

Widespread body pain and mortality: prospective population based study

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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

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. Alternatively, it may be a consequence of an underlying physical process giving rise to heightened pain perception. 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.^{1,6} We sent a postal questionnaire to all selected participants aged 18-85 years (with follow up reminders to non-responders) inviting them to participate in a health survey. The questionnaires gathered information on potential aetiological factors of pain. Together, the studies involved 6569 people, with participation rates of 65% and 75%.

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,⁷ regional pain, and no pain. One study, 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.⁸

If the participant died during follow up the Office for National Statistics provided information on the date and underlying cause of death coded according to ICD-9.

Statistical analysis

The person years at risk (of dying) was calculated for each participant, from the date of the original survey until 30 September 1999 or, if the person had died, until the date of death. 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.

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 were older and more likely to be female (median age 55 years; 66% women) 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 virtually unchanged after adjustment for age group, sex, and study location.



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Most of the deaths in the study cohort were due to cardiovascular disease (40%), cancer (31%), or respiratory disease (16%), and 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). There was no relation between pain status reported on the original survey and subsequent mortality from either cardiovascular or respiratory disease. The excess risk was almost all due to deaths from cancer.

Widespread pain may be evidence of cancer, particularly if metastasis throughout the body is present. 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.

We adjusted for current smoking status and level of psychological distress but the doubling in risk of death from cancer associated with widespread pain remained (1.91, 1.04 to 3.49).

The three most common fatal cancers in the study were lung cancer, cancers of the gastrointestinal tract (upper and lower), and breast cancer. A separate analysis of these cancers in relation to widespread pain suggests a general rather than site specific excess risk of cancer among people reporting widespread pain.

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. We combined two population based studies. Both were conducted according to similar protocols, and the results with respect to the relation between widespread pain and mortality and specifically cancer mortality 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.⁹ 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 one of the studies information was available on the duration of pain reported. 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 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 cancer¹⁰ and is also common among people with widespread pain.¹¹ 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 sites 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 12} Overall there is little evidence that pain reporting, particularly widespread pain, varies by social class. Specifically, a previous report from one of the studies 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.¹³ Further, we did adjust for study area in the analysis.

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

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.

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

increased perception of pain may also be associated with an increased risk of cancer. Secondly, patients who report widespread pain may be less likely to survive when they develop cancer. High levels of psychological distress, a feature of widespread pain, particularly depression, have been associated with reduced survival from cancer.^{14 15} 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.¹⁶ Many of these factors have also been linked to widespread body pain.^{17 18} 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 may have 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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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.

Drug points

Premature osteonecrosis and sirolimus treatment in renal transplantation

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The incidence of osteonecrosis or avascular necrosis has fallen as a result of new advances in immunosuppression and lower corticosteroid regimens.^{1,2} Mycophenolate mofetil and sirolimus are associated with an increase in surgical complications.^{3,4} Sirolimus may also be associated with avascular necrosis in patients after renal allograft transplantation. This could be attributed to sirolimus's adverse lipid profile, its potent bone marrow suppressive effect, or perhaps an idiosyncratic effect

A 39 year old man with IgA nephropathy received a cadaveric renal transplant. He was a non-smoker and non-drinker. Seven months after receiving the transplant he developed an acute painful left leg. He was taking prednisone 10 mg, cyclosporin 300 mg, and sirolimus 5 mg daily. His trough sirolimus concentration was 20.7 ng/ml (range 5-20). Hip x ray and magnetic resonance imaging confirmed avascular necrosis in both hips. Sirolimus was discontinued, and tacrolimus and mycophenolate mofetil were introduced. Disodium pamidronate treatment produced symptomatic improvement.

A 49 year old man with polycystic kidney disease received a cadaveric renal transplant. He was a non-smoker and non-drinker. Six months after the transplantation he developed hip pain. Investigations confirmed bilateral avascular necrosis. He was taking prednisone 10 mg, cyclosporin 200 mg, and sirolimus 5 mg daily. His trough sirolimus concentration was 5.8 ng/ml. Sirolimus was changed to mycophenolate mofetil, and elective bilateral hip replacements were arranged.

Avascular necrosis, a recognised complication of transplantation, is commonly associated with prolonged high doses of corticosteroid.^{1,2} Occurring 6-12 months after transplantation, it is less likely to result from corticosteroid treatment. In our transplant population the prevalence of avascular necrosis is 2% in patients on standard treatment, with less than 0.5% in the first year (unpublished data). In those patients receiving sirolimus the prevalence is 3.8% (2 from 52 cases). Data sheets suggest a frequency of 1-10% with corticosteroids. No other reports have been published. Although our data are compared with historical controls, we believe that sirolimus may be a cause of early post-transplant bone pain because of avascular necrosis.

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Endpiece

Death

Death is the dark backing a mirror needs if we are to see anything.

Saul Bellow