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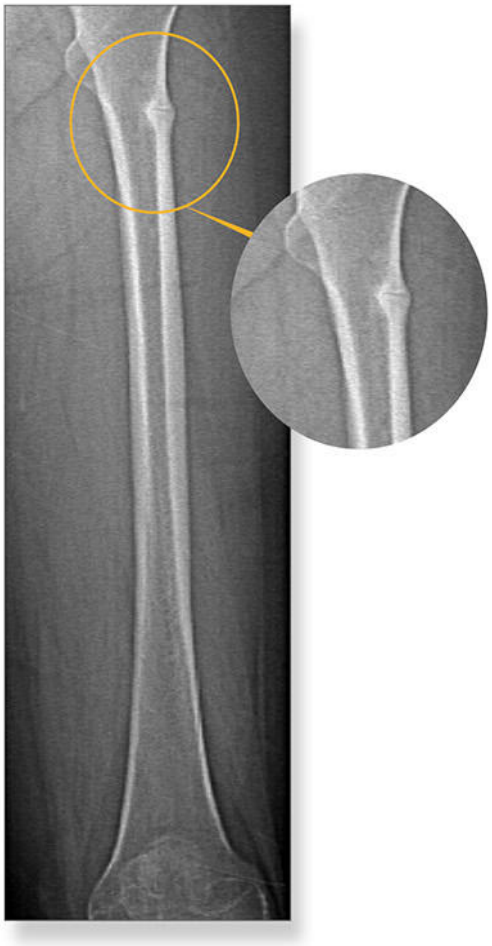

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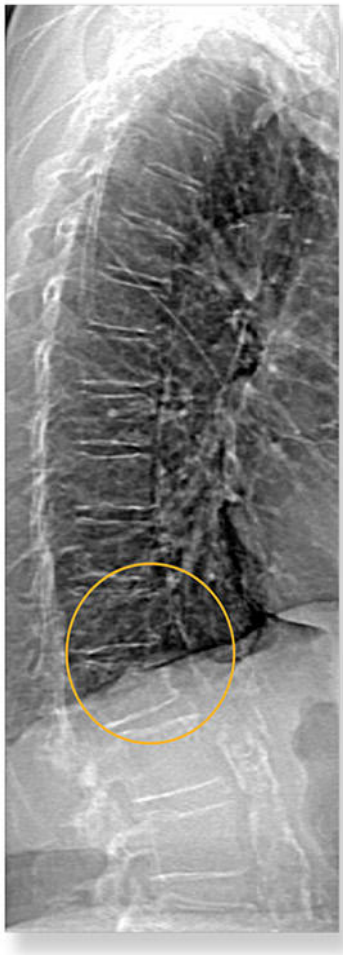

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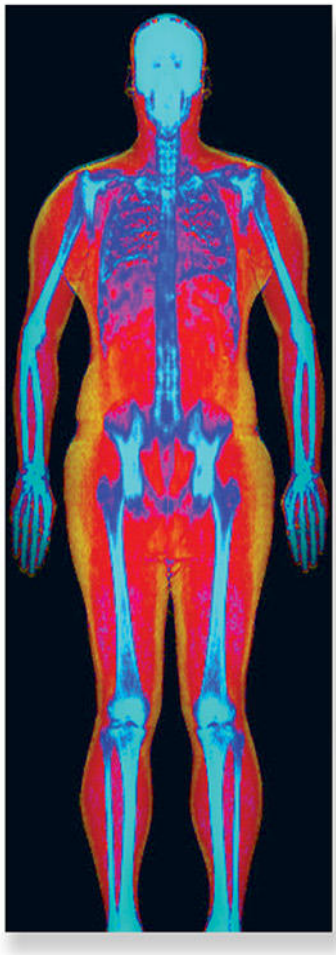

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Pain at multiple sites is associated with prevalent and incident fractures in older adults

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Disclosures: The authors declare no conflict of interest.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jbmr.3817.

Abstract

Musculoskeletal pain is common and typically occurs at multiple sites. Pain has been shown to be associated with falls risk; however, whether increased risk for falls associated with multi-site pain (MSP) translates into an increased risk of fractures has not been investigated. This study aimed to describe the associations of number of painful sites with prevalent and incident fractures. Data from a longitudinal population-based study of older adults (mean age 63 years) were utilised. Follow-up was performed at 2.6, 5.1 and 10.7 years later, respectively. Presence/absence of pain at the neck, back, hands, shoulders, hips, knees and feet was assessed by questionnaire at baseline. Participants were classified into three groups according to the total number of painful sites (0-2, 3-4 and 5-7 painful sites). Fractures were self-reported at each time-point. Bone mineral density (BMD) was measured by Dual-energy X-ray absorptiometry. Falls risk was calculated based on the short form Physiological Profile Assessment. Log-binomial regression was used for the analyses. A total of 450 fractures at baseline and 154 new fractures were reported during a mean follow-up period of 10.7 years (range 9.2-12.5 years). In multivariable analyses, number of painful sites was associated with prevalent fractures at any site and non-vertebral. Furthermore, participants with 5-7 painful sites had an increased risk of incident fractures at any site [relative risk (RR) 1.69, 95%CI 1.13-2.53], major (including the femur, radius, ulnar, vertebral, rib and humerus) (RR 2.17, 95%CI 1.12-4.22) and vertebral (RR 6.44, 95%CI 1.64-25.33) compared to those with pain at 0-2 sites. These associations remained significant after further adjustment for falls risk, BMD and confounders. Pain at multiple sites was associated with incident fracture risk in a dose-response manner, suggesting that widespread pain is an independent contributor

to fracture risk. The potential for pain management in fracture prevention warrants further exploration.

Keywords: Musculoskeletal pain, multi-site pain, fracture, prospective study

Introduction

Musculoskeletal pain is common particularly in the elderly, with a prevalence as high as 74% in community-based older adults (1-3). It poses a huge individual and societal health burden leading to restricted physical function, reduced quality of life and disability (4). Pain in the low back and neck was ranked as 1st and 6th of years lived with disability (YLDs) among 30 leading diseases and injuries in 2016 from a most recent report of the global burden, respectively (5).

Pain often occurs at multiple sites with 41-75% of persons from various studies reporting pain occurring at two or more sites depending on differences in study population and number of painful sites measured [3, 6, 7]. We previously reported that 59% of people had pain at more than two sites in our population-based cohort with a mean age of 63 years (8). Epidemiological studies have shown that multisite pain (MSP) is linked to worse health outcomes as compared to single-site pain, including poorer physical health (9) , worse health-related quality of life (10), more severe depressive symptoms (11), cognitive impairments (12), and poorer sleep quality (13).

Fracture is also a major health care burden worldwide, leading to an increased risk of recurrent fractures and mortality (14-16). Ageing, osteoporosis and falls are the main risk factors for fracture (17, 18). Two recent systematic reviews and meta-analyses have demonstrated a link between pain and falls, and prospective studies included in the reviews provided the evidence that pain is associated with increased risk of falls in the general older population (19, 20). This is further supported by the recent findings

from prospective studies (21-25). In addition, the associations appear to be more pronounced with increasing number of painful sites (26, 27). Pain has also been shown to be associated with bone mineral density (BMD) but results are mixed with some reporting positive and some negative associations (28-30). This has led to several investigations of whether increased risk for falls and/or changed BMD associated with pain translates into an increased risk of fractures, but these studies have been focusing on single-site pain and the results are conflicting (31-34). No study has examined the associations with MSP. We hypothesised that people with greater number of painful sites have a higher risk of fractures. The aims of this study were, therefore, to examine the association between number of painful sites and prevalent and incident fractures, and to determine whether these associations are independent of falls risk, BMD and other potential confounders in a community-dwelling older population.

Patients and Methods

Participants

This study utilised data from the Tasmanian Older Adult Cohort Study (TASOAC), a longitudinal, observational population-based study. A total of 1,099 participants aged 50–80 years (mean age 63 years) were randomly selected using computer generated random numbers from the electoral roll in Southern Tasmania (population 229,000), with an equal number of men and women. Baseline measures were conducted in 2002 (Phase 1). The follow-up measures were performed approximately 2.6 years (Phase 2, n=875), 5.1 years (Phase 3, n=768) and 10.7 years (Phase 4, n=563) later. Supplementary Figure 1 shows reasons for non-participation at each follow-up. The

study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and all participants provided written informed consent.

Fracture

Fracture events occurring at any site were recorded at each visit, and then were categorised into five groups: any fractures, vertebral, non-vertebral, hip and major fractures (defined as involving the femur, radius, ulnar, vertebral, rib and humerus). At baseline, participants were asked to report any fractures they ever had. During the follow-up, participants were asked to report any fractures since last visit. Those who experienced any fractures from baseline (i.e. those reported fractures at Phase 2, Phase 3 and/or Phase 4) were considered incident fracture.

Number of painful sites

The location of sites at which the participants experienced pain was self-reported at baseline. Participants were asked whether they had pain (yes/no) in the following sites at present: neck, back, hands, shoulders, hips, knees or feet. The total number of painful sites (range 0 to 7) was categorised into three groups (0-2, 3-4 and 5-7 painful sites).

Anthropometrics

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) calibrated using a known weight at the beginning of each clinic. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Height and weight were measured at baseline and were then used to calculate body mass index (BMI) (kg/m^2).

Physical activity

Physical activity was assessed at baseline as steps/day determined by pedometer (Omron HJ –003 & HJ–102, Omron Healthcare, Kyoto, Japan), as previously described (35). Briefly, participants were instructed to wear a pedometer for seven consecutive days and to record the number of steps each day and the duration and type of physical activity for any activities in which the pedometer could not be worn (for example, swimming). This was repeated six months later to account for seasonal variation. Mean steps/day was calculated as the average of the days worn at both time points.

Smoking history

Smoking history was assessed at baseline by asking 'Have you ever smoked at least seven cigarettes, cigar or pipes every week for at least 3 months?'.

Use of pain medication

Participants were asked to list all medication prescribed by a doctor, and any other over-the-counter medications they had taken in the last two weeks, including dosage and frequency. Medications used for pain relief were extracted from this list, and dichotomised into whether they were used or not (yes/no). A list of reported use of pain medications is shown in Supplementary Table 1.

Comorbidities

Common conditions including diabetes, heart attack, hypertension, thrombosis, asthma, bronchitis/emphysema, hyperthyroidism, hypothyroidism, rheumatoid arthritis, were collected by a self-reported comorbidity questionnaire. The participants were also asked to list any doctor diagnosed osteoarthritis at neck, back, hands, shoulders, hips, knees and feet. The presence of osteoarthritis was defined as

osteoarthritis occurring at any one or more sites. Each condition was summed to create a total of number of comorbidities (range 0-10), which was also grouped as a categorical variable (any comorbidities defined as having one or more comorbidities).

Falls risk

The short form Physiological Profile Assessment (PPA) (Prince of Wales Medical Research Institute, Sydney, Australia) was used to identify individuals who are at risk of falls (36). The PPA is a valid and reliable tool and measures five physiological domains including visual contrast sensitivity, reaction time, knee extension strength, proprioception and postural sway on foam. Based upon these five domains, a standardized falls risk score at baseline was then calculated.

BMD

Femoral neck BMD was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic Delphi densitometer (Model: Hologic Discovery QDR; Software: Apex system software 2.4.2; Manufacturer: Hologic, Waltham, MA, USA) at baseline.

Statistical analysis

T-tests and Chi-square were used to compare differences in means and percentages between the participants included and the rest of cohort where appropriate. ANOVA and ordinal $\chi 2$ test (Kruskal-Wallis test) were used to test if there was a trend of mean of each continuous and categorical variable across pain groups. Log-binomial regression was used to examine the associations between number of painful sites and prevalent and incident fractures at different sites. Regression models were performed stepwise: 1) adjusted for age, sex, BMI, physical activity, smoking history, pain medication and comorbidities; 2) further adjusted for falls risk and hip BMD. Inverse probability weighting was applied to examine whether loss to follow-up influenced

our results of incident fractures. All statistical analyses were performed using Stata V.15 (StataCorp, USA). P values less than 0.05 (two-tailed) were regarded as statistically significant.

Results

Of 1,099 participants attending baseline examination, 1,000 participants had complete interview, questionnaire and clinical assessment data at baseline. Table 1 shows characteristics of participants by number of painful sites. Those who reported greater number of painful sites were more likely to be female, heavier and shorter, have a greater BMI, be physically inactive, have more comorbidities, a higher reported use of pain medication, a greater falls risk score as well as higher prevalent and incident fractures. There were no statistically significant differences across the pain categories in terms of age, smoking history and hip BMD.

There were 450 fractures reported at baseline in total. Of these, 32 vertebral, 441 non-vertebral, eight hip and 244 major fractures were reported. During a mean follow-up period of 10.7 years (range 9.2-12.5 years), a total of 154 participants reported fractures, of whom 21 experienced a vertebral fracture, 134 a non-vertebral fracture and only three a hip fracture and 60 had fractures occurring at the major. Figure 1 presents prevalent and incident fractures at these sites broken down by category of number of painful sites. Prevalent fractures increased with increasing number of painful sites in a dose-response manner for fractures at any site, non-vertebral, and hip (all adjusted P for trend<0.05), while results did not achieve statistical significance for major and vertebral fractures. Similarly, incidence of fractures at any site, major, and vertebral was higher in those in a greater number of painful sites. There was also a dose-response relationship between incident fractures and number of painful sites (all

adjusted P for trend<0.05). No statistical significance for non-vertebral and hip fractures was observed.

Adjusted associations between number of painful sites and prevalent and incident fractures are presented in Table 2 and 3. After adjustment for potential confounders (including age, sex, BMI, physical activity, smoking history, pain medication and comorbidities), number of painful sites was associated with prevalent and incident fractures at any site. Number of painful sites was associated with prevalent fractures at non-vertebral, while it was associated with an increased risk of incident vertebral and major fractures. After further adjustment for falls risk and hip BMD, these associations remained significant. Also, there was a dose-response relationship between number of painful sites and risk of fractures at these sites.

Compared to those who were lost to follow-up, participants who completed the study at 10.7 years were younger, had a lower BMI, were more physically active, had a greater number of comorbidities, higher hip BMD and lower falls risk score. There was a lower proportion of participants who had ever smoked, reported the use of pain medications and had a greater number of painful sites in the cohort with follow-up (Supplementary Table 2). We reanalysed the data using inverse probability weighting, the results remained consistent (data not shown).

Discussion

This study found that number of painful sites is associated with prevalent fractures in a dose-response manner among a general community-based older population. In addition, greater number of painful sites was associated with an increased risk of incident fractures, independent of falls risk, BMD and other potential confounders, suggesting that MSP in older adults may be considered an independent risk factor or

marker for fractures. The associations of MSP with prevalent and incident fractures differed across different sites, which may reflect some differences in underlying mechanisms of fractures at different sites and/or the lower numbers of some fracture types.

Musculoskeletal pain is highly prevalent and commonly occurs at multiple sites in older adults. MSP has been shown to be associated with multiple health outcomes including physical and psychological domains and is being recommended as a geriatric syndrome (37). A link between pain and risk of falls has been documented in prior studies (19, 20) and recent studies (21-25). Further, risk for falls was more pronounced with increasing number of painful sites (26, 27). It has been postulated that the increased risk of falls is due to local joint pathology, leg muscle weakness or slowed neuromuscular responses, and cognitive and executive function (19, 20, 26). Given that a fall is one of main risk factors for fractures, we hypothesised that participants having more painful sites had a higher risk of prevalent and incident fractures which was largely mediated by increased risk of falls. Partially consistent with our hypotheses, our study found higher prevalence and incidence of fractures at any site in those with greater painful sites. However, our findings that the associations between MSP and fractures are independent of falls risk, BMD and other potential confounders suggest that increased risk of fractures in those with a greater number of painful sites is not explained by increased risk of falls and other factors. Indeed, there was no evidence that these factors act as confounders in the models (data not shown). This supports that MSP can be regarded as an independent factor in the assessment of fracture risk in older population.

To the best of our knowledge, our study is the first to investigate the association between MSP and prevalent and incident fractures. There have been few attempts to

explore the association between single-site pain and risk of fractures, but the results are mixed (31-34). Arden et al (33) reported that knee pain was associated with an increased risk of non-vertebral and hip fracture over a 3-year period in women and men aged ≥75 years old. In a Japanese postmenopausal women cohort with a mean follow-up of 5.7 years, back pain was found to be associated with incident vertebral fractures (32). In contrast, a study in women aged ≥65 years old did not find an increased risk of incident vertebral fractures in those with back pain (34). In a recent study with a mean follow-up of 9.7 years, neither hip nor knee pain were reported to be associated with future hip and non-spine fractures in a community-dwelling older men population (31). These discrepancies may be explained by the differences in participants' characteristics, assessment in pain and fractures sites, and length of follow-up. The findings of the current study are not directly comparable with prior studies, but this study extends previous studies into assessing MSP and different types of fractures, and a longer time of follow-up. Our study, combined with these studies, provides a support for the adverse impacts of pain on health outcomes, with a greater impact of MSP.

The current study found that number of painful sites was associated with higher prevalent fractures at non-vertebral, but not at vertebral. This may reflect that risk factors for fractures vary according to different sites, despite several common risk factors for all types of fractures (e.g. age and low BMD). In this study, pain was assessed at baseline while prevalent fractures may have occurred several years before, making it difficult to make causal interpretation.

In contrast, we found an increased risk of fractures at vertebral but not non-vertebral in those with a greater number of painful sites. The mechanisms underlying the link of MSP—vertebral fractures are not clear, but systemic inflammation due to pain is one

of the suggested explanations. Systemic inflammation has been suggested a crucial role in bone remodelling with human studies showing increased risk of fractures associated with pro-inflammatory cytokines (38-40). There is some evidence that participants with widespread pain (e.g. fibromyalgia), have modestly elevated levels of systemic inflammation (41), reduced anti-inflammatory markers (42) and enhanced innate immune response (43). In light of this, it is plausible that participants with MSP had higher levels of inflammation, which lower bones strength through bone remodelling, thereby increasing risk of fractures. Despite no statistically significant association for incident non-vertebral fractures, we observed a numerically greater risk in those people with more painful sites suggesting a longer follow-up or larger sample size may be needed. The findings from this study have several implications for research and clinical practice. First, the observed relationship between MSP and prevalent fractures emphasises pervasive MSP in the older population and its correlation with fractures. It is important that clinicians should routinely count and assess number of painful sites in relation to fractures. Second, increased risk of incident fractures in participants with a greater number of painful sites suggests that MSP is an important risk factor for fractures in older adults. One implication from this finding is that treatment and management of pain may have the potential to prevent and reduce fracture risk in older population, thereby leading to a reduction in mortality related to fractures. However, treatments targeted at single-site pain may only have small effects on fractures reduction in those with MSP. MSP may reflect a dysfunction in pain processing (44), therefore, it is worthwhile testing centrally acting agents such as antidepressants in future well-designed trials. More importantly, the underlying causes of MSP should also be sought and targeted.

The strengths of this study include a large sample of general older population with a long-time period of follow-up. There are several potential limitations needed to acknowledge. First, pain was measured by a simple self-reported questionnaire with no assessment of pain intensity, duration and pattern; therefore, we are unable to assess whether these pain features are associated with fractures. Second, although multiple common comorbidities in older adults were considered in this study, it is still possible that some unidentified conditions associated with pain may be a driver for fracture risk. Third, self-reported fracture without X-ray confirmation may lead to over-reporting of fractures (45). We may have overestimated the relative risks (RRs) if fractures were randomly reported in relation to different pain categories. Alternatively, participants with a greater number of painful sites may be more likely to remember and report fractures more accurately than those without pain or fewer painful sites, then the RRs may have been underestimated. This underestimated effect may get stronger with a longer recall period since fracture may be more likely to be forgotten in those with fewer painful sites. In addition, fractures (especially hip fractures) increase mortality rates in the elderly (46). This may lead to under-reporting of fractures in some people if they did not survive to next assessment, so the association between pain and fracture risk may be underestimated. Fourth, we were unable to estimate hazard ratios of incident fractures given the fact that the exact time of the occurrence of fractures was not ascertained, and the follow-up time cannot accurately represent the time to the event (fractures). Therefore, our results may be affected by loss to follow-up and death while using log-binomial regression. However, we found similar results after using inverse probability weighting to address the issue of loss to follow-up, suggesting that our results are robust. Fifth, participants who were lost to follow-up were likely to have a greater number of painful sites

compared to those who completed the study. Therefore, this may have weakened the association between MSP and fracture risk. Lastly, there were only eight and three hip fractures reported at baseline and during follow-up, respectively, leading to no observations in one pain category. Therefore, we were unable to estimate the risk of hip fractures.

In conclusion, pain at multiple sites was associated with prevalent fractures, independent of falls risk, BMD and potential confounders, providing the evidence of general link between MSP and fractures. Incident fracture risk increased with greater number of painful sites suggesting that widespread pain is an independent contributor to fracture risk. The potential of pain management for fracture prevention warrants further exploration.

Acknowledgements

We thank the study participants for volunteering for the study, and Catrina Boon and Pip Boon for their role in data collection. FP is funded by the National Health and Medical Research Council (NHMRC) of Australia Early Career Fellowship; DA is funded NHMRC Career Development Fellowship; GJ is funded by NHMRC Practitioner Fellowship. This work was supported by grants from the NHMRC (302204), the Tasmanian Community Fund (D0015018), the Arthritis Foundation of Australia (MRI06161), and the University of Tasmania Grant-Institutional Research Scheme (D0015019).

Authors' roles: Study design and conduct: FP, FC and GJ; Data collection: FP, DA, FC, and GJ; Data analysis: FP and JT. Data interpretation: FP, JT, DA, and GJ; Drafting and Revising manuscript: FP, JT, DA, FC and GJ. FP and GJ take responsibility for the integrity of the data analysis.

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Figure

Figure 1. Prevalent and incident fractures occurring in each category of number of painful sites. P for trend from tests of trend of fractures on number of painful sites determined by the log-binomial regression with adjustment for age, sex, body mass index, physical activity, smoking history, pain medication, comorbidities, falls risk, and hip bone mineral density.

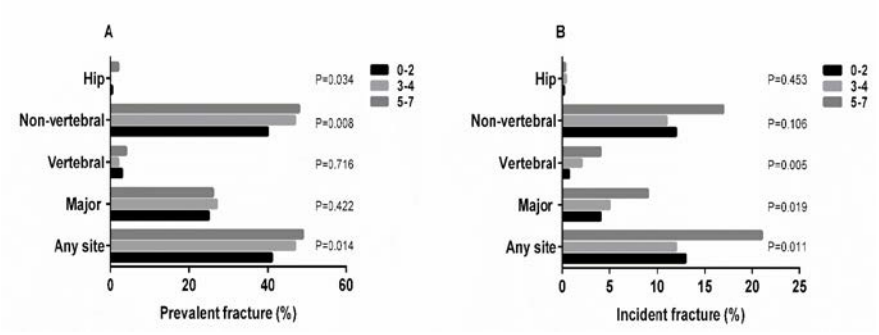

Table 1 Descriptive characteristics of participants, by number of painful sites*

	Number of painful sites			P value
	0-2 (n=425)	3-4 (n=281)	5-7 (n=294)	
Age, years	63.0±7.5	62.3±7.1	63.3±7.7	0.721
Female (%)	46	54	57	0.003
Weight (kg)	76.1±14.8	78.7±15.0	79.2±14.6	0.004
Height (cm)	167.7±9.2	167.4±8.6	165.9±8.8	0.014
Body mass index (kg/m^2)	27.0±4.3	28.0±4.5	28.7±5.2	<0.001
Ever smoking (%)	48	49	55	0.101
Physical activity (steps/day)	8995.3±3375.4	8616.9±3245.5	8052.2±3352.7	<0.001
Number of comorbidities (0-10)	1.0±1.1	1.5±1.2	2.0±1.4	<0.001
Any comorbidities (%)	61	77	88	<0.001
Any pain medications (%)	45	59	73	<0.001
Hip bone mineral density (g/cm^2)	0.96±0.15	0.98±0.15	0.97±0.16	0.239
Falls risk (z score)	0.11±0.77	0.08±0.75	0.30±0.91	0.004
Prevalent fractures (%)	41	47	49	0.026
Incident fractures (%)	13	12	21	0.004

*Values are the Mean±SD except for percentages; ANOVA and ordinal $\chi 2$ test (Kruskal-Wallis test) were used to test if there was a trend of mean of each continuous and categorical variable (increase or decrease) across pain groups.

Table 2 Association between number of painful sites and prevalent fractures*

	No. of participants	*No. of participants with fracture*	number of painful sites	Multivariable†		Multivariable‡	
				PR	95% CI	PR	95% CI
Fractures at any site							
	425	174	0-2	REF		REF	
	281	132	3-4	1.16	0.98, 1.37	1.17	0.99, 1.37
	294	144	5-7	1.19	1.01, 1.41	1.23	1.04, 1.46
			P for trend	0.035		0.014	
Vertebral fractures							
	425	12	0-2	REF		REF	
	281	7	3-4	0.77	0.30, 1.97	0.78	0.30, 1.99
	294	13	5-7	1.13	0.48, 2.65	1.16	0.50, 2.72
			P for trend	0.763		0.716	
Non-vertebral fractures							
	425	169	0-2	REF		REF	
	281	131	3-4	1.19	1.00, 1.41	1.19	1.01, 1.41

	294	141	5-7	1.22	1.03, 1.44	1.26	1.06, 1.49
			P for trend	0.021		0.008	
Major fractures							
	425	94	0-2	REF		REF	
	281	75	3-4	1.21	0.93, 1.57	1.23	0.94, 1.60
	294	75	5-7	1.09	0.83, 1.45	1.11	0.84, 1.47
			P for trend	0.487		0.422	

Bold denotes statistically significant result. REF, reference group.

*PR (95% CI): Prevalence ratio (95% confidence interval) representing the risk of having fractures associated with greater number of painful sites;

†Adjusted for age, sex, body mass index, physical activity, smoking history, pain medication and comorbidities;

‡Further adjusted for falls risk and hip bone mineral density.

Table 3 Association between number of painful sites and incident fractures*

	No. of participants	*No. of participants with fracture*	number of painful sites	Multivariable†		Multivariable‡	
				RR	95% CI	RR	95% CI
Fractures at any site							
	425	56	0-2	REF		REF	
	281	35	3-4	0.93	0.59, 1.45	0.95	0.61, 1.50

	294	63	5-7	1.69	1.13, 2.53	1.70	1.13, 2.55
			P for trend	0.012		0.011	
Vertebral fractures							
	425	3	0-2	REF		REF	
	281	6	3-4	3.29	0.77, 14.02	3.30	0.78, 14.01
	294	12	5-7	6.44	1.64, 25.33	6.54	1.67, 25.60
			P for trend	0.005		0.005	
Non-vertebral fractures							
	425	53	0-2	REF		REF	
	281	30	3-4	0.83	0.51, 1.35	0.86	0.53, 1.40
	294	51	5-7	1.45	0.93, 2.26	1.46	0.94, 2.27
			P for trend	0.109		0.106	
Major fractures							
	425	19	0-2	REF		REF	
	281	14	3-4	1.11	0.53, 2.33	1.14	0.54, 2.40
	294	27	5-7	2.17	1.12,	2.21	1.14,

		4.22	4.31
	P for trend	0.021	0.019

Bold denotes statistically significant result. REF, reference group.

*RR (95% CI): Relative risk (95% confidence interval) representing the risk of having fractures associated with greater number of painful sites;

†Adjusted for age, sex, body mass index, physical activity, smoking history, pain medication and comorbidities;

‡Further adjusted for falls risk and hip bone mineral density.