Predictors of pain interference and potential gain from intervention in community dwelling adults with joint pain

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Title: Predictors of pain interference and potential gain from intervention in community dwelling adults with joint pain: prospective cohort study

Running head: Modifiable predictors of pain interference

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Abstract

Introduction: There is little research on identifying modifiable risk factors that predict future interference of pain with daily activity in people with joint pain, and the estimation of corresponding population attributable risk. This study therefore investigates modifiable predictors of pain interference and estimates maximum potential gain from intervention in adults with joint pain.

Methods: A population-based cohort aged ≥50 years was recruited from eight general practices in North Staffordshire, UK. Participants (n=1878) had joint pain at baseline lasting ≥3 months and indicated no pain interference. Adjusted associations of self-reported, potentially modifiable, prognostic factors (body mass index, anxiety/depressive symptoms, widespread pain, inadequate joint pain control, physical inactivity, sleep problems, smoking and alcohol intake) with onset of pain interference three years later were estimated via Poisson regression, and corresponding population attributable risk (PAR) estimates were obtained.

Results: Inadequate joint specific pain control, insomnia and infrequent walking are independently significantly associated with onset of pain interference after three years, with associated PARs of 6.3%, 7.6% and 8.0% respectively, however only PAR for infrequent walking was statistically significant. The PAR associated with inadequate control of joint pain, insomnia and infrequent walking simultaneously was 20.3% (95%CI 8.6, 30.4).

Conclusions: There is potential to moderately reduce the onset of pain interference from joint pain in the over-50s if clinical and public health interventions targeted pain management and insomnia and promoted active lifestyle. Most of the onset of significant pain interference in the over 50s, however, would not be prevented even assuming these factors could be eliminated.

1. INTRODUCTION

Joint pain, including joint pain attributable to osteoarthritis (OA), is one of the most common reasons for consulting primary care. A study based in North Staffordshire, UK, has found that 10% of adults aged 45 years and over consult primary care annually for joint pain (Jordan et al., 2014). This burden has huge cost implications for society, both in terms of work-loss (Sharif et al., 2016) and health care use (Xie et al., 2016). The goal of treatment is to reduce joint pain, maintain function and optimise lifestyle choices based on individual patient needs (NICE, 2014).

In primary care, advice and decisions regarding initial treatment of OA is based on a clinical assessment of patients presenting with joint pain, without imaging or other investigations, with agreed criteria for a clinical diagnosis of OA including age >45 years and movement-related chronic joint pain, without morning stiffness lasting more than 30 minutes (NICE 2014). Although OA can occur at any synovial joint, the knees, hips, hands and feet are most commonly affected (Bijlsma et al., 2011; Roddy et al., 2015). The natural history of OA onset and progression at each of these body sites is variable, indicating that OA is not one disease entity but rather a disease process with a number of site-specific phenotypes (Bijlsma et al., 2011), that may benefit from targeted site-specific management. There has been increased interest in symptom trajectory analyses specifically for the hip (Verkleij et al., 2012), knee (Holla et al., 2014), or hand (Green et al., 2016), and the design of site-specific prediction models (Kerkhof et al., 2014), attempting to subgroup patients into distinct prognostic categories, which may benefit from targeted site-specific management.

However, optimal clinical and public health interventions for joint pain should not only target individual joint site features, such as specific muscle weakness, but also person-level characteristics that could help symptom control, such as weight loss and active lifestyle. The emphasis on joint sites in isolation does not always reflect the fact that people with joint pain are likely to have symptoms across multiple joint sites (Birrell, 2004; Peat et al., 2006; Keenan et al., 2006). Whilst previous studies have developed models to predict onset of joint pain (Takahashi et al., 2010; Kerkhof et al., 2014) or specific treatment outcomes (French et al., 2014; Wright et al., 2011), the focus has predominantly been joint-specific, particularly at the knee (Jinks et al., 2008; Zhang et al., 2011; Yusuf et al., 2011). Prospective evidence of how potentially modifiable person-level risk factors can alter the course and impact of joint pain at multiple sites of the body remains unclear. Furthermore, it has been argued that OA should be regarded as a chronic condition, and the models of prevention and early care applied as is common with other chronic conditions (Roos and Arden, 2016).

The aim of this study was to investigate the association of potentially modifiable prognostic factors, identified from previous research, including obesity, sleep or mood problems, physical inactivity, pain severity, and multisite pain, with future (3-year) risk of pain interference in a population-based sample of older adults with joint pain. Additionally, population attributable risk was estimated for these

prognostic factors to allow better understanding of their potential impact at a population level and clinical importance as potential targets for treatment.

2. PATIENTS AND METHODS

2.1 Design and study population

Data were used from the North Staffordshire Osteoarthritis Projects (NorStOP), which consist of a series of population-based prospective cohorts of adults aged 50 years or more registered with 8 general practices in North Staffordshire (UK) (Thomas et al., 2004). A substantial proportion (98%) of the British population is registered with a general practice making it a suitable sampling frame for a population study. A two stage mailing strategy was used consisting of a health survey sent to all individuals between 2002 and 2005, and a subsequent regional pain questionnaire sent to those who responded, gave consent to further contact, and indicated they had experienced pain in the hip, knee, hand or foot in the previous year. Participants received similar follow-up questionnaires 3 years later (Thomas et al., 2004). The North Staffordshire Local Research Ethics Committee approved the study (NS-LREC 1351 and 1430). For this analysis we identified all responders who reported hand, hip, knee or foot joint pain at baseline that had lasted three months or more over the last 12 months and indicated no pain interference with daily activities.

2.2 Outcome: interfering pain at 3-year follow-up

The outcome of interest was onset of pain interference at 3-year follow-up and consisted of a single item from the MOS SF-12 reflecting the current interference of pain in everyday activities (Ware et al., 1996): “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)”. The five possible response options were grouped as interfering pain (“Moderately”, “Quite a bit” or “Extremely”) versus no interfering pain (“Not at all” or “A little bit”). This dichotomy to differentiate between those with considerable versus minimal or no interfering pain has been used previously (Campbell et al., 2013; Thomas et al., 2014).

2.3 Potential prognostic factors

The baseline health survey included a wide range of socio-demographic, lifestyle, general health, joint pain, physical functioning and comorbidity variables. Full details of these variables and their descriptions have been reported in detail elsewhere (Thomas et al., 2004).

Modifiable prognostic factors

Factors were selected based on their already established relationship with outcomes of hip, knee or hand pain (Chapple et al., 2011; Nicholls et al., 2012; de Rooij et al., 2016), and/or their potential to be modifiable via interventions (Uthman et al., 2013; Zhang et al., 2017; Springer et al., 2017). These included:

(i) Being overweight or obese (as defined by Body Mass Index (BMI) of ≥25-29.99 and ≥30 respectively).

(ii) Anxiety or depression measured as score 8+ on either the Hospital Anxiety or Depression Scales (Zigmond and Snaith, 1983).

(iii) Widespread pain: defined by ACR 1990 criteria for fibromyalgia requiring presence of pain above and below the waist, in the right and left sides of the body and in the axial skeleton (Wolfe et al., 1990).

(iv) Inadequate control of joint pain: defined as a high score on pain subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for hip or knee pain (Bellamy 1996), Australian Canadian Osteoarthritis Hand Index (AUSCAN) for hand pain (Bellamy et al., 2002), and Manchester Foot Pain and Disability Index (MFPDI) for foot pain (Garrow et al., 2000). The following cut-off points were used in the analysis sample: WOMAC knee pain score of ≥10, WOMAC hip pain score of ≥10, AUSCAN hand pain score ≥10, MFPDI foot Rasch pain score ≥0.7485. All these cut off points are the 91st percentile for their respective scale, reflecting high levels of pain likely to require additional treatment (over and beyond simple analgesics).

(v) Insomnia: measured via Jenkins Sleep Questionnaire (Morphy et al., 2007), comprised of four items regarding common sleep problems over the past 4 weeks, namely "having trouble falling asleep", "waking up several times per night", "having trouble staying asleep" and "waking up after usual amount of sleep feeling tired and worn out", each presenting three response options: "not at all", "on some nights" and "on most nights". Insomnia was defined as those responding "on most nights" on at least one item. This definition of insomnia has been used previously (Morphy et al., 2007, Campbell et al., 2013).

(vi) Physical inactivity: measured using responses to four questions (playing sports, heavy DIY, housework and gardening) which were scored as "All days", "Most days", "Some days", "Few days" or "No days" in the last 4 weeks. Physical inactivity was defined as response of few days/no days on all four items.

(vii) Infrequent walking: defined as frequency of <1 per week or never for both short and long walks in last 4 weeks.

(viii) Smoking status

(ix) High and moderate alcohol intake: daily and monthly/weekly versus once/twice a year or never.

2.4 Potential confounders

Potential confounding variables were chosen on the basis of having previously been shown to be associated with future outcomes in people with joint pain, but cannot be modified, or their risk cannot

be fully addressed by interventions (Chapple et al., 2011; Nicholls et al., 2012; de Rooij et al., 2016). These included:

(i) Age and gender

(ii) Living alone

(iii) Higher education

(iv) Employment categorised as employed, retired or ill/unemployed/housewife/other.

(v) Financial strain: measured using responses to perceived income adequacy question, with financial strain indicated with responses "Strain" or "Need to be careful" versus no financial strain, indicated with a response of "can manage" or "comfortably well off".

(vi) Social networks: measured using Berkman-Syme Network Index (Berkman and Syme, 1979), comprised of four types of social connection: marital status (married/unmarried), sociability (number of frequent contacts with children, close relatives, and close friends), church group membership (yes/no) and membership in other community organizations (yes/no). Responses were combined and categorized into two levels: socially isolated (including those classed as isolated or moderately isolated) and socially integrated (including those classed as moderately integrated or integrated).

(vii) Cognitive impairment: measured using alertness behaviour subscale of Sickness Impact Profile (Bergner et al., 1981), consisting of 10 binary items measuring alertness and ability to concentrate; composite score was categorised as no cognitive impairment (score 0) versus cognitive impairment (score>0).

(viii) Comorbidities: number of existing health conditions (chest problems, heart problems, diabetes; categorised as 0/1/2-3) and number of impairments (deafness, eyesight problems, cough with spit, breathless when walking, dizziness, weakness in arms/legs; categorised as 0/1/2-6).

(ix) Injury: defined as ever having had injury in one or more of knee, hip, hand and foot.

(x) Pain relief: measured via three variables: pain medications and anti-inflammatories (e.g. paracetamol, aspirin, Diclofenac, Ibuprofen), creams and gels (e.g. Ibuleve, Ibuprofen, Ralgex), natural medicines (e.g. herbal remedies, cod liver oil); all categorised as "No", "Few/Some days" and "Most/All days".

2.5 Statistical analysis

Responders and non-responders at 3 years were compared in terms of prognostic factors considered in this study.

Poisson regression models were used to obtain estimates of associations between modifiable prognostic factors and onset of pain interference at 3 years, quantified in terms of relative risks (RRs) and associated 95% confidence intervals (CIs). Robust variance estimator was used to account for

excess zeros in the data (Zou, 2004). Unadjusted associations were obtained first followed by adjustment for potential confounders (i)-(x) above. Subsequently, a full multivariable model was fit, where all modifiable factors were entered into the model simultaneously, adjusted for potential confounders. Pearson chi-square goodness of fit test was used in each case to assess how well the assumed Poisson model fit the observed data.

To estimate the individual contribution of identified modifiable prognostic factors at the population level, PAR was estimated for each. PAR represents the proportion of the risk of pain interference in the whole population that is explained by a particular factor and would be removed if exposure to that factor was eliminated. Greenland and Drescher's specification of model-based adjusted PAR was used (Greenland and Drescher, 1993), expressed as $1 - \sum_j \sum_i \frac{p_{ij}}{\mathrm{RR}_{i|j}}$ where sum over j represents sum over all adjustment factors and sum over i represents sum over all levels of modifiable factors of interest. p_{ij} is a model-based estimate of the proportion of those with pain interference among those with modifiable factor level i and level j of adjustment factors. $\mathrm{RR}_{i|j}$ are obtained from the final multivariable regression model outlined above. Corresponding variance estimates are obtained using standard delta method.

Primary analysis was based on participants with complete data. Multiple imputation by chained equations (White et al., 2011), using 100 imputations, was subsequently used to impute missing data and all analyses re-performed in order to assess sensitivity of results to missing data. All analyses were performed using STATA version 12.

4. RESULTS

4.1 Study sample

A total of 26,625 people aged ≥50 were identified from eight general practices, found eligible to take part and mailed the health survey. Seventy-one percent (18,497 participants) responded and the regional pain questionnaire was subsequently sent to 10,057 people who gave consent for further contact and specified any joint pain in the last year (response rate 87%). Two thousand two hundred and seventy-two participants indicated hand, hip, knee or foot pain lasting three or more months over the last 12 months on the regional pain questionnaire and reported no interference of pain with daily activities, 1878 (83%) of whom responded to 3-year health survey. These participants formed the analysis sample for this study; the corresponding flowchart is given in Fig 1.

[Figure 1 to be inserted here]

They were more likely to be female compared to the 394 non-responders (60% vs 51.5%, p-value=0.001), less likely to suffer with cognitive impairment (35% vs 41%, p-value=0.033) and less

likely to be a current smoker (11% vs 16%, p-value=0.006). They did not differ significantly with respect to any other factors considered.

The mean age of the 1878 participants was 62.7 years (standard deviation (SD) 8.2) and 60% were female. The majority reported hand pain and knee pain at baseline (63 and 62% respectively), followed by foot pain (47%) and hip pain (37%). 33% reported pain in only one joint (typically hand or knee) and 10% in all four joints considered. Mean WOMAC knee and hip pain subscale scores at baseline were 4.3 (SD 3.3) and 4.7 (SD 3.1) respectively, mean AUSCAN score was 4.7 (SD 3.7) and median MFPDI score was -0.96 (inter-quartile range -1.6, 0.004).

4.2 Prognostic factors

Table 1 and Table 2 give baseline distribution of all prognostic factors and confounders respectively considered in the study. At 3-year follow-up, 503 (27%) patients reported onset of pain interference with everyday life.

Table 1: Distribution of all considered prognostic factors at baseline

		Pain interference at 3 years	
	All (1878) N(%)†	**No (1332) N(%)†**	**Yes (503) N(%)†**
BMI			
Normal† □	769 (41)	552 (41)	205 (41)
Overweight	769 (41)	552 (41)	205 (41)
Obese	320 (17)	211 (16)	99 (20)
Anxiety/depression			
No□	1269 (68)	933 (70)	307 (61)
Yes	582 (31)	380 (29)	188 (37)
Widespread pain			
No□	1344 (72)	992 (74)	322 (64)
Yes	366 (19)	225 (17)	133 (26)
Inadequate joint specific pain control			
No□	1513 (81)	1129 (85)	350 (70)
Yes	354 (19)	195 (15)	151 (30)
Insomnia			
No□	1303 (69)	949 (71)	325 (65)
Yes	570 (30)	382 (29)	174 (35)
Infrequent walks in last 4 weeks			
No□	187 (10)	136 (10)	48 (10)
Yes	1663 (89)	1178 (88)	446 (89)
Smoking			
No□	860 (46)	634 (48)	207 (41)
Previous	793 (42)	546 (41)	227 (45)
Current	212 (11)	141 (11)	67 (13)
Alcohol intake			
Never/yearly□	382 (20)	257 (19)	115 (23)
Monthly/weekly	1018 (54)	715 (54)	278 (55)
Daily	462 (25)	348 (26)	106 (21)

BMI Body mass index; † Percentages may not add up to 100 due to missing data; ‡ Normal BMI category includes underweight patients (<2%); □ Used as a reference category in Poisson regression analyses.

Table 2: Distribution of all considered confounders at baseline

		Pain interference at 3 years	
	All (1878) N(%)†	**No (1332)** N(%)†	**Yes (503)** N(%)†
Age, mean(SD)	62.7 (8.2)	65.0 (9.1)	63.4 (8.6)
Gender			
Male	743 (40)	541 (41)	185 (37)
Female	1135 (60)	791 (59)	318 (63)
Living alone			
No	1484 (79)	1072 (80)	378 (75)
Yes	324 (17)	209 (16)	106 (21)
No higher education			
No	293 (16)	235 (18)	55 (11)
Yes	1558 (83)	1075 (81)	444 (88)
Employment			
Employed	683 (36)	529 (40)	141 (28)
Retired	914 (49)	626 (47)	267 (53)
Other‡	232 (12)	148 (11)	77 (15)
Financial strain			
No	1210 (64)	892 (67)	290 (58)
Yes	647 (34)	427 (32)	205 (41)
Social networks			
Integrated	696 (37)	519 (39)	170 (34)
Isolated	860 (46)	590 (44)	241 (48)
Cognitive impairment			
No	1173 (62)	868 (65)	282 (56)
Yes	639 (34)	419 (31)	202 (40)
Health conditions			
None	1281 (68)	958 (72)	297 (59)
1	486 (26)	317 (24)	159 (32)
2-3	111 (6)	57 (4)	47 (9)
Impairments			
None	704 (37)	563 (42)	127 (25)
1	616 (33)	420 (32)	180 (36)
2-3	558 (30)	349 (26)	196 (39)
Injury			
No	1035 (55)	747 (56)	266 (53)
Yes	835 (44)	578 (43)	236 (47)
Painkillers/Anti-inflammatories			
No days	632 (34)	505 (38)	115 (23)
Few/Some days	802 (43)	580 (44)	204 (41)
Most/All days	362 (19)	191 (14)	162 (32)
Creams and gels			
No days	1140 (61)	860 (65)	256 (51)
Few/Some days	396 (21)	263 (20)	124 (25)
Most/All days	92 (5)	45 (3)	44 (9)
Natural medicine			
No days	886 (47)	637 (48)	226 (45)
Few/Some days	123 (7)	89 (7)	33 (7)
Most/All days	649 (35)	467 (35)	170 (34)

SD Standard deviation; † Percentages may not add up to 100 due to missing data; ‡ Consisting of those ill, unemployed, housewives or other.

All modifiable prognostic factors, except being overweight and alcohol intake, were individually significantly associated with pain interference at 3-year follow-up (Table 3). Following adjustment for

confounding variables (from Table 2), the significant associations remained for widespread pain, inadequate joint specific pain control, insomnia and infrequent walking. In the full multivariable model including all modifiable prognostic factors adjusted for confounders, infrequent walking was the strongest predictor of incidence of pain interference at 3 years (RR 1.26; 95%CI 1.02, 1.57) that had a significant estimated PAR: 8.0 (95%CI 0.1, 15.2) i.e. 8% of incident cases could potentially be prevented if infrequent walking was fully addressed. Even though those with inadequate control of joint pain and those reporting insomnia were 20-30% more likely to report onset of pain interference (RR 1.28; 95%CI 1.01, 1.64 and RR 1.25; 95%CI 1.01, 1.56 respectively), the associated PARs were not statistically significant (6.3; 95%CI -0.3, 12.4 and 7.6; 95%CI -0.4, 15.0). The PAR associated with inadequate control of joint pain, insomnia and infrequent walking simultaneously was 20.3% (95%CI 8.6, 30.4).

Table 3: Modifiable predictors of pain interference at 3 years: Relative risk and population attributable risk

			Full multivariable model‡	
	Unadjusted RR (95% CI)	**Adjusted models† RR (95% CI)**	**RR (95% CI)**	**Adjusted PAR (95%CI)**
BMI				
Overweight	1.06 (0.89, 1.26)	1.08 (0.87, 1.35)	1.08 (0.85, 1.36)	4.3 (-9.1, 16.1)
Obese	1.25 (1.02, 1.53)	1.18 (0.90, 1.54)	1.21 (0.90, 1.62)	8.4 (-2.8, 18.3)
Anxiety/depression	1.34 (1.15, 1.56)	1.13 (0.90, 1.41)	1.11 (0.87, 1.41)	3.7 (-5.3, 12.0)
Widespread pain	1.52 (1.29, 1.79)	1.29 (1.03, 1.63)	1.27 (1.00, 1.61)	6.7 (-0.4, 13.4)
Inadequate joint specific pain control	1.84 (1.59, 2.14)	1.29 (1.04, 1.60)	1.28 (1.01, 1.64)	6.3 (-0.3, 12.4)
Insomnia	1.23 (1.05, 1.43)	1.23 (1.01, 1.51)	1.25 (1.01, 1.56)	7.6 (-0.4, 15.0)
Physical inactivity	1.20 (1.02, 1.40)	1.16 (0.94, 1.43)	1.12 (0.89, 1.40)	3.5 (-4.0, 10.4)
Infrequent walks in last 4 weeks	1.37 (1.18, 1.59)	1.32 (1.09, 1.61)	1.26 (1.02, 1.57)	8.0 (0.1, 15.2)
Smoking				
Previous	1.19 (1.02, 1.40)	1.16 (0.93, 1.44)	1.18 (0.93, 1.50)	N/A□
Current	1.31 (1.04, 1.65)	1.28 (0.93, 1.75)	1.37 (0.96, 1.94)	6.0 (-1.4, 13.0)
Alcohol intake				
Monthly/weekly	0.91 (0.76, 1.09)	1.09 (0.86, 1.39)	1.11 (0.85, 1.44)	4.9 (-15.3, 21.5)
Daily	0.76 (0.60, 0.95)	0.99 (0.73, 1.33)	1.02 (0.74, 1.40)	2.1 (-16.7, 17.9)

RR Relative risk; PAR Population attributable risk; N/A Non-applicable; †All models adjusted for confounders in Table 2; ‡All modifiable predictors entered in the model, adjusted for confounders (based on 1018 participants, Pearson goodness of fit p-value=0.921); □ Previous smoking status not considered modifiable risk factor.

Most prognostic factors and confounders had some degree of missing data with social networks and widespread pain having the most (17 and 9% respectively). Redoing analyses following multiple imputation of the missing data (Table 4) left the results almost unchanged in terms of the direction and magnitude of estimates. Exceptions were inadequate joint pain control which on adjustment for confounders had a higher RR of 1.42 (95%CI 1.19, 1.70), compared to a RR of 1.29 in complete case analysis (this observation persisted in full multivariable model), and being a smoker which was

significantly associated with onset of pain interference on adjustment for confounders (adjusted RR 1.35; 95%CI 1.04, 1.75 compared to 1.28; 95%CI 0.93, 1.75).

Table 4: Modifiable predictors of pain interference at 3 years: findings following multiple imputation

	Unadjusted RR (95% CI)	Adjusted models† RR (95% CI)	Full multivariable model‡ RR (95% CI)
BMI			
Overweight	1.06 (0.90, 1.26)	1.09 (0.91, 1.31)	1.08 (0.90, 1.30)
Obese	1.27 (1.04, 1.55)	1.18 (0.94, 1.49)	1.18 (0.93, 1.49)
Anxiety/depression	1.33 (1.14, 1.55)	1.17 (0.97, 1.40)	1.11 (0.92, 1.33)
Widespread pain	1.54 (1.31, 1.82)	1.29 (1.07, 1.57)	1.29 (1.06, 1.56)
Inadequate joint specific pain control	1.85 (1.59, 2.15)	1.42 (1.19, 1.70)	1.39 (1.16, 1.67)
Insomnia	1.22 (1.05, 1.43)	1.20 (1.01, 1.43)	1.18 (0.99, 1.41)
Physical inactivity	1.19 (1.02, 1.40)	1.13 (0.95, 1.34)	1.08 (0.90, 1.29)
Infrequent walks in last 4 weeks	1.37 (1.18, 1.60)	1.28 (1.09, 1.52)	1.25 (1.05, 1.49)
Smoking			
Previous	1.20 (1.02, 1.41)	1.23 (1.02, 1.48)	1.19 (0.98, 1.43)
Current	1.32 (1.05, 1.66)	1.35 (1.04, 1.75)	1.37 (1.05, 1.78)
Alcohol intake			
Monthly/weekly	0.91 (0.76, 1.09)	1.12 (0.91, 1.38)	1.16 (0.94, 1.44)
Daily	0.76 (0.60, 0.95)	0.98 (0.75, 1.27)	1.00 (0.77, 1.31)

RR Relative risk; PAR Population attributable risk; †All models adjusted for confounders in Table 2;
‡ All modifiable predictors entered in the model, adjusted for confounders.

5. DISCUSSION

Using a large population-based cohort study, we aimed to examine the importance of a variety of known predictors of poor outcome in people reporting joint pain in the hand, hip, knee or foot, and to estimate potential gains if they were successfully eliminated through intervention. Among prognostic factors considered, we found inadequate joint specific pain control, insomnia and infrequent walking to be independently significantly associated with onset of pain interference after three years, with associated PARs of 6.3%, 7.6% and 8.0% respectively, noting that only PAR for infrequent walking was statistically significant. We estimated that approximately 20% of incident cases of pain interference could potentially be prevented if all three of these modifiable factors could be successfully eliminated through interventions.

Our analyses have enabled us to compare the relative independent contribution of a number of prognostic factors with an already established relationship with joint pain. In terms of comparison with other studies, few have reported prognostic factors expressed as PARs and the magnitude of estimated PARs will vary between studies depending on the distribution of prognostic factors and exact outcome measures used. For example, in one previous study it was found that 17% of cases of onset of severe knee pain 3 years after reporting non-severe knee pain could be prevented if obesity was eliminated (Jinks et al., 2006), however PARs were not obtained using the Greenland and Drescher approach (Greenland and Drescher, 1993). Although in our study obesity did not demonstrate a statistically significant association with pain interference in our adjusted models, it

resulted in a highest adjusted PAR (8.4%), although it was not statistically significant. On this basis, and given previous research findings (Chapple et al., 2011; Muthuri et al., 2011; de Rooij et al., 2016; Messier et al., 2018), we recognise that weight loss should feature as a core recommendation as part of preventative strategies for joint pain and OA (NICE, 2014).

Based on the view that OA should be considered as whole-organ disease that is amenable to prevention and early intervention (Roos and Arden, 2016), this study aimed to estimate maximum potential gain from clinical and public health interventions. Although it is unlikely that all prognostic factors can be fully eliminated and thus their impact on prognosis completely removed, each of these factors was considered to potentially form a relevant part of clinical or public health intervention for patients with joint pain, and could alert healthcare professionals to those individuals where there is a high risk of developing pain that interferes with daily life. By conducting our analysis within a population sample we demonstrated that interfering pain is a common problem that impacts many community-dwelling adults with joint pain, irrespective of whether they consult healthcare. This illustrates that key clinical messages about joint pain could also be directed at the general population, particularly in terms of prevention among groups of people with characteristics that make them more vulnerable to developing moderate to severe pain interference (Blyth et al., 2015). Increased attention to modifiable factors as part of interventions aimed at prevention and early management of joint pain has been suggested to help people make informed decisions and better maintain their long-term joint health. Although their impact is to be demonstrated, experts in OA and consumers have identified and prioritized 21 key messages for people with joint pain associated with OA, which may be used to inform the content of educational materials about important aspects of OA and its management (French et al, 2014).

The true extent to which the selected and identified prognostic factors are modifiable is difficult to quantify, and this study was not designed to establish causality. It may be argued that the reported PAR estimates are not very large, significant ones combined amounting to just over 20%, and representing factors that are difficult to shift, such as sedentary behaviour and sleeping problems, with complete elimination of the risk being implausible. Numerous systematic reviews of randomised clinical trials have supported the role of therapeutic exercise for joint pain, consistently demonstrating that it can improve pain and function (Uthman et al, 2013), however, reported mean effect sizes are small to moderate, and often decline over time. For interventions to impact on outcomes beyond the several months of follow-up generally reported in clinical trials, and to be effective in whole populations, wide access to interventions as well as high adherence is essential. Recent reviews have highlighted the need for identifying predictors of adherence to lifestyle interventions and barriers to behaviour change with more emphasis on the design and evaluation of interventions to improve adherence (Nicolson et al, 2017).

We have used a validated question on pain interference as the outcome. In contrast to the more commonly used joint specific outcomes, for example WOMAC (Bellamy, 1996), and AUSCAN

(Bellamy et al., 2002), our outcome reflects the impact of pain more holistically in the person across joint sites (Thomas et al., 2014). The chosen cut-off points used for the construction of inadequate joint pain control were high, reflecting high levels of pain likely to require management beyond simple analgesics.

The potential confounders available in the self-report survey data were scrutinised carefully in order to select those that have previously been shown to relate to outcomes of joint pain and pain interference (Chapple et al., 2011; Nichols et al., 2012; de Rooij et al., 2016), and/or are related to pain interference in this particular study sample. However, not all important confounders will have been fully measured and accounted for (e.g. detailed history of occupational work load, other relevant co-morbidities), and a number of those measured may have been subject to some degree of measurement error, e.g. self-reported measures of physical activity and body weight. Therefore, our risk estimates and resulting PARs need to be interpreted with caution. A further possible limitation of this study is that we have assumed that the baseline values of predictors remained unchanged until three-year follow-up; these may have changed as a result of self-management or clinical care, or the management of other relevant health conditions (e.g. cardiovascular disease or diabetes). Estimates of prognosis need to be interpreted in the context of care, including self-management and treatment received for joint pain, however this may not have been fully represented by our measure of pain relief via self-reported use of pain medications, anti-inflammatories, creams/gels and natural remedies; more definitive measures of self-management, treatment options and healthcare use over the three-year follow-up were not available, such as participation in exercise or weight loss programmes, physiotherapy, occupational therapy, joint injection, or surgical intervention. We dichotomised some confounders in order to facilitate multiple imputation, for example employment and financial strain; however, retaining these variables in their originally grouped forms did not alter complete case analyses.

In conclusion, this analysis of a population-based cohort of older people with joint pain shows that there is potential for a moderate reduction in onset of pain interference with daily life if clinical and public health interventions targeted pain management and insomnia and promoted active lifestyles. The majority of pain interference onset in the over-50s, however, would not be prevented even under the assumption that these factors could be completely eliminated.

Author contributions

All authors contributed to the conception of the study. MBB, JW and DAvdW designed the analysis plan, performed statistical analyses and drafted the initial manuscript. All authors participated in the design of the study, interpretation and discussion of the results, and drafting of the manuscript. All authors read and approved the final manuscript.

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