Title: Pathways to premature mortality for hand, hip, knee and foot osteoarthritis

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**Purpose:**

Evidence of an association between osteoarthritis and mortality is conflicting; differences in definitions and anatomical sites explain some of the discordance**.**

. The sheer frequency and increasing prevalence of osteoarthritis highlights the need to understand if and why osteoarthritis is linked with premature mortality. The aims of this study are to (i) identify which site specific definitions of osteoarthritis (hand, hip, knee and foot) are associated with premature mortality and (ii) identify the role of potentially modifiable factors on the pathway between osteoarthritis at each site and premature mortality using a novel approach to examine mediation (path analysis) within a Cox proportional hazard model (survival analysis).

**Methods:**

A population-based prospective cohort study was conducted using data from the North Staffordshire Osteoarthritis Project (NorStOP), in which primary care medical record data was linked to self-report information collected by questionnaire in adults aged 50 years and over (n=8066). Osteoarthritis at each site was defined as those who had consulted general practice for osteoarthritis and at baseline indicated moderate to severe pain interference and experienced pain in the hand, hip, knee or foot. A Cox proportional hazards analysis was performed to determine the total effect (TE) of joint specific osteoarthritis on mortality with adjustment for confounders (age, gender, education, occupation, non-steroidal anti-inflammatory use, ischaemic heart disease and diabetes). Within the Cox model, path analysis was used to decompose the TE to assess the indirect (IE) and direct effects (DE) for potential mediators (walking frequency, depression, anxiety, insomnia and cognitive impairment*).* Results are expressed as hazard ratios (HR); bootstrap resampling was used to generate 95% confidence intervals (95% CIs).

**Results:**

Mean age of participants was 65.2 (SD 9.8) years and 51.6% were female. 1515 (18.8%), 1323 (16.4%), 1774 (22.0%) and 1387 (17.2%) had hand, hip, knee and foot osteoarthritis respectively. Participants were followed up over 10 years during which time 1188 (14.7%) died. Hand, foot and knee osteoarthritis were significantly associated with premature mortality (Adjusted HR 1.18 [1.02-1.36], 1.21 [1.05-1.4] and 1.1 [1.01-1.33] respectively); the increased hazard ratio for hip osteoarthritis was not significant (1.10; 0.94, 1.27). Low walking frequency, depression, anxiety, insomnia and cognitive impairment were significant mediators of the relationship between premature mortality and hand, knee and foot osteoarthritis (p<0.05). Taking knee osteoarthritis to illustrate this, the indirect effects for walking frequency, depression, anxiety, insomnia and cognitive impairment were 1.13 (1.11-1.15), 1.13 (1.11-1.16), 1.03 (1.01-1.05), 1.03 (1.02-1.05), 1.08 (1.06-1.10) respectively.

**Conclusions:**

This novel approach to understanding pathways within a survival model indicates that potentially modifiable factors explain the link between hand, knee and foot osteoarthritis and premature mortality. Increasing walking, and exercise and activity in general, may also reduce the impact of depression and insomnia, and subsequent comorbidity.