The relationship between back pain and mortality in older adults varies with disability and gender – results from the Cambridge over-75s Cohort (CC75C) study

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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What is already known about this topic?

1. Disabling back pain increases into the oldest old
2. In working ages, there is an association between regional pain and excess mortality

What does this study add?

1. We provide new data to show that the excess in mortality evident in working ages is also present in older adults
2. We further demonstrate that this association may be limited to disabling pain
2. Finally, we demonstrate that it exists solely in women, rather than men

ABSTRACT

Background

To determine whether older adults reporting back pain (BP) are at increased risk of premature mortality, specifically, to examine the association with disabling/non-disabling pain separately.

Methods

Participants aged ≥75yrs were recruited to the Cambridge City over-75s Cohort (CC75C) study. Participants answered interviewer-administered questions on BP and were followed until death. The relationship between BP and mortality was examined using Cox regression, adjusted for potential confounding factors. Separate models were computed for men and women.

Results

From 1174 individuals with BP data, the date of death was known for 1158 (99%). A significant association was found between disabling BP and mortality (hazard ratio: 1.4; 95% confidence interval: 1.1-1.8) and this remained, albeit of borderline significance, following adjustment for socio-demographic variables and potential disease markers (1.3; 0.99-1.7). Further, this association was found to vary with sex: women experienced a 40% increase in the risk of mortality associated with disabling BP (1.4; 1.1-1.9) whereas no such increase was observed for men (1.0; 0.5-1.9). Participants with non-disabling BP were not at increased risk of mortality.

Conclusions

This study confirmed previous findings regarding a relationship between pain and excess mortality. Further, we have shown that, among older adults, this association is specific to disabling pain and to women. Clinicians should be aware, not only of the short-term implications of disabling BP, but the longer-term effects. Future research should attempt to understand the mechanisms underpinning this relationship to avoid excess mortality, and should aim to determine why the relationship differs in men and women.

INTRODUCTION

There has been growing interest in the association between pain and mortality. Macfarlane et al (2001) found 18-75yr olds who reported regional/widespread pain were at increased risk of all-cause mortality over subsequent eight years. Excess deaths were attributable to external causes (accidents/suicides) and cancer–higher incidence of cancer, and a poorer prognosis (McBeth et al, 2003).

Several studies attempt to replicate these findings. McBeth et al (2009) demonstrated an increase in all-cause, cancer-related and cardiovascular mortality associated with regional/widespread pain in individuals ≥16yrs. Torrance et al (2010) demonstrated individuals reporting severe chronic pain experienced a 50% increase in risk of all-cause mortality over 20yrs compared to those with milder symptoms.

Jordan et al (2010) examined mortality in the year following consultation for musculoskeletal problems in those >50yrs. Mortality was higher for individuals presenting with a new episode of back/hip/shoulder pain, which could not be fully explained by cancer or other comorbidities. Hochberg (2008) conducted a review of articles examining the relationship between osteoarthritis and increased mortality risk and found a moderate increase of mortality in those with osteoarthritis compared to the general population. Risk factors for mortality in this group included advanced age, increased burden of osteoarthritis and presence of comorbid conditions.

In contrast, Macfarlane et al (2007) failed to show any association between multiple regional pain(s) and mortality. Also, Smith et al (2003) found no association between chronic pain reporting and all-cause mortality, however persons with chronic pain did experience an increase in the risk of death from respiratory disease over a 6yr period.

The possible mechanisms underpinning any association between pain and mortality are unclear, although the relationship with cancer is site specific–prostate, breast, some gastro-intestinal cancers–all of which have been associated with poor diet/lifestyle. Recent evidence is consistent with the hypothesis that individuals with CWP report a prior lifestyle (lower levels of physical activity/poorer diet) that may predispose them to such cancers in later life (Vandenkerkhof et al, 2011). However, evidence is sparse and inconclusive.

The majority of previous work has involved general population samples with older individuals only appearing in the proportion that they occur in that population. In older adults, generally, absolute risk of mortality and prevalence of co-morbid conditions are higher. Further, the experience of pain is more likely to be disabling, lifestyle implications greater, and it may have a greater impact on mortality. Recent findings suggest that disabling pain-sufficient to interfere with life-increases in the oldest old (Thomas et al, 2007; Docking et al, 2011) yet while previous studies have considered chronic pain, there is no data examining differences between disabling/non-disabling pain on risk of mortality.

In addition, no previous studies have examined the differences between males and females. Women report more pain than men (and poorer self-rated health generally) although, conversely, they experience a lower age-specific risk of mortality. This relationship may be explained by increased healthcare seeking, generally, in women (Office for National Statistics, 2011). Stessman et al (1995) found chronic back pain was protective, in terms of the risk of 12yr mortality, authors speculate this could be due to an increase in visits to the doctors, emergency department and medication use. Intriguingly, however, this relationship was only observed in males.

In summary, the nature of the association between pain and mortality is equivocal and further clarification is required. In addition, it is important to examine the relationship in older adults where risk of mortality, pain-related disability, and co-morbidities is higher. Thus, using back pain as an exemplar, this study examined the relationship between pain and mortality in older adults, specifically (a) to examine the association with disabling and non-disabling pain separately; and (b) to examine the relationship stratified by gender.

METHODS

The Cambridge City over-75s Cohort (CC75C) study is one of the longest and largest population-based prospective cohort studies of the very old (Fleming et al, 2007), for which comprehensive methods, including details of consent, are provided elsewhere (www.cc75c.group.cam.ac.uk). In brief, in 1985-87, all men and women aged ≥75yrs from a selection of geographically and socially representative primary care practices in Cambridge were contacted, of whom 95% participated. Each CC75C study phase was approved by the local research ethics committee and participants gave written informed consent at each survey. Successive interviews and assessments have been carried out since baseline. BP questions were first asked in 1988-89, when 83% of survivors participated (n=1174).

The interview-administered study questionnaire gathered a wide range of information in addition to demographics (age; gender; marital status; place of residence; social class). Participants were asked: "Have you recently had an illness or condition which prevented you carrying out your normal day to day routine?", and persons answering positively were then asked whether this was related to a number of specific conditions, including BP (BP). Possible responses were: (1) No; (2) Yes; or (3) Yes, but not disabling. Disabling BP was defined as BP that interfered with daily tasks within the last month. All participants were flagged at the Office for National Statistics (UK) who provided notification of all deaths. Survival (time from initial questionnaire completion to mortality by censoring date: 11 November 2008) was then computed for all individuals based on a follow-up of 20 years.

Analysis

All analysis was conducted using Stata v10.1 (StataCorp LP, College Station, Texas) with CC75C study data version 3.0.

Differences in all-cause mortality between the three BP groups were initially examined using Kaplan-Meier survival curves. Differences between curves were assessed using the log-rank test. This allowed for an initial examination of the data to determine whether there were any clear differences between the groups' survival rates and log-log survival plots.

Secondly, a Cox proportional hazard regression model was used to estimate the magnitude of any differences in survival in the two BP groups versus the group with no BP. Results are expressed as hazard ratios (HR) with 95% confidence intervals (95%CI) and were adjusted for age, sex, place of residence, social

class, marital status and factors which could be potential markers for disease that could therefore confound the relationship, including self-reported: arthritis/rheumatism; use of medication; previous use of general anaesthetic; chest pain; shortness of breath; and falls. This was then stratified by gender to examine potential differences in mortality between men and women.

RESULTS

Demographic characteristics of the study sample

1174 individuals had BP data and the date of death was known for 1158 individuals (99%; 15 were known to be still living when the data was censored, and one was untraced since moving abroad). The mean age of participants when BP was recorded was 83yrs (range: 77-101yrs) and 65% were female. The majority of participants were either married (39%) or widowed (47%); most still lived in their own home (86%) and the majority of participants (61%) were social class IIIm (i.e. previously in skilled manual occupations) or lower. The majority of participants were on medication (82%).

BP and mortality

The prevalence of disabling and non-disabling BP was 6% (n=65) and 23% (n=274) respectively. Figure 1 shows the Kaplan-Meier survival curves for participants with no BP, non-disabling, and disabling BP respectively. Examination of Schoenfeld residuals demonstrated that the proportional hazard assumptions were justified.

<<Figure 1 here>>

While there was no difference with age in the reporting of non-disabling BP, the prevalence of disabling BP increased with age: those who were ≥90yrs were more than twice as likely to report disabling BP than participants aged 77-79yrs (risk ratio: 2.6; 95%CI: 1.1-6.2) (detailed in previous study (Docking et al, 2011)). Women were more likely to report disabling BP (7.2% versus 2.7%; difference: 4.5%; 95%CI of difference: 2.0-6.9%) and the same was true of non-disabling BP (25.9% versus 17.5%; difference: 8.4%; 95%CI of difference: 3.5-13.2%).

Participants with disabling BP experienced an increase in risk of mortality compared to those with no BP (HR: 1.4; 95%CI: 1.1-1.8), see Table 1. This remained after adjusting for socio-demographic variables: age; sex; residence; social class; marital status (1.5; 1.2-1.9) and all measured potential confounders, albeit of borderline significance (1.3; 0.99-1.7). Individuals with non-disabling BP did not experience an increase in the risk of mortality.

<<Table 1 here>>

Differences between men and women

In both men and women although there was an increase in the risk of premature mortality associated with disabling BP (1.4; 0.8-2.6 and 1.5; 1.2-2.0, respectively) in men, this was completely attenuated by adjustment for socio-demographic and health-related variables (1.0; 0.5-1.9) whereas, in women, the relationship remained (1.4; 1.1-1.9). Null effects were found for both women and men with respect to non-disabling BP and risk of mortality (0.9; 0.8-1.1 and 0.9; 0.7-1.2 respectively).

<<Table 2 here>>

DISCUSSION

We have confirmed findings from working age populations that persons with pain experience an increase in the risk of mortality in the medium-term and further provide supporting data for Jordan et al (2010) regarding a relationship between back pain reporting and increased mortality. We have further demonstrated that this association, in older adults, is specific to disabling pain and we provide new evidence to suggest that the association occurs in women, but not in men.

When interpreting these findings there are a number of methodological issues that one must consider. Firstly, we have only considered BP at a single point in time and this is, arguably, not a good measure of an individual's continuous exposure. We know, for example, that only 19% of participants who initially reported disabling BP still reported disabling BP at their next follow-up interview, four years subsequently. It is possible, statistically, to examine BP as a time-varying covariate. However, although we know the exact date of the outcome measurement (mortality) we do not know the exact date of any change in pain status– where this occurred. Indeed, even for participants who apparently did not change status, we cannot be certain that they did not have fluctuating or recurrent BP, as opposed to chronic symptoms. Thus, while mathematically possible, adjusting for BP as a time varying covariate would make a number of assumptions about BP status over time that we cannot be certain are true. Our approach, considering pain at a single point, is more conservative in that any misclassification would bias our results towards the null, and makes the fact that we have observed any effect at all the more remarkable, particularly with a relatively small sample size.

Secondly, while we were able to adjust for a number of important co-morbidities that may have confounded the pain-mortality relationship, the list is not exhaustive and information on other diseases was not available. Of particular interest would have been cancer, which has been shown to be responsible for the excess mortality in working age populations (McBeth et al, 2003). One of the hypotheses that might have explained this relationship between disabling pain and increased mortality is that pain (in this case back pain) is a symptom of an underlying condition that may be associated with premature mortality e.g. cancer. However, the survival curve indicates that the difference in mortality did not start until approximately 4-5 years after the pain report. Although not conclusive, this would suggest that underlying morbidity, such as cancer at the time of reporting pain, is not the explanation for the findings. In addition, in the review by Hochberg (2008) he proposed that excess mortality in those with osteoarthritis may be explained not only by the presence of comorbid conditions, but also reduced physical activity and adverse side effects of medications used to treat

symptomatic osteoarthritis. For any of these explanations to completely explain the current findings, one would have to hypothesise that they were associated not only with mortality, and disabling BP, but not with non-disabling BP. Furthermore, they would need to be associated with disabling BP in women, but not in men. We consider this to be unlikely. However, it may be the case that disabling BP is related to undiagnosed osteoporotic fractures, and these are both (a) more common in women; and (b) more likely in those who are physically frail, generally. It would have been interesting to have had information on both the prevalence of osteoporotic fractures and cause of death, however this is currently unavailable.

Could the relationship be due to residual confounding? There were a number of known risk factors for mortality that were unmeasured in the current analysis (e.g. body mass index, smoking) and, while these have been previously associated with pain Hildebrandt et al, 2000; John et al, 2006), it is unlikely that these would be limited to persons with disabling, but not non-disabling, pain. Social class is a strong marker of both body mass index and smoking status (Power et al, 2005) and, therefore, adjusting for social class will have controlled, in part, for the effect of these two potential confounders and such adjustment had little impact on the results. Thus, while one cannot rule out residual confounding, we consider it unlikely that the omission of these factors will have had a major impact on the findings.

Previous evidence found that chronic widespread pain (CWP) carried a higher future mortality risk than regional pain (Macfarlane et al, 2001; McBeth et al, 2003). While our findings are specific to regional pain and therefore we can only make conclusions regarding regional pain, the definition of CWP used in earlier studies includes spinal pain as a necessary component ("axial skeleton pain in addition to pain in two contralateral body quadrants"; Wolfe et al, 1990). Therefore, while we did not measure CWP within this study, it is highly plausible that many of those within the disabling back pain group would also have been categorised as having CWP. Therefore the finding that mortality risk increases in those with disabling back pain is consistent with the previous findings regarding CWP.

The mechanisms of the observed relationship between pain and mortality are unclear. One possible explanation is that individuals with disabling or chronic pain may have a lifestyle characterised by factors likely to increase mortality, such as lower levels of physical activity, professional hazards (e.g. manual work), and a poor diet. While those with pain are very likely to change their lifestyle, we have also previously shown that individuals with CWP at age 45yrs reported a lifestyle at age 33yrs that was characterised by high fat diet, high BMI, and low levels of physical exercise(Vandenkerkhof et al, 2011). And, interestingly,

these associations were stronger in women than in men. However, although these data were collected longitudinally (i.e. the measurement of diet and lifestyle preceded the measurement of pain) information regarding the timing of onset of pain was lacking and, therefore, one can only speculate about the prospective nature of the relationship. However, it is certainly consistent with the hypothesis that these factors may be responsible for the observed association with mortality, at least in part. What is not clear is why the association is limited to disabling BP.

Also unclear is why the association appears to be limited to women and not men. It also contradicts the previous findings relating to pain and mortality, where the opposite relationship was found (Stessman et al, 1995). Women are more likely than men to report more pain, higher pain severity, and a greater frequency of pain (Racine et al, 2012). There are also sex differences in experimental pain reporting (Racine et al, 2012), and in opioid requirements post-surgery (Fillingim et al, 2009). There is an increased fracture risk associated with the use of strong opioids and older adults are more likely to be prescribed painkillers, with or without other medications (Macfarlane et al, 2012). However, our findings are robust to adjustment for falls. Indeed, among women, the hazard ratio associated with disabling BP is twice that associated with falls: 1.4 (1.1-1.9) versus 1.2 (1.03-1.4) respectively. The prevalence of disabling BP was more common in women than in men, although the current data does not allow us to examine the issue more thoroughly and therefore this remains speculative. As mentioned earlier, it could be that disabling BP is related to undiagnosed osteoporotic fractures. An alternative explanation may be due to cancer: breast cancer typically metastasizes to the bone, and this would be negatively associated with survival, and positively associated with pain. However, survival with metastatic breast cancer is poor – around 50% at 5yrs (Nieto et al, 2002). The fact that the difference in mortality did not start until approximately 4-5 years after the pain report, suggests that this is unlikely to be the case. Finally, there could potentially be a methodological explanation for this, for example healthy survivors in our older cohort, perhaps random error or indeed a differential mortality with respect to cancers or chronic heart disease in men and women. However, while our findings do not support those of the Jerusalem Longitudinal Study (Stessman et al, 1995), which found that chronic back pain was associated with a lower mortality in men but not women, there are similarities in that we have both demonstrated that there are sex differences between mortality risk related to pain in older adults, and therefore it may be that chronic or disabling pain may be aetiologically different between men and women.

In summary: our findings, confirm those from working age populations regarding a relationship between pain and an increase in the risk of early mortality. In addition, we present new data to suggest that this

association may be limited to disabling pain, and appears to be specific to women. Future research should attempt to determine the mechanisms underpinning this relationship, including further examination of specific conditions causing disabling BP, with a view to considering secondary prevention; and to determine why the relationship differs in men and women.

KEY MESSAGES

- We confirm previous findings, from working age populations, demonstrating an association between regional pain, and subsequent increase in the risk of mortality
- We provide new data to show that the excess in mortality, firstly, may be limited to disabling pain; and secondly, exists solely in women, rather than men

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AUTHOR CONTRIBUTIONS

R.E.D. conducted the analysis and produced the first draft of the manuscript. J.F. was the CC75C study investigator and commented on the draft of manuscript – including comments on analysis, results and interpretation. C.B. was the CC75C study principal investigator and commented on the draft of the manuscript – including comments on results and interpretation. J.Z. was the CC75C study investigator and helped prepare data for analysis and commented on the draft of the manuscript – including comments on results and interpretation. G.J.M. oversaw analysis and commented on the draft of the manuscript. G.T.J. supervised analysis and drafting of the manuscript.

ETHICAL APPROVAL

Each CC75C study phase was approved by Cambridge Research Ethics Committee (current reference numbers: 08_H0308_3).

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FIGURE 1 **Cumulative survival**

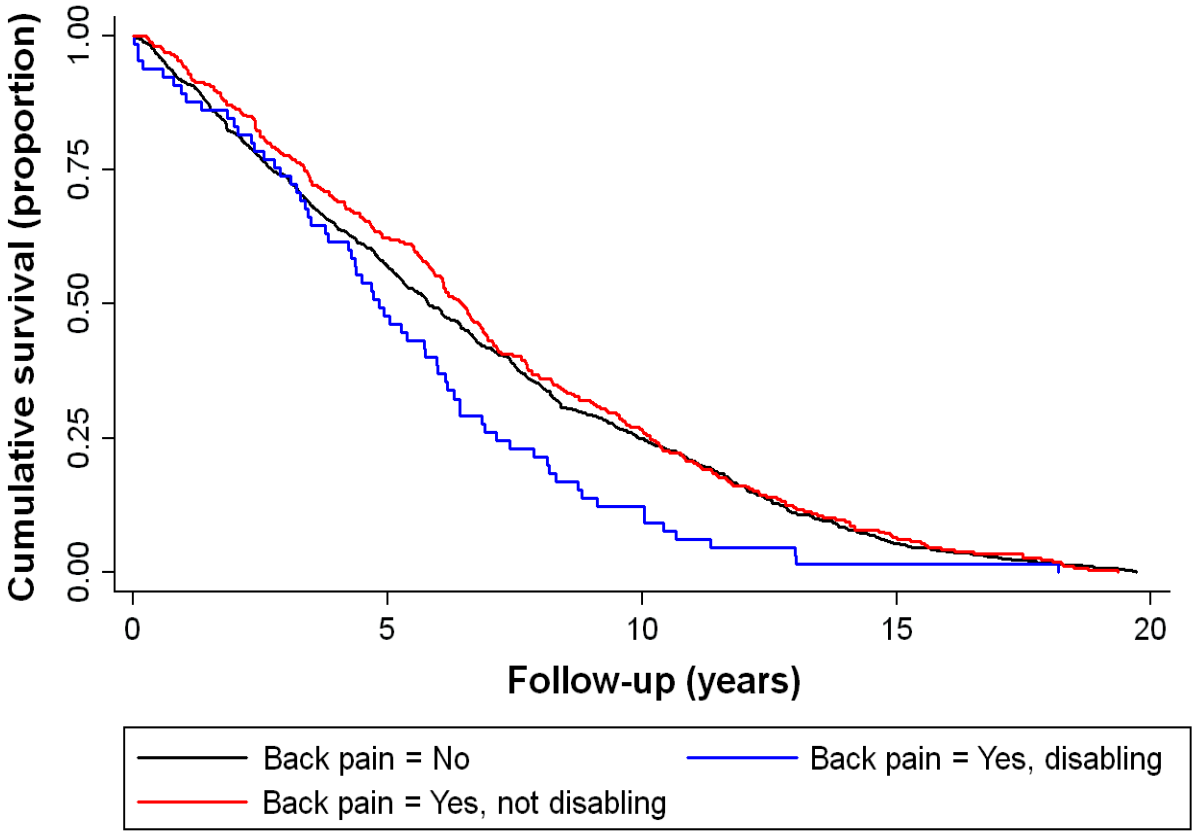

TABLE 1 Cox proportional hazard model

Back pain	Hazard ratios (95% confidence intervals)		
	Crude analysis	Adjusted[1]	Adjusted[2]
No back pain	1.0	1.0	1.0
Disabling back pain	1.4 (1.1-1.8)	1.5 (1.2-1.9)	1.3 (0.99-1.7)
Non-disabling back pain	0.9 (0.8-1.1)	1.0 (0.9-1.1)	0.9 (0.8-1.1)

1 Adjusted for socio-demographic variables (age; sex; residence; social class; marital status)

2 Further adjusted for health-related potential confounding variables (arthritis/rheumatism; use of medication; previous use of general anaesthetic; chest pain; shortness of breath; falls)

TABLE 2 Cox proportional hazard model (sex-stratified analysis)

Back pain	Hazard ratios (95% confidence intervals)			
	Men		Women	
	Crude	Adjusted[1]	Crude	Adjusted[1]
No back pain	1.0	1.0	1.0	1.0
Disabling back pain	1.4 (0.8-2.6)	1.0 (0.5-1.9)	1.5 (1.2-2.0)	1.4 (1.1-1.9)
Non-disabling back pain	1.0 (0.8-1.3)	0.9 (0.7-1.2)	1.0 (0.8-1.1)	0.9 (0.8-1.1)

1 Adjusted for socio-demographic variables (age; residence; social class; marital status) and health-related potential confounding variables (arthritis/rheumatism; use of medication; previous use of general anaesthetic; chest pain; shortness of breath; falls)