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Painful knee but not hand osteoarthritis is an independent predictor of mortality over 23 years follow-up of a population-based cohort of middle-aged women

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Abstract

To assess whether joint pain or radiographic osteoarthritis (ROA) of the knee and hand is associated with all-cause and disease specific mortality in middle-aged women.

Methods:

Four subgroups from the prospective community-based Chingford Cohort Study were identified based on presence/absence of pain and ROA at baseline: (Pain-/ROA-; Pain+/ROA-; Pain-/ROA+; Pain+/ROA+). Pain was defined as side-specific pain in the preceding month, while side-specific ROA was defined as K-L Grade ≥2. All-cause, cardiovascular (CVD) and cancer related mortality over the 23-year follow-up was based on information collected by the Office for National Statistics. Associations between subgroups and all-cause/cause-specific mortality were assessed using Cox regression, adjusting for age, BMI, typical cardiovascular risk factors, occupation, past physical activity, existing CVD disease, glucose levels and medication use.

Results:

821 and 808 women were included for knee and hand analyses respectively. Compared to the knee Pain-/ROA- group, the Pain+/ROA- group had an increased risk of CVD-specific mortality (hazard ratio 2.93 (95%CI, 1.47-5.85)), while the knee Pain+/ROA+ group had an increased HR of 1.97 (95%CI, 1.23-3.17) for all-cause and 3.57 (95%CI, 1.53-8.34) for CVD-specific mortality. We found no association between hand OA and mortality.

Conclusions:

We found a significantly increased risk of all-cause and CVD-specific mortality in women experiencing knee pain with or without ROA but not ROA alone. No relationship was found between hand OA and mortality risk. This suggests that

knee pain, more than structural changes of OA is the main driver of excess mortality in patients with OA.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and a significant contributor of musculoskeletal disability burden in the developed world. (1) In the population above 55 years old, one in four

reports frequent knee pain and have evidence of radiographic knee osteoarthritis (KOA). (2) The lifetime risk of receiving a total knee replacement at age 50 is of 8.1% for men and 10.8% for women. (3) The prevalence of symptomatic hand OA is 8.2% and 15.9% in men and women respectively. (4)

There is growing evidence that low-grade systemic inflammation, linked with adipose tissue, is associated with joint pain (5-7), incidence of radiographic changes (8, 9), development of cardiovascular disease (CVD), (10-12) and also have a role in the cancer pathogenesis. (13) Compared to individuals with no OA, participants with total joint replacements have a 26% increased risk of CVD. (14) Furthermore, a younger middle-aged population with OA have a 5-fold increased prevalence of metabolic syndrome. (15, 16)

The strongest evidence of a relationship between OA and mortality comes from an observational study where patients with symptomatic radiographic KOA and/or hip OA were selected and found to be at increased mortality risk compared with general population. (17) A more recent study demonstrates a borderline significant association between excess mortality and symptomatic (but not radiographic) KOA alone.(18) Hand OA was associated with a risk of premature CVD death in the Finnish population aged 30 years and over. (19, 20) In

contrast, a more recent publication demonstrates no association with an excess mortality and hand OA, despite increased risk of coronary heart disease events in a population with symptomatic hand OA. (21) It is currently unclear whether symptomatic or radiographic only OA is associated with excess mortality. The aim of our study was to examine the relationship between knee and hand OA and the risk of mortality in a longitudinal community-based cohort with 23 years of follow-up. Participants were divided into four subgroups based on presence or absence of pain and radiographic OA (ROA).

METHODS

Study Population

Characteristics of the Chingford study have been described in detail previously. (22) Briefly, in Chingford, North London, UK, all women aged 45-64 years from the register of a large general practice were contacted in 1988-1989 and asked to participate in a population-based study to evaluate risk factors for osteoporosis and OA. Among 1353 women contacted, 1003 (78% response rate) attended the baseline visit and have since been examined annually. This cohort has been shown to be representative of women in England. (22)

Inclusion criteria

We included 821 women for knee and 808 for hand analyses with available data on both pain and radiographic KOA or hand OA. Women with the following diseases (n=43) at baseline or any point of follow-up were excluded from analysis: Rheumatoid arthritis, psoriatic arthritis, gout, Paget's disease, polio, cerebral palsy and chronic inflammatory demyelinating neuropathy. Two participants were excluded due to lack of time-to-death data. Further 137 women for knee and 150 for hand analyses were excluded due to lack of pain and/or radiographic data at baseline (Figure 1). Characteristics of the participants without baseline radiographic or pain data were similar with those included for analyses.

Assessment of Mortality

The outcomes of interest were all-cause and cause-specific mortality from cardiovascular (CVD) and cancer, based on available data up to August 2014. The Health and Social Care Information Centre provided detailed mortality information on the Chingford cohort based on the information collected by the Office for National Statistics from civil registration records. The cause of death was based on the information from death certificates. For the cause specific mortality, we reviewed all CVD and cancer related deaths data from death certificates. In seven cases of cardiovascular mortality the cause of death was changed to

cancer related mortality, if the direct cause of death was a complication of cancer or its treatment. The cumulative number of deaths over the 23 years (median 21.7 years (IQR: 21.2-22.3)) of follow-up was 223 women (22.2%) out of the total sample of 1,003 women. CVD mortality accounted for 29% (n=64), cancer for 45% (n=100) and other diseases for 26% (n=59) of all-cause mortality. Time to event was assessed from year 3 until death, or the end of the follow-up (August 15, 2014).

Assessment of joint-specific OA and pain

A physical examination at baseline (year 1) was performed to assess anteroposterior (AP) radiographs of the hands and weight-bearing AP radiographs of the knees. The protocols for radiographic grading and reproducibility for both knee and hand OA and for this study have been previously reported. (23-26)

Women were classified as having radiographic KOA if they had a Kellgren-Lawrence (K/L) OA grade of 2 or more in at least one knee at baseline. Hand radiographs were also graded for OA. Summary scores of distal interphalangeal (DIP), proximal interphalangeal (PIP) and first carpometacarpal (CMC) joints were defined as the number of joints with K/L grade≥2, while radiographic hand OA in any hand joint

was defined as positive if the K/L score in at least one joint was 2 or greater.

Knee and hand pain was assessed at year 3 as part of a self-administered questionnaire. (27) Women were asked if they had experienced any knee/hand pain in the past month and the number of days this had occurred. Knee/hand pain was classified as positive for either knee/hand if "yes" and "more than 0 days" were reported.

Joint-specific OA and pain was classified into four subgroups based on presence and absence of pain and ROA:

1) Neither ROA nor pain (Pain-/ROA-: reference category).

2) ROA (Pain-/ROA+).

3) Pain only (Pain+/ROA-).

4) Painful ROA (Pain+/ROA+: joint(s) with ROA and pain in the same side).

Women with ROA only in one side and pain only in the contralateral side were classified as having ROA+/Pain- only.

Potential confounders

We assessed information on potential confounders at year 3. *Socio-demographic covariates* included age and occupation ("Manual" versus

"Non-manual"). *Health-related behaviours* were physical activity at age 30 and smoking. Physical activity (PA) at age 30 was assessed by the following question: "Were you a physically active person at age 30?". Smokers were classifies as never smoked/ex-smoker or currently smoking. *Current and past CVD disease* was ascertained by asking the women if they had any CVD disease. We included all risk factors for heart disease that are part of the Framingham Heart Study Risk Assessment. (28) The *biological factors* included were body mass index (BMI), systolic blood pressure (BP), total and high-density lipoprotein (HDL) cholesterol and glucose. Body mass index (BMI) was calculated at baseline and divided into two groups: "non-obese" (BMI<30 kg/m^2) and "obese" (BMI ≥30 kg/m^2). Total and HDL cholesterol and glucose were measured by fasting serum samples taken (29). For the analysis, systolic BP, total and HDL cholesterol and glucose were treated as continuous variables. BP medication, anti-inflammatory drugs (NSAIDs) and hormone replacement therapy (HRT) use were coded as dichotomous variables with a value of 1 if the women reported taking the medication and 0 otherwise.

Statistical Analysis

All analyses were conducted using Stata version 13 statistical software (StataCorp, College Station, Texas) and took place separately for knee and hand. Multiple imputation using chained equations was used to investigate the impact of missing potential confounders, while 100 imputed datasets were generated using all potential confounders (including all-cause mortality and log transformed survival time) and estimated parameters were combined using Rubin's rules. Kaplan-Meier survival curves for all-cause mortality in joint-specific OA and pain subgroups were estimated.

The association between joint-specific OA and pain subgroups (knee and hand) and all-cause and cause-specific mortality was assessed using Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (95%CI). Three models were used to assess this association:

Model 1) was age-adjusted.

Model 2) added risk factors from Framingham Risk Score (smoking, total cholesterol, HDL-cholesterol, systolic BP and BP medication).

Model 3) added the remaining potential confounders (occupation, HRT use, past physical activity, BMI, current/previous CVD disease, Non-ASA NSAIDs and glucose levels).

In the analyses of specific cause of death, deaths attributed to other causes were treated as censored at the time of death. Proportional hazards assumption was examined by Schoenfeld residuals. There was no evidence showing that the hazards were not proportional over the follow-up period studied.

Four sensitivity analyses were conducted. First, we excluded women who underwent joint-specific surgery at any point during follow-up. Second, all deaths occurring during the first 12 months of follow-up were excluded. Third, with a radiographic hand OA defined as positive if the K/L score in at least two joints was 2 or greater. Forth, with available crude measures of PA. This was assessed by the following question ''How many times per week do you engage in activity that makes you sweat?".

RESULTS

From 1993 to 2014 (median follow-up of 21.7 years (range: 21.2-22.3)), 166 and 163 deaths (~20%) were confirmed by death certificate among the knee and hand OA and pain study sample, respectively. Potential confounders according to knee and hand OA and pain categories are presented in Table 1 and 2, respectively. Compared with women without OA (Pain-/ROA-), women with ROA (Pain+ and Pain-) were older and had higher systolic BP levels (Tables 1 and 2).

Women with painful knee (ROA+ or ROA-) were more likely to use Non-ASA NSAIDs. (Table 1) Women with knee or hand pain (Pain+/ROA-) were also more likely to be using HRT medication, compared with the other subgroups.

Kaplan-Meier survival curves for all-cause mortality according to KOA and pain (fig. 2a) and hand OA and pain categories (fig. 2b) are presented in figure 2. Women with painful knee/hand ROA had a greater risk of all-cause mortality compared with women with neither knee/hand pain nor ROA (log-rank test p-value ≤ 0.001).

Results from Cox proportional hazard models estimating the mortality risk according to knee and hand OA and pain categories are shown in tables 3 and 4. In the age-adjusted model, women with knee pain and no ROA had a 49% increased risk of dying from all-cause mortality, compared with those with neither knee pain nor ROA [HR 1.49 95%CI 1.04-2.14; p-value=0.029]. The mortality risk was stronger among women with painful knee ROA, reaching a 97% increase in mortality risk in an age-adjusted model [HR 1.97 95%CI, 1.23-3.17; p-value=0.005] (Model 1; Table 4).

After adjustment for the factors from Framingham Risk Score Factors(Table 4; Model 2), the HRs increased slightly for painful knee subgroups (ROA+, ROA-) (1.55 [95%CI, 1.07-2.22] and 2.06 [95%CI,

1.27-3.33], respectively) (Model 2; Table 4). The relationship remained unchanged even after further adjusting for all other covariates (Model 3; Table 4). In contrast, knee ROA alone was not associated with mortality in any of the three models.

The magnitude of association between knee pain subgroups (Pain+/ROA- and Pain+/ROA+) and mortality was the strongest for CVD-specific mortality in all models. Compared with women with neither knee pain nor ROA, the HR associated with knee pain only (Pain+/ROA-) was 3.25 [95%CI, 1.64-6.43] and with painful knee ROA (Pain+/ROA+) was 4.19 [95%CI, 1.87-9.40], after adjustment for Framingham Risk Score factors (Model 2; Table 4). Further inclusion of all other covariates produced an almost negligible reduction in the HR for CVD-specific mortality (Model 3; Table 4). No statistically significant associations were found for cancer-specific mortality.

Additionally, there were no associations between hand pain, with or without ROA, and all-cause or cause-specific mortality after adjustment for other covariates (Table 4).

No substantial differences in the results were observed when women who died during the first 12 months of follow-up (n=2), or when women who underwent knee replacement (for knee analysis) during the follow-up (n=29) were excluded (data not shown).

DISCUSSION

In this prospective community-based study of middle-aged women, we found a significant association between knee pain, with or without radiographic OA, and an increased risk of all-cause and CVD-specific mortality. We found no association between knee ROA only (Pain-/ROA+) and decreased survival, although subjects with symptomatic ROA (Pain+/ROA+) had the highest risk of both all-cause and CVD-specific mortality. No relationship was found between hand OA and mortality risk.

There are conflicting results between observational studies on the impact of knee and hand OA on early mortality. Cerhan *et al*, found that radiographic OA of hands, knees and the cervical spine was associated with decreased survival of middle-aged women who worked in the radium dial-painting industry, when compared to participants without ROA. (30) A systematic review on this subject found moderate evidence of increased mortality among participants with OA compared with the general population. (31) Two studies based on the Finish national health survey reported modest association between advanced radiographic hand OA and risk of early

mortality. (19, 20) However, Haugen et al have not confirmed those findings in the Framingham Study. (21)

Nüesch and colleagues utilised a large selected population-based sample of men and women with symptomatic radiographic knee and/or hip OA and compared age and sex standardised mortality ratios after a median of 14 years' follow-up. (17, 32) They reported a significant excess in all-cause, CVD- and dementia-related mortality. Liu *et al* found that participants from two different cohorts of patients consulting health professionals for their OA were not at higher risk of death than the general population (mean follow-up time below 7 years). (33) Hawker and colleagues showed that increased walking disability, use of walking aids and poor baseline function are associated with excess all-cause mortality in individuals with hip and KOA symptoms. (32) . The main limitations of the previous studies include:

- Relatively short follow-up,
- Selection towards participants with symptomatic radiographic OA (34),

- Comparison with controls from population mortality registers or participants with no ROA, with no study using a comparison group without pain and ROA.

This paper confirms strong independent associations between painful knee (but not hand) OA and excess mortality. (17, 21) This relationship is independent from the majority of known CVD risk factors and not attenuated by non-ASA NSAIDs use, which corresponds with previous findings (35).

We have found that any self-reported knee pain in the past month, with or without radiographic KOA changes, but not symptomatic hand OA or radiographic KOA alone, is a significant predictor of early CVD mortality. There are number of plausible explanations for our findings, which are not mutually exclusive. The most biologically plausible mechanism for the causal association is that the knee pain results in sedentary behaviour, poor cardiovascular fitness and early mortality. This is supported by some observational studies(32, 36, 37) and by the fact that only 7.7% women with KOA meet recommended PA guidelines.(38) However, an alternative pathway might be presented where painful KOA is an early sign of metabolic dysregulation, leading to CVD problems and premature death. Adipose tissue associated

inflammation is considered to be a common mechanism precipitating development of CVD and painful OA. (8, 11, 39, 40) Women with KOA have higher levels of markers of atherosclerosis.(41) Physical activity is also an important mediator of this inflammatory response (42) and inactivity linked with painful KOA might accelerated metabolic dysregulation.(43, 44) The pain in KOA fluctuates (27) and people commonly limit the activities associated with their symptoms and perceive physical activity (PA) to lead to the disease progression.(45, 46) Despite, clear evidence suggesting that PA improves pain, quality of life and minimises disability in individuals with KOA (47), we lack evidence supporting that any interventions in KOA patients improve PA levels or cardiovascular fitness in the longer term.(48, 49)

To our knowledge, this is the first longitudinal prospective community-based cohort with over two decades follow-up looking at the effect of knee and hand pain with and without radiographic OA on all-cause and disease specific mortality in middle-aged women. Participants' selection to enter this study was not based on symptomatology or radiographic features. The comparison group is part of the same population and has no radiographic disease at baseline nor side-specific pain. With comprehensive baseline data, we adjusted our

analysis for potentially important multiple confounders, including all risk factors from the Framingham Heart Study. We performed a sensitivity analysis with a radiographic hand OA was defined as positive if the K/L score in at least two joints was 2 or greater, that when adjusted for, did not attenuate the findings.

Some potential limitations are worth mentioning. Findings of this study are limited to middle-aged and predominantly Caucasian women. In multivariable analysis of groups, we used baseline values of covariates, but those values may change over time and have time-dependent effects on OA and mortality outcomes that we would not be able to comment on in this analysis. This analysis is likely to underestimate the absolute risk of the exposure groups due to the fact that participants from the control group (ROA-/Pain-) remain in the original group even if they develop pain and/or ROA over time. .In this study all exposure categories have this immortal time period. (50) The other important limitation of this study is the fact that radiographs of the hands and knees were taken three years before knee and hand pain assessment. To mitigate against this, outcomes were measure from year 3 onwards. The physical activity and function is another potential

residual confounding. We performed a sensitivity analysis using an available crude measures of PA, that when adjusted for, did not attenuate the findings.

In conclusion, knee pain with or without radiographic OA in middle-aged women is associated with an increased all-cause and CVD mortality only. The highest risk was found in subjects with both pain and ROA, with no association found with ROA alone. In addition, there were no associations between hand pain, with or without ROA, and all-cause and specific-cause mortality. The link behind this relationship is not completely understood. Further research analysing the longitudinal differences in the groups' characteristics associated with CVD mortality is required to identify potential underlying mechanisms. Additional studies of men-only or mixed gender cohorts are needed to confirm generalizability of these findings.

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COMPETING INTEREST

The Authors declare that there is no conflict of interest.

CONTRIBUTORSHIP

Authors made substantial contributions to conception and design, analysis, data interpretation and drafting and/or revising the article: SK MS KL AJ CC JN NA

Authors made a substantial contribution to acquisition of data: TS DH KL NA

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ETHICS APPROVAL

The Outer North East London Research Ethics Committee approved the study.

DATA SHARING STATEMENT

For information about the access to the Chingford 1000 Women Study data, please email chingford@ndorms.ox.ac.uk.

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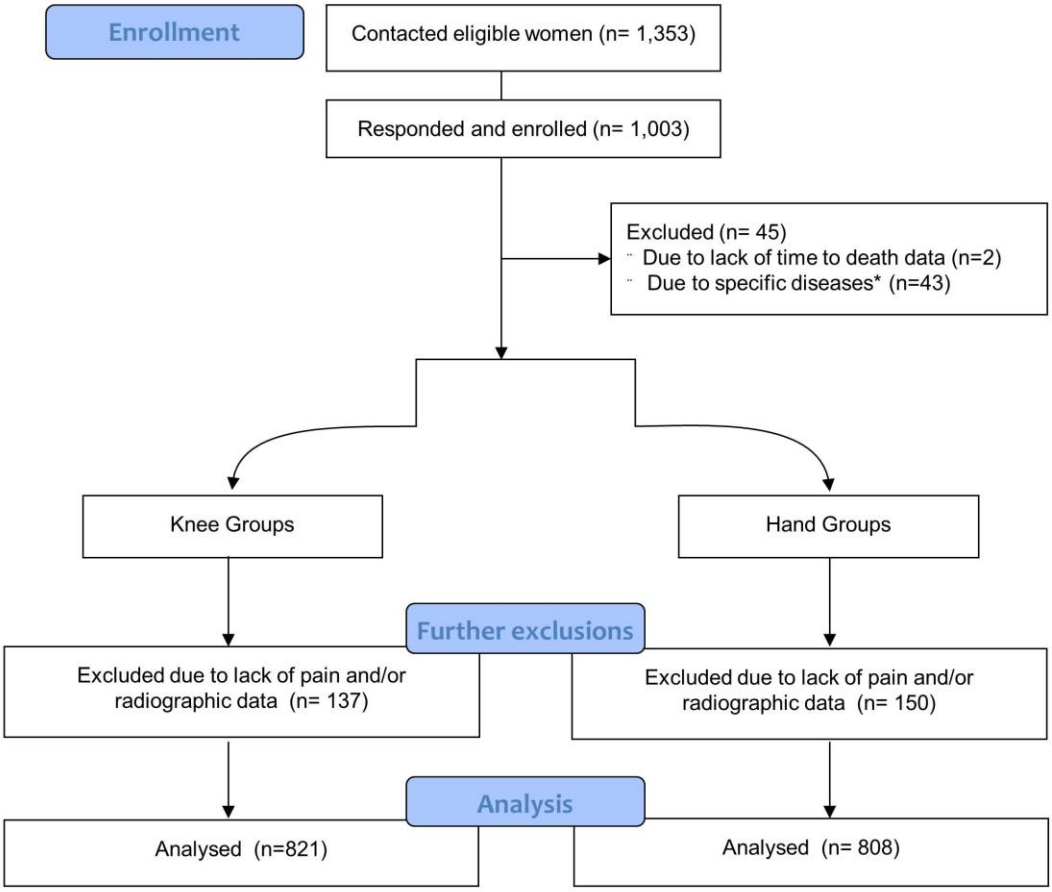
Figure 1. *A flow diagram of participants included and excluded for each analysis.*



* Rheumatoid arthritis, psoriatic arthritis, gout, Paget's disease, polio, cerebral palsy and chronic inflammatory demyelinating neuropathy

Table 1. *Descriptive characteristics across knee status categories*

Characteristic	Neither ROA nor pain (n=524)	ROA only (n=64)	Pain only (n=176)	Symptomatic OA (n=57)	p-value
Age, years, mean (SD)	55.2 (5.8)	58.7 (6.3)	56.4 (5.8)	59.6 (4.9)	**0.000**
Occupation, n (%)					**0.042**
Manual	79 (15.1)	11 (17.2)	40 (22.7)	8 (8.8)	
Non-Manual	440 (84.0)	52 (81.3)	135 (76.7)	52 (91.2)	
HRT, n (%)					**0.045**
No	343 (65.5)	44 (68.8)	100 (56.8)	39 (68.4)	
Yes	164 (31.3)	16 (25.0)	74 (42.1)	17 (29.8)	
Smoking, n (%)*					0.706
Never/ex-smoker	401 (76.5)	53 (82.8)	137 (77.8)	45 (79.0)	
Smoker	123 (23.5)	11 (17.2)	39 (22.2)	12 (21.1)	
Physical activity at age 30, n (%)					0.328
No	101 (19.3)	13 (20.3)	25 (14.2)	8 (14.0)	
Yes	413 (78.8)	50 (78.1)	150 (85.2)	49 (86.0)	
Body Mass Index, n (%)					**0.002**
Non-obese (<30 kg/m²)	316 (60.3)	39 (60.9)	118 (67.1)	34 (59.7)	
Obese (≥30 kg/m²)	41 (7.8)	14 (21.9)	25 (14.2)	13 (22.8)	
Previous CVD disease, n (%)					0.436
No	489 (93.3)	58 (90.6)	163 (92.6)	53 (93.0)	
Yes	18 (3.4)	2 (3.1)	11 (6.3)	3 (5.3)	
BP medication, n (%)*					**0.008**
No	454 (86.6)	51 (79.7)	149 (84.7)	40 (70.2)	
Yes	70 (13.4)	13 (20.3)	27 (15.3)	17 (29.8)	
Non-ASA NSAIDs medication, n (%)					**0.010**
No	507 (96.8)	63 (98.4)	163 (92.6)	51 (89.5)	
Yes	17 (3.2)	1 (1.6)	13 (7.4)	6 (10.5)	
Systolic BP, mmHg, mean (SD)*	124.8 (20.5)	129.7 (17.6)	127.1 (17.7)	132.8 (19.7)	**0.029**
Total cholesterol, mg/dL, mean (SD)*	6.6 (1.4)	6.7 (1.3)	6.8 (1.4)	7.1 (1.2)	0.072
HDL-cholesterol, mg/dL, mean (SD)*	1.7 (0.4)	1.6 (0.4)	1.7 (0.4)	1.7 (0.5)	0.263
Glucose, mmol/L, mean (SD)	4.9 (0.6)	5.0 (0.8)	4.9 (0.7)	5.1 (0.6)	0.130

OA=Osteoarthritis; IQR=Interquartile range; SD= Standard deviation; BP= blood pressure; HDL= High-density lipoprotein; NSAIDs=nonsteroidal anti-inflammatory drugs.*Framingham Risk Score Factors

Table 2. *Descriptive characteristics across hand status categories*

Characteristic	Neither ROA nor pain (n=416)	ROA only (n=166)	Pain only (n=127)	Symptomatic OA (n=99)	p-value
Age, years, mean (SD)	54.0 (5.5)	59.3 (5.5)	55.4 (5.3)	60.0 (5.1)	**0.000**
Occupation, n (%)					0.688
Manual	70 (16.8)	24 (14.5)	24 (18.9)	14 (14.1)	
Non-Manual	341 (82.0)	141 (84.9)	103 (81.1)	85 (85.9)	
HRT, n (%)					**0.012**
No	271 (65.1)	114 (68.7)	67 (52.8)	64 (64.7)	
Yes	130 (31.3)	46 (27.7)	58 (45.7)	34 (34.3)	
Smoking, n (%)*					0.996
Never/ex-smoker	323 (77.6)	130 (78.3)	98 (77.2)	77 (77.8)	
Smoker	93 (22.4)	36 (21.7)	29 (22.8)	22 (22.2)	
Physical activity at age 30, n (%)					0.176
No	79 (19.0)	35 (21.1)	15 (11.8)	16 (16.2)	
Yes	331 (79.6)	128 (77.1)	110 (86.6)	82 (82.8)	
Body Mass Index, n (%)					0.272
Non-obese (<30 kg/m²)	225 (54.1)	110 (66.3)	85 (66.9)	77 (77.8)	
Obese (≥30 kg/m²)	40 (9.6)	26 (15.7)	17 (13.4)	8 (8.1)	
Previous CVD disease, n (%)					0.901
No	384 (92.3)	154 (92.8)	121 (95.3)	93 (93.9)	
Yes	17 (4.1)	6 (3.6)	4 (3.2)	5 (5.1)	
BP medication, n (%)*					0.085
No	360 (86.5)	131 (78.9)	110 (86.6)	80 (80.8)	
Yes	56 (13.5)	35 (21.1)	17 (13.4)	19 (19.2)	
Non-ASA NSAIDs medication, n (%)					0.110
No	404 (97.1)	154 (92.8)	121 (95.3)	93 (93.9)	
Yes	12 (2.9)	12 (7.2)	6 (4.7)	6 (6.1)	
Systolic BP, mmHg, mean (SD)*	122.6 (18.4)	130.7 (19.9)	127.4 (20.1)	132.8 (21.3)	**0.000**
Total cholesterol, mg/dL, mean (SD)*	6.5 (1.4)	7.0 (1.3)	6.7 (1.3)	7.1 (1.3)	**0.000**
HDL-cholesterol, mg/dL, mean (SD)*	1.7 (0.4)	1.7 (0.5)	1.8 (0.5)	1.7 (0.4)	0.168
Glucose, mmol/L, mean (SD)	4.9 (0.7)	5.0 (0.7)	4.9 (0.5)	5.0 (0.8)	0.184

OA=Osteoarthritis; IQR=Interquartile range; SD= Standard deviation; BP= blood pressure; HDL= High-density lipoprotein; NSAIDs=nonsteroidal anti-inflammatory drugs. *(Framingham Risk Score Factors)

Figure 2.

All-cause mortality stratified by A) Knee status; and B) Hand status. Kaplan-Meier survival plots of all-cause mortality up to 23 years.

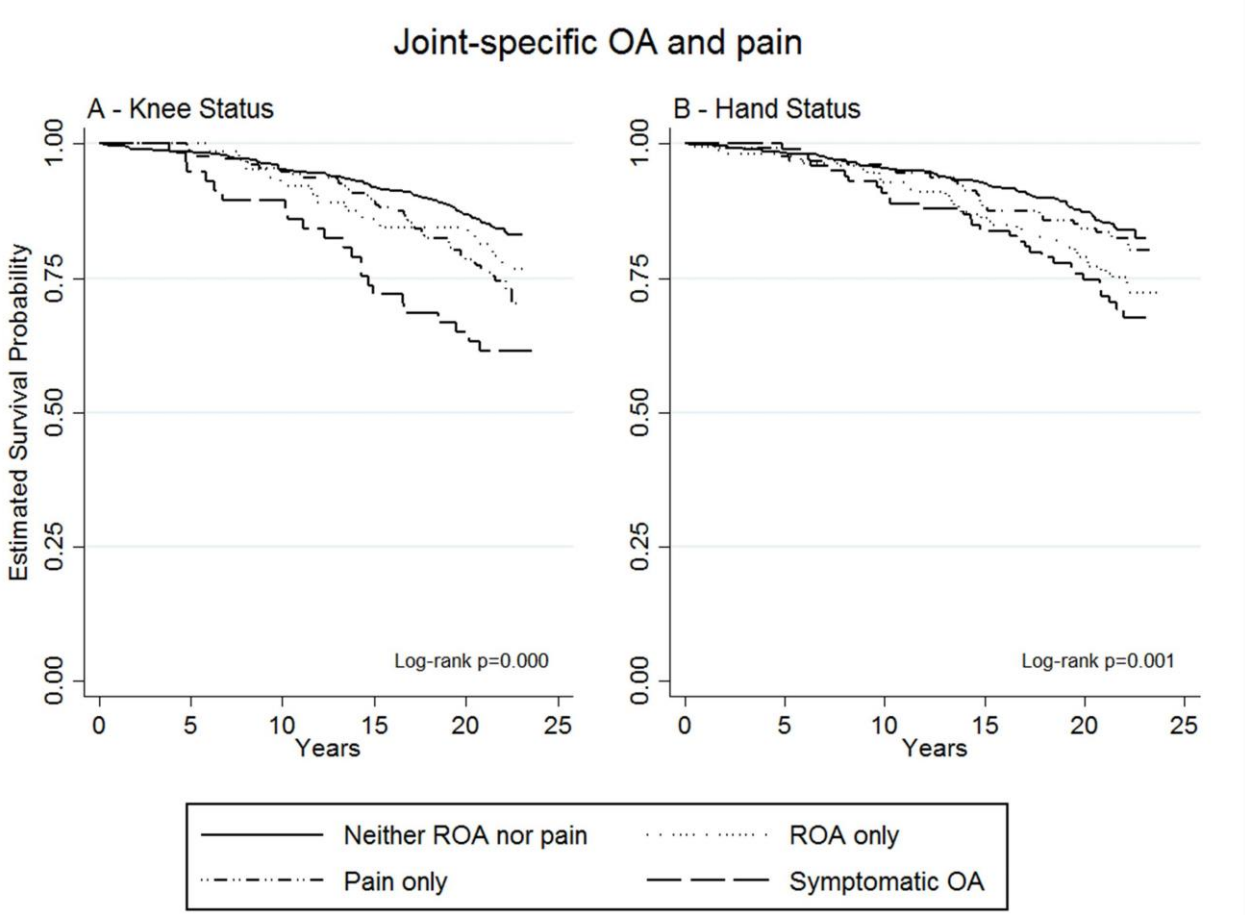


Table 4.

Number of deaths (N) and Hazard Ratio (95%CI) of all-cause and disease specific mortality by KOA categories.

Outcome KOA status	No. of deaths (%)	Model 1		P-value	Model 2		P-value	Model 3		P-value
		HR	95%CI		HR	95%CI		HR	95%CI	
All-causes										
Neither ROA nor pain	84 (16.0)	1.00			1.00			1.00		
ROA only	14 (21.9)	0.95	0.54-1.69	0.865	1.01	0.57-1.80	0.968	1.05	0.58-1.88	0.876
Pain only	46 (26.1)	**1.49**	**1.04-2.14**	**0.029**	**1.55**	**1.07-2.22**	**0.019**	**1.44**	**0.99-2.08**	**0.055**
Painful ROA	22 (38.6)	**1.97**	**1.23-3.17**	**0.005**	**2.06**	**1.27-3.33**	**0.003**	**1.97**	**1.20-3.22**	**0.007**
CVD disease										
Neither ROA nor pain	17 (3.2)	1.00			1.00			1.00		
ROA only	4 (6.3)	1.14	0.38-3.43	0.811	1.47	0.48-4.49	0.498	1.45	0.47-4.48	0.521
Pain only	18 (10.2)	**2.78**	**1.43-5.41**	**0.003**	**3.25**	**1.64-6.43**	**0.001**	**2.93**	**1.47-5.85**	**0.002**
Painful ROA	10 (17.5)	**3.98**	**1.81-8.76**	**0.001**	**4.19**	**1.87-9.40**	**0.001**	**3.57**	**1.53-8.34**	**0.003**
Cancer disease										
Neither ROA nor pain	44 (8.4)	1.00			1.00			1.00		
ROA only	7 (10.9)	1.08	0.48-2.41	0.860	1.11	0.49-2.51	0.801	1.10	0.48-2.51	0.818
Pain only	19(10.8)	1.23	0.72-2.12	0.444	1.23	0.72-2.12	0.451	1.12	0.64-1.94	0.693
Painful ROA	6 (10.5)	1.17	0.49-2.78	0.719	1.33	0.56-3.16	0.523	1.18	0.49-2.88	0.712

Model 1: adjusted for age

Model 2: Model 1 + Smoking, total cholesterol, HDL-cholesterol, systolic BP and BP medication (Framingham Risk Score Factors)

Model 3: Model 2 + occupation, BMI, HRT use, past physical activity, current/previous CVD disease, Non-ASA NSAIDs and glucose levels

Table 4. Number of deaths (N) and Hazard Ratio (95%CI) of all-cause and disease specific mortality by hand OA categories.

Outcome Hand OA status	No. of deaths (%)	Model 1		P-value	Model 2		P-value	Model 3		P-value
		HR	95%CI		HR	95%CI		HR	95%CI	
All-causes										
Neither ROA nor pain	66 (15.9)	1.00			1.00			1.00		
ROA only	43 (25.9)	0.94	0.62-1.41	0.754	0.86	0.57-1.30	0.465	0.91	0.60-1.39	0.667
Pain only	23 (18.1)	1.02	0.64-1.65	0.920	1.02	0.63-1.64	0.947	0.98	0.60-1.60	0.946
Painful ROA	31 (31.3)	1.13	0.72-1.77	0.591	1.05	0.67-1.65	0.835	1.05	0.66-1.66	0.850
CVD disease										
Neither ROA nor pain	18 (4.3)	1.00			1.00			1.00		
ROA only	10 (6.0)	0.60	0.27-1.34	0.212	0.48	0.21-1.10	0.081	0.57	0.25-1.33	0.196
Pain only	10 (7.9)	1.54	0.71-3.33	0.276	1.66	0.75-3.66	0.210	1.53	0.67-3.50	0.313
Painful ROA	8 (8.1)	0.80	0.34-1.91	0.620	0.76	0.32-1.82	0.541	0.75	0.30-1.87	0.539
Cancer disease										
Neither ROA nor pain	33 (7.9)	1.00			1.00			1.00		
ROA only	22 (13.3)	1.28	0.71-2.29	0.407	1.24	0.69-2.24	0.477	1.27	0.70-2.30	0.432
Pain only	9 (7.1)	0.85	0.41-1.78	0.665	0.83	0.39-1.75	0.626	0.78	0.34-1.66	0.522
Painful ROA	12 (12.1)	1.17	0.58-2.35	0.662	1.13	0.55-2.29	0.743	1.16	0.57-2.39	0.679

Model 1: adjusted for age

Model 2: Model 1 + Smoking, total cholesterol, HDL-cholesterol, systolic BP and BP medication (Framingham Risk Score Factors)

Model 3: Model 2 + occupation, BMI, HRT use, past physical activity, current/previous CVD disease, Non-ASA NSAIDs and glucose levels