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Cause-specific mortality in osteoarthritis of peripheral joints

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SUMMARY

Purpose: To estimate cause-specific mortality in osteoarthritis patients compared to the general population.
Methods: We identified all residents in southern Sweden aged 45–84 years in 2003. Through the Skåne Healthcare Register (SHR) we identified those diagnosed with osteoarthritis in peripheral joints between 1998 and 2003. We followed all residents from 2004 until relocation outside of the region, death, or end of 2014. We classified the underlying cause of death from death certificates into: cardiovascular and neoplasms, diabetes, infections, dementia, diseases of digestive system, or other causes. For estimation, we used multi-state adjusted Cox proportional hazards models.
Results: We identified 15,901 patients (mean age [SD] 67 years [10], 41% men) with prevalent doctor-diagnosed osteoarthritis in knee, 9347 in hip, 4004 in hand and 5447 in other peripheral joints among 469,177 residents. For most causes of death in osteoarthritis patients, we found no increased mortality, with hazard ratios (HRs) close to 1, similar for men and women. However, for knee and hip osteoarthritis and cardiovascular death, HRs were non proportional and increased to 1.19 (95%CI 1.10, 1.28) and 1.13 (1.03, 1.24) during 9–11 years of follow-up, mostly due to excess mortality from chronic ischemic heart diseases and heart failure.
Conclusions: The risk of cardiovascular excess deaths increases with duration of knee and hip osteoarthritis. The major contributors are chronic ischemic heart diseases and heart failure. Our results call for improved implementation of osteoarthritis treatment guidelines, with major focus on interventions to address mobility limitations and maintaining or increase physical activity level.

Introduction

Mortality as an outcome of osteoarthritis (OA) was neglected in the past[1], but in the previous decade a number of prospective studies have estimated all-cause mortality associated with OA of knee, hip and hand compared to persons without OA[2–11]. These reports have been conflicting, but in general, persons with knee and hip OA have somewhat higher hazard of death compared to persons without OA. This excess mortality has been related to mobility limitations[12] and was an important factor contributing to classifying OA as a serious disease by the United States Food and Drug Administration.[13]

However, our knowledge about cause-specific mortality in OA is still limited and the results for all-cause mortality may conceal a substantial heterogeneity of the associations between OA and specific causes of death. A given candidate are cardiovascular diseases, which have been reported to be one of the major consequences of OA and reduced physical activity[2,7,14–16]. However, cardiovascular *mortality* has been much less studied[5,9,10,17]. There is even greater paucity of data about the mortality from specific causes other than cardiovascular, such as cancer, diabetes, dementia or diseases of digestive system[5,9,17]. Taking into account the side effects of pain medications commonly used in OA, such as non-steroidal anti-inflammatory drugs[18], and recently reported associations between diabetes and OA[14,19], mortality from diseases of digestive system or diabetes are of particular interest in patients with OA. Thus, in the present study, we aimed to estimate associations between OA in knee, hip, hand or other peripheral joints and *cause-specific mortality*, taking into account a wide range of underlying causes of death in a large population-based cohort.

Methods

Data sources

The study is based on register data for entire population of Skåne, the southernmost region in Sweden with 1.15 million

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inhabitants in the year 2003. We used data on date of birth, age, sex, and residential addresses from the Swedish Population Register. From the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by Swedish acronym) we retrieved individual-level data on the following socioeconomic and related variables: income, education, occupation, marital status and country of birth, as reported in the year 2003. When an item was missing, we used the most recent non-missing data from the years 2001 or 2002. The Skåne Healthcare Register (SHR) is a regional legislative, mandatory register based on physicians' International Classification of Diseases (ICD) 10 diagnostic codes. From this register, we extracted information about diagnoses set on any healthcare visit to a physician in public specialist healthcare (both in- and out-patient) between the years 1998 and 2003. The positive predictive value of a knee OA diagnosis in this register has been reported to be 88%, based on the same underlying population as the present study[20]. The validity of comorbid diagnoses is available from inpatient data only with typically high positive predictive values, but lower sensitivity[21]. The Cause of Death Register (CDR) was used to identify persons that deceased between the years 2004 and 2014 and to classify the underlying cause of death. The CDR contains information about death dates and causes of death registered through ICD-10 codes, as listed on the official death certificate and in line with World Health Organization's guidelines for registration of causes of death, for all inhabitants in Sweden. We chose year 2004 for start of follow-up to enable enough years for both assembling a large OA cohort as well as for sufficient comorbidity assessment (1998–2003). It also enabled monitoring of deaths for a relatively long period, 11 years (2004–2014). The study has been approved by the Regional Ethical Review Board in Lund, Sweden.

Study cohort, exposures and outcomes

The study cohort consisted of all persons being residents in Skåne at Dec 31st 2003 and aged 45–84 years. In this cohort, we identified all patients diagnosed with OA between Jan 1st 1998 and Dec 31st 2003 by a physician within specialist care (>99% of all persons with OA were diagnosed by a specialist in orthopaedics, rheumatology, internal medicine or emergency medicine, hand or jaw surgery or physician under specialty training within these specialties). The exposures of interest were OA in knee, hip, hand or other peripheral joints. We required at least one diagnosis of knee OA (ICD-10: M17), hip OA (M16), hand OA (M18, M15.1, M15.2) or other peripheral joint OA (codes M15 to M19 excluding knee, hip and hand) for a person to be classified as having OA in these joints, respectively. All other included persons were classified as not having peripheral joint OA. If a person was diagnosed with the disease in more than one joint, this person was included as exposed in all relevant analyses. The follow-up time was from Jan 1st 2004 until relocation outside of the region, death, or Dec 31st 2014, whichever came first. We classified the causes of death into 7 broad categories: cardiovascular, neoplasms, diabetes, infectious diseases, dementia, diseases of digestive system, or other causes. The cardiovascular causes and neoplasms were further subdivided into 4 and 7 subcategories, respectively, based on the frequency of the distinct causes of death (Supplementary Table 1).

Covariates and comorbidities

We categorized education depending on its length: <10 years (reference category), 10–12 years, 13–14 years, and 15 + years. Marital status (married/registered partner or other) and country of birth (Sweden or outside Sweden) were binary. Residential area was included as municipality, while the smallest municipalities were combined into bigger groups based on geographical and/or economic similarity. Occupation was classified into 9 major groups (military excluded due to low numbers), based on the major occupation categories defined in SSYK 96 classification (the Swedish adaptation of ISCO-88, https://www.scb.se/dokumentation/klassifikationer-och-standarder/standard-for-svensk-yrkesklassificering-ssyk/). We retrieved information about diagnosed type I diabetes (ICD-10: E10) or obesity (ICD-10: E66) from diagnoses registered in SHR during the years 1998–2003. For descriptive purposes, using SHR data (specialist care) from years 1998–2003, we collected information about chronic comorbidities present at the beginning of follow-up. We did not update data on confounders during follow-up time to avoid adjusting for intermediates.

Statistical analyses

We present descriptive baseline data on the study cohort, by exposure status. To estimate the hazard ratios (HRs) of death we used a multistate Cox proportional hazards regression models. In this model we considered 7 distinct causes of death. The HRs for all included causes of death were estimated simultaneously through a stratified analysis, where each subject was included 7 times (i.e., the number of distinct causes of death) with the outcome of either 0 (no death from the specific cause) or 1 (death from the specific cause). We used robust standard errors to account for dependence of observations coming from the same individual. For further discussion of this analysis approach please see the work of Putter *et al*[22]. We evaluated the proportional hazards assumption using plots of Schoenfeld residuals[23]. When non-proportionality was detected, we performed an analysis after partitioning the time scale in 3 intervals (first 4 years, 5–8 years, and ≥9 years of follow-up). Based on the literature on risk factors for doctor-diagnosed OA and mortality, we hypothesized that following factors preceding the OA incidence could be confounders of the OA-death association: age, sex, occupation, genetic factors, body mass, level of physical activity, socioeconomic status (residential area, income and education), if being born outside Sweden, if married, and diabetes. In the primary regression analysis, we adjusted for all the above confounders, apart from those that we could not measure (or had unknown temporal order): genetic factors, physical activity, body mass and diabetes. We adjusted for occupation only in the analysis of persons up to age 70 years, as the data on occupation (in years 2001–2003) for older persons had high proportion of missing values (the common retirement age in Sweden was 65 years). We repeated the main analyses stratified on sex.

Sensitivity analyses

We repeated the analyses with additional adjustment for diagnosed obesity and diagnosed type I diabetes (we were not able to adjust for diagnosed type II diabetes due to often unknown temporal order of diabetes and OA incidence). Further, we analysed mortality after excluding all persons that underwent a knee or hip replacement surgery due to knee or hip OA (knee or hip OA registered as the primary diagnosis at the time of the surgery) between 1998 and 2003. We also performed an additional analysis of a potential confounding effect of body mass index on our results (Supplementary Fig. 3).

Results

Study sample

We identified 29,189 patients with doctor diagnosed OA in any peripheral joint among 469,152 Skåne residents aged 45 to 84

(Table I). Patients with OA were on average older, more often women and had considerably higher prevalence of comorbidities, especially cardiovascular diseases and musculoskeletal disorders (other than OA).

The mean observed follow-up time was 9.6 years for those with OA and 10.0 years for those without. During this time 97,410 persons died. The crude mortality rates per 1000 person-years were 30.1, 40.2, 20.8, 24.3 and 20.3 for persons with knee, hip, hand or other OA and those without OA, respectively. The most common causes of death were neoplasms and cardiovascular diseases, which together accounted for 66% of all deaths.

Cause-specific mortality

In the adjusted Cox regression model, the estimated HRs were close to 1 for most OA sites and causes of death (Table II). However, the hazards were not proportional when modelling knee or hip OA and cardiovascular deaths. The HRs increased to 1.16 (95%CI 1.07,1.26) and 1.13 (95%CI 1.03,1.25) during 9 + years of follow-up for knee OA and hip OA, respectively (Supplementary Figs. 1 and 2, Supplementary Table 2). The estimates were similar in the analyses stratified by sex (Figs. 1 and 2, Table III) These results were mostly driven by mortality from heart failure (and other forms of heart disease) and chronic ischemic heart diseases (Figs. 1 and 2). No clear pattern could be found for the association between cancer types and OA, however, persons with knee OA had generally lower cancer related mortality than persons without (HR 0.89 [0.83,0.94]).

Sensitivity analyses

Results were generally similar in a sensitivity analysis, where we additionally adjusted for diagnosed obesity and type I diabetes (Supplementary Table 3) as well as when additionally adjusting for tobacco use and comorbid type II diabetes (Table IV). However, the association between knee OA and death from diabetes was markedly attenuated to HR close to 1 in both these analyses. Additional adjustment for occupation in persons under age of 70 yielded similar results. However, the uncertainty was larger due to lower sample size and less events (Supplementary Table 4).

Among persons with knee OA, 26% underwent knee replacement surgery during the 5 years preceding the follow-up start and the corresponding proportion among those with hip OA was 55%. After excluding all persons that underwent joint replacement surgery (both among those with and without OA) the results were similar (Supplementary Table 5).

Discussion

In this population-based study of half a million inhabitants in Sweden, we found that persons with knee and hip OA have increased cardiovascular mortality as compared to the general population. We found little evidence of increased mortality from any cause among persons with hand OA or OA of other peripheral joints. Importantly, due to the large sample size, we were able to provide estimates for specific subgroups of cardiovascular diseases and cancer. The major contributors to excess mortality in persons with OA were found to be chronic ischemic heart diseases and heart failure, but not cerebrovascular or gastrointestinal diseases.

Cardiovascular diseases have been recognized as one of major consequences of OA, but precise estimates of the associated cause-specific mortality were scarce[13]. Our results suggest a somewhat increased risk for cardiovascular mortality, as has been previously reported for cardiovascular comorbidities in Canada[15,24]. In the present study, we found that knee and hip OA leads to higher mortality from chronic ischemic heart diseases and heart failure with HRs close to 1.2. Similar findings were reported previously for the association between OA and cardiovascular *comorbidities*[15,16], while a bit higher estimate was found in a US population with radiographic knee OA[17]. There seem not to be a simple explanation of the apparent differential effect of OA on different cardiovascular outcomes. The relative lower incidence of myocardial infarction but higher of ischemic heart disease and heart failure warrants further investigation. We suggest that a distinction between different OA phenotypes in relation to CVD outcomes may shed further light on this issue." This means that the higher proportion of persons with cardiovascular diseases among those with OA translates also into higher mortality. Considering OA is a highly prevalent disease and these are among the most frequent causes of deaths, the increase in

Table I
Descriptive characteristics of the study sample, at baseline in the year 2003

	Knee OA	Hip OA	Hand OA	Other OA	No OA	Any OA
	N = 14,728	*N* = 8809	*N* = 3607	*N* = 5447	*N* = 439 966	*N* = 29,186
Age at beginning of follow-up, mean (SD)	66.8 (10.4)	69.9 (9.5)	63.7 (9.2)	63.8 (10.1)	61.1 (10.8)	66.6 (10.3)
Male sex, n (%)	6486 (44)	3824 (43)	758 (21)	2152 (40)	213,410 (49)	12,088 (41)
Income* in 100 000 SEK, mean (SD)	1.5 (1)	1.4 (1.3)	1.5 (.8)	1.5 (1.1)	1.7 (2.5)	1.5 (1.1)
Education*, up to 9 years, n (%)	6507 (45)	3978 (46)	1231 (34)	2174 (40)	155,747 (36)	12,423 (43)
Education, 10–12 years, n (%)	5537 (38)	3222 (37)	1606 (45)	2236 (41)	172,418 (40)	11,264 (39)
Education 13–14 years, n (%)	1102 (8)	661 (8)	317 (9)	468 (9)	43,386 (10)	2291 (8)
Education 15 + years, n (%)	1358 (9)	840 (10)	430 (12)	529 (10)	61,209 (14)	2855 (10)
Married*, n (%)	11,161 (76)	6327 (72)	2908 (81)	4314 (79)	341,535 (78)	22,166 (76)
Born outside Sweden*, n (%)	1752 (12)	908 (10)	456 (13)	691 (13)	66,856 (15)	3445 (12)
Diabetes, type I, n (%)	1062 (7)	602 (7)	180 (5)	319 (6)	18,049 (4)	1909 (7)
Diabetes, type II or unspecified, n (%)	445 (3)	283 (3)	98 (3)	136 (2)	8592 (2)	847 (3)
Hypertension, n (%)	2023 (14)	1477 (17)	317 (9)	622 (11)	26,206 (6)	3857 (13)
Ischemic heart disease, n (%)	1493 (10)	1041 (12)	260 (7)	489 (9)	26,377 (6)	2888 (10)
Heart failure, n (%)	697 (5)	482 (5)	112 (3)	202 (4)	9582 (2)	1282 (4)
Cerebrovascular disease, n (%)	697 (5)	493 (6)	113 (3)	261 (5)	13,700 (3)	1382 (5)
Other cardiovascular, n (%)	3008 (20)	1885 (21)	555 (15)	1015 (19)	46,620 (11)	5647 (19)
Neoplasm, n (%)	1545 (10)	1044 (12)	389 (11)	524 (10)	31,642 (7)	3102 (11)
Musculoskeletal diseases, n (%)	8174 (55)	4064 (46)	2006 (56)	3692 (68)	76,585 (17)	15,655 (54)
Dementia, n (%)	218 (1)	168 (2)	29 (1)	76 (1)	4411 (1)	436 (1)
Diseases of liver, n (%)	118 (1)	83 (1)	25 (1)	57 (1)	2170 (0)	235 (1)

* Percentage of missing data: income (0.02%), education (1.61%), married (0.02%), born outside Sweden (0.02%). Those with missing data were excluded from adjusted regression models.

Table II
Adjusted hazard ratios (95% confidence intervals) of specific causes of death

Specific causes of death	Number of deaths	Knee OA		Hip OA		Hand OA		Other OA	
Malignant neoplasms, all	29,204	0.89	[0.83,0.94]	1.02	[0.95,1.09]	1.12	[0.99,1.27]	1.06	[0.96,1.17]
Digestive organs	8856	0.91	[0.81,1.01]	1.12	[1.00,1.26]	1.01	[0.80,1.28]	1.09	[0.91,1.30]
Respiratory and intrathoracic organs	5889	0.75	[0.64,0.87]	0.94	[0.79,1.11]	1.28	[0.99,1.66]	1.10	[0.88,1.37]
Male genital organs	2923	1.06	[0.89,1.27]	0.99	[0.81,1.22]	0.93	[0.53,1.64]	1.12	[0.80,1.57]
Lymphoid, hematopoietic and related tissue	2521	0.87	[0.71,1.07]	0.93	[0.73,1.18]	1.25	[0.83,1.87]	1.18	[0.85,1.63]
Breast*	1904	1.12	[0.90,1.40]	1.07	[0.82,1.41]	1.14	[0.78,1.69]	1.18	[0.83,1.67]
Urinary tract	1778	0.83	[0.65,1.07]	1.00	[0.77,1.31]	0.67	[0.33,1.34]	0.70	[0.42,1.17]
Other	5333	0.87	[0.75,1.00]	0.98	[0.83,1.15]	1.07	[0.81,1.41]	0.93	[0.73,1.19]
CVD, all	35,553	Supplementary Figs. 1 and 2				0.95	[0.84,1.07]	1.02	[0.93,1.12]
Myocardial infarction	8901	0.80	[0.71,0.89]	0.92	[0.81,1.03]	0.98	[0.76,1.26]	0.89	[0.73,1.09]
Ischemic heart diseases		Supplementary Figs. 1 and 2				1.02	[0.77,1.33]	1.11	[0.92,1.36]
Heart failure (and other forms of heart disease)	7659	1.18	[1.07,1.30]	1.17	[1.05,1.31]	1.03	[0.80,1.33]	1.03	[0.84,1.26]
Cerebrovascular diseases	7411	0.88	[0.79,0.99]	0.83	[0.73,0.95]	0.67	[0.49,0.92]	1.03	[0.84,1.25]
Other CVD	4173	1.14	[0.99,1.30]	0.96	[0.81,1.13]	1.29	[0.94,1.76]	1.10	[0.85,1.43]
Diabetes	2240	1.22	[1.01,1.47]	1.14	[0.92,1.42]	1.06	[0.66,1.72]	1.22	[0.86,1.71]
Infection	3081	1.02	[0.87,1.20]	0.92	[0.76,1.12]	0.86	[0.55,1.36]	1.35	[1.03,1.79]
Dementia related disorders	5011	0.92	[0.81,1.05]	0.90	[0.78,1.04]	1.25	[0.94,1.65]	0.93	[0.72,1.20]
Diseases of digestive system	3226	1.13	[0.96,1.33]	1.04	[0.85,1.27]	0.93	[0.62,1.41]	1.20	[0.90,1.59]
Other	19,120	0.96	[0.89,1.03]	0.95	[0.87,1.03]	0.96	[0.81,1.13]	1.09	[0.97,1.23]

* in women only; CVD – cardiovascular diseases; the Cox regression model was adjusted for age, sex, if married, residential area, education, income, if born outside Sweden. Similar results were obtained after additional adjustment for diagnosed obesity and type I diabetes (Supplementary Table 3).

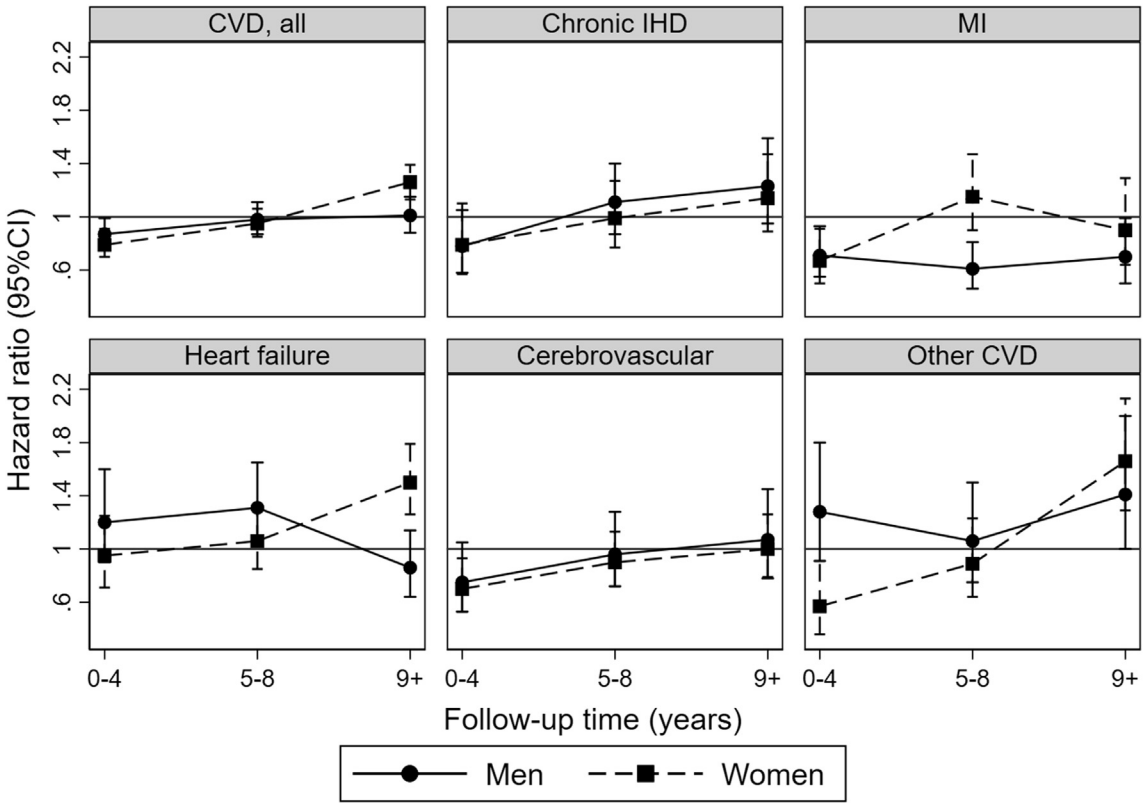

Fig. 1. Cardiovascular mortality in patients with knee OA as compared to the general population, by sex - adjusted hazard ratios with 95%CI from Cox regression model during 3 periods of the follow-up time. *CVD – cardiovascular diseases, IHD – ischemic heart diseases, MI – myocardial infarction.

hazard may have relevant impact on absolute mortality. Importantly, the mortality gap between persons with knee or hip OA and the general population increased with time. The main mechanism reported in the literature is mobility limitation[12]. Our results support this indirectly, as we found the increased cardiovascular mortality for persons with OA in knees and hips – potentially affecting mobility, but not for OA of hand or other peripheral joints.

Several previous studies reported higher relative CVD risk in women with OA than in men[15,25]. Thus, in this study we also presented results stratified on sex. For most causes of death, the estimated hazards ratios were similar for men and women. The differences in estimates for myocardial infarction and heart failure were not consistent. They might suggest slightly higher relative hazard of death from myocardial infarction among women with knee OA.

We found that persons with knee OA have lower cancer-specific mortality than persons without, while no similar association could be observed for OA in hip, hand or other joints. We speculate, that

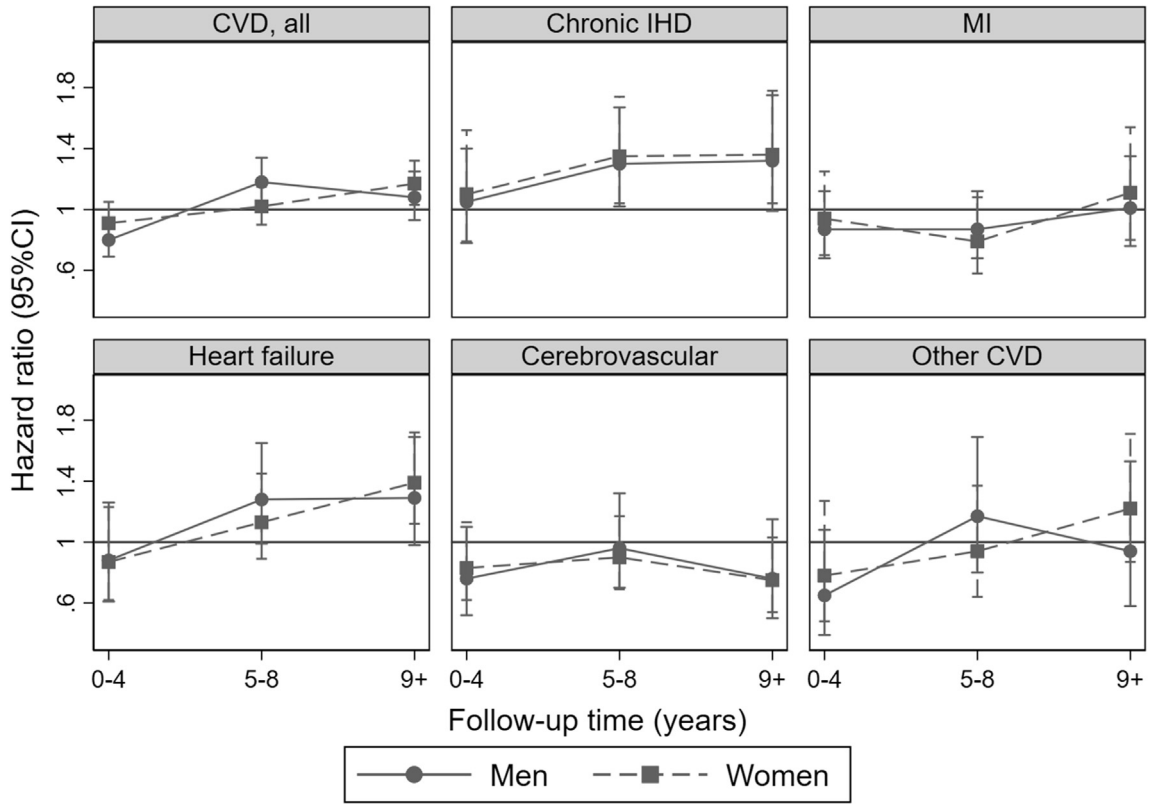

Fig. 2. Cardiovascular mortality in patients with hip OA as compared to the general population, by sex - adjusted hazard ratios with 95%CI from Cox regression model during 3 periods of the follow-up time. *CVD – cardiovascular diseases, IHD – ischemic heart diseases, MI – myocardial infarction.

Table III
Hazard ratios (95% confidence intervals) of specific causes of death, by sex

Specific causes of death	Sex	Knee OA		Hip OA		Hand OA		Other OA	
Malignant neoplasms, all	Men	0.94	[0.86,1.02]	0.99	[0.90,1.09]	1.14	[0.90,1.45]	1.06	[0.91,1.23]
	Women	0.87	[0.80,0.95]	1.06	[0.97,1.17]	1.08	[0.93,1.26]	1.07	[0.94,1.23]
CVD*, all and subgroups	Men	Figs. 1 and 2				0.88	[0.70, 1.11]	0.95	[0.82, 1.10]
	Women					1.00	[0.87, 1.16]	1.08	[0.96, 1.22]
Diabetes	Men	1.20	[0.92,1.56]	1.29	[0.97,1.73]	1.36	[0.65,2.85]	1.19	[0.72,1.98]
	Women	1.24	[0.96,1.60]	0.99	[0.71,1.38]	0.92	[0.49,1.72]	1.24	[0.78,1.98]
Infection	Men	1.12	[0.89,1.40]	1.00	[0.76,1.30]	0.69	[0.29,1.67]	1.44	[0.96,2.15]
	Women	0.95	[0.75,1.19]	0.85	[0.64,1.13]	0.94	[0.55,1.59]	1.29	[0.88,1.89]
Dementia related disorders	Men	1.00	[0.80,1.24]	0.86	[0.66,1.11]	1.07	[0.55,2.06]	0.94	[0.59,1.50]
	Women	0.89	[0.76,1.04]	0.93	[0.77,1.11]	1.29	[0.95,1.75]	0.92	[0.68,1.25]
Diseases of digestive system	Men	1.16	[0.92,1.48]	1.02	[0.75,1.37]	1.34	[0.70,2.59]	1.05	[0.66,1.67]
	Women	1.09	[0.88,1.36]	1.05	[0.81,1.37]	0.79	[0.47,1.35]	1.31	[0.91,1.88]
Other	Men	0.95	[0.85,1.06]	0.93	[0.82,1.06]	0.84	[0.60,1.19]	0.99	[0.81,1.21]
	Women	0.96	[0.88,1.05]	0.95	[0.86,1.07]	1.01	[0.84,1.22]	1.17	[1.00,1.36]

* CVD – cardiovascular diseases; the Cox regression model was adjusted for age, sex, if married, residential area, education, income, if born outside Sweden.

Table IV
The adjusted hazard ratios of death from specific causes in persons with knee or hip OA compared to general population without

Specific causes of death	Knee OA		Hip OA		Hand OA		Other OA	
Malignant neoplasms, all	0.88	[0.83,0.94]	1.01	[0.95,1.09]	1.11	[0.98,1.26]	1.05	[0.95,1.16]
Diabetes	0.97	[0.81,1.16]	1.07	[0.86,1.33]	0.97	[0.60,1.56]	1.04	[0.74,1.46]
Infection	1.00	[0.85,1.17]	0.91	[0.75,1.11]	0.86	[0.55,1.35]	1.33	[1.01,1.76]
Dementia related disorders	0.92	[0.81,1.05]	0.90	[0.78,1.05]	1.25	[0.94,1.65]	0.93	[0.72,1.20]
Diseases of digestive system	1.11	[0.94,1.30]	1.03	[0.84,1.26]	0.93	[0.61,1.40]	1.18	[0.89,1.57]
Other	0.94	[0.88,1.01]	0.94	[0.86,1.02]	0.95	[0.81,1.13]	1.08	[0.95,1.21]
CVD*					0.94	[0.83,1.06]	1.00	[0.91,1.10]
≤4 years of follow-up	0.81	[0.73,0.89]	0.84	[0.76,0.94]				
5–8 years of follow-up	0.94	[0.87,1.02]	1.09	[1.00,1.19]				
>9 years of follow-up	1.14	[1.05,1.23]	1.12	[1.02,1.24]				

* CVD – cardiovascular diseases; the Cox regression model was adjusted for age, sex, if married, residential area, education, income, if born outside Sweden and additionally adjusted for diagnosed obesity and type I or II diabetes and diagnosed tobacco use.

this may reflect a potentially large proportion of persons with post-traumatic disease among those who consult a physician for knee OA. These persons may have high levels of physical activity preceding the OA incidence and in general better health on average. Unfortunately, we did not have individual-level data on physical activity level to adjust for its potential confounding effect. Recently, a similar finding was reported for persons with radiographic knee OA[17].

We found weak evidence of increased mortality from diabetes among persons with knee OA. The point estimate was almost completely attenuated when adjusting for type I diabetes, and with further adjustment for tobacco use and type II diabetes. Diabetes has previously been reported to be an independent risk factor for OA[26], as well as type II diabetes to be a consequence of OA[27,28]. The attenuation of the association in our data could be a consequence of both this issue.

The estimates of the association between OA in peripheral joints and other causes of death were all close to one. In particular, we found no evidence of increased mortality from dementia, infections or other causes in patients with OA as compared to the general population. Also deaths from diseases of digestive system were not more common in persons with OA than in those without, but this cause of death was relatively uncommon and the confidence intervals do not exclude a possibility of a weak effect.

Our study has several limitations worth discussing. First, we were not able to adjust for body mass, only for diagnosed obesity. High body mass is a major risk factor for OA and is also associated with higher all-cause mortality and lack of adjustment could bias our estimates upwards[29]. However, the prevalence of obesity (body mass index $\geq$35) estimate from population surveys in Sweden from the years 1980 and 1988, suggest that in our cohort the pre-OA obesity prevalence was around 5.5%. Our sensitivity analysis of potential impact of bias suggests that is unlikely to explain all the observed associations (Supplementary Fig. 3). We included persons with OA at different stages of the disease but we lacked information about diseases severity. Those diagnosed with OA during the 5 year inclusion period were a mixture of prevalent and incident cases and many underwent a joint replacement surgery for their OA. However, in a sensitivity analysis, where we excluded those who underwent knee or hip replacement, we found very similar results as for the whole cohort. As not all persons consult a physician for their OA, and we only included those who consulted specialist care, we likely included persons with OA in the unexposed group. However, as this group could only be a small proportion among all unexposed, it could have only a minor impact on the estimates. On the other hand, those who did consult may have had recent onset of pain and/or more severe symptoms, as reported previously[30]. The same report concluded though that comorbidities seem to have only minor impact on the decision to consult for knee pain. However, as persons with OA in this study were diagnosed within specialist care, they may not be representative for the entire underlying population with OA. In Sweden a consultation with a specialist is available within the common tax-based healthcare system and we would not expect major socioeconomic differences, especially after adjusting for individual level education, residential area and income. We could expect though, that those consulting a specialist would experience higher OA-burden, pain or disability. Lastly, the underlying cause of death was retrieved from the CDR, and reflected the judgment of the physician filling in the death certificate as of what the underlying cause of death was. It is known that cancer and cardiovascular diseases are more likely to be considered as underlying cause of death, than other diseases and administrative records of causes of death have some limitations. However, this is the only source of information available for a large cohort and validity of coding in CDR has been reported to be high with respect to major disease groups, as used in this work[31]. There are several strengths of the current work. We limited a potential impact of selection bias by including all residents of a well-defined region. The assessment of exposure, confounders and outcome was consistent for all included persons. The large sample size enabled us to study a number of distinct causes of death, including subgroups or malignant cancer and cardiovascular diseases. These analyses were crucial for identification of the major causes of excess mortality in knee and hip OA.

In conclusion, we found two major groups of cardiovascular diseases that lead to increased mortality in persons with OA as compared to those without, i.e., ischemic heart diseases and heart failure, and that this gap in mortality increases over time. At the same time, mortality from other causes is comparable between persons with and without OA. OA remains one of the leading causes of disability[32], while there is a clear potential for improved management of persons with OA[33]. Thus, we reinforce the need to address the most important known modifiable intermediate factor, i.e., mobility limitations, in treatment of persons with OA. Considering that regular exercise is an effective but underused treatment for knee and hip OA and has a potential for improved mobility and cardiovascular health, our results reinforce the need for better implementation of OA treatment guidelines[34].

Author contributions

AT and ME has conceived the study and obtained the data. AT has performed statistical analyses and drafter the manuscript. All authors contributed to the study design, interpretation of the results, revised the text for important intellectual content and approved the final version of the manuscript before submission.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary data

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