Impact of the definition of osteoarthritis and of the timing of its onset on the association between type 2 diabetes mellitus and osteoarthritis: Clinical Practice Research Datalink

Johannes T.H. Nielen [a,b], Pieter C. Dagnelie [c], Annelies Boonen [d], Olaf Klungel [a], Bart van den Bemt [e,f,g], Frank de Vries [a,g,*]

[a] Department of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
[b] Department of Epidemiology, CAPHRI School for Public Health and Primary Care, Maastricht University, Maastricht, the Netherlands
[c] Department of Epidemiology, CAPHRI School for Public Health and Primary Care, and CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, the Netherlands
[d] Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center+, Maastricht, the Netherlands
[e] Department of Pharmacy, Sint Maartenskliniek, Nijmegen, the Netherlands
[f] Department of Pharmacy, Radboud University Medical Center, Nijmegen, the Netherlands
[g] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Center+, Maastricht, the Netherlands

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ABSTRACT

Aims: In a previous case-control study in a large primary care database, the Clinical Practice Research Datalink (CPRD), type 2 diabetes mellitus (T2DM) was associated with a decreased rate of total joint replacement (TJR). As this was in contrast to the hypothesis, selection bias due to the used definition of osteoarthritis (OA) or misclassification of the onset of OA were raised as possible explanations. We therefore aimed to explore the effect of the definition of OA, and hypothesized timing of its onset on the association between T2DM and OA.

Methods: All patients using a non-insulin anti-hyperglycaemic drug (NIAD) between 1989 and 2012 in the CPRD were included and matched to unexposed patients. Cox proportional hazard models were fitted estimating the risk of TJR or OA in T2DM patients compared to patients without T2DM. These analyses were repeated in sensitivity scenarios and joint-specific analyses. To assess whether misclassification of onset of OA may affect the association, analyses were repeated with addition of a latency period of up to 10 years after start of follow-up.

Results: The use of TJR as a proxy for OA (hazard ratio (HR) = 0.74; 95% Confidence Interval (CI) = 0.70–0.78) resulted in a HR that was approximately 0.2 lower than when OA diagnostic

* Corresponding author at: Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands.
   E-mail address: f.devries@uu.nl (F. de Vries).

codes were used (HR = 0.93; 95% CI = 0.90–0.95). The joint-specific subgroup analyses, sensitivity scenarios, and latency analyses showed similar results.

Conclusion: When examining the association between T2DM and OA, the use of TJR as a proxy for OA resulted in a 20% lower estimate than the OA diagnosis.

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1.   Introduction

Osteoarthritis (OA) is the main cause of pain and disability in the United Kingdom (UK), affecting around a third of people aged 45 years and older [1]. The most commonly affected joints are the knee and the hip [1]. When this disease progresses, pain and disability may deteriorate, and in patients with severe knee and hip OA, total joint replacement (TJR) may be the only remaining treatment option providing improvement of mobility, symptom relief, and quality of life [2].

Previous studies have suggested that type 2 diabetes mellitus (T2DM) may be an independent risk factor for OA [3–6]. However, in a recent case-control study we found a 15% reduced risk of TJR in T2DM patients compared to non-T2DM patients [7]. This study was conducted using a large primary care database, the UK Clinical Practice Research Datalink (CPRD). This database has the advantage of conducting studies on risk factors of diseases quickly and with low costs. Furthermore, the CPRD has been widely used to study risk factors of a variety of outcomes such as fractures, cardiovascular events, and mortality [8,9]. However, as coding for a diagnosis of OA is not yet validated in the CPRD, epidemiological studies have used TJR surgery (as proxy of severe OA) as the outcome of interest [7,10]. To the best of our knowledge, however, it has never been explored whether TJR is a reliable proxy of OA when conducting longitudinal studies of risk or effectiveness with OA as the outcome of interest. Generally, when using a proxy indicator of the outcome, the hazard function of the association under investigation, should reflect the intended hazard function as closely as possible. However, as TJR is likely to represent a subgroup of patients with more severe OA, TJR may not reflect OA and its hazard function properly. Consequently, the unexpected results obtained in our previous study may be the result of selection bias due to the use of TJR as proxy of OA.

In our previous study, patients with T2DM, especially those with severe T2DM, were possibly less eligible for TJR surgery due to an increased risk of surgical complications. For example, the risk of infection associated with surgery is higher in T2DM patients compared to patients who do not have T2DM [11]. More specifically, high HbA1c levels have been associated with more complications following TJR [12,13], and more surgical site infections in particular [14]. On a same line, HbA1c levels have been associated with increased mortality rates in non-orthopaedic surgical procedures [15]. Based on these reports of increased risks of potential surgical complications, surgeons may be less tempted to operate on patients with T2DM. Consequently, when TJR is used as a proxy for OA, patients with OA and high risk of surgical complications (and therefore do not undergo TJR) may be misclassified as non-OA patients.

In addition, timing of the onset of OA may be important when assessing the association between T2DM and OA. As the date of OA diagnosis is suggested to reflect the actual date of onset of the disease with an average delay of 7.7 years [16], and a T2DM diagnosis shortly before an OA diagnosis (or a TJR surgery) is unlikely to have influenced the course of OA substantially, misclassification of the date of onset of OA may result in biased estimates when assessing the association between T2DM and OA.

In short, due to selection bias or misclassification of the onset of OA, by using TJR as a proxy for OA, results may be biased. If these biases are indeed present the unexpected results from our previous study may be explained and use of TJR as proxy for OA should not be used in this setting. In order to evaluate the effect of these potential biases, we aimed to explore the effect of the definition of OA as outcome measure in the CPRD, and misclassification of its onset on the association between T2DM and OA. To determine the effect of the definition of the outcome, the risk of TJR or OA in T2DM patients compared to patients without T2DM was assessed. To evaluate whether misclassification of onset of OA may affect the association, we determined the effect of addition of a latency period of up to 10 years after start of follow-up.

2.   Methods

2.1.   Data source

A population-based cohort study was performed using the CPRD. The CPRD collates the computerized medical records of general practitioners (GPs) [17,18]. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, and hospital admissions.

2.2.   Study population

In the CPRD database, all patients aged 18 years or older who received their first non-insulin anti-hyperglycaemic drug (NIAD) prescription between January 1987 and October 2012 were selected. Follow-up started at the date of the first NIAD prescription. A period of at least one year between registration in the database and the first NIAD prescription was required. Patients with a recorded diagnosis of rheumatoid arthritis (RA) or hip/femur fracture ever before start of follow-up or during follow-up were excluded. Patients with an OA diagnosis or a recorded TJR prior to start of follow-up were also excluded. For each NIAD user, one patient not using
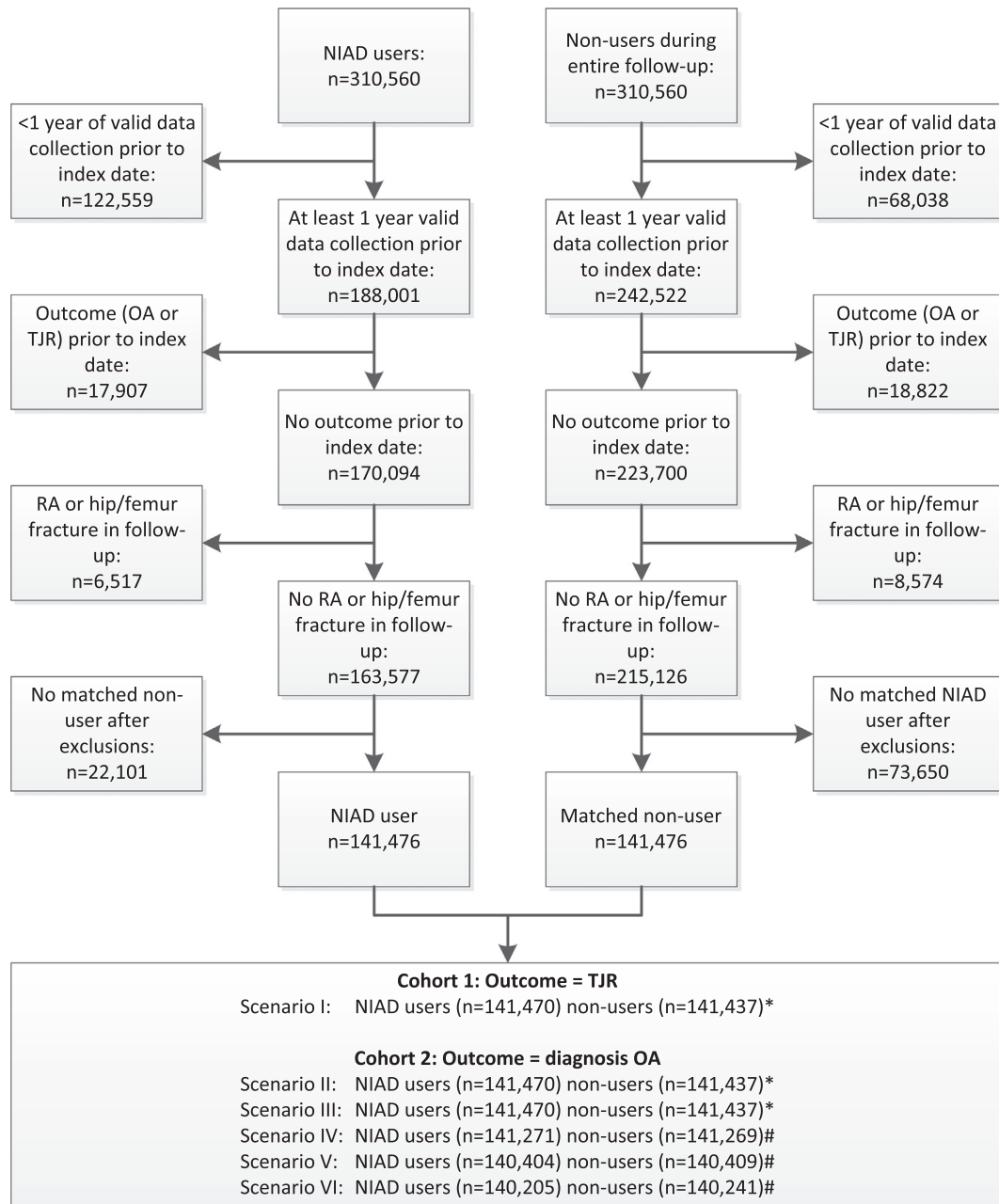
Fig. 1 – Exclusion flowchart. * Loss of patients due to lack of follow-up. # Additional loss of patients due to exclusion of specific patient types (Scenario IV: patient type 5 excluded; Scenario V: patient type 3 excluded; Scenario VI: patient type 3 and 5 excluded). NIAD = non-insulin anti-hyperglycaemic drug, TJR = total joint replacement, OA = osteoarthritis.

a NIAD during the entire follow-up was selected and matched by year of birth, sex, and GP practice. The non-users started follow-up at the same date as their matched NIAD user (Fig. 1).

2.3. Exposure

Exposure to an incident NIAD prescription was used as a proxy for T2DM. NIADs included metformin, sulfonylurea, glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, thiazolidine-diones, or acarbose.

2.4. Outcomes

For data analysis, two cohorts were created based on the out-come: TJR (total knee replacement (TKR) or total hip replace-ment (THR); Cohort 1) on one hand, or a diagnosis of any OA (Cohort 2) registered by the GP on the other hand. In both cohorts, patients were followed up to either the end of data collection, the date of the patient's transfer out of the practice area, the patient's death, or the first registration of the out-come of interest. Within these cohorts, five potential types of patients were considered (Fig. 2). Type 1 patients had an OA diagnosis followed by a TJR later during follow-up. Type
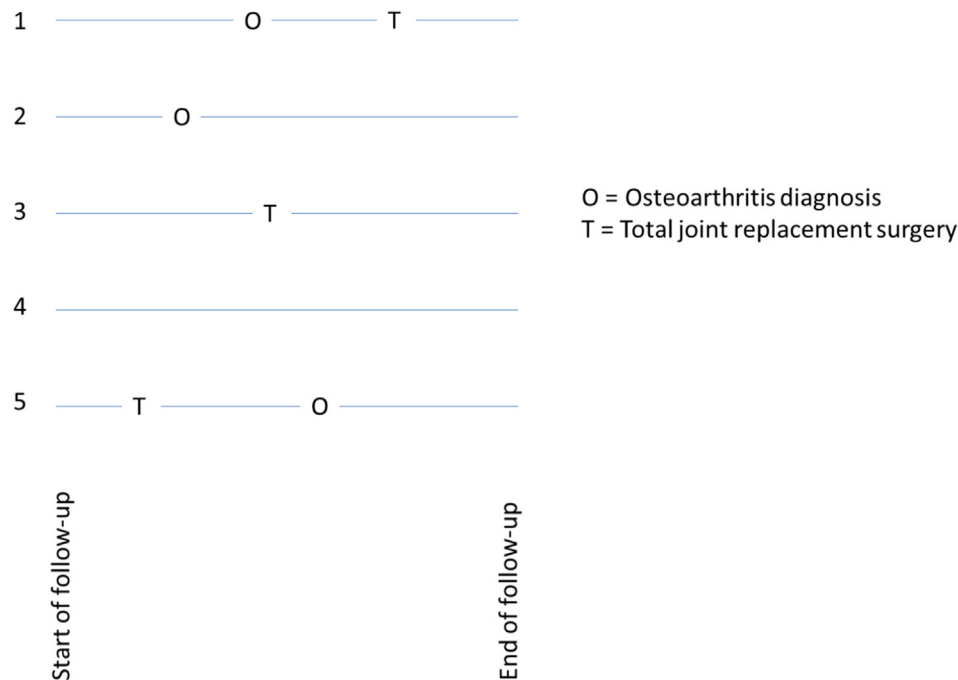
Fig. 2 – Potential patient types. Type 1 (n = 3133), Type 2 (n = 22,296), Type 3 (n = 2094), Type 4 (n = 255,062), Type 5 (n = 367).

2 patients only had an OA diagnosis during follow-up, and no TJR surgery. Type 3 patients only had a recording of TJR surgery during follow-up, and no OA diagnosis. Type 4 patients had no recordings of OA or TJR during follow-up. Type 5 patients had a recording of TJR surgery which was followed by an OA diagnosis during follow-up.

2.5. Potential confounders

Sex, age, and body mass index (BMI) at start of follow-up were considered as potential confounders.

2.6. Statistical analysis

Cox proportional hazard models were used to estimate the hazard ratios (HR) for the outcomes in patients with T2DM compared to patients without T2DM. Based on the abovementioned potential patient types (Fig. 2), six scenarios were analysed and are listed in detail in Table 1. In brief, we used the following analytical strategy: using six different scenarios, we moved stepwise from the original case-control study that used TJR surgery as the outcome [7], towards the scenario which may have had the lowest risk of bias and used an OA diagnosis as the outcome.

In scenario I, the risk of TJR was assessed while ignoring a potential record of an OA diagnosis. This analysis is comparable with a previous case-control study that was conducted within the largely same source population [7]. In this scenario, the outcome (TJR) occurred in patient types 1, 3, and 5 at some point during follow-up. In scenario II, the risk of an OA diagnosis while ignoring any potentially recorded TJR surgery was assessed. In this scenario, the outcome (OA diagnosis) occurred in patient types 1, 2, and 5 at some point during

follow-up. In scenario III, the risk of an OA diagnosis was assessed while censoring patients at the date of TJR surgery if there was only a TJR (and no recorded OA diagnosis) or when TJR surgery had preceded the OA diagnosis. In this analysis, patient types 3, and 5 were censored, and the outcome (OA diagnosis) occurred in patient types 1 and 2. In scenario IV, we used the same cohort as in scenario II, but now excluded patients with an OA diagnosis after TJR surgery (type 5 patients). Scenario V was another variation on scenario II, but now excluded all patients with TJR surgery during follow-up, who had no diagnosis of OA (type 3 patients). In scenario VI, the risk of an OA diagnosis was assessed while patients with a TJR surgery only (patient type 3), and patients with an TJR surgery prior to the OA diagnosis (patient type 5) were excluded (Table 1).

Cox proportional hazard models were also applied to determine the impact of misclassification of the date of onset of OA by adding a latency period up to 10 years after start of follow-up to scenario VI. In these models, patients with T2DM and patients without T2DM who experienced the outcome (OA diagnosis) within a specified latency period after start of follow-up were excluded from the analyses. As the date of OA diagnosis reflects the actual date of onset with an average delay of 7.7 years [16], we varied the latency period from 0 to 10 years after start of follow-up. A smoothing spline regression plot was drafted to visualise the effect of varying latency periods on the association between T2DM and OA in Scenario VI.

Subgroup analyses were conducted assessing the risk of joint-specific surgery (TKR and THR) and OA (knee OA (KOA), hip OA (HOA), or other OA) in six scenarios that were constructed in the same way as the primary analysis. Latency analyses were also conducted in these joint-specific sub-

Table 1 – Detailed information about six analytical scenarios.

Scenario	Cohort	Outcome	Description	Patient type (outcome in follow-up)				
				1 (OA diagnosis followed by TJR)	2 (OA diagnosis only)	3 (TJR only)	4 (no outcome)	5 (TJR followed by OA diagnosis)
I	1	TJR	Similar to original analysis by Nielen et al. [5]. The occurrence of an OA diagnosis any time during follow-up was ignored (patient types 1, 2, and 5)	+	−	+	−	+
II	2	OA	The occurrence of a TJR any time during follow-up was ignored (patient types 1, 3, and 5)	+	+	−	−	+
III	2	OA	Follow-up is censored at TJR if the patient only had a TJR (patient type 3) or if the TJR preceded the OA diagnosis (patient type 5)	+	+	−	−	−
IV	2	OA	Patients were excluded if the patient had a TJR that was followed by an OA diagnosis (patient type 5). If the patient only had a TJR then the TJR was ignored (patient type 3)	+	+	−	−	Excluded
V	2	OA	Patients were excluded if the patient only had a TJR (patient type 3). If a TJR was followed by an OA diagnosis, then the TJR was ignored (patient type 5)	+	+	Excluded	−	+
VI	2	OA	Patients were excluded if the patient only had a TJR (patient type3) or if the TJR preceded the OA diagnosis (patient type 5)	+	+	Excluded	−	Excluded

Excluded = in this scenario this patient type was excluded from the analyses.
+ = in this patient type the outcome does occur.
− = in this patient type the outcome does not occur.
Patient types (Supplementary Fig. 1):
Type 1: In this patient type, first an OA diagnosis was registered, followed by a TJR.
Type 2: In this patient type, only an OA diagnosis was registered.
Type 3: In this patient type, only a TJR was registered.
Type 4: In this patient type, no outcomes occur during follow-up.
Type 5: In this patient type, first a TJR was registered, followed by an OA diagnosis.
Abbreviations: TJR = total joint replacement, OA = osteoarthritis.

Table 2 – Baseline characteristics.		
Characteristic	T2DM n = 141,476 n (%)	No T2DM n = 141,476 n (%)
Age (years; mean (SD))	58.3 (14.9)	58.3 (14.9)
<40	17,857 (12.6)	17,857 (12.6)
41–65	76,165 (53.8)	76,165 (53.8)
>65	47,454 (33.5)	47,454 (33.5)
BMI (kg/m^2; mean(SD))	31.4 (6.7)	26.7 (5.0)
$\leq$20	1993 (1.4)	6961 (4.9)
21–25	18,442 (13.0)	42,895 (30.3)
26–30	45,257 (32.0)	47,098 (33.3)
>30	71,938 (50.8)	24,783 (17.5)
BMI missing	3846 (2.7)	19,739 (14.0)
Sex (female)	63,860 (45.1)	63,860 (45.1)
Any outcome after start of follow-up	14,678 (10.4)	13,212 (9.3)
TJR only after start of follow-up	1066 (0.8)	1028 (0.7)
OA only after start of follow-up	11,975 (8.5)	10,321 (7.3)
TJR and OA after start of follow-up	1637 (1.2)	1863 (1.3)
Abbreviations: T2DM = type 2 diabetes mellitus, OA = osteoarthritis, TJR = total joint replacement, SD = standard deviation.		

groups analyses. In all analyses, age, sex, and BMI adjusted estimates were calculated. SAS version 9.3 (PHREG procedure) was used for all analyses.

3. Results

Baseline characteristics of T2DM patients (n = 141,476) and patients without T2DM (n = 141,476) are presented in Table 2. On average both T2DM patients and patients without T2DM were 58.3 years of age, and 45.1% were female. T2DM patients had a mean BMI of 31.4 kg/m^2, versus 26.7 kg/m^2 for patients without T2DM. The T2DM patients were more likely to have either one of the outcomes (OA or TJR) in follow-up (10.4%), as compared to the patients without T2DM (9.3%).

The risk of TJR or OA for T2DM patients compared to patients without T2DM, determined in the various scenarios, is depicted in Table 3. The risk of TJR in scenario I (HR = 0.74 [95% Confidence Interval (CI) = 0.70–0.78]), and the risk of OA in scenario II (HR = 0.93 [95% CI = 0.90–0.95]) were both lower in T2DM patients compared to patients without T2DM. Furthermore, the HRs computed in the scenarios that censored follow-up at the date of TJR surgery (Scenario III), or excluded specific patient types with TJR surgery (Scenarios IV-VI) were largely comparable to the scenario without these restrictions (Scenario II). The results were similar in the joint-specific subgroup analyses.

The risk of any OA did not substantially change when a latency period up to 10 years after start of follow-up was added (Fig. 3). Similar results were found when a latency period was added to the joint-specific subgroup analyses (Supplementary Figs. 2-4).

4. Discussion

This study demonstrates that, when evaluating the association between T2DM and OA, the use of either a surgical or a diagnostic proxy of OA resulted in a reduced risk of the outcome. However, the risk of a TJR surgery was approximately 20% lower than the risk of an OA diagnosis for patients with T2DM. Furthermore, by excluding and censoring patients with possible registration errors in a stepwise manner, a "close to ideal" study population was evaluated. The results of these scenarios (Scenarios III–VI) were similar to the primary scenario (Scenario II). The results were also similar in the joint-specific subgroup analyses. Overall, this may suggest that the use of TJR as a proxy for OA may introduce bias when assessing the association between T2DM and OA. Adding a latency period up to 10 years after start of follow-up did not change the results, which suggests that misclassification of start of onset of OA does not play a major role.

Our findings are partially in line with those from our previous case-control study which showed a 15% reduced risk (OR = 0.85; 95% CI = 0.76–0.94) of TKR and a 12% reduced risk (OR = 0.88; 95% CI = 0.83–0.94) of THR in patients with T2DM compared to those without T2DM [7]. In the present study, the risks of TKR and THR were reduced by 23% (HR = 0.77; 95% CI = 0.72–0.84) and 30% (HR = 0.70; 95% CI = 0.65–0.76), respectively. The differences between these studies could be due to a difference in confounder adjustment. In the present study, the main objective was to determine whether there was a difference between a surgical and a diagnostic proxy of the outcome when assessing the association between T2DM and OA, rather than to assess the actual risk of T2DM on OA. Therefore, we did not include all potentially relevant confounders that were included in the previous case-control study. As a result, the current findings differ from those in our previous case-control study in a largely comparable study population.

In this study, the use of either a surgical or a diagnostic proxy for OA resulted in a reduced risk of the outcome in T2DM patients compared to subjects without T2DM. However, the HR for TJR was approximately 20% lower than the HR for the OA diagnosis. As suggested previously, this difference may have been caused by selection bias. Due to the presence of contraindicating comorbidities or risk factors, patients with T2DM may have a reduced eligibility to undergo elective joint surgery compared to patients without T2DM [15,16]. The reduced eligibility may be cause by an increased risk of infec-

	TJR – Scenario I HR (95% CI)	OA – Scenario II HR (95% CI)	OA – Scenario III HR (95% CI)	OA – Scenario IV HR (95% CI)	OA – Scenario V HR (95% CI)	OA – Scenario VI HR (95% CI)
No T2DM	ref	ref	ref	ref	ref	ref
T2DM (TJR and any type of OA)	0.74 (0.70–0.78)	0.93 (0.90–0.95)	0.93 (0.90–0.95)	0.93 (0.90–0.95)	0.92 (0.90–0.95)	0.92 (0.90–0.95)
TKR and KOA	0.77 (0.72–0.84)	0.94 (0.89–0.99)	0.94 (0.89–0.99)	0.94 (0.89–0.99)	0.93 (0.89–0.98)	0.94 (0.89–0.99)
THR and HOA	0.70 (0.65–0.76)	0.89 (0.82–0.96)	0.89 (0.83–0.97)	0.90 (0.83–0.97)	0.88 (0.82–0.96)	0.89 (0.82–0.96)
Other type of OA	n/a	0.92 (0.89–0.95)	0.92 (0.89–0.95)	0.92 (0.89–0.95)	0.91 (0.89–0.94)	0.91 (0.89–0.94)

Table 3 – Primary, and subgroup analyses assessing risk of TJR or OA in T2DM patients compared to patients without T2DM.[a]

Abbreviations: T2DM = type 2 diabetes mellitus, OA = osteoarthritis, KOA = knee osteoarthritis, HOA = hip osteoarthritis, TJR = total joint replacement, TKR = total knee replacement, THR = total hip replacement, HR = hazard ratio, CI = confidence interval. BMI = body mass index.
[a] All analyses adjusted for: age, sex and BMI.

tions associated with surgery in T2DM patients compared to patients without T2DM [11]. Previous studies have shown that high HbA1c levels are associated with more complications and more surgical site infections [12–14]. Furthermore, HbA1c levels have been associated with higher mortality rates in non-orthopaedic surgical procedures [15]. Based on these increased risks of complications, surgeons may be less tempted to operate on patients with T2DM. Consequently, some T2DM patients may not undergo TJR due to a high risk of surgical complications even though they may have OA. In contrast to TJR, this type of bias is unlikely to have affected the recording of an OA-diagnosis potentially explaining the 20% difference found in this study.

Furthermore, we found no differences in the risk of OA when a latency period up to 10 years after start of follow-up was added. In fact, the HR remained the same with a latency period varying from 0 to 10 years after start of follow-up. The results were similar for the overall and the joint-specific sub-group analyses. Although the date of OA diagnosis is estimated to reflect the actual date of onset with an average delay of 7.7 years [16], the results from this study suggest that the impact of misclassification the date of onset of OA is limited.

This study has several strengths. First, by using the world's largest primary care database representative for the British population we were able to analyse a population of over 140,000 T2DM patients and an equal number of randomly selected controls. Second, to our knowledge, this was the first study evaluating the effect of timing of the outcome by comparing different proxies, when evaluating the association between T2DM and OA. However, as with all studies there are some limitations to consider. First, a NIAD prescription was used as a proxy for T2DM. This proxy, however, does not include early stage T2DM patients as they are generally treated with lifestyle interventions, rather than pharmacological therapy. However, these early stage patients may have had deregulated glucose levels for a shorter period of time than the T2DM population using anti-hyperglycaemic drug. The bio-pathological effects suggested to be involved in the development and progression of OA may therefore be limited in this population. Consequently, the effect of not including these early stage patients is probably limited. Second, this study is based on the assumption that once treated with a single NIAD, the patient has T2DM and will continue to have T2DM during the entire follow-up. Although T2DM is suggested to be reversible in some cases [19], it is generally considered to be an enduring progressive disease, despite the use of glucose-lowering treatment [20]. Furthermore, NIADs are selectively prescribed to treat T2DM. Consequently, it is unlikely that non-T2DM patients were misclassified as T2DM patients. Finally, TJR is a generally well registered outcome, as this is a major medical event that is unlikely to go unnoticed. However, this is possibly not the case for the outcome "OA diagnosis", as the codes for an OA diagnosis in the CPRD have not yet been validated, and potentially codes for RA and OA may have been used interchangeably. Consequently, misclassification of this outcome may have occurred. This misclassification may be differential, as T2DM patients visit their GP on a regular basis, and therefore the threshold to address OA related issues may be relatively lower in these
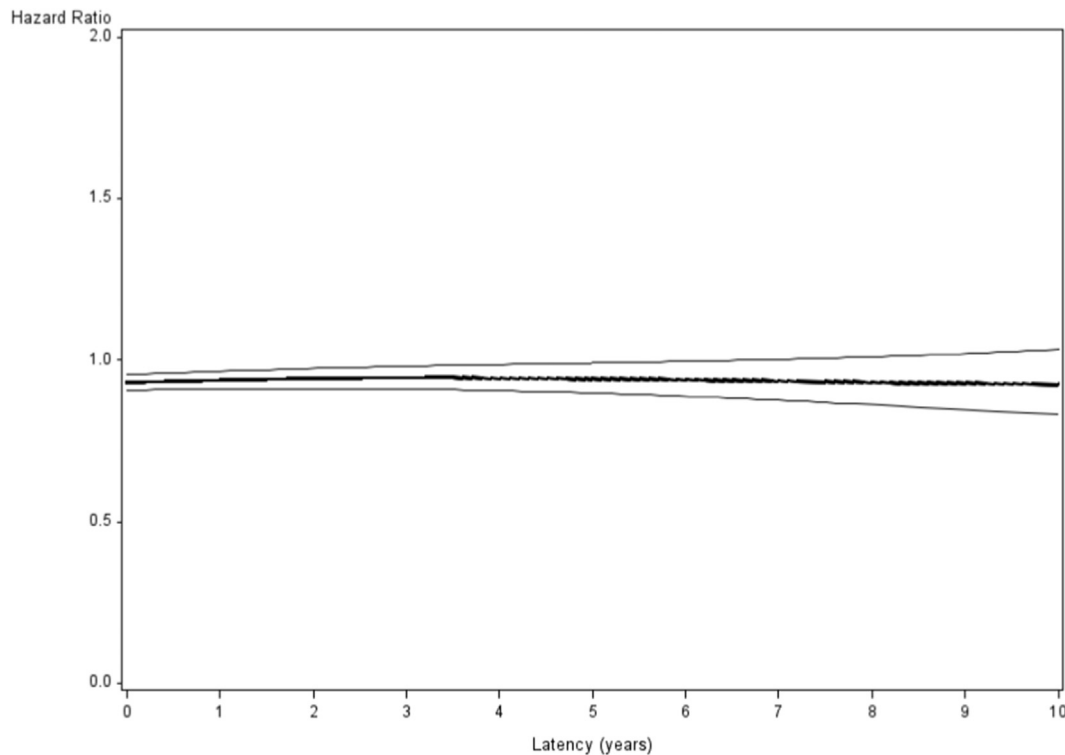
Fig. 3 – Risk (HR (bold line) and 95% CI) of OA in T2DM patients compared to patients without T2DM with varying latency period after start of follow-up. Analyses conducted in Scenario VI. Adjusted for: age, BMI, and sex. Abbreviations: T2DM = type 2 diabetes mellitus, OA = osteoarthritis, HR = hazard ratio, CI = confidence interval, BMI = body mass index.

patients compared to healthy individuals. Alternatively, GPs may be less likely to register a secondary diagnosis (i.e. OA) if they already have a primary diagnosis (i.e. T2DM). Overall, there may be counteracting possibilities for differential mis-classification and the effects on the results of this study may therefore be limited.

In conclusion, the use of either a surgical or a diagnostic proxy for OA when examining the association between T2DM and OA resulted in a reduced risk of the outcome. However, the point estimate for TJR was approximately 20% lower than the OA diagnosis. This may have been caused by selection bias as especially severe T2DM patients may not be eligible to undergo elective joint surgery. It should be emphasized that due to the methodological nature of this study, a limited number of potential confounders were included, and, consequently, the presented risk estimates should be interpreted as comparative numbers only, not as absolute risk estimates.

Conflict of interest/Acknowledgements

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.021.

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