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ARTICLE

The impact of hip and knee osteoarthritis on the subsequent risk of incident diabetes: a population-based cohort study

Tetyana Kendzerska[1,2] · Lauren K. King[3] · Lorraine Lipscombe[3,4,5] · Ruth Croxford[5] · Ian Stanaitis[4] · Gillian A. Hawker[3,4,5]

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Abstract

Aims/hypothesis This study examined the relationship between hip/knee osteoarthritis and incident diabetes. We hypothesised that hip/knee osteoarthritis would be independently related to an increased risk of incident diabetes and that this relationship would be due, at least in part, to walking difficulty. We also hypothesised a stronger relationship with incident diabetes for knee than hip osteoarthritis because of the higher prevalence in the former of obesity/the metabolic syndrome.

Methods A population cohort aged ≥55 years recruited from 1996 to 1998 was followed through provincial health administrative data to 2014. Participants with baseline diabetes were excluded. Hip/knee osteoarthritis was defined as swelling, pain or stiffness in any joint lasting 6 weeks in the past 3 months and indication on a joint homunculus that a hip/knee was 'troublesome'. Walking limitation was defined as self-reported difficulty standing or walking in the last 3 months (yes/no). Using Cox regressions, we examined the relationship of baseline hip/knee osteoarthritis with incident diabetes as defined from health administrative data, controlling for age, sex, BMI, income, prior hypertension, cardiovascular disease and primary care exposure. We tested whether the observed effect was mediated through walking limitation.

Results In total, 16,362 participants were included: median age 68 years and 61% female. Of these, 1637 (10%) individuals met the criteria for hip osteoarthritis, 2431 (15%) for knee osteoarthritis and 3908 (24%) for walking limitation. Over a median follow-up of 13.5 years (interquartile range 7.3–17.8), 3539 individuals (22%) developed diabetes. Controlling for confounders, a significant relationship was observed between number of hip/knee joints with osteoarthritis and incident diabetes: HR for two vs no osteoarthritic hips 1.25 (95% CI 1.08, 1.44); HR for two vs no osteoarthritic knees 1.16 (95% CI 1.04, 1.29). From 37% to 46% of this relationship was explained by baseline walking limitation.

Conclusions/interpretation In a large population cohort aged ≥55 years who were free of diabetes at baseline, and controlling for confounders, the presence and burden of hip/knee osteoarthritis was a significant independent predictor of incident diabetes. This association was partially explained by walking limitation. Increased attention to osteoarthritis and osteoarthritis-related functional limitations has the potential to reduce diabetes risk.

Keywords Hip and knee osteoarthritis · Incident diabetes · Population cohort · Walking limitation

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✉ Tetyana Kendzerska
tkendzerska@toh.ca

[1] Division of Respirology, Ottawa Hospital Research Institute, University of Ottawa, Ottawa Hospital, Civic Campus, 1053 Carling Ave, Ottawa, ON K1Y 4E9, Canada

[2] Institute for Clinical Evaluative Sciences, Ottawa, ON, Canada

[3] Department of Medicine, University of Toronto, Toronto, ON, Canada

[4] Women's College Research Institute, Women's College Hospital, Toronto, ON, Canada

[5] Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

Research in context

What is already known about this subject?

- Osteoarthritis and type 2 diabetes are common chronic health conditions that frequently co-occur
- Potential explanations for the frequent coexistence of these two conditions include shared risk factors, common pathogenetic mechanisms and the effects of osteoarthritis-related functional limitation on diabetes risk factors
- Current evidence of a causal relationship between osteoarthritis and diabetes is limited

What is the key question?

- Are the presence and burden of hip and knee osteoarthritis associated with increased risk for developing diabetes and, if so, might this association be explained by reduced mobility?

What are the new findings?

- After controlling for multiple confounders, bilateral hip or knee osteoarthritis was significantly associated with a 16–25% increased risk for incident diabetes
- 37% to 46% of this relationship was explained by limitation in walking at baseline

How might this impact on clinical practice in the foreseeable future?

- Increased attention to osteoarthritis and osteoarthritis-related functional limitation has the potential to reduce diabetes risk

Abbreviations

ACR American College of Rheumatology
ADG Johns Hopkins' Aggregated Diagnosis Group
CVD Cardiovascular disease
HCN Unique health card number
ICES Institute for Clinical Evaluative Sciences
IQR Interquartile range
ODD Ontario Diabetes Database

Introduction

Osteoarthritis and type 2 diabetes are common chronic health conditions that frequently co-occur [1, 2]. In meta-analyses performed by Louati and colleagues on 1,040,175 individuals, the risk of diabetes in people with osteoarthritis compared with individuals without osteoarthritis was 40% higher (unadjusted OR 1.41 [95% CI 1.21, 1.65; $p < 0.001$]) [1].

Potential explanations for the frequent coexistence of these two conditions include shared risk factors (ageing, obesity, lack of physical activity and socioeconomic disadvantages) [3, 4], common pathogenetic mechanisms (inflammation, oxidative stress and endothelial dysfunction) [5, 6] and the effects of osteoarthritis-related functional limitations on these diabetes risk factors (e.g. sedentary behaviour exacerbates the metabolic syndrome) [7–9]. Further, knee and hip osteoarthritis may have differential relationships with diabetes development. Specifically, obesity/the metabolic syndrome have been linked more strongly with knee osteoarthritis than hip osteoarthritis, whereas genetic factors affecting bone shape have been linked more strongly with hip osteoarthritis than knee osteoarthritis [10–12]. Given the relationship of diabetes incidence to obesity/the metabolic syndrome, one might expect the relationship between incident diabetes and knee osteoarthritis to be stronger, because of common risk factors, than the relationship with hip osteoarthritis.

However, current evidence of a causal relationship between osteoarthritis and diabetes is limited. Only two studies have investigated the longitudinal relationship between osteoarthritis and diabetes [13, 14]. Rahman and colleagues used physician claims and hospital discharge abstract data to identify people with osteoarthritis and incident diabetes from 1991 to 2009 [13]. Individuals with osteoarthritis were matched with control individuals without osteoarthritis by age, sex and year of administrative records. Over a mean follow-up of 12 years, the adjusted RRs for diabetes were significantly higher in most individuals with osteoarthritis, ranging from 1.16 to 1.27 for younger men and both younger and older women. Given the risk of misclassification bias using diagnostic codes that have not been validated to identify osteoarthritis and diabetes, this finding warrants confirmation. A second study, published in abstract form only, which used self-reported diabetes as the outcome, found no association [14].

In prior qualitative research [15–17] we identified that the high prevalence of comorbidities (e.g. hypertension) in people

with osteoarthritis was a major barrier to osteoarthritis care. People with osteoarthritis tended to reduce their physical activity (i.e. moving, walking) to manage their osteoarthritis symptoms rather than use 'risky painkillers' that might exacerbate these conditions. Given that lack of physical activity is a known risk factor for diabetes and heart disease, we used existing data from a population cohort to examine the relationship between osteoarthritis and incident diabetes and to determine whether the relationship, if found, was explained by reduced mobility as measured by walking difficulty. We hypothesised that hip and knee osteoarthritis would be independently related to increased risk of incident diabetes and that this relationship would be due, at least in part, to walking difficulty. We also hypothesised a stronger relationship with incident diabetes for knee than hip osteoarthritis because of the higher prevalence in the former of obesity/the metabolic syndrome.

Methods

A population-based cohort study was conducted using linked data from a prospective community-based cohort followed from 1996 to 1998, and retrospectively collected provincial health administrative data from 1991 to 2014 (electronic supplementary material [ESM] Fig. 1).

Data sources Information on demographics, self-reported height and weight, joint complaints, functional limitations and self-reported comorbidity was collected through a standardised mail/telephone survey (72.3% response rate) of all individuals aged 55+ years who lived in two regions of Ontario, Canada—one rural and one urban—between 1996 and 1998 [18]. These baseline data were linked to provincial health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES). Probabilistic matching (AUTOMATCH 4.022, 23) using the participant's name, address, month/year of birth and sex was used to match the 28,451 survey respondents with records in Ontario's healthcare registry, the Registered Persons Database, to obtain their unique health card numbers (HCNs). An encryption of the HCN was used to link the survey data with the ICES databases of interest. Overall, 25,388 of 28,451 individuals (89%) were successfully linked to provincial health administrative data.

The ICES data repository consists of high-quality individual-record-level coded and linkable longitudinal databases (www.ices.on.ca/Data-and-Privacy/ICES-data [accessed 7 June 2018]). It encompasses most publicly funded health services for the Ontario population (about 13 million people) eligible for universal health coverage since 1986. Legislation prohibits the private delivery of services covered under the Ontario Health Insurance Plan (OHIP), including laboratory testing (www.ontario.ca/page/what-ohip-covers [accessed 7 June 2018]). These databases include information on outpatient visits, discharge summaries of emergency department visits and hospital stays and, for those 65 years and older, medical drug claims to the Ontario Drug Benefit Program. The Registered Persons Database was used to document deaths. An additional database used for this analysis, the Ontario Diabetes Database (ODD), was developed to estimate population-based incidence and prevalence of diabetes in Ontario [19, 20]. Details on databases used and variables included are available from the ICES data repository at https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx (accessed 7 June 2018). These datasets were linked using unique, encoded identifiers and analysed at ICES.

The study was conducted in accordance with the Declaration of Helsinki and guidelines for good clinical practice, and was approved by the institutional ethics review boards at Sunnybrook Health Sciences Centre and Women's College Hospital, Toronto, ON, Canada. ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. Section 45 authorises ICES to collect personal health information, without consent, for the purposes of analysis and compiling statistical information about the health system. While data-sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria (available at www.ices.on.ca/DAS [accessed 7 June 2018]) for confidential access. The full dataset creation plan is available from the authors on request.

Study participants Screening survey respondents who were unable to self-complete the screening questionnaire, who self-reported lower-limb amputation or wheelchair use, or with baseline rheumatic diseases (based on self-report or health administrative data) were excluded (ESM Fig. 2).

To define our diabetes-free cohort, we also excluded individuals with diabetes defined as: (1) physician-diagnosed diabetes based on the validated case definition from the ODD; (2) self-reported diabetes on the survey; or (3) use of diabetes medications (oral glucose-lowering agents or insulin) prescribed during a 1 year period prior to enrolment date.

Participant involvement As noted above, this study was directly informed by prior qualitative research on participants with osteoarthritis (focus groups and one-to-one interviews) by our group [15–17].

Exposures We defined symptomatic hip or knee osteoarthritis as: (1) self-reported swelling, pain or stiffness in any joint lasting ≥6 weeks in the past 3 months; and (2) indication on a joint homunculus that a hip or knee was 'troublesome'. In a random subset of cohort participants with and without osteoarthritis, as we defined it, 96% met American College of Rheumatology (ACR) criteria for hip or knee osteoarthritis

[21, 22] based on self-reported joint pain, age >50 years and findings on joint examination (sensitivity of 74% and specificity of 76%) (unpublished data, Principal Investigator: G. A. Hawker) and 66% met ACR criteria for hip or knee osteoarthritis based on joint pain and radiographs (sensitivity of 78% and specificity of 25%) [18]. Osteoarthritis burden was assessed by the number of hips or knees affected (0–2 for each of hip or knee osteoarthritis). In secondary analyses, we considered the total number of joints (knees or hips) affected by osteoarthritis as an exposure.

Outcomes The primary outcome was time from baseline to incident physician-diagnosed diabetes derived from the ODD [19]. In this database, people with diabetes were identified using a validated algorithm as those having at least one hospitalisation or at least two outpatient visits bearing a diagnosis of diabetes within a 2 year period (sensitivity of 86%, specificity of 97% and positive predictive value of 80%) [19]. For validation, diagnostic data abstracted from the primary care charts ($n = 3317$) of 57 randomly selected physicians were linked to the administrative data cohort, and sensitivity and specificity were calculated. We considered the first service date as the incident diabetes date. Participants were followed from baseline to the end of March 2014 or the occurrence of the primary outcome or all-cause death, whichever occurred first.

Risk factors and confounders Potential baseline risk factors and confounders considered were age, BMI and sex defined from clinical data, and hypertension, cardiovascular diseases (CVD) and neighbourhood income status defined from health administrative data [23, 24]. The severity of comorbidities at baseline was approximated using an aggregated score, the Johns Hopkins' Aggregated Diagnosis Group (ADG) categories (using the Johns Hopkins ACG System, Version 10; https://www.hopkinsacg.org/). Other factors considered were location (rural vs urban region) and number of outpatient visits to primary care physicians in the 2 years prior to the baseline assessment as a measure of healthcare utilisation. Baseline walking limitation was considered a potential mediator of the relationship between osteoarthritis and incident diabetes. Walking limitation was defined as self-reported difficulty standing or walking in the last 3 months (yes/no). Details of definitions are provided in ESM Table 1.

Analyses Baseline cohort characteristics were summarised overall, by presence of hip or knee osteoarthritis, and by outcome using means (SD), medians (interquartile range [IQR]) and proportions as appropriate. Unadjusted diabetes-free survival was estimated using the Kaplan–Meier method, and strata defined by the number of hips or knees affected (0–2 for each of hip or knee osteoarthritis) were compared using the logrank test.

For the primary analysis we used Cox proportional hazards regressions to assess the relationship between baseline self-reported knee or hip osteoarthritis, separately (by the number of hips or knees affected by osteoarthritis), and incident diabetes, controlling for covariates selected based on the literature review and expert opinion: age, BMI, sex, prior hypertension and CVD, income status, region and prior healthcare utilisation. Given potential differential relationships with incident diabetes, we considered hips and knees separately in our main analytic approach. The Cox proportional hazards regression assumptions for each variable were tested using traditional approaches [25]. Interactions between osteoarthritis, sex, age and BMI, specified a priori, were also evaluated. The main-effects-only models were compared with the full models that included interactions using likelihood ratio tests.

To investigate whether functional limitations explained the association between osteoarthritis and incident diabetes, we examined the effect of including walking limitation in our final models, and also separately assessed the effect of walking limitation on the risk of incident diabetes controlling for confounders. The interaction between functional limitation and affected joint (hip/knee) was tested to see if there was any evidence of a differential impact associated with the joint. To test if the observed association between hip or knee osteoarthritis and incident diabetes was mediated through walking limitation, we used the methods proposed by Lange and colleagues [26] and presented by Rochon and colleagues [27] to assess mediation in survival data. This approach is based on the counterfactual framework [28] and allows decomposition of the total effect of a given exposure A on the outcome Y into a natural direct effect ($A \rightarrow Y$) and a natural indirect effect through a mediator M ($A \rightarrow M \rightarrow Y$). In the case of a time-to-event outcome Y, a binary exposure A, a binary mediator M and a number of baseline confounders C, Lange and colleagues showed that unbiased estimates for the direct and indirect effect may be obtained from Cox regression [26]. The corresponding code written in the R statistical programming language was used, as published by Rochon and colleagues [27].

To account for the competing risk of death, we also investigated the effect of hip/knee osteoarthritis and walking limitation on incident diabetes using Fine and Gray's competing-risk regressions [29]. As we expected there to be high all-cause mortality in our population, death was considered as a competing event that might preclude individuals from being diagnosed with diabetes or alter the chances of observing it, resulting in a biased estimate of the risk of diabetes development as a standalone outcome [30].

Missing data were observed on income status (0.1%), height (18.0%) and weight (7.2%). To address missing values, we previously used two approaches: (1) considering missing baseline values as a 'missing' category; and (2) multivariate imputation by chained equations (details are presented in ESM Methods) [31, 32]. As the results were similar for both approaches [33], for uniform presentation, we used the first approach in the current study.

Analyses were conducted using R Version 3.1.2: a language and environment for statistical computing (www.r-project.org).

Results

Diabetes-free cohort Of 25,388 individuals linked to provincial health administrative data to enable assessment of healthcare use from 1991 to 2014, 16,362 participants free of diabetes at baseline were included after applying exclusion criteria (ESM Fig. 2). Participants' median baseline age was 68 years (IQR 61–75), 61% were female and median BMI was 25.3 kg/m^2 (IQR 22.9–28.0) (Table 1). 1637 (10%) individuals met criteria for hip osteoarthritis, 2431 (15%) for knee osteoarthritis, and 3908 (24%) for walking limitation. Individuals with hip or knee osteoarthritis were more likely than those without osteoarthritis to be female with higher BMI, to live in a low-income quintile neighbourhood, to be hypertensive, to have comorbidities and to report walking limitation (Table 1).

Primary analyses Over a median follow-up of 13.5 years (7.3–17.8), 3539 individuals (21.6%) experienced incident diabetes, giving an overall diabetes incidence in our cohort of 17.8 per 1000 person-years. Individuals who developed diabetes were more likely to be men living in a low-income area, to have higher BMI, to be hypertensive, and to have comorbidities and symptomatic knee and hip osteoarthritis with walking limitation (ESM Table 2).

In unadjusted analyses, individuals with knee or hip osteoarthritis were significantly more likely to develop diabetes (ESM Table 2). Diabetes-free survival at 10 years ranged from 85.9% (85.2–86.5) among individuals without knee osteoarthritis to 82.0% (79.9–84.2) in individuals with bilateral knee osteoarthritis (Fig. 1), and from 85.7% (85.1–86.3) among individuals without hip osteoarthritis to 80.8% (77.7–84.0) in individuals with bilateral hip osteoarthritis (Fig. 2). Diabetes-free survival at 15 years ranged from 75.8% (75.0–76.7) among individuals without knee osteoarthritis to 69.8% (67.1–72.5) in individuals with bilateral knee osteoarthritis (Fig. 1), and from 75.5% (74.7–76.3) among individuals without hip osteoarthritis to 68.1% (64.2–72.2) in individuals with bilateral hip osteoarthritis (Fig. 2). Compared with individuals with no hip/knee osteoarthritis, a dose–response relationship was observed between number of joints affected by knee/hip osteoarthritis and incident diabetes in the univariable model (ESM Table 2).

Controlling for baseline age, sex, income, BMI, pre-existing hypertension and CVD, region and prior primary care exposure, a significant dose–response relationship was observed between number of hip/knee joints with osteoarthritis and incident diabetes: HR for two vs no osteoarthritic hips 1.25 (95% CI 1.08, 1.44; $p < 0.01$); HR for two vs no osteoarthritic knees 1.16 (95% CI 1.04, 1.29; $p < 0.01$). Further adjustment for walking limitation resulted in attenuation of these relationships, which became non-significant (Table 2 and ESM Table 3). No significant improvement in model fit was observed between the main-effects-only models and full models with interactions. The interactions between osteoarthritis and walking limitation were not significant ($p > 0.4$ for both).

Taking into account the baseline confounders included in the full model, the overall adjusted HR of incident diabetes associated with the presence of hip or knee osteoarthritis was 1.16 (95% CI 1.07, 1.26). The proportion of individuals who reported walking limitation was 61% in individuals with hip or knee osteoarthritis and 15% in those without any hip or knee osteoarthritis (adjusted OR 8.28 [95% CI 7.56, 9.06]). The total HR of 1.16 was decomposed into a direct HR of 1.10 and an indirect HR of 1.05, which corresponds to the mediator effect. This suggests that about 37% of the effect of hip or knee osteoarthritis on incident diabetes was mediated by difficulty walking. Applying similar statistical techniques, about 37% of the effect of bilateral hip osteoarthritis and 46% of the effect of bilateral knee osteoarthritis was mediated by difficulty walking.

Secondary analyses When the number of joints (0 to 4) affected by osteoarthritis was considered as an ordinal variable, we found that risk of incident diabetes increased with each additional joint affected: HR per one joint 1.06 (95% CI 1.02, 1.09; $p < 0.01$) (Table 2).

Among 8164 individuals who died in follow-up, 6690 (81.9%) died without developing diabetes and 1474 died after developing diabetes. When analysed using a competing-risk approach, after further adjustment of the full model for walking limitation, the relationship between bilateral hip/knee osteoarthritis and diabetes remained significant (adjusted HR for bilateral hip osteoarthritis vs none, 1.21 [95% CI 1.04, 1.41]; adjusted HR for bilateral knee osteoarthritis vs none, 1.14 [95% CI 1.02, 1.28]) (ESM Table 4).

Discussion

In a large population cohort aged ≥55 years and free of diabetes at baseline, bilateral hip or knee osteoarthritis was associated with a 16–25% increased hazard of developing incident diabetes after controlling for known risk factors. A dose–response relationship was observed; individuals with a higher number of affected hips or knees experienced a higher risk for developing diabetes. From 37% to 46% of this relationship was explained by walking limitation at baseline. The effects of hip/knee osteoarthritis were consistent in a model adjusting for the competing risk of all-cause mortality. These findings provide compelling evidence to suggest that hip/knee osteoarthritis is a clinically relevant and potentially modifiable risk factor for the development of type 2 diabetes.

Table 1 Baseline cohort characteristics for the excluded individuals, cohort of interest and by presence of hip or knee osteoarthritis

Baseline covariate	Population with diabetes at baseline ($n = 2128$)	Population free of diabetes at baseline			p value
		Overall ($n = 16,362$)	Presence of OA (knee/hip)		
			Yes ($n = 3046$)	No ($n = 13,316$)	
Sociodemographic					
Age (years), median (IQR)	70 (64–76)	68 (61–75)	68 (62–75)	68 (61–75)	0.02
Sex (female), *n* (%)	1144 (54)	9978 (61)	2100 (69)	7878 (59)	<0.0001
Income, *n* (%)					
Quintile 1	440 (21)	2553 (16)	512 (17)	2041 (15)	0.01
Quintile 2	338 (16)	2347 (14)	406 (13)	1941 (15)	
Quintile 3	512 (24)	3890 (24)	681 (22)	3209 (24)	
Quintile 4	452 (21)	3765 (23)	697 (23)	3068 (23)	
Quintile 5	384 (18)	3794 (23)	749 (25)	3045 (23)	
BMI (kg/m^2), median (IQR)	27.2 (24.3–30.5)	25.3 (22.9–28.0)	26.5 (23.6–29.5)	25.1 (22.7–27.6)	<0.0001
Categories, *n* (%)					
Underweight (<18.5 kg/m^2)	25 (1)	306 (2)	36 (1)	270 (2)	<0.0001
Normal (18.5–24.9 kg/m^2)	482 (23)	5668 (35)	817 (27)	4851 (36)	
Pre-obese (25.0–29.9 kg/m^2)	665 (31)	5086 (31)	917 (30)	4169 (31)	
Obese I (30.0–34.9 kg/m^2)	339 (16)	1430 (9)	397 (13)	1033 (8)	
Obese II (35.0–39.9 kg/m^2)	96 (5)	261 (2)	101 (3)	160 (1)	
Obese III (≥40 kg/m^2)	25 (1)	85 (1)	37 (1)	48 (0)	
Missing	496 (23)	3526 (22)	741 (24)	2785 (21)	
Health conditions					
CVD, *n* (%)					
AMI	109 (5)	296 (2)	53 (2)	243 (2)	0.81
Angina	150 (7)	424 (3)	106 (4)	318 (2)	<0.001
CHF	133 (6)	276 (2)	53 (2)	223 (2)	0.86
CABG/PCI	66 (3)	204 (1)	43 (1)	161 (1)	0.41
Hypertension, *n* (%)	1273 (60)	6514 (40)	1368 (45)	5146 (39)	<0.0001
Stroke, *n* (%)	93 (4)	267 (2)	53 (2)	214 (2)	0.66
Respiratory, *n* (%)					
Asthma	129 (6)	730 (5)	180 (6)	550 (4)	<0.0001
COPD	257 (12)	1303 (8)	292 (10)	1011 (8)	<0.001
Malignancy (self-report), *n* (%)	62 (3)	321 (2)	74 (2)	247 (2)	0.05
Mental health, *n* (%)	30 (1)	127 (1)	35 (1)	92 (1)	0.01
ADG category, *n* (%)					
High	487 (23)	2438 (15)	664 (22)	1774 (13)	<0.0001
Medium	819 (38)	5600 (34)	1193 (39)	4407 (33)	
Low	822 (39)	8324 (51)	1189 (39)	7135 (54)	
Osteoarthritis (1+ joint), *n* (%)					
Knee (1+ joint)	399 (19)	2431 (15)	2431 (80)	–	
One knee	129 (6)	990 (6)	990 (33)	–	
Two knees	270 (13)	1441 (9)	1441 (47)	–	
Hip	219 (10)	1637 (10)	1637 (54)	–	
One hip	113 (5)	931 (6)	931 (31)	–	
Two hips	106 (5)	706 (4)	706 (23)	–	
Walking limitation, *n* (%)	782 (37)	3908 (24)	1849 (61)	2059 (16)	<0.0001
Being seen by primary care physician, *n* (%)	2049 (96)	14,773 (90)	2867 (94)	11,906 (89)	<0.0001
Outcome					
Diabetes *n* (%)	–	3539 (22)	772 (25)	2767 (21)	

Detailed descriptions of the covariates are provided in ESM Table 1

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; OA, osteoarthritis; PCI, percutaneous coronary intervention

The overall diabetes incidence in our cohort of 17.8 per 1000 person-years is at the upper limits of prior population estimates. Incidence rates of diabetes among individuals aged 55 years and older in Canada in 2008/09 ranged between 11.2 (55–59 years) and 17.9 (75–79 years) per 1000 individuals [34]. The diabetes incidence was significantly higher among those with hip or knee osteoarthritis (21.3 per 1000 person-years).

Our results are consistent with those of Rahman and colleagues and with proposed pathophysiological mechanisms linking osteoarthritis to diabetes [13]. However,

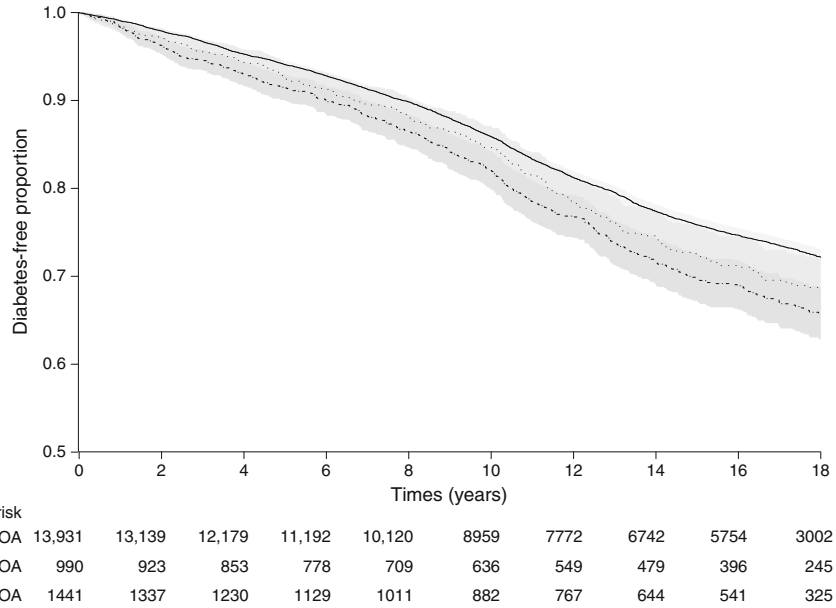

Fig. 1 Unadjusted Kaplan–Meier estimates of diabetes-free survival by the number of joints affected by knee osteoarthritis with 95% CIs: solid line, no knee osteoarthritis (NKOA); dotted line, unilateral knee osteoarthritis (UKOA); dotted–dashed line, bilateral knee osteoarthritis (BKOA). The numbers at risk are presented below the *x*-axis

contrary to our hypothesis, walking limitation explained only 37% of the effect of bilateral hip osteoarthritis and 46% of the effect of bilateral knee osteoarthritis on incident diabetes, suggesting that factors other than functional limitation play an important role. Among other factors, chronic inflammation and pain from osteoarthritis may play a significant role in diabetes development. Low-grade inflammation has been shown to be associated with insulin resistance and diabetes development [5]. Further, individuals with progressively painful osteoarthritis may restrict weight-bearing activities, including walking, to manage their symptoms, contributing to weight gain and sedentary behaviour and thus risk for diabetes.

Future prospective studies and, ultimately, clinical trials are needed to confirm the effects of symptomatic hip/knee osteoarthritis on diabetes development [35]. Clinical trials to elucidate the impact of interventions designed to reduce osteoarthritis pain and disability, such as with therapeutic exercise, biomechanical interventions [36], topical non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine and, ultimately, joint replacement surgery, on diabetes development should be considered.

Study strengths include reliance on a large population cohort, long and near complete follow-up, use of a validated case definition for our outcome using health administrative data and validated measures of self-reported hip/knee osteoarthritis and disability, careful control for known risk factors for diabetes

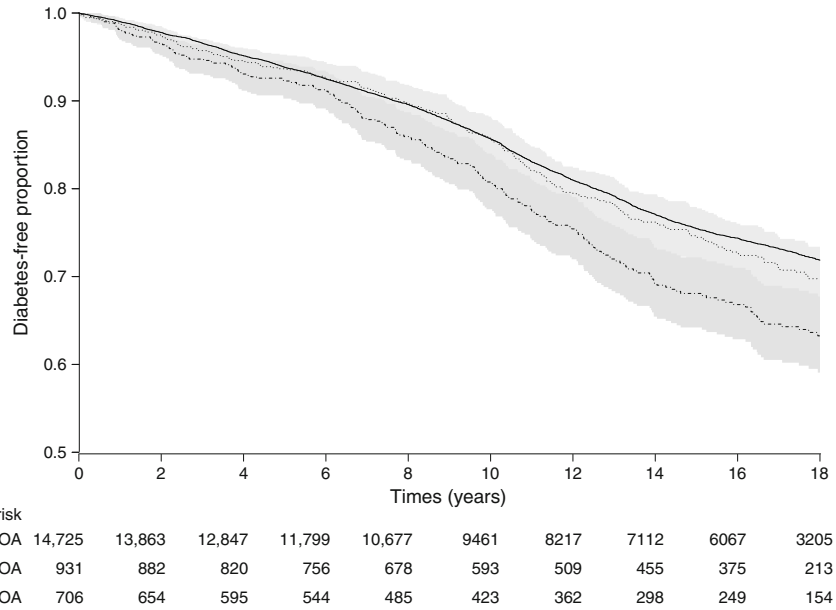

Fig. 2 Unadjusted Kaplan–Meier estimates of diabetes-free survival by the number of joints affected by hip osteoarthritis with 95% CIs: solid line, no hip osteoarthritis (NHOA); dotted line, unilateral hip osteoarthritis (UHOA); dotted–dashed line, bilateral hip osteoarthritis (BHOA). The numbers at risk are presented below the *x*-axis

Table 2 Effect of knee or hip osteoarthritis and walking limitation on incident diabetes controlling for known risk factors estimated using Cox proportional hazards regressions

Exposure	Model 1			Model 2		
	HR (95% CI)	*p* value for HR	*p* value for trend	HR (95%CI)	*p* value for HR	*p* value for trend
Knee OA						
One joint	1.08 (0.95, 1.24)	0.23	<0.01	1.03 (0.90, 1.18)	0.65	0.16
Two joints	1.16 (1.04, 1.29)	0.01	<0.01	1.09 (0.97, 1.22)	0.16	0.16
Hip OA						
One joint	1.01 (0.88, 1.17)	0.84	<0.01	0.96 (0.83, 1.11)	0.60	0.16
Two joints	1.25 (1.08, 1.44)	<0.01	<0.01	1.16 (0.99, 1.35)	0.06	0.16
No. joints affected, 0–4 (per additional joint affected)	1.06 (1.02, 1.09)	<0.01	–	1.03 (1.00, 1.07)	0.09	–
Presence of walking limitation	1.17 (1.08, 1.26)	<0.001	–	1.14 (1.04, 1.24)[a]	<0.01	–

Model 1, each exposure separately additionally adjusted for age, sex, region, income status, BMI, prior hypertension, acute myocardial infarction, angina, congestive heart failure, revascularisation procedures, stroke, exposure to healthcare (being seen by a primary care physician)

Model 2, model 1 + walking limitation

[a] Controlling additionally for knee and hip osteoarthritis

No., number of; OA, osteoarthritis

development and use of a competing-risk approach to account for the competing risk of death. Thus, we believe our findings are generalisable to the broader population of older adults living with osteoarthritis.

Some study limitations should be noted. First, as in all observational studies, there is the potential effect of unmeasured confounders (e.g. lack of information on physical activity, diet, smoking status, ethnic group or a family history of diabetes) [23, 24]. We did not adjust for changes over time in osteoarthritis symptom severity or other covariates, as we were interested in the effect of presence of hip or knee osteoarthritis at baseline on incident diabetes. The presence of walking limitation was self-reported, which may over- or underestimate an individual capacity; however, concordance between self-reported and performance-based measures of mobility is high [37]. Further, we were unable to distinguish between type 2 and type 1 diabetes using the ODD. However, given the age of our cohort we expect the vast majority of diabetes to be type 2. Although we used validated algorithms to define incident diabetes and prior comorbidities from health administrative data, these algorithms are characterised by certain specificity and sensitivity resulting in possible misclassification bias. If differential, this bias could go in either direction, while if non-differential, the estimated effect of osteoarthritis on incident diabetes is more likely to fall below the true value [38, 39]. There is also potential for misclassification bias given the sensitivity/specificity of our osteoarthritis definition [40].

In a large population cohort aged ≥55 years free of diabetes at baseline and after controlling for multiple confounders, the presence and burden of hip and knee osteoarthritis was a significant independent predictor of incident diabetes. This association was explained in part by osteoarthritis-related walking limitation. Increased attention to management of hip and knee osteoarthritis with a view to improving mobility has the potential to reduce risk of incident diabetes.

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The severity of comorbidities at baseline was approximated using an aggregated score, the Johns Hopkins' Aggregated Diagnosis Groups categories (The Johns Hopkins ACG® System, Version 10).

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Data availability While data-sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria (available at www.ices.on.ca/DAS [accessed 7 June 2018]) for confidential access. The full dataset creation plan is available from the authors on request.

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Contribution statement All authors contributed to study design and interpretation of data. TK, RC and GAH were responsible for the statistical analysis. TK and GAH drafted the manuscript. All authors critically revised the manuscript for important intellectual content, read and approved the final manuscript and approved the decision to submit for publication. TK and GAH are the guarantors and had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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