Widespread body pain and mortality: prospective population based study

Gary J Macfarlane, John McBeth, Alan J Silman

Abstract

Objective To determine whether there is excess mortality in groups of people who report widespread body pain, and if so to establish the nature and extent of any excess.

Design Prospective follow up study over eight years. Mortality rate ratios were adjusted for age group, sex, and study location.

Setting North west England.

Participants 6569 people who took part in two pain surveys during 1991-2.

Main outcome measures Pain status at baseline and subsequent mortality.

Results 1005 (15%) participants had widespread pain, 3176 (48%) had regional pain, and 2388 (36%) had no pain. During follow up mortality was higher in people with regional pain (mortality rate ratio 1.21, 95% confidence interval 1.01 to 1.44) and widespread pain (1.31, 1.05 to 1.65) than in those who reported no pain. The excess mortality among people with regional and widespread pain was almost entirely related to deaths from cancer (1.55 (1.09 to 2.19) for regional pain and 2.07 (1.37 to 3.13) for widespread pain). The excess cancer mortality remained after exclusion of people in whom cancer had been diagnosed before the original survey and after adjustment for potential confounding factors. There were also more deaths from causes other than disease (for example, accidents, suicide, violence) among people with widespread pain (5.21, 0.94 to 28.78).

Conclusion There is an intriguing association between the report of widespread pain and subsequent death from cancer in the medium and long term. This may have implications for the long term follow up of patients with "unexplained" widespread pain symptoms, such as those with fibromyalgia.

Introduction

Widespread body pain is the cardinal symptom of fibromyalgia. It is commonly reported in the general population. Studies have shown that the one month period prevalence is about 9-10%.[1–4] Such pain is associated with high levels of psychological distress, features of the process of somatisation, and comorbidities such as fatigue.[5] Although widespread pain is common, little is known about the natural course. Studies of clinic patients with fibromyalgia have suggested that it is a difficult condition to treat and symptoms resolve infrequently.[6 7]

Widespread pain may reflect underlying organic disease. However, studies on patients with fibromyalgia find an organic basis for symptoms in only a small proportion of people. The symptom may nevertheless be a marker for poor general health including, for example, high levels of psychological distress. Alternatively, it may be a consequence of an underlying physical process giving rise to heightened pain perception. Under any of these hypotheses, the report of widespread pain could be associated with subsequent increased mortality. We tested the hypothesis that widespread body pain is associated with increased mortality and examined the nature and extent of any excess.

Methods

We carried out a population based, prospective cohort study. Participants were those people who had taken part in two population surveys conducted in north west England during 1991-2.

Study A took place in 1992 in a residential area of the city of Manchester. Study B took place in 1991 in two areas: a commuter suburb and a town in a semi-rural area. Together these areas provide a range of socioeconomic conditions. These studies have been described in detail previously and were conducted with similar protocols.[1 8] The sampling frame in each study was the age-sex registers of two local general practices. From both registers used in study A we drew a simple random sample of participants aged 18-75 years, while from both registers used in study B we drew an age stratified random sample of participants aged 18-85 years. We sent a postal questionnaire to all selected participants (with follow up reminders to non-responders) in both studies inviting them to participate in a health survey. The studies primarily related to pain and gathered information on potential aetiological factors. Together, the studies involved 6569 people, with participation rates in studies A and B of 65% and 75%, respectively.

In both studies, participants were asked "During the past month, have you experienced pain lasting at least one day?" If they responded positively they were invited to indicate the site(s) of pain on blank body manikins. This allowed participants to be classified into three groups: widespread pain, regional pain, and no

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Table 1 Pain status at baseline and subsequent mortality during eight year follow up

Characteristic	Person years of follow up	No of deaths	Mortality rate ratio (95% CI)*
Pain status:			
No pain	19 368	196	1.00
Regional pain	25 086	329	1.21 (1.01 to 1.44)
Widespread pain	7 942	129	1.31 (1.05 to 1.65)
Age group (5 year bands)	—	—	1.68 (1.62 to 1.75)
Men	21 712	329	1.00
Women	30 684	325	0.63 (0.54 to 0.74)

*Derived from multivariate regression model, adjusted for study location.

Table 2 Pain status at baseline and subsequent mortality during eight year follow up: specific causes of death

Cause of death	ICD-9 codes	No of deaths	Mortality rate ratio (95% CI)*	
			Regional pain	Widespread pain
All causes	001-999	654	1.21 (1.01 to 1.44)	1.31 (1.05 to 1.65)
All cancers	140-208	201	1.55 (1.09 to 2.19)	2.07 (1.37 to 3.13)
Cardiovascular disease	390-459	261	1.14 (0.86 to 1.49)	1.12 (0.78 to 1.61)
Respiratory disease	460-519	106	1.00 (0.65 to 1.53)	1.01 (0.57 to 1.79)
Other diseases	—†	72	1.36 (0.81 to 2.29)	0.91 (0.45 to 1.85)
All external causes	800-999	14	3.01 (0.64 to 14.21)	5.21 (0.94 to 28.78)

*Participants classified as having "no pain" form reference group; results adjusted for age, sex, and study.
†All codes 001-799 excluding 140-208 and 390-519.

pain. Widespread pain was defined according to the American College of Rheumatology (ACR) criteria for fibromyalgia: this requires axial skeleton pain in addition to pain in two contralateral body quadrants.[9] Participants who reported pain but who did not meet this definition were classified as having regional pain. In addition study A, which contributed 65% of all study participants, collected information on current smoking status and on levels of psychological distress. The latter was measured with the 12 item general health questionnaire.[10]

Details of participants were sent to the Office for National Statistics to be identified on the NHS central register. All participants were identified on the register and their vital status determined. If the participant was registered as having died, the Office for National Statistics provided information on the date and underlying cause of death coded according to ICD-9 (international classification of diseases, ninth revision). Information on deaths up to and including 30 September 1999, about eight years of follow up, were included.

The study gained approval from the Office for National Statistics and from the ethical committee of the University of Manchester.

Statistical analysis

The person years at risk (of dying) was calculated for each participant, from the date of the original survey until the 30 September 1999 or, if the person had died, until the date of death. This allowed us to determine the mortality in each of the three pain groups (widespread pain, regional pain, no pain). Thereafter we used Cox proportional hazards modelling to take account of the possible confounding effects of age (in five year age groups), sex, and study location. The results are presented, with the "no pain" group as reference, as mortality rate ratios with 95% confidence intervals. Similar analyses were conducted according to specific causes of death.

Table 3 Pain status and subsequent mortality from cancer (in subcohort free from cancer diagnosis at time of original survey)

	Person years of follow up	Deaths		Mortality rate ratio (95% CI)†
		No	Rate*	
No pain	18 862	38	2.01	1.00
Regional pain	24 281	88	3.62	1.66 (1.13 to 2.43)
Widespread pain	7 588	42	5.54	2.27 (1.46 to 3.54)

*Per 1000 person years.
†Adjusted for age, sex, and study population.

Results

Of the 6569 participants, at baseline 1005 (15%) had widespread pain, 3176 (48%) had regional pain, and 2388 (36%) had no pain. People with widespread pain (median age 55 years; 66% women) were older and more likely to be female than those with regional pain (median age 49 years; 59% women) and no pain (median age 42 years; 54% women). In total there were 654 deaths among participants during the follow up period. Mortality was lowest in those who originally reported no pain (10.1 per 1000 person years) and increased across regional pain (13.1/1000 person years) and widespread pain (16.2/1000 person years) groups. The mortality in both the regional pain (mortality rate ratio 1.21, 95% confidence interval 1.01 to 1.44) and widespread pain groups (1.31, 1.05 to 1.65) remained significantly increased after adjustment for age group, sex, and study location (table 1).

Most of the deaths in the study cohort were due to cardiovascular disease (40%), cancer (31%), or respiratory disease (16%), with only 11% due to other diseases. In addition, 2% of deaths were due to violence, accidents, or suicide. Participants with regional pain and widespread pain were, respectively, three times and five times more likely to die from causes not related to disease during the follow up period (table 2). However, the wide confidence intervals around the mortality rate ratios are indicative of the small number of deaths from these cause. There was no relation between pain status reported on the original survey and subsequent mortality from either cardiovascular or respiratory disease (table 2). The excess risk was almost all due to deaths from cancer. After adjustment for age group and sex, participants with regional pain (1.55, 1.09 to 2.19) and widespread pain (2.07, 1.37 to 3.13) were significantly more likely to die from cancer during the follow up period compared with those with no pain.

Widespread pain may be evidence of cancer, particularly if metastasis throughout the body is present. For this reason we subsequently used the NHS central register to identify all participants in our studies who had been diagnosed as having cancer before the original study questionnaire was completed. In total, 236 participants had been diagnosed as having cancer. They were removed from subsequent analyses. The increased risk of death from cancer among participants with regional pain (1.66, 1.13 to 2.43) and widespread pain (2.27, 1.46 to 3.54) was, however, still evident (table 3).

Such an observation may arise because of confounding factors. Therefore we used data from study A to adjust for current smoking status and level of psychological distress. However, the doubling in risk

of death from cancer associated with widespread pain remained (table 4).

The three most common fatal cancers in the study, which accounted for more than half the total, were lung cancer, cancers of the gastrointestinal tract (upper and lower), and cancer of the female breast. Table 5 shows a separate analysis of these cancers in relation to widespread pain. Although these site specific analyses have large confidence intervals, they are suggestive of a general rather than site specific excess cancer risk among people reporting widespread pain.

Table 4 Pain status and subsequent mortality from cancer in study A (in subcohort free from cancer diagnosis at time of original survey)

	Mortality rate ratio (95% CI)*	
Adjustment	**Regional pain**	**Widespread pain**
Age, sex	1.40 (0.85 to 2.33)	2.06 (1.15 to 3.70)
Age, sex, current smoking status	1.39 (0.84 to 2.30)	2.07 (1.15 to 3.71)
Age, sex, current smoking status, level of psychological distress	1.19 (0.71 to 2.01)	1.91 (1.04 to 3.49)

*Participants classified as "no pain" form reference group.

Table 5 Pain status and subsequent mortality from cancer: site specific analysis (in subcohort free from cancer diagnosis at time of original survey)

		Mortality rate ratio (95% CI)*	
Cancer site	**ICD codes**	**No of deaths**	**Widespread pain**
All cancers	140-208	168	2.07 (1.37 to 3.13)
Upper GI† tract	150-1	11	2.21 (0.43 to 11.31)
Lower GI† tract	153-4	17	3.25 (0.75 to 14.01)
Lung	162	51	3.09 (1.45 to 6.62)
Female breast	174	9	∞ (1.03 to ∞)
Other	—‡	80	1.63 (0.82 to 3.24)

*Participants classified as "no pain" form reference group; results adjusted for age, sex, and study.
†GI=gastrointestinal.
‡All codes 140-208 excluding 150-1, 153-4, 162, and 174.

Discussion

This study has shown that people who report widespread pain have an increased risk of death, mainly from cancer, over the subsequent eight years.

Methodology

Several methodological aspects need to be considered in the interpretation of these results. The two population based studies involved were conducted according to similar protocols, and the results with respect to the relation between widespread pain and mortality (study A 1.24 (0.91 to 1.60), study B 1.41 (1.01 to 1.97)) and specifically cancer mortality (study A 1.93 (1.14 to 3.25), study B 2.07 (1.08 to 3.94)) are consistent. There were no selection factors involving the participants, apart from their decision on whether to take part in the original pain surveys. The prevalences of regional and widespread pain in these surveys are similar to those reported by other population surveys.[2 3 5] A comparison between the causes of death in the study population and mortality among adults aged 18-84 years in England and Wales during 1998 also shows these to be similar: cancer (30.7% versus 30.5%), circulatory (39.9% versus 40.4%), respiratory (16.2% versus 13.5%), external (2.1% versus 3.5%), other causes (11.0% versus 12.1%).[11] It is highly improbable that those who chose not to take part would exhibit a different relation between their original pain status and mortality over the subsequent eight year period.

Pain was reported at a single point in time (referring to the preceding month). In study B information was available on the duration of pain reported. Of those with widespread pain, 83% satisfied the definition of "chronic pain" from the International Association for the Study of Pain (IASP).[12] So in most participants with widespread pain these were not transient symptoms. Nevertheless, some people will have been misclassified according to their usual pain state, and others will have changed pain state during follow up. Such misclassification, however, would result in an underestimate of the strength of the association. Errors in vital status on the NHS central register are rare. The effect of any error in coding of cause of death would be random across pain groups. It is inconceivable that responses to a postal survey up to 10 years previously could influence the chance of an error on cause of death being made on a death certificate. Such errors would again result in an underestimate of the strength of the association.

Confounding factors

We are not aware of any previous large scale population study examining pain status with future cause specific mortality, and we did not have an a priori hypothesis that excess mortality in people with widespread pain would principally be related to deaths from cancer. Could such an association be due to artefact? Participants who reported widespread pain differed in several respects from those who reported no pain. They were older and more were women, but the excess mortality was still evident after we adjusted for age and sex. The observed association may be due to confounding factors. Smoking is one of the most important risk factors for death from cancer, and it is also more common among people with widespread pain. Similarly, psychological distress has been reported as a predictor of future death from cancer[13] and is also common among people with widespread pain.[14] However, even after we adjusted for these additional factors we still found an approximate doubling of risk of death from cancer among people with widespread pain. Although we lacked information on other potential confounders, the observation that the increased risk of death from cancer may be consistent across cancer site makes identification of "missing" confounding variables difficult.

Social class is a marker for risk of dying from cancer. Is reported pain status also a measure of social class, thus explaining the association? Studies in different countries among populations of widely differing social status have shown remarkably similar rates of reported regional and widespread pain.[1–3 5 8 15] Overall there is little evidence that pain reporting, particularly widespread pain, varies by social class. Specifically, a previous report from study A has shown neither a strong nor a significant link between reporting of back pain—the most common regional pain syndrome—and a measure of social status derived from occupation.[16] Although there were differences in social status between the areas in which the studies were conducted, we did adjust for study area in the analysis. Within each study, because the study population was sampled from people registered with selected general practices, the variation in measures of social status (particularly if based on area of residence) would be small.

What is already known on this topic

Widespread body pain, the cardinal symptom of fibromyalgia, is common

An organic basis for symptoms is found in only a small proportion of people

Treatment is difficult, and studies with short term follow up have shown that symptoms commonly persist

What this study adds

This was the first study with long term follow up of people with widespread pain in the community

These people experience an increased mortality and the excess is principally related to deaths from cancer

Mechanisms

If the association is true, what are the possible mechanisms? The association may be with cancer occurrence or survival, and the precise nature of any association is necessarily speculative. Mechanisms associated with increased perception of pain may also be associated with an increased risk of cancer. Secondly, patients who reported widespread pain may have worse survival when they develop cancer. High levels of psychological distress, a feature of widespread pain, particularly depression, have been associated with reduced survival from cancer.[17 18] However, in the current study excess mortality from cancer was evident both in those with low and high levels of distress (data not shown). Some studies have provided evidence that certain psychosocial factors may predispose people to the development of cancer. These include the inability to release emotion, the experience of stressful life events, psychosexual disturbance, and parental problems or separation in early life.[19] Many of these factors have also been linked to widespread body pain.[20 21] Lifestyle factors subsequent to these adverse events, possibly in combination with changes in neuroendocrine function, may result in both an increased reporting of pain and an increased risk of cancer.

In summary, we have shown an association between the report of widespread pain and excess mortality from cancer in the medium and long term. This has implications for the long term follow up of patients with "unexplained" widespread pain symptoms, such as those with fibromyalgia. However, it is important to set the risk in context: the vast majority of such people did not die from cancer. The risk increased from about one in 60 among people reporting no pain to one in 20 among those with widespread pain. Future studies are needed to confirm this association and to investigate the possible mechanisms.

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Contributors: GJM conceived the idea, designed the study, and, together with AJS, monitored study conduct and supervised the analysis of data. JM coordinated receipt of the data and conducted data analysis. GJM wrote the paper which was then reviewed and revised by the other authors. All authors are guarantors.

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Commentary: An interesting finding, but what does it mean?

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This is an intriguing paper. New insights into possible risk factors for death from cancer are greatly to be welcomed. If this study's findings are true then having pain for at least one day can increase the risk of death from cancer by over 20%. The risk is higher in the group who have widespread as opposed to regional pain, possibly suggesting a dose-response relation. The finding needs to be taken seriously because the study seems to have been well conducted and competently analysed. However, the finding implies a major cancer burden; even a 20% increase in the risk of death from cancer is serious when it applies to 48% of the population. Thus the paper deserves careful review. Are the findings plausible, what other explanation could there be, and what should be done next?

The finding of an increased death rate from cancer is partly serendipitous. The authors were looking for some increase in mortality, but they had no a priori hypothesis that the risk would be seen in deaths from cancer. As the authors suggest, the association could be due to an increase in the incidence of cancer or to a reduced survival among those with the disease. Each explanation has potential weaknesses.

An effect on increased incidence seems unlikely because there is an increased risk at all sites of cancer. Even cigarette smoking restricts its effects to a small number of sites. This lack of specificity makes a causal association less likely. It also introduces a related problem. What plausible biological mechanism could explain the finding? The authors mention psychosocial factors, lifestyle factors, and neuroendocrine function but do not explain how these could have a carcinogenic effect on all body systems. Furthermore, in a subgroup analysis the authors show that adjusting for psychological distress does not reduce the risk of cancer associated with widespread pain.

Plausibility is also challenged because the increased risk of cancer is not restricted to a specific group of pain sufferers but is seen in the heterogeneous group with regional pain. It is unlikely that the risk is due to some small subgroup with regional pain, as a subgroup would have to have a substantially increased risk for the effect to be seen in the whole group. Plausibility is further threatened because this study was unable to take account of potential confounding factors. The authors have shown that the findings are robust to adjustment for current smoking status, but this is only one in a many potential lifestyle and environmental confounding factors. But if it were due to confounding, this would have to operate in a curious way. It is difficult to think of confounding factors that would act with such complete lack of specificity.

An effect on reduced survival would be more easily understood than an effect on an increase in incidence: psychosocial wellbeing or diet or other factors could have a generalised effect on survival. However, exclusion of participants with a previous diagnosis of cancer from the analysis led to an increased risk of mortality. This leaves the possibility that the pain is an early symptom of undiagnosed cancer.

We are thus left with an unexplained but potentially important finding. As the authors state the association needs to be assessed in other studies and possible mechanisms investigated. It seems unlikely that confounding could be the explanation. However the finding could be due to some unrecognised bias or may simply be a statistical fluke. It would be much more interesting if the effect were real because of the potential insights into the development of cancer. But, as so often, the answer will require further research.

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