the current study,

lending support to our original observation. We have also observed an increased risk of cardiovascular mortality that we had not observed in our previous study, although that relationship did not reach statistical significance after adjustment was made for putative confounding factors. On examination of the relationship between these specific causes of death we found that the risk of death increased as the number of reported pain sites increased.

Although these results replicate our previous findings of cancer-related mortality in a separate cohort of subjects, we have not necessarily identified incident cases of cancer. One could argue that the musculoskeletal pain reported at baseline may be symptomatic of underlying disease, i.e. cancer, and that it is unsurprising to observe the relationship. If that were true we would expect that the relationship would primarily be evident during the immediate period of follow-up. However, this was not the case as the relationship was proportional across all years of follow-up and persisted after excluding those subjects who had died during the first year of follow-up. In addition, we have previously demonstrated that widespread pain is associated with both cancer incidence and, following cancer onset, reduced survival [11].

There have been relatively few studies that have examined the mortality experience of persons with regional or widespread pain disorders. A clinic-based study [14] explored the cancer incidence experience of 1353 patients (1269 women, 84 men) referred to secondary care with 'possible' fibromyalgia. Of those, 1189 (88%) cases satisfied the ACR criteria [1], 131 (10%) did not fulfil criteria, while medical records were unavailable for 33 (2%) subjects. There was an increased risk of cancer among women (standardized incidence ratio = 1.4; 95% CI 1.1, 1.9) although these analyses were based on a small number of cancers ($n = 50$). In a cohort study, fibromyalgia patients who satisfied the ACR criteria were found to have an increased risk of all-cause mortality (SMR = 1.5; 95% CI 1.2, 1.9) and specifically accidental deaths (SMR = 4.5; 95% CI 2.0, 10.1), infections (SMR = 4.5; 95% CI 1.7, 11.9) and pneumonia (SMR = 3.3; 95% CI 1.2, 8.8) over 25 yrs of follow-up [20]. A population-based study reported a higher 10-yr mortality rate among persons with fibromyalgia (22.6/1000 person-years) when compared to those without fibromyalgia (16.6/1000 person-years) [21]. The difference in mortality rates was not significant when adjusted for age and gender using a proportional hazards model. However, this analysis was based on only 54 subjects with fibromyalgia and 12 deaths over the study period. In a population-based study of women, reporting 'any' [odds ratio (OR) = 1.1; 95% CI 0.9, 1.4] or 'chronic' (OR = 1.01; 95% CI 0.8, 1.3) pain [12], symptoms were

not associated with increased all-cause mortality. Women with chronic chest pain had an increased all-cause mortality (OR = 1.75; 95% CI 1.2, 2.6). The authors were unable to identify and explore the relationship among subjects with widespread pain although reporting pain at regional sites was associated with an increased risk of developing cancer: head (OR = 1.5; 95%CI 1.03, 2.2) and abdominal (OR = 1.6; 95%CI 1.01, 2.4) pain.

More recently, we explored the mortality experience among subjects reporting 'widespread pain' (reporting pain in four or more joints) in a population-based cohort study conducted in Finland [13]. Overall, the risk of death was not increased among those with 'widespread pain' (relative risk = 0.9; 95% CI 0.7, 1.00). This discrepancy with our original and current observation could be explained by the different populations studied, the different aetiological processes by which these two populations may come to have widespread pain and the associated comorbidities. It is less important that the studies were conducted in rural vs urban areas, but more important that the factors associated with the presence of symptoms are likely to differ. Thus, in the Finnish study we could hypothesize that reports of widespread pain are more likely to be associated with mechanical factors and in the UK study with psychological factors. That alone would not be important; however, it may also be the case that the two populations also have different factors associated with the presence of widespread pain—for example, low physical activity that may explain the increase in mortality.

It is important to note that there may be unmeasured factors including smoking and morbidity at the time of survey completion, that may be independently associated with regional and widespread pain and cancer mortality, and that may act to confound the relationship we have observed. However, we have previously adjusted the relationship for the possible confounding effects of socioeconomic status, smoking and levels of psychological distress [10], and in the current study for ethnic group and found that the relationship persisted.

The replication of a relationship between musculoskeletal pain and mortality should encourage the investigation of the mechanism of association, and in particular the determination of whether premature mortality can be avoided. The relationship is with both regional and widespread pain. We have also reported a novel observation of an increasing risk of mortality with an increasing number of pain sites reported suggesting a dose-response relationship. We have previously proposed a number of mechanisms that may explain this observation [11] including the influence of insulin-like growth factor-1 and low levels of physical exercise. In our previous report, widespread pain was most strongly associated with female breast and prostate cancer and both cancers are associated with low levels of physical exercise. We have reported in this study a moderate relationship with cardiovascular mortality, an outcome that is also associated with reduced physical activity levels. The interesting question arises whether the onset of regional and widespread pain leads to long-term reduced levels of physical exercise that ultimately lead to an increased risk of cancer and cardiovascular mortality. One could hypothesize a negative correlation between an increasing number of pain sites reported and levels of physical activity that may lead to an increased mortality risk. Studies are under way to help elucidate possible mechanisms underlying these relationships.

Rheumatology key messages

- Chronic widespread pain is associated with an increased risk of mortality.
- Pain is associated with cancer and cardiovascular deaths.
- The mechanism of association is unclear.

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