



The association between preexisting conditions and osteoarthritis development in peripheral joints: A population based nested case-control study



Andrea Dell'Isola ^{a,*}, Aleksandra Turkiewicz ^a, Weiya Zhang ^b, Sita Bierma-Zeinstra ^{c,d}, Jos Runhaar ^c, Daniel Prieto-Alhambra ^e, Subhashisa Swain ^f, Ali Kiadaliri ^a, Martin Englund ^a

^a Clinical Epidemiology Unit, Orthopedics, Department of Clinical Sciences Lund, Lund University, Lund, Sweden

^b Academic Rheumatology, Pain Centre Versus Arthritis, School of Medicine, University of Nottingham

^c Department of General Practice, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

^d Department of Orthopedics & Sports Medicine, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

^e Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford

^f Nuffield Department of Primary Health Care Sciences, University of Oxford, Oxford, UK

ARTICLE INFO

Keywords:

Osteoarthritis
Knee
Hip
Multimorbidity
Incidence

ABSTRACT

Aim: To study the risk of receiving a new (incident) osteoarthritis (OA) diagnosis in different joint sites based on conditions diagnosed in the 20 years prior the OA diagnosis.

Methods: We used register data for the entire population of the Skåne region (Sweden) to perform a nested case-control study. The outcome was newly diagnosed (incident) OA in peripheral joints, i.e. knee (ICD-10 code M17), hip (M16) and other joints (M15, M18, M19), diagnosed in 2018 or 2019 in persons aged 45+ years with 20 years of register coverage. For each OA case, we sampled 1 control matched on age (1-year strata), sex and residential area in the year of index date using incidence density sampling. The exposures of interest comprised 50 comorbidities. We used adjusted conditional logistic regression for analysis.

Results: Between January 1st 2018 and December 31st 2019, we identified 7 201, 2 895, and 7863 persons, respectively, with newly diagnosed knee, hip and other OA. Hypertension, back pain, gout, allergy, depression, anxiety and migraine were all associated with increased risk of knee OA diagnosis, while only gastroesophageal reflux disease and back pain were associated with newly diagnosed hip OA. Interestingly, many of the analysed conditions were associated with increased risk of OA diagnosis in other peripheral joints, including diagnosed generalised OA.

Conclusions: The risk of being diagnosed with OA increases with the presence of multimorbidity earlier in life, but the associations seem to differ between weight-bearing and non-weight-bearing joints.

1. Introduction

Osteoarthritis (OA) affects more than 500 million individuals globally and is a major cause of pain and functional disability worldwide [1]. Part of the burden linked to OA is due to the high rate of coexisting chronic conditions which are present in roughly 7 out of 10 people with OA, 20% more often than in age- and sex-matched controls [2]. The high prevalence of comorbidities further impacts mental and physical function and can increase the risk of hospitalisation and mortality [2]. However, except for few known shared risk factors, such as obesity and ageing, there is little evidence about the mechanisms and the temporality of OA

and comorbidities. Recent longitudinal studies suggest that OA is an independent risk factor for the development of numerous chronic conditions including depression, cardiovascular diseases, back pain, and osteoporosis [3,4]. Nevertheless, those and other conditions are often already present when OA is diagnosed suggesting that the potential temporal link between OA and comorbidities may be bi-directional. However, OA is a slowly progressive disease that may be present many years before the symptoms become severe enough for the person to seek care and receive a diagnosis. Studies using cross-sectional designs or follow-ups shorter than 10 years may have thus observed reverse causality of OA rather than the effect of other conditions on OA incidence.

* Corresponding author. Clinical Epidemiology Unit, Orthopedics Department of Clinical Sciences, Lund Wigerthuset, Remissgatan 4, Lund, 22185, Sweden.

E-mail address: andrea.dellisola@med.lu.se (A. Dell'Isola).

<https://doi.org/10.1016/j.ocarto.2022.100265>

Received 21 December 2021; Accepted 28 April 2022

2665-9131/© 2022 The Authors. Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International (OARSI). This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Moreover, epidemiological and genetic evidence seems to suggest that OA in different joints may, to some extent, be distinct conditions thus limiting the possibility to extend the results from knee OA research to other joints [5–7].

Systemic factors such as low-grade inflammation and metabolic dysregulation are associated with the development of numerous chronic conditions through complex networks of environmental and genetic factors and have been advocated as key steps on the causal pathway for the development of OA [7]. This newly discovered complexity calls for greater attention to multimorbidity and disease interaction [8]. Considering the dearth of longitudinal evidence, this study aims to provide a comprehensive overview of the association between a large set of conditions and newly diagnosed OA in different joints. In this exploratory work, we included conditions for which an association with incident OA is expected (e.g. painful conditions), debated or possible (e.g. diabetes) or scarcely explored (e.g. irritable bowel syndrome). Our hypothesis is that studying a wide range of comorbidities using the same data source and consistent methodology can shed new light on the pathways leading to OA and multimorbidity and may help to develop new prevention strategies that may target persons at higher risk of developing OA. Thus, using a nested case-control study design and healthcare data prospectively collected over 20 years, we aimed to explore the associations between a number of pre-specified conditions and incident diagnosis of OA of the knee, hip or other joints.

2. Methods

2.1. Data sources

We used prospectively collected healthcare data for the population of Skåne, the southernmost region in Sweden with ~1.4 million inhabitants (1/8 of the Swedish population in the year 2019). From the Swedish Population Register, we retrieved data on age, sex, and residential addresses. Individual-level data on income, education, marital status, and country of birth were retrieved from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by Swedish acronym). Information on the date of death was obtained from the Swedish Causes of Death register. Lastly, from the Skåne Healthcare Register (SHR) we extracted information about diagnoses set on any physical healthcare visit. SHR is a regional mandatory register that contains the diagnostic codes from publicly funded clinics according to the International Classification of Diseases (ICD) 10 system. These codes are assigned at the time of the healthcare visit by the physicians themselves and are automatically transferred to the register from the electronic medical records. The positive predictive value of a knee OA diagnosis in SHR has previously been reported to be high at 88% [9]. All data from the different registers were linked through the coded personal unique identification number that is assigned to all residents in Sweden by the Swedish Tax Agency. The study was approved by the Regional Ethical Review Board in Lund, Sweden, and is reported The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement [10]. The study was approved by the Regional Ethical Review Board in Gothenburg (1059-16).

2.2. Study design, exposures and outcomes

We performed a nested case-control study. The outcome was newly diagnosed (incident) OA diagnosis in peripheral joints, i.e. knee (ICD-10 code M17), hip (M16) and other peripheral joints (incl first carpometacarpal joint [M18]; foot, shoulder, hand, or elbow OA [M19 subcodes]; generalised OA [M15] and unspecified OA [M19.9]), diagnosed in 2018 or 2019 in persons aged 45+ years at the time of diagnosis. All persons with any OA diagnosed before Jan 1st 2018 were excluded. Further, we required that the persons were residents in Skåne between 1998 and 2017 to enable the assessment of conditions preceding OA diagnosis. For each OA case, we sampled one control matched on exact age (1-year

strata), sex and residential area in the year of index date using incidence density sampling, i.e. from those at risk. The inclusion and exclusion criteria for controls were the same as for the cases, apart from the OA diagnosis. The date of OA was used as the index date for cases and their matched controls.

2.3. Definitions and extraction of conditions

A large set of 50 conditions were selected from a previous systematic review and previous studies from Sweden and England studying the association between OA and incident comorbidities ([4–6]). For each included person we assessed if each condition was present up to 20 years preceding the index date. The conditions were grouped into musculoskeletal (MSK), metabolic, cardiovascular (CV), immune system, respiratory, neuro-psychological, cancer and other conditions (supplementary Table 1). The presence of more than one condition was defined as multimorbidity to estimate the risk of developing OA among people with multiple conditions.

2.4. Confounders

We considered the following factors measured in the year 1998, i.e. preceding the diagnosis of the analysed conditions, as potential confounders: education level (up to 9 years, 10–13 years, 13–14 years, 15+ years), income (categorised into 6 groups using 10th, 25th, 50th, 75th and 90th percentile), if married/registered partner, if born outside Sweden. Further, we controlled for obesity, alcohol consumption and tobacco addiction using the registered ICD10 codes E66 (obesity), F10 (alcohol addiction) and F17 (mental disorders and behavioural disorders caused by tobacco). We considered these to be risk factors for the analysed conditions (not the conditions being risk factors for them), therefore we adjust for obesity, alcohol and tobacco use irrespectively of the date of diagnosis during the 20 year exposure period.

2.5. Statistical methods

Descriptive data are provided as means (SD) or frequencies and percentages. Considering the study design we used conditional logistic regression for analysis. The model was adjusted for the confounders listed above. We fitted a separate model for each OA type. We first fitted models with specific disease groups (as defined above) as exposure. In a second step, we used each specific condition as exposure, excluding those with low counts (total count less than 250) due to the challenge of producing reliable estimates. We did not adjust for other conditions than the one of interest. Considering the nested case-control design and the equal 20 years period of exposure assessment, the estimates obtained are risk ratios (RR), we provide them with 95% confidence intervals. As a sensitivity analysis to enable comparisons with previous studies, we repeated the above analyses using conditions diagnosed up to 5, 10 and 15 years prior to the index date. Further, considering that OA is a slowly developing disease and many patients do not seek care for their OA symptoms, we considered as exposure only conditions diagnosed within 10–20 years preceding the index date (i.e. excluding conditions diagnosed within 10 years preceding the index date).

3. Results

Between January 1st 2018 and December 31st 2019, we identified 17,959 persons with newly diagnosed OA of whom 7201 (40%), 2895 (16%), and 7863 (44%) with newly diagnosed knee, hip and other OA respectively. The age, sex and socio-economy distribution were similar across the different joint sub-groups (Table 1).

3.1. Knee OA

Overall, 82% (5877) of the persons who were diagnosed with knee

Table 1
Demographic variables by case status and OA site.

	Knee OA, controls	Knee OA, cases	Hip OA, controls	Hip OA, cases	Other OA, controls	Other OA, cases
Age in years at index date, mean (SD)	66.28 (11.23)	66.28 (11.23)	69.03 (11.43)	69.03 (11.43)	66.32 (11.73)	66.32 (11.73)
Education, up to 9 years, n(%)	1800 (26)	1864 (27)	827 (29)	791 (28)	1989 (26)	2084 (28)
Education, 10–12 years, n(%)	3127 (45)	3197 (46)	1201 (43)	1243 (44)	3439 (45)	3526 (47)
Education 13–14 years, n(%)	962 (14)	888 (13)	384 (14)	386 (14)	1048 (14)	962 (13)
Education 15+ years, n(%)	1041 (15)	985 (14)	400 (14)	414 (15)	1105 (15)	966 (13)
If born outside Sweden, n(%)	1101 (16)	1090 (16)	377 (13)	322 (11)	1190 (16)	1252 (16)
Income, annual, in 100,000 SEK, mean (SD)	1.43 (1.18)	1.44 (1.08)	1.43 (1.21)	1.45 (.85)	1.4 (.85)	1.39 (1.48)
Male, n(%)	3056 (42)	3056 (42)	1268 (44)	1268 (44)	2937 (37)	2937 (37)
Married or registered partner, n(%)	5135 (74)	5304 (76)	2135 (75)	2206 (77)	5565 (73)	5704 (75)
Alcohol related disorders, n(%)	260 (4)	221 (3)	84 (3)	110 (4)	280 (4)	306 (4)
Obesity, n(%)	853 (12)	1345 (19)	359 (12)	405 (14)	962 (12)	1196 (15)
Nicotine dependence, n(%)	453 (6)	411 (6)	178 (6)	187 (6)	473 (6)	587 (7)
OA						
Foot/ankle, n(%)	–	–	–	–	–	362 (5)
Generalised, n(%)	–	–	–	–	–	657 (8)
Hip, n(%)	–	–	–	2895 (100)	–	–
Knee, n(%)	–	7201 (100)	–	–	–	–
Unspecified, n(%)	–	–	–	–	–	5492 (70)
Wrist/hand, n(%)	–	–	–	–	–	1352 (17)

OA: Osteoarthritis, n: number, SD: Standard deviation, SEK: Swedish korona

OA had multimorbidity in the 20 years preceding the diagnosis, compared to 74% (5296) of the matched controls (Table 2). Cardiovascular (55%) and MSK (48%) conditions were the most prevalent, while respiratory conditions were the least common (16%). Multimorbidity was associated with a 43%–72% higher risk of being diagnosed with knee OA (Fig. 1, Supplementary Table 2). Among the studied cardiovascular and MSK diseases, only hypertension, back pain and gout were associated with newly diagnosed OA (Supplementary Table 3). Allergy was associated with a 24% (RR:1.24, 95%CI 1.13; 1.35) increased risk of knee OA diagnosis. Interestingly, depression, anxiety and migraine were all associated with increased risk of knee OA diagnosis. Persons with COPD, diabetes, dementia, heart failure or peripheral vessel diseases had a lower risk of being diagnosed with knee OA.

3.2. Hip OA

Overall, 83% (2394) of the people who were diagnosed with hip OA had multimorbidity, compared to 74% (5296) of the matched controls. Cardiovascular (58%) and MSK (52%) conditions were the most prevalent, while respiratory conditions were the least common (17%). People with multimorbidity had a 33%–79% higher risk of being diagnosed with hip OA, while the presence of MSK conditions was associated with a 28%–59% higher risk. Due to the lower number of persons with hip OA (as compared to knee and other joints), the confidence intervals are wide, but generally suggest no association between specific conditions and hip OA diagnosis except for back pain (RR 1.55, 95%CI 1.39; 1.74) and gastroesophageal reflux disease (GERD) (RR 1.27, 95%CI 1.01; 1.47). Furthermore, of the conditions with high prevalence, the wide CIs do not exclude the possibility that hypertension is associated with newly diagnosed hip OA.

3.3. OA in other peripheral joints (including diagnosed generalised OA)

Overall, 85% (6702) of the people who were diagnosed with OA in other peripheral joints had multimorbidity, compared to 75% (5296) of the matched controls. Cardiovascular (56%) and MSK (56%) conditions were the most prevalent, while respiratory conditions were the rarest (18%). People with multimorbidity had a 78%–115% higher risk of being diagnosed with OA in other joints, while the presence of MSK, CV, immune system, neuro-psychological, metabolic, and cancer conditions were associated with a 7%–82% higher risk. Almost all studied conditions were associated with a higher risk of being diagnosed with OA in other joints (including diagnosed generalised OA). In particular, a strong increase in the risk of being diagnosed with OA in other joints was seen

for people with fibromyalgia (1.98, 95%CI 1.53; 2.56), back pain (1.60, 95%CI 1.49; 1.71) and irritable bowel syndrome (IBS) (1.51, 95%CI 1.30; 1.77). All types of peripheral joint OA were less commonly diagnosed in persons with dementia.

3.4. Sensitivity analyses

The estimates obtained using up to 5, 10 or 15 years were very similar to the overall results (supplementary Table 4–6). Using only conditions that likely preceded true incidence of OA (diagnosed within 10–20 years preceding index date) to prevent potential reverse causality gave also similar results for most conditions, even though often the point estimates were attenuated (supplementary Table 7–8). The two important discrepancies that emerged from this sensitivity analysis were hypertension, which was not associated with OA in any joint, and multimorbidity, which was not associated with a knee or hip OA diagnosis and had a much weaker association with an OA diagnosis in other joints (RR 1.20, 95%CI 1.12; 1.29).

4. Discussion

In this population-based study, utilising over 20 years of healthcare data, we found that the presence of the analysed conditions was associated with later diagnosis of OA, but differently for different joint sites. We found that the presence of hypertension, back pain, gout, allergy, depression, anxiety and migraine were all associated with increased risk of knee OA diagnosis, while only GERD and back pain were associated with newly diagnosed hip OA. Interestingly, we found that most of the analysed conditions were associated with increased risk of OA diagnosis in other peripheral joints, including diagnosed generalised OA.

Particularly, conditions of the immune system (e.g. allergy, inflammatory bowel syndrome), dyslipidemia, depression, polymyalgia and fibromyalgia appear to be strongly associated with an OA diagnosis in other peripheral joints than knee or hip. Low-grade inflammation has been suggested to be a key factor linking comorbidities and OA [11]. However, it could not explain why the observed risks vary between joints. Thus, it can be hypothesised that systemic factors may be more prominent in the pathogenesis of OA in non-weight-bearing joints, while biomechanical factors may be more prominent in the pathogenesis of knee and hip OA. This hypothesis is supported by previous studies suggesting that systemic processes may be important risk factors for hand OA but not for knee OA, where surrogates for mechanical stress, such as high body weight, appear to explain the observed associations [12,13].

Another possible explanation is the existence of joint-specific single

Table 2
Prevalence of diagnosed conditions in the 20 years preceding the index date.

	Knee OA control	Knee OA case	Hip OA control	Hip OA case	Other OA control	Other OA case
Musculoskeletal, n(%)	3014 (42)	3467 (48)	1248 (43)	1501 (52)	3278 (42)	4365 (56)
Fibromyalgia, n(%)	95 (1)	105 (1)	32 (1)	35 (1)	99 (1)	203 (3)
Gout, n(%)	263 (4)	352 (5)	142 (5)	147 (5)	295 (4)	434 (6)
Osteoporosis, n(%)	566 (8)	540 (7)	257 (9)	255 (9)	602 (8)	793 (10)
Polymyalgia, n(%)	134 (2)	137 (2)	73 (3)	78 (3)	136 (2)	216 (3)
Back pain, n(%)	2543 (35)	2968 (41)	1028 (36)	1312 (45)	2779 (35)	3742 (48)
Metabolic, n(%)	2214 (31)	2363 (33)	972 (34)	1012 (35)	2467 (31)	2812 (36)
Diabetes, n(%)	932 (13)	924 (13)	424 (15)	392 (14)	1008 (13)	1082 (14)
Dyslipidaemia, n(%)	1325 (18)	1396 (19)	594 (21)	592 (20)	1435 (18)	1644 (21)
Hyperthyroidism, n(%)	157 (2)	179 (2)	58 (2)	83 (3)	179 (2)	212 (3)
Hypothyroidism, n(%)	614 (9)	661 (9)	247 (9)	293 (10)	731 (9)	877 (11)
Cardiovascular, n(%)	3566 (50)	3952 (55)	1612 (56)	1671 (58)	3929 (50)	4417 (56)
Cardiac arrhythmia, n(%)	920 (13)	941 (13)	464 (16)	445 (15)	990 (13)	1049 (13)
Coronary heart disease, n(%)	969 (13)	958 (13)	487 (17)	474 (16)	1075 (14)	1233 (16)
Heart failure, n(%)	434 (6)	358 (5)	228 (8)	189 (7)	459 (6)	441 (6)
Hypertension, n(%)	2990 (42)	3374 (47)	1370 (47)	1447 (50)	3304 (42)	3774 (48)
Peripheral vascular disease, n(%)	187 (3)	131 (2)	88 (3)	85 (3)	189 (2)	249 (3)
Stroke, n(%)	571 (8)	626 (9)	318 (11)	282 (10)	724 (9)	699 (9)
Immune system, n(%)	2067 (29)	2360 (33)	817 (28)	855 (30)	2310 (29)	2917 (37)
Ankylosing spondylitis, n(%)	33 (0)	23 (0)	12 (0)	9 (0)	24 (0)	33 (0)
Rheumatoid arthritis, n(%)	85 (1)	99 (1)	47 (2)	38 (1)	133 (2)	129 (2)
Inflammatory bowel disease, n(%)	423 (6)	470 (7)	169 (6)	169 (6)	447 (6)	608 (8)
Multiple sclerosis, n(%)	24 (0)	19 (0)	12 (0)	8 (0)	31 (0)	22 (0)
Psoriasis, n(%)	339 (5)	366 (5)	133 (5)	153 (5)	358 (5)	502 (6)
Allergy, n(%)	1234 (17)	1484 (21)	459 (16)	488 (17)	1369 (17)	1777 (23)
Sjögren's syndrome, n(%)	36 (0)	45 (1)	16 (1)	19 (1)	42 (1)	77 (1)
Systemic lupus erythematosus, n(%)	13 (0)	12 (0)	4 (0)	6 (0)	16 (0)	15 (0)
Respiratory, n(%)	1030 (14)	1139 (16)	421 (15)	479 (17)	1193 (15)	1400 (18)
Asthma, n(%)	698 (10)	865 (12)	285 (10)	313 (11)	841 (11)	1037 (13)
Chronic obstructive pulmonary disease, n(%)	500 (7)	425 (6)	222 (8)	246 (8)	550 (7)	582 (7)
Neuro-Psychological, n(%)	2051 (28)	2315 (32)	883 (31)	881 (30)	2384 (30)	2878 (37)
Dementia, n(%)	182 (3)	144 (2)	94 (3)	72 (2)	206 (3)	154 (2)
Depression, n(%)	1185 (16)	1363 (19)	509 (18)	538 (19)	1388 (18)	1755 (22)

Table 2 (continued)

	Knee OA control	Knee OA case	Hip OA control	Hip OA case	Other OA control	Other OA case
Anxiety, n(%)	968 (13)	1118 (16)	420 (15)	423 (15)	1108 (14)	1452 (18)
Migraine, n(%)	380 (5)	451 (6)	122 (4)	140 (5)	432 (5)	600 (8)
Parkinson's disease, n(%)	41 (1)	41 (1)	30 (1)	18 (1)	66 (1)	45 (1)
Epilepsy, n(%)	111 (2)	98 (1)	59 (2)	39 (1)	124 (2)	126 (2)
Schizophrenia, n(%)	57 (1)	54 (1)	14 (0)	16 (1)	55 (1)	30 (0)
Eating disorder, n(%)	14 (0)	16 (0)	2 (0)	0 (0)	9 (0)	19 (0)
Fatigue, n(%)	9 (0)	4 (0)	2 (0)	1 (0)	8 (0)	7 (0)
Sleep disorders, n(%)	15 (0)	21 (0)	9 (0)	11 (0)	11 (0)	31 (0)
Other, n(%)	3685 (51)	4005 (56)	1635 (56)	1702 (59)	4148 (53)	4633 (59)
Irritable bowel syndrome, n(%)	269 (4)	303 (4)	110 (4)	137 (5)	307 (4)	464 (6)
Cancer, n(%)	1414 (20)	1377 (19)	623 (22)	629 (22)	1567 (20)	1561 (20)
GERD, n(%)	1040 (14)	1209 (17)	426 (15)	520 (18)	1137 (14)	1502 (19)
Gastrointestinal bleed, n(%)	45 (1)	41 (1)	25 (1)	23 (1)	54 (1)	51 (1)
Chronic kidney disease, n(%)	187 (3)	167 (2)	95 (3)	88 (3)	191 (2)	244 (3)
Gall bladder stones, n(%)	454 (6)	525 (7)	164 (6)	194 (7)	520 (7)	595 (8)
Renal stones, n(%)	405 (6)	439 (6)	181 (6)	184 (6)	430 (5)	491 (6)
Liver diseases, n(%)	45 (1)	34 (0)	21 (1)	20 (1)	40 (1)	48 (1)
Anaemia, n(%)	767 (11)	718 (10)	331 (11)	320 (11)	887 (11)	932 (12)
Cataract, n(%)	1730 (24)	1814 (25)	875 (30)	883 (31)	2023 (26)	2206 (28)
Vision problems, n(%)	542 (8)	572 (8)	272 (9)	267 (9)	640 (8)	712 (9)
Hearing problems, n(%)	845 (12)	907 (13)	414 (14)	423 (15)	928 (12)	1077 (14)
Sinusitis, n(%)	105 (1)	100 (1)	40 (1)	37 (1)	118 (2)	164 (2)
HIV/AIDS, n(%)	5 (0)	3 (0)	1 (0)	2 (0)	6 (0)	3 (0)
Tuberculosis, n(%)	9 (0)	10 (0)	4 (0)	5 (0)	13 (0)	10 (0)
Multimorbidity, n(%)	5296 (74)	5877 (82)	2222 (77)	2394 (83)	5887 (75)	6702 (85)
Multimorbidity count, median (25th, 75th percentile)	3 (1, 6)	4 (2, 6)	4 (2, 6)	4 (2, 7)	3 (1, 6)	4 (2, 7)

OA: Osteoarthritis, n: number, GERD: Gastroesophageal reflux disease, HIV: Human Immunodeficiency Virus, AIDS: Acquired Immunodeficiency Syndrome.

nucleotide variants that may explain why certain factors or conditions are more strongly associated with OA in specific joints [5]. Genetic studies seem also to confirm the association of OA with certain conditions including low back pain, which was the only condition to increase the risk of OA in all the joint sites [5]. The inclusion of the M47 code (i.e. spondylosis, also known as spine OA) in our definition of back pain has also identified subjects with spine OA who may have a higher risk for developing OA in multiple joints, which could partially explain the strong association between back pain and OA. Of all persons diagnosed with back pain, 9% (in both cases and controls) were diagnosed with spine OA specifically, which suggest that there were no essential differences in registration of spine OA vs back pain between cases and controls. Nevertheless, genes act through a complex web of mechanisms involving injury, body weight, muscle mass and other environmental factors ultimately leading to the development of OA [14]. Among these

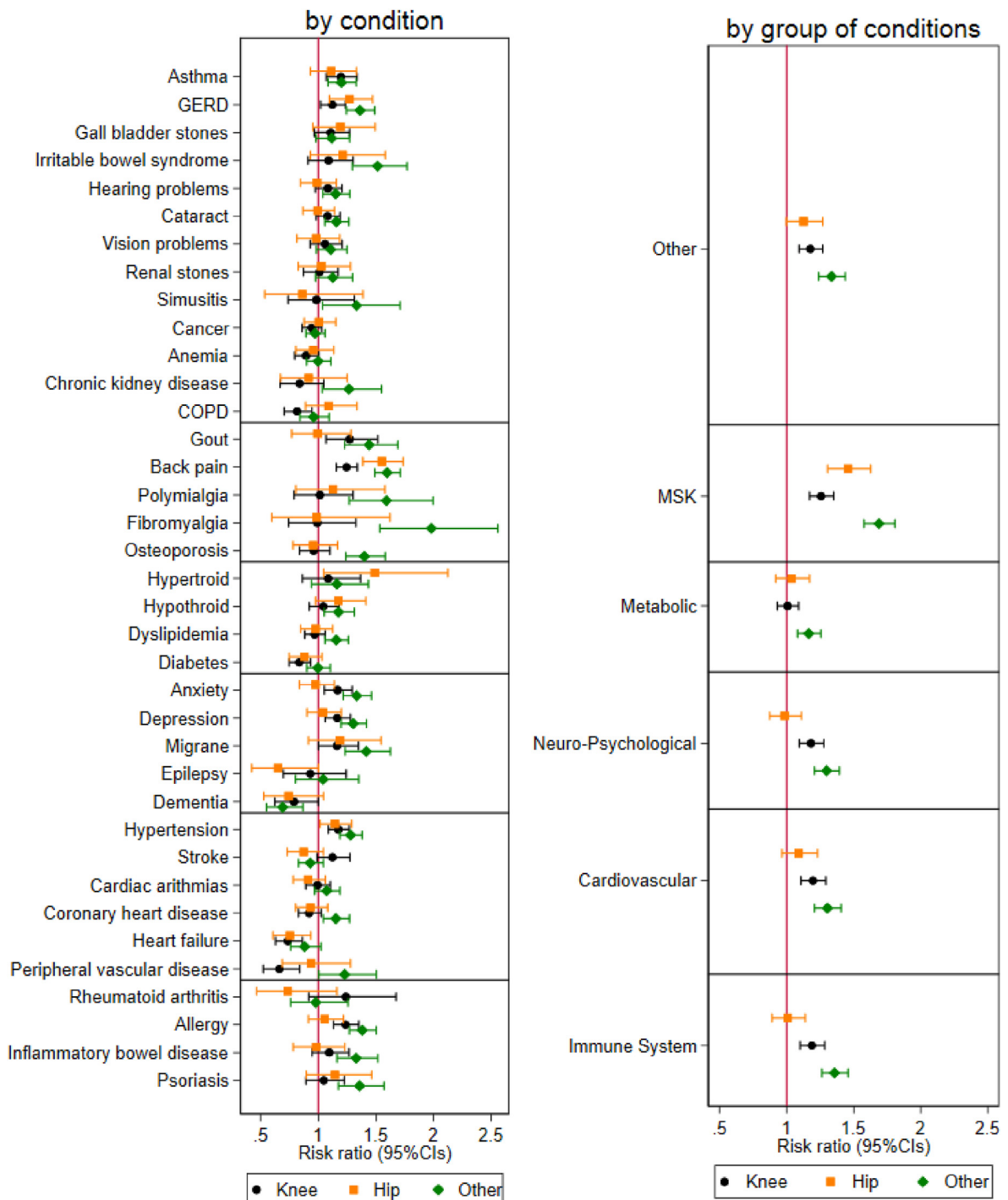


Fig. 1. Risk ratio of developing osteoarthritis by single condition and by group of conditions diagnosed within 20 years prior osteoarthritis diagnosis.

mechanisms, neuronal plasticity in pain coding pathways resulting in maladaptive pain sensitisation is known to occur in chronic painful conditions and to favour the onset of widespread pain [15]. Depression appears to influence the same pathways through the depression of serotonin and norepinephrine [16]. Thus, the presence of pain may in itself explain the observed association between painful conditions, depression and OA. The differences observed in this study may thus be attributed to the multifactorial nature of OA and its complex aetiology, which seems to be, at least to some extent, joint-specific.

Interestingly, persons with COPD, diabetes, heart failure or peripheral vessel diseases had a lower risk of being diagnosed with knee OA. This might be because lower-limb OA, to a larger extent than OA in other

joints, is a result of overloading [17]. People with heart failure and COPD are less likely to engage in sporting activity leading to joint overloading thus partially explaining the observed protective association. Another possible explanation is that when more severe conditions are present, joint problems may be overlooked by the clinicians or underreported by the patient. Moreover, the association between diabetes and incident OA is currently debated, with recent reports suggesting that excess weight may be the main factor behind this association [18]. While our results seem to be in line with these observations, using primary care diagnosis may imply that the observed effect showed in our study reflects more how patients are managed in clinical settings rather than a true protective effect. In a prior study, we have reported an elevated risk of

developing diabetes and heart failure after newly diagnosed knee OA [3]. This suggested that lifestyle changes that may happen consequently to the development of OA (e.g. reduced physical activity) may explain the directionality of the observed associations. People with dementia appear to have a lower risk of being diagnosed with OA. This is likely a result of consultation bias, i.e., people with symptoms of dementia may simply consult a clinician for joint problems to a lesser extent than persons mentally fully alert.

A recent study using healthcare register data from the UK to analyse the associations between >40 conditions and newly diagnosed OA found similar associations regardless of the joint that developed OA [4]. More so, the study reported that nearly all the analysed conditions were associated with OA. A potential explanation of the discrepancy with our results could be differences in the healthcare systems and/or general population health in the UK vs Sweden. These discrepancies require further investigation through comparative studies.

Interestingly, previous evidence showed that OA is a risk factor for the development of comorbidities, such as back pain and hypertension, that were found to precede OA in this study [3]. These findings suggest that the relationship between OA and certain chronic conditions, but not all, is likely bidirectional. Finally, the association of GERD with later OA diagnosis may be explained by the often-high use of NSAIDs in people with other MSK conditions, such as low back pain, which in turn are associated with an OA diagnosis. In addition, symptomatic but still undiagnosed OA could yield higher consumption of over-the-counter NSAIDs.

Our results can have important clinical implications. For instance, treatment strategies targeting shared risk factors and/or disease mechanisms might be beneficial for more than a single condition. For example, lifestyle interventions aimed at modifying dietary habits while promoting increased physical activity are advised for many metabolic, cardiovascular and MSK conditions and may potentially delay or prevent the onset of OA [19,20]. This is particularly important given the fact that people with OA and other pre-existing conditions report worse symptoms and more restricted social participation than individuals with OA and no comorbidities [21,22]. However, to fully appreciate this, a better understanding of the causal mechanisms by which OA may cause other conditions is needed.

This study is an exploratory study of associations, and it has several limitations that need to be acknowledged. Despite we included only persons with newly diagnosed OA, certain subjects may have had undiagnosed OA in other joints potentially being a confounder or an intermediate on the path from comorbidity to newly diagnosed OA. Nevertheless, we believe that people receiving a diagnosis of OA would often report, and be screened for, pain in other joint sites thus minimising the risk of undiagnosed OA. People with multimorbidity tend to have more frequent contacts with healthcare which in turn increases the likelihood of receiving further diagnosis which may partially explain the strong association between multimorbidity and OA in all joint sites. However, all but 130 persons (<0.01%) in our study sample had at least one physical healthcare visit to a physician with at least one diagnosis registered before the index date. Moreover, the median number of visits was 37 among the cases and 31 among the controls, suggesting that both groups were users of healthcare and thus eligible for an OA diagnosis if having the disease. Nevertheless, not all persons with a condition seek care for their symptoms or receive a diagnosis. However, the validity of codes set in in-patient care for many of the conditions included in this study (such as myocardial infarction, heart failure, stroke, RA, diabetes, inflammatory diseases and others) have been validated, with generally good results [9,23]. The group "OA in other joints" includes people that received a diagnosis of OA of the first carpometacarpal joint (M18), foot, shoulder, hand, or elbow OA (M19 subcodes), generalised OA (M15) and unspecified OA (M19.9). The majority of the codes were set in primary care settings, where only a general code M19 (without further specification) is used to diagnose OA in other joints than hip or knee and thus we were not able to study further specific peripheral joints. Moreover,

joint-specific estimates could naturally be affected by residual confounding, however, we believe that the overall pattern of associations is informative as unmeasured confounding could largely be expected to affect each OA site to a similar extent.

We did not adjust for other conditions due to unknown causal structures between them, which may have resulted in residual confounding. To adjust for obesity, smoking and alcohol consumption we used registered ICD-10 codes. This implies that there may be some misclassification, especially due to underdiagnosing. Additionally, OA is known to be a slowly progressive disease with symptoms often arising many years before a diagnosis is made in the healthcare system. Therefore, it is possible that a part of the observed associations is due to reverse causality. However, we performed a sensitivity analysis using only conditions that likely preceded true incidence of OA (diagnosed within 10–20 years preceding index date). This analysis led to similar results for most conditions, even though often the point estimates were attenuated suggesting that the problem of reverse causality may explain parts of the observed associations.

Lastly, considering the large number of analyses, the interpretation of the results should take into consideration the uncertainties of the estimates shown by the confidence intervals without relying on the dichotomization of the results.

The study has also important strengths. We have minimised the potential for selection bias using population-based registered data. All included persons had healthcare data available from 20 years preceding the diagnosis of OA, which is an exceptionally long time for assessment of diagnosed conditions and presence of OA and should minimise the risk of misclassification. We were able to adjust for individual-level data on socioeconomic variables known to affect health, such as education, income and place of birth. Thanks to the relatively large sample size, we were able to study 37 specific conditions, while 50 conditions were included in the groupings.

5. Conclusions

This study suggests that the risk of receiving a diagnosis of OA increases with the presence of multimorbidity and that the pattern of conditions linked to newly diagnosed OA is joint-specific. These results add another piece to the puzzle of OA aetiology, providing another indication that OA is a heterogeneous condition, resulting from a variety of different exposures.

Author contributions

Conception and design: AD, AT, WZ, SB-Z, JR, DP-A, SS, AK, ME. Collection and assembly of data: AT and ME. Analysis and interpretation of data: AD, AT and ME. Drafting manuscript: AD, AT. Revising manuscript and approving the final version of manuscript: AD, AT, WZ, SB-Z, JR, DP-A, SS, AK, ME. Final approval of the version to be published: AD, AT, WZ, SB-Z, JR, DP-A, SS, AK, ME. All authors take responsibility for the integrity of the data analysis.

Role of the funding sources

This work was supported by funds from the Foundation for Research in Rheumatology (FOREUM), The Swedish Research Council, Greta and Johan Kock Foundation, The Swedish Rheumatology Association, and Governmental Funding of Clinical Research within National Health Service (ALF). The funders did not have any role in the study other than to provide funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ocarto.2022.100265>.

References

- [1] D.J. Hunter, L. March, M. Chew, Osteoarthritis in 2020 and beyond: a Lancet commission, *Lancet* 396 (2020) 1711–1712.
- [2] S. Swain, A. Sarmanova, C. Coupland, M. Doherty, W. Zhang, Comorbidities in osteoarthritis: a systematic review and meta-analysis of observational studies, *Arthritis Care Res.* 72 (2020) 991–1000.
- [3] A. Dell'Isola, K. Pihl, A. Turkiewicz, V. Hughes, W. Zhang, S. Bierma-Zeinstra, et al., Risk of comorbidities following physician-diagnosed knee or hip osteoarthritis: a register-based cohort study, *Arthritis Care Res.* (2021), <https://doi.org/10.1002/acr.24717>.
- [4] S. Swain, C. Coupland, C. Mallen, C.F. Kuo, A. Sarmanova, S.M.A. Bierma-Zeinstra, et al., Temporal relationship between osteoarthritis and comorbidities: a combined case control and cohort study in the UK primary care setting, *Rheumatology* 60 (2021) 4327–4339, <https://doi.org/10.1093/rheumatology/keab067>. Oxford.
- [5] C.G. Boer, K. Hatzikotoulas, L. Southam, L. Stefánsdóttir, Y. Zhang, R. Coutinho de Almeida, et al., Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations, *Cell* 184 (2021) 4784–4818, e4717.
- [6] A. Dell'Isola, M. Steultjens, Classification of patients with knee osteoarthritis in clinical phenotypes: data from the osteoarthritis initiative, *PLoS One* 13 (2018), e0191045.
- [7] A. Dell'Isola, R. Allan, S.L. Smith, S.S. Marreiros, M. Steultjens, Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature, *BMC Musculoskel. Disord.* 17 (2016) 425.
- [8] K.-I. Goh, I.-G. Choi, Exploring the human diseaseome: the human disease network, *Briefings in Functional Genomics* 11 (2012) 533–542.
- [9] A. Turkiewicz, I.F. Petersson, J. Björk, G. Hawker, L.E. Dahlberg, L.S. Lohmander, et al., Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032, *Osteoarthritis Cartilage* 22 (2014) 1826–1832.
- [10] E.I. Benchimol, L. Smeeth, A. Guttman, K. Harron, D. Moher, I. Petersen, et al., The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement, *PLoS Med.* 12 (2015), e1001885.
- [11] J.M. Bennett, G. Reeves, G.E. Billman, J.P. Sturmberg, Inflammation-Nature's way to efficiently respond to all types of challenges: implications for understanding and managing "the epidemic" of chronic diseases, *Front. Med.* 5 (2018), 316–316.
- [12] A.W. Visser, R. de Mutsert, S. le Cessie, M. den Heijer, F.R. Rosendaal, M. Kloppenburg, et al., The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study, *Ann. Rheum. Dis.* 74 (2015) 1842–1847.
- [13] M.T. Sanchez-Santos, A. Judge, M. Gulati, T.D. Spector, D.J. Hart, J.L. Newton, et al., Association of metabolic syndrome with knee and hand osteoarthritis: a community-based study of women, *Semin. Arthritis Rheum.* 48 (2019) 791–798.
- [14] T.D. Spector, A.J. MacGregor, Risk factors for osteoarthritis: genetics, *Osteoarthritis Cartilage* 12 (Suppl) (2004) S39–S44.
- [15] R.-R. Ji, A. Nackley, Y. Huh, N. Terrando, W. Maixner, Neuroinflammation and central sensitization in chronic and widespread pain, *Anesthesiology* 129 (2018) 343–366.
- [16] M.J. Bair, R.L. Robinson, W. Katon, K. Kroenke, Depression and pain comorbidity: a literature review, *Arch. Intern. Med.* 163 (2003) 2433–2445.
- [17] E. Poulsen, G.H. Goncalves, A. Bricca, E.M. Roos, J.B. Thorlund, C.B. Juhl, Knee osteoarthritis risk is increased 4–6 fold after knee injury - a systematic review and meta-analysis, *Br. J. Sports Med.* 53 (2019) 1454–1463.
- [18] L. Kuusalo, D.T. Felson, N. Wang, C.E. Lewis, J. Torner, M.C. Nevitt, et al., Relation of Diabetes and Cardiovascular Disease with Knee Osteoarthritis, *Osteoarthritis and Cartilage*, 2020.
- [19] S.T. Skou, B.K. Pedersen, J.H. Abbott, B. Patterson, C. Barton, Physical activity and exercise therapy benefit more than just symptoms and impairments in people with hip and knee osteoarthritis, *J. Orthop. Sports Phys. Ther.* 48 (2018) 439–447.
- [20] A. Mobasheri, M. Batt, An update on the pathophysiology of osteoarthritis, *Annals of Physical and Rehabilitation Medicine* 59 (2016) 333–339.
- [21] P. Calders, A. Van Ginckel, Presence of comorbidities and prognosis of clinical symptoms in knee and/or hip osteoarthritis: a systematic review and meta-analysis, *Semin. Arthritis Rheum.* 47 (2018) 805–813.
- [22] R. Wilkie, M. Blagojevic-Bucknall, K.P. Jordan, R. Lacey, J. McBeth, Reasons why multimorbidity increases the risk of participation restriction in older adults with lower extremity osteoarthritis: a prospective cohort study in primary care, *Arthritis Care Res.* 65 (2013) 910–919.
- [23] J.F. Ludvigsson, E. Andersson, A. Ekblom, M. Feychting, J.-L. Kim, C. Reuterwall, et al., External review and validation of the Swedish national inpatient register, *BMC Publ. Health* 11 (2011), 450–450.