Yannick Nielen was born in Nijmegen, the Netherlands, on the 25th of June 1988. In 2006 he graduated from secondary school at the Stedelijk Gymnasium Nijmegen. Hereafter, he moved to Groningen to study pharmacy at the University of Groningen. In the final years of his studies he did an internship at the University of Sydney, on the topic of anticholinergic drug use in elderly men. This internship stimulated him to continue working in the field of pharmacoepidemiology. In September 2013, he started his PhD project at the department of Clinical Epidemiology at Maastricht University under the supervision of prof. dr. A.E.R.C.H. Boonen, prof. dr. ir. P.C. Dagnelie, dr. F. de Vries, and dr. B.J.F. van den Bemt. During his PhD, he also started his training to become a clinical pharmacologist. As of September 2017, he is appointed as a pharmacist at the department of Clinical Pharmacy and Toxicology at the Maastricht University Medical Center+.

Osteoarthritis: diabetes mellitus, and treatment-related outcomes

Yannick Nielen

DE MAASTRICHT STUDIE

OSTEOARTHRITIS:
association with diabetes mellitus, and treatment-related outcomes

Yannick Nielen

DE MAASTRICHT STUDIE

Osteoarthritis is one of the most common chronic diseases worldwide and the prevalence of this painful disease is likely to increase in the following years. Furthermore, recent studies have suggested that diabetes mellitus might be an independent risk factor for osteoarthritis. However, the heterogeneity in the available literature suggests more research is required. Additionally, effectiveness and safety outcomes of some of the therapies used to treat osteoarthritis are unknown. Therefore, the objective of this thesis was to assess the association between diabetes mellitus and osteoarthritis of the knee and hip, and to gain insight into outcomes associated with the treatment of knee and hip osteoarthritis. Based on the studies presented in this thesis diabetes mellitus does not appear to be an independent risk factor for knee or hip osteoarthritis, but there may be, yet unidentified, specific types of osteoarthritis that are affected by diabetes mellitus independently. These types might be joint specific, or rather share a similar clinical or molecular phenotype. Furthermore, there is an increasing medical and societal need for new effective treatment strategies for osteoarthritis. With the increasing knowledge on the complex underlying pathophysiology and the associated multifactorial approach in finding disease-modifying osteoarthritic drugs, future treatment is likely to contain a broad spectrum of therapeutic options tailored to the patient-specific needs.

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Johannes Theodorus Hendrikus Nielen

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Contents

Chapter 1

Introduction

This thesis explores the association between osteoarthritis (OA) and diabetes mellitus (DM), and several outcomes associated with the treatment of OA. In this first chapter the relevant background and objectives of this thesis will be introduced. First, a general description of OA will be provided. This general description will include information on the epidemiology, pathophysiology, classification criteria, and treatment options for OA. In the following section, the current evidence of the association between DM and OA will be introduced and hypotheses and knowledge gaps regarding the link between DM and OA that are addressed in this thesis will be described. Then, uncertainties regarding effectiveness and safety outcomes associated with existing and potentially new treatment options for OA will be discussed. Again, hypotheses and knowledge gaps will be identified. Next, the data sources that are used in this thesis will be summarized and based on the knowledge gaps and hypotheses, the objectives of this thesis will be stated. Finally, the outline of this thesis will be described.

Osteoarthritis

OA is the most prevalent chronic disease in the Netherlands with an estimated 1.2 million (~70/1000 persons) diagnosed patients in 2015[1]. From a global perspective, OA is one of the most common musculoskeletal diseases[2,3,4]. An estimated 27 million people in the United States (US) were diagnosed with OA in 2005 (~90/1000 persons)[5] and in the United Kingdom (UK), approximately 8.8 million people (~145/1000 persons) have sought treatment for OA[6]. Due to the global increase of life expectancy, and the strong relationship with obesity, the prevalence of this painful and immobilizing disease is likely to increase in the next decades[2].

Traditionally, OA is considered to be a "wear and tear" disease characterized by the gradual loss of cartilage. However, in the past decades this paradigm has shifted towards a more complex disease involving degradation of the cartilage, bone remodelling, and inflammation of the synovium (synovitis)[7,8,9]. Mediators such as matrix metalloproteinases (MMP), serine proteinases, cysteine proteinases[10] and (pro-)inflammatory factors, such as interleukins (IL) IL-1 beta, IL-6, and IL-8, and tumour necrosis factor alpha (TNF-alpha)[11] are the main suspects with regard to the development and progression of OA. Recognized risk factors for OA of the hip and knee are age, sex, overweight, physical activity (occupational and leisure), and genetic features[12,13,14,15,16,17].

For clinical research, different classification criteria are used. Radiographically, OA is characterized by narrowing of the joint space, remodelling of the bone, presence of osteophytes and sclerosis of the subchondral bone. Grading methods, such as the Kellgren and Lawrence scale define OA based on these characteristics[18]. However, the clinical symptoms, such as pain and stiffness are not necessarily captured using this method. The American College of Rheumatology (ACR) has provided classification criteria in which these symptoms are included with or without radiographic or laboratory findings. The ACR has published joint-specific criteria for OA of the hip[19] and the knee[20].

The treatment of OA is mainly focussed on pain relief and optimizing functioning. It can be divided into three main strategies or combinations of these strategies: conservative, pharmacological, and surgical. Regardless of the strategy, the choice of therapy should be individualized and effectiveness may differ between joint locations. The conservative treatment options include education, exercise, weight loss (for overweight patients), and supportive devices[21,22,23]. Pharmacological therapies are mainly focussed on pain relief, as drugs with disease modifying properties are lacking. The use of paracetamol, non-steroidal anti-inflammatory drugs (NSAID), tramadol, and intra-articular corticosteroid injections are recommended[21,24]. Other substances such as hyaluronic acid, glucosamine sulphate, chondroitin sulphate are either not recommended or have been discouraged by the ACR[21]. In severe cases of OA with inadequate response to analgesic therapy, surgical therapy, including joint replacement procedures, may be considered.

The association between diabetes mellitus and osteoarthritis

The relationship between DM and OA has been the subject of research since the early 1960s[25]. As a shared risk factor, overweight has been suggested to be the main causative feature within the concept of DM-induced OA. However, recent studies and meta-analyses have suggested that DM might be an independent risk factor for OA[26,27,28,29,30]. Metabolic features of DM, such as hyperglycaemia, are suggested to trigger mechanisms involved in the association between DM and OA[31]. Pro-inflammatory cytokines[32], the glucose transporter-1 (GLUT-1)[33], advanced glycation end products (AGE)[34], peroxisome proliferator-activated receptor (PPAR) gamma[34], the polyol pathway[32], and reactive oxygen species (ROS)[32,33] are potentially part of the underlying bio-pathological mechanism of DM-induced OA (Figure 1.1).

Despite the existing evidence and plausible underlying metabolic pathways, other studies have shown no association between DM and OA[35,36,37,38]. Consequently, the heterogeneity in the currently available literature suggests more research is required.

Effectiveness and safety outcomes associated with the treatment of osteoarthritis

As previously mentioned, intra-articular glucocorticoid (GC) injections are used for the treatment of OA. Similar to oral GC, these injections may unintentionally increase the risk of hyperglycaemia and DM[39]. However, the association between parenteral GC use and hyperglycaemia and DM is unknown.

Among patients with severe OA, with inadequate response to analgesic therapy, surgical therapy, including joint replacement procedures, may be considered. The incidence and associated costs of these procedures in the Netherlands are largely unknown. Moreover, it has been suggested that nowadays joint surgery is performed at a younger age[40]. However, these procedures are not without risk. On the one hand, the risk of bleeding may increase following the total joint replacement (TJR) surgery[41]. On the other hand, the risk of venous

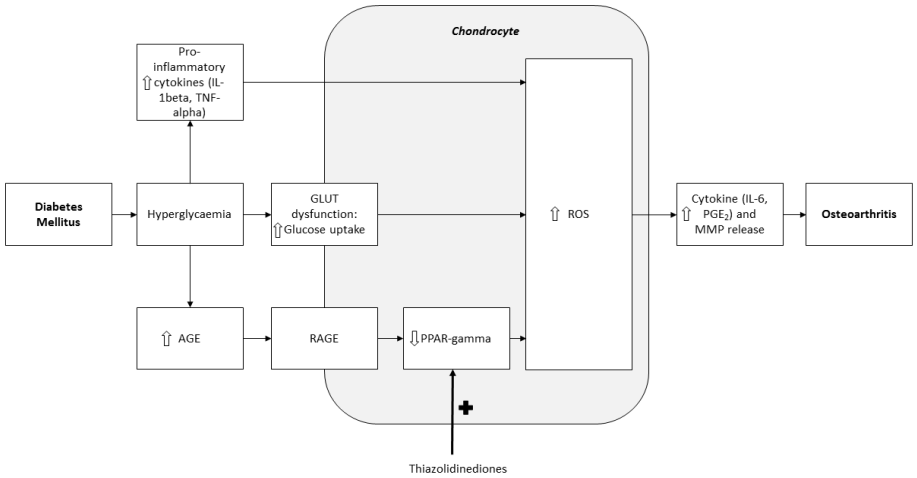

FIGURE 1.1: The proposed mechanism of diabetes-induced osteoarthritis in the chondrocyte. Adapted from Courties el al.[31]. AGE = advanced glycation end products, GLUT = glucose transporter, IL = interleukin, MMP = matrix metalloproteinase, PGE_2 = prostaglandin-E_2, PPAR = peroxisome proliferator-activated receptor, RAGE = receptor for AGE, ROS = reactive oxygen species, TNF = tumour necrosis factor

thromboembolic (VTE) events, such as deep venous thrombosis (DVT) and pulmonary embolism (PE), may increase 14-fold in the first six weeks following TJR[42]. A VTE event can be prevented by antithrombotic treatment options including aspirin, coumarins, heparins, and new (or direct) oral anticoagulants (NOAC/DOAC)[43]. However, with the recent introduction of the NOACs, there has been much discussion on the risk-benefit profiles of the antithrombotic agents following TJR. Several randomized controlled trials (RCT) that compared NOACs to low molecular weight heparins (LMWH) have been conducted, but post-marketing observational studies comparing the safety and effectiveness of the NOACs with other agents are limited.

Although there are no drugs available with proven disease modifying properties in OA, several existing drugs (e.g. doxycycline, statins, and bisphosphonates) and new chemical entities are being examined for their potential to act as disease modifying osteoarthritic drugs (DMOAD)[44,45]. For instance, in vitro and in vivo OA models have shown that PPAR-gamma can be activated by the anti-hyperglycaemic thiazolidinediones (TZD), such as rosiglitazone and pioglitazone (Figure 1.1)[34,46,47,48]. Based on these findings, PPAR-gamma activation was suggested to reduce the development and progression of OA[47,48]. However, the association between TZD use and OA has not yet been assessed in a human population.

DATA SOURCES

In this thesis three data sources will be used: the Maastricht Study, the Clinical Practice Research Datalink (CPRD), and the Achmea Health Database (AHD).

The Maastricht Study is an observational prospective population-based cohort study, initiated in 2010, assessing the aetiology, pathophysiology, complications, and comorbidities

of type 2 DM. Eligible for participation are all individuals aged between 40 and 75 years living in the southern part of the Netherlands. Participants are recruited through mass media campaigns, from the municipal registries, and the regional Diabetes Patient Registry via mailings. The Maastricht Study includes demographic information, self-reported medical history, longitudinal drug dispensing data, a variety of clinical measurements (e.g. cardiovascular, rheumatological, and laboratory tests), and imaging techniques[49]. The examinations of each participant are performed within a time window of three months. Currently, cross-sectional data from the first 3451 participants are available.

The CPRD, formerly known as the General Practice Research Database (GPRD), is world's largest primary care database with full access to qualified researchers. It contains historical data on >14 million inhabitants of the UK, and it is representative of the total UK population. All care events that general practitioners (GP) have chosen to record as part of their usual medical practice are included in the CPRD. Recorded data includes demographic information, socioeconomic status, prescription details, clinical events, specialist referrals, lifestyle parameters, and laboratory test results. Clinical information is largely coded, but GPs write additional notes and letters as free text. Data on prescriptions in secondary care and over the counter (OTC) medication use are often lacking. Furthermore, while some data (e.g. Body Mass Index (BMI), cholesterol levels, or smoking status) may be well recorded in specific groups, it could be largely missing in others[50].

The AHD, formerly known as the Agis Health Database, is a medical claims database representative of the Dutch urban population[51]. It includes demographic data (on patients, and health care professionals), reimbursement data, and information regarding health services provided by GPs, specialists, physiotherapists, and pharmacists. Drug prescription data is classified according to the Anatomical Therapeutic Chemical (ATC) coding system, and information regarding hospital care is based on the diagnosis related groups (DRG) coding system. The AHD is primarily used for administrative purposes rather than clinical or research. Therefore, detailed clinical information is lacking and follow-up may be limited due to patients switching to other health insurers[51].

Objectives

The overall objective of this thesis is to assess the association between DM and OA of the knee and hip, and to gain insight into outcomes associated with the treatment of knee and hip OA. In part one we aim to improve our knowledge about the association between DM and OA of the knee and hip. In part two we aim to evaluate effectiveness and safety outcomes associated with a broad spectrum of treatment strategies for knee and hip OA.

Outline of thesis

Part one of this thesis consist of four studies evaluating the association between DM and OA of the knee and hip. In order to assess representativeness of the population included

in the Maastricht Study, drug utilisation is compared to nationwide data in Chapter 2. Subsequently, data from the Maastricht Study are used to assess the association between knee OA and DM in Chapter 3. In Chapter 4, a case-control study assessing the association between DM and OA of the knee and hip in the CPRD is described. As multiple definitions of OA in different stages of the disease are used throughout this thesis, the impact of timing of onset of OA when assessing the association between OA and DM is appraised in Chapter 5. In part two, five studies assessing effectiveness and safety outcomes associated with broad spectrum of treatment strategies for OA are described. A case-control study on the use of parenteral glucocorticoids and the risk of type 2 DM is described in Chapter 6. In Chapter 7, the disease burden of knee OA patients with joint replacement is compared to patients without OA related joint replacement in a population-based analysis. A search strategy aiming to increase the identification of anticoagulant drug use related to TJR by using free text notes in the CPRD is described in Chapter 8. In Chapter 9, this strategy is subsequently applied to a study assessing the safety and effectiveness of post-surgery NOAC or LMWH use compared to use of aspirin. The potential protective effect of TZDs on knee and hip OA in patients with DM is evaluated in Chapter 10. This thesis concludes with a general discussion of the main findings, methodological considerations, implications, and future recommendations in Chapter 11.

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Part 1

The association between diabetes mellitus and osteoarthritis

Chapter 2

Drug utilisation in the Maastricht Study: a comparison with nationwide data

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Submitted

Abstract

Background: Within the southern region of the Netherlands, the Maastricht Study is an on-going observational prospective population-based cohort study that focuses on the aetiology of type 2 diabetes mellitus (T2DM). Representativeness of the participating population is a crucial but often an unknown factor in population-based cohort studies such as the Maastricht Study.

Objective: To assess the representativeness of the study population by comparing drug utilisation of the participants of the Maastricht Study with the general population of the Netherlands.

Methods: Since T2DM patients were oversampled in this study, a sampling method was applied in order to ensure a similar distribution of T2DM over the study populations. Drug use in the study population was compared to drug use in the population of the Netherlands, using a Z-test test to compare two independent proportions.

Results: In general, drug use in the study was similar compared to national data. However, in the age group 65-74 years total drug use was lower in the study population (833/1000 persons) versus nationwide data (882/1000 persons). The use of pulmonary medications was lower (104/1000 persons vs. 141/1000 persons) and the use of hypnotics/anxiolytics was higher (90/1000 persons vs. 36/1000 persons) in the Maastricht Study as compared to national data.

Conclusions: Drug use in the Maastricht Study is largely comparable to that in the total Dutch population. Therefore, data on drug utilisation by participants in the Maastricht Study are useful for the assessment of drug utilisation or the association of drug use with outcomes.

Introduction

In 2013 on average 677 out of 1000 inhabitants of the Netherlands received at least one drug prescription. This equals approximately 11.6 million inhabitants, which is ~70% of the national population. It has been estimated that this has led to 4.3 billion euro nationwide annual costs for drugs in 2013[1,2]. In 2011, 6.5% and 16.1% of the population aged 45-64 and 65-74 respectively have been diagnosed with type 2 diabetes mellitus (T2DM)[3].

Interestingly, in the southern region of the Netherlands (Zuid-Limburg), drug use is higher as compared to the national average. Drug utilisation in this area in 2013 is estimated to be 720 users per 1000 insured inhabitants[1]. Within this region, the Maastricht Study is an on-going observational prospective population-based cohort study including individuals aged between 40 and 75 years living in the southern region of the Netherlands. Details regarding this study have been reported elsewhere[4].

Representativeness of the participating population is a crucial but often an unknown factor in population-based cohort studies such as the Maastricht Study. In order to extrapolate findings from this type of studies to the general population it is important to assess the representativeness of the study population and to be aware of deviations. More specifically, in order to compare results of drug outcome studies in studies such as the Maastricht Study to outcome studies in the general population drug use should be similar in these populations. Therefore, the objective of this study was to assess the representativeness of drug use of the Maastricht Study by comparing drug utilisation of the participants with the general population of the Netherlands.

Methods

Data sources

Data from the Maastricht Study and the Drug Information System of the National Health Care Institute ("Genees- en hulpmiddelen Informatie Project" [GIP]) were used[2]. The Maastricht Study is an observational prospective population-based cohort study. The study focuses on the aetiology, pathophysiology, complications and comorbidities of T2DM and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of three months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Information regarding drug use was available from electronic dispensing records obtained from community pharmacies. Aggregated national data on drug use per 1000 insured inhabitants of the Netherlands were available from the Drug Information System of the National Health Care Institute (GIP).

Study population

This study was conducted in Maastricht Study participants who were included between 2011 and 2013. Participants younger than 45 and older than 74 years at the date of inclusion (index date) were excluded from the analyses, because aggregated national data were not available on drug use for these age categories. If no informed consent was given for the collection of pharmacy data, participants were excluded. Participants with a diagnosis of type 1 diabetes mellitus (T1DM) were excluded because they were clinically aberrant compared to both T2DM and other non-T2DM participants (Figure 2.1).

Two methods were applied in order to achieve a study population with 6.5% and 16.1% T2DM patients aged 45-64 and 65-74 respectively[3]. First, by randomly excluding patients with T2DM. Second, by randomly selecting non-T2DM patients with replacement in the selection pool. The age categories were selected based on the availability of national reference data.

Random exclusion

For the main analyses, T2DM patients were randomly excluded from the study population in order to achieve a distribution of T2DM representative for the general Dutch population. Consequently, the study population consisted of all participants without T2DM and a random sample of T2DM participants (Figure 2.1, left panel). Sensitivity analyses were conducted in order to take into account age distribution within the previously specified categories. In these analyses, overrepresented age categories were reduced in order to achieve a population comparable with the national age distribution.

Random selection

In additional analyses, all T2DM patients were retained and non-T2DM patients were randomly selected, with replacement in the selection pool. Non-T2DM patients may therefore have been included more than once in this population, while no data was lost by excluding T2DM patients (Figure 2.1, right panel).

Diabetes Mellitus status and drug exposure

T2DM status was determined by an oral glucose tolerance test (OGTT). Participants with a fasting plasma glucose level of ≥7.0 mmol/l (126mg/dl) or a two-hour plasma glucose level ≥11.1 mmol/l (200mg/dl) were defined as T2DM according to the World Health Organisation (WHO) guidelines. Others were defined as non-T2DM. Drug use in the year prior to index date

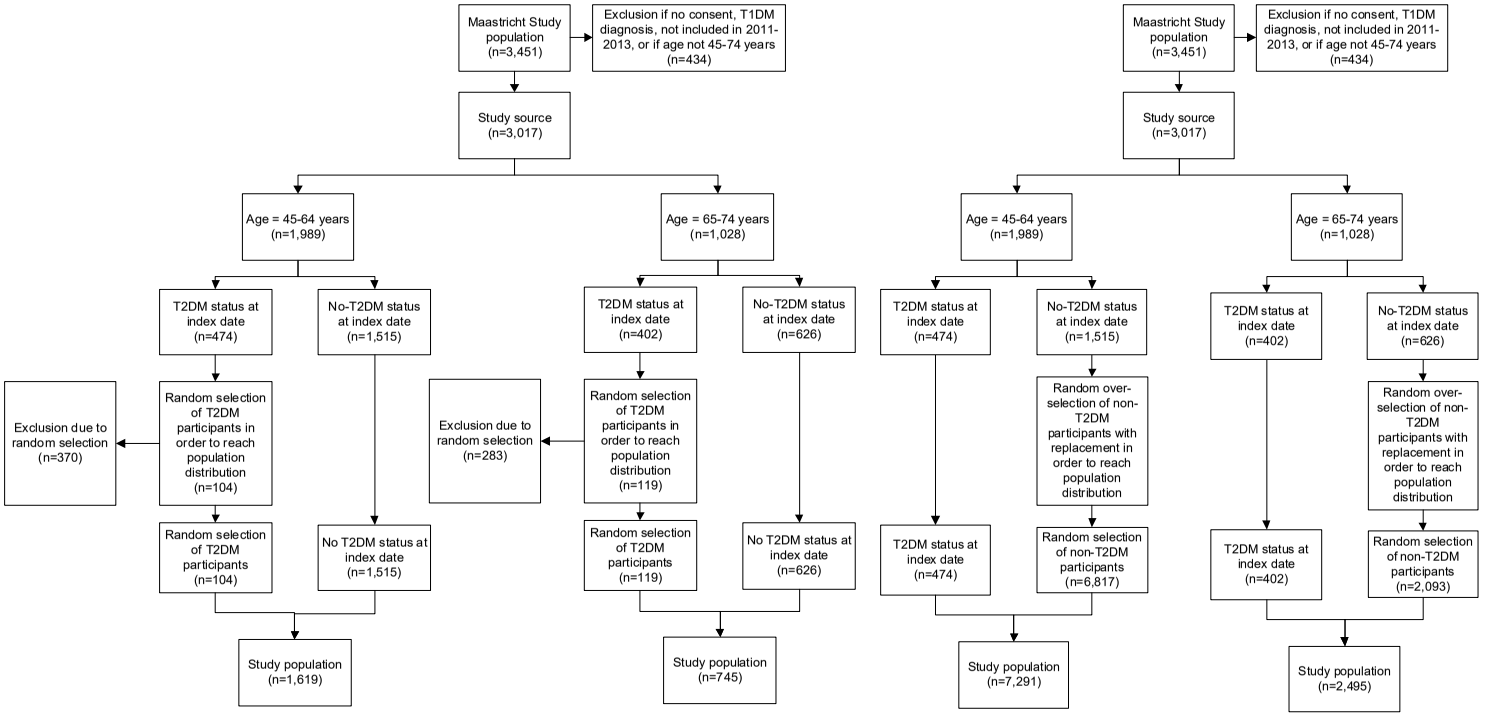

FIGURE 2.1: Two methods of selection of study population. In the left panel, the study population is obtained by random exclusion of T2DM patients. In the right panel, the study population is obtained by random selectoin of non-T2DM patients with replacement. The latter results in a study population in which a single subject is included multiple times. Abbreviatons: T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus

was determined by at least one drug dispensing according to community pharmacy data. We calculated drug use per 1000 participants of the study population. By assessing drug use in the year prior to index date, potential variability in seasonal prescription patterns was taken into account. In order to deal with regulatory or guideline changes throughout the study period, patients contributed to drug exposure in two calendar years. The proportion contributing to a specific calendar year depended on the index date. If the index date was July 1st 2012, a prescription in the year prior contributed for 50% to 2012 and for 50% to 2011. Consequently, if the index date was April 1st 2012, a prescription contributed for 25% to 2012 and for 75% to 2011 (Figure S.2.1). Drugs were classified according to the WHO's Anatomical Therapeutic (ATC) Chemical classification[5]. Drug use was categorized into the following groups (ATC codes): histamine 2(H2)-receptor antagonists and proton pump inhibitors (PPI) (A02), lipid lowering drugs (C10), anti-hyperglycaemic drugs (A10), asthma/COPD treatment (R03, R05CB), antidepressants (N06A), antipsychotics (N05A), and hypnotics/anxiolytics (N05BA, N05CD, N05CF).

Statistical analysis

We compared drug use in the study population in 2013 to nationwide drug use in the same year, using a Z-test test to compare two independent proportions. The Z-test allows an overlap of not more than 10% of the total population[6].

Results

Random exclusion

Baseline characteristics of the national and the study populations are depicted in Table 2.1. On average, when compared to the national population, the study population aged 45-64 years were older (56.5 years versus 54.6 years), while age was comparable for participants aged 65-74 years (68.5 years versus 68.9 years). More specifically, there was an underrepresentation for the age categories 45-49 years, 50-54 years and 70-74 years in the study population, and an overrepresentation among categories 55-59 years, 60-64 years and 65-69 years, when compared to the national population. Furthermore, among those aged 45-64 years, there were more females in the study population (55.8%) compared to the national population (49.8%), yet the opposite was observed for the 65-74 years category (study population: 44.0%, national: 51.1%).

Table 2.2 presents the total drug use in the study population and the national population among those aged 45-64 years of age. For the year 2013, we identified that the total drug use was comparable between the study population (687.0/1000 persons 95% [confidence interval (CI): 624.0-750.0/1000 persons]) and the national population (718.8/1000 persons). The use of hypnotics/anxiolytics was significantly higher in the study population, as compared to the national population, while use of asthma/chronic obstructive pulmonary disease (COPD) medication, H2-receptor antagonists and PPIs tended to be lower in the

Table 2.1: Baseline characteristics of the Dutch national population and the study population. A representative study population was acquired by randomly excluding a proportion of T2DM patients from the Maastricht Study population. Categorized by age and years of inclusion.

		45-64 years			65-74 years		
Characteristic	Study population 2011-2013 n=3,017 (%)	Study population randomly excluded T2DM 2011-2013 n=1,619 (%)	Study population randomly excluded T2DM 2013 n=679 (%)	National population 2013 n=4,693,909 (%)	Study population randomly excluded T2DM 2011-2013 n=745 (%)	Study population randomly excluded T2DM 2013 n=306 (%)	National population 2013 n=1,609,394 (%)
Number of females	1,449 (48.0)	904 (55.8)	391 (57.6)	2,336,655 (49.8)	328 (44.0)	147 (48.0)	822,596 (51.1)
Age (mean years, SD)	60.7 (7.3)	56.5 (5.4)	56.4 (5.4)	54.6	68.5 (2.8)	68.5 (2.7)	68.9
Age by category (years)							
45-49	263 (8.7)	228 (14.1)	100 (14.7)	1,292,024 (27.5)			
50-54	378 (12.5)	315 (19.5)	130 (19.1)	1,234,911 (26.3)			
55-59	624 (20.7)	508 (31.4)	212 (31.2)	1,115,177 (23.8)			
60-64	724 (24.0)	568 (35.1)	237 (34.9)	1,051,797 (22.4)			
65-69	655 (21.7)				497 (66.7)	201 (65.7)	941,814 (58.5)
70-74	373 (12.4)				248 (33.3)	105 (34.3)	667,580 (41.5)
Education							
Low	1,029 (34.1)	430 (26.6)	173 (25.5)	-	303 (40.7)	133 (43.5)	-
Medium	809 (26.8)	483 (29.8)	210 (30.9)	-	149 (20.0)	66 (21.6)	-
High	1,108 (36.7)	675 (41.7)	288 (42.4)	-	277 (37.2)	101 (33.0)	-
Missing	71 (2.4)	31 (1.9)	8 (1.2)	-	16 (2.1)	6 (2.0)	-
Alcohol use							
Non	542 (18.0)	261 (16.1)	122 (18.0)	-	94 (12.6)	34 (11.1)	-
Low	1,631 (54.1)	914 (56.5)	407 (59.9)	-	395 (53.0)	167 (54.6)	-
High	780 (25.9)	419 (25.9)	146 (21.5)	-	241 (32.3)	104 (34.0)	-
Missing	64 (2.1)	25 (1.5)	4 (0.6)	-	15 (2.0)	1 (0.3)	-
Smoking status							
Never	1,023 (33.9)	595 (36.8)	266 (39.2)	-	252 (33.8)	112 (36.6)	-
Former	1,557 (51.6)	785 (48.5)	327 (48.2)	-	422 (56.6)	173 (56.5)	-
Current	378 (12.5)	216 (13.3)	83 (12.2)	-	58 (7.8)	20 (6.5)	-
Missing	59 (2.0)	23 (1.4)	3 (0.4)	-	13 (1.7)	1 (0.3)	-
History of COPD	234 (7.8)	112 (6.9)	42 (6.2)	-	58 (7.8)	20 (6.5)	-
Missing	813 (26.9)	489 (30.2)	280 (41.2)	-	176 (23.6)	106 (34.6)	-
History of CVD	500 (16.6)	161 (9.9)	58 (8.5)	-	160 (21.5)	65 (21.2)	-
Missing	96 (3.2)	44 (2.7)	7 (1.0)	-	22 (3.0)	2 (0.7)	-

- Data not available. Abbreviations: COPD = chronic obstructive pulmonary disease, CVD = cardiovascular diseases, SD = standard deviation, T2DM = type 2 diabetes mellitus.

Table 2.2: Drug use per 1000 inhabitants/participants aged 45-64 years. A representative study population was acquired by randomly excluding a proportion of T2DM patients from the Maastricht Study population.

	Dutch national population	Study population		
Drug class	2013	2011 (95% CI) [a]	2012 (95% CI) [a]	2013 (95% CI)
Total	718.8	747.7 (706.3-789.1)	759.1 (730.7-787.4)	687.0 (624.0-750.0)
H2-receptor antagonists and PPIs	144.5	190.4 (153.0-227.9)	186.6 (160.8-212.4)	140.2 (93.0-187.4)
Lipid lowering drugs	146.9	229.6 (189.5-269.7)	179.2 (153.8-204.6)	170.8 (119.7-222.0)
Anti-hyperglycaemic drugs	58.6	54.9 (33.2-76.6)	45.7 (31.9-59.5)	50.3 (20.6-80.0)
Asthma/COPD treatment	97.6	84.5 (58.0-111.1)	78.8 (60.9-96.6)	58.1 (26.3-89.9)*
Antidepressants	89.5	91.1 (63.6-118.5)	76.5 (58.9-94.1)	73.1 (37.8-108.5)
Antipsychotics	21.4	12.6 (2.0-23.3)	11.7 (4.6-18.8)	10.5 (-3.4-24.3)
Hypnotics and anxiolytics	31.2	81.2 (55.2-107.3)	94.3 (75.0-113.7)	65.0 (31.5-98.5)*

[a] No data available for reference group/year, therefore not statistically tested. * Significantly different as compared to drug use in same year in the national population (p<0.05). Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, H2 = histamine 2, PPI = proton pump inhibitor, T2DM = type 2 diabetes mellitus.

Table 2.3: Drug use per 1000 inhabitants/participants aged 65-74 years. A representative study population was acquired by randomly excluding a proportion of T2DM patients from the Maastricht Study population.

	Dutch national population	Study population		
Drug class	2013	2011 (95% CI)[a]	2012 (95% CI) [a]	2013 (95% CI)
Total	881.8	840.1 (792.0-888.2)	856.4 (821.2-891.7)	833.3 (758.5-908.2)*
H2-receptor antagonists and PPIs	282.6	268.1 (209.9-326.2)	246.9 (203.5-290.2)	213.7 (131.4-296.1)*
Lipid lowering drugs	374.3	431.0 (366.0-496.0)	390.6 (341.6-439.6)	371.9 (274.8-469.0)
Anti-hyperglycaemic drugs	142.4	127.5 (83.7-171.3)	97.2 (67.4-126.9)	157.8 (84.6-231.0)
Asthma/COPD treatment	141.0	104.1 (64.0-144.2)	78.9 (51.8-105.9)	103.8 (42.5-165.0)*
Antidepressants	83.9	61.6 (30.1-93.2)	70.7 (45.0-96.5)	72.8 (20.6-125.0)
Antipsychotics	18.5	6.5 (-4.0-17.1)	6.4 (-1.6-14.5)	0.0 (0.0-0.0) *
Hypnotics and anxiolytics	36.3	115.8 (73.8-157.9)	93.4 (64.2-122.7)	90.0 (32.5-147.5)*

[a] No data available for reference group/year, therefore not statistically tested. * Significantly different as compared to drug use in same year in the national population (p<0.05). Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, H2 = histamine 2, PPI = proton pump inhibitor, T2DM = type 2 diabetes mellitus.

Table 2.4: Drug use per 1000 inhabitants/participants, adjusted for age distribution in 2013. A representative study population was acquired by randomly excluding a proportion of T2DM patients from the Maastricht Study population.

	Dutch national population		Study population	
Drug class	45-64 years	65-74 years	45-64 years (95% CI)	65-74 years (95% CI)
Total	718.8	881.8	705.6 (623.6-787.5)	865.9 (787.2-944.6)
H2-receptor antagonists and PPIs	144.5	282.6	147.6 (83.8-211.3)	230.7 (133.3-328.0)*
Lipid lowering drugs	146.9	374.3	185.7 (115.8-255.7)*	392.4 (279.6-505.2)
Anti-hyperglycaemic drugs	58.6	142.4	69.0 (23.4-114.6)	138.7 (58.8-218.5)
Asthma/COPD treatment	97.6	141.0	53.7 (13.2-94.2)*	107.8 (36.1-179.4)*
Antidepressants	89.5	83.9	81.4 (32.2-130.6)	75.0 (14.2-135.9)
Antipsychotics	21.4	18.5	2.6 (-6.6-11.8)*	0.0 (0.0-0.0) *
Hypnotics and anxiolytics	31.2	36.3	46.7 (8.8-84.7)	118.9 (44.1-193.7)*

* Significantly different as compared to drug use in same year in the national population (p<0.05). Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, H2 = histamine 2, PPI = proton pump inhibitor, T2DM = type 2 diabetes mellitus.

study population. However, only asthma/COPD medication use was significantly lower. All other medication use was similar between the two groups.

In the study population aged 65-74 years (Table 2.3) total drug use (833.3/1000 persons [95% CI: 758.5-908.2/1000 persons]) was significantly lower compared to the national population (881.8/1000 persons). Similar to the 45-64 age group, the use of hypnotics/anxiolytics was significantly higher, while the use of asthma/COPD medication, H2-receptor antagonists, and PPIs was lower in the study population. Notably, there was no use of antipsychotic drugs in the study population aged 65-74.

Sensitivity analyses accounting for age distribution within the pre-specified age categories revealed similar results to our primary analysis (Table 2.4). In contrast to the primary analysis, among those aged 45-64 years, the use of lipid lowering medications was significantly higher, while the use of antipsychotics was significantly lower in the study population, as compared to the national population. In the analyses of the population aged 65-74 years, trends by specific drug remained consistent with our primary analysis; however, the total drug use was no longer significantly lower in the study population (865.9 [95% CI: 787.16-944.63/1000 persons]) when compared to the national population (881.8/1000 persons).

Random selection

The study population consisting of all participants with T2DM, and a selection with replacement of participants without T2DM (Table S.2.1), showed similar baseline characteristics to the primary analysis (Table 2.1, i.e. study population of all participants without T2DM and a random exclusion of T2DM patients). In the population aged 45-64 years, the total drug use in the study population aged 45-64 years was comparable with drug use in the national population (Table S.2.2). Among the study population, the use of lipid lowering drugs (182.5/1000 persons [95% CI: 152.8-212.1/1000 persons]) and hypnotics/anxiolytics (67.9 95% CI: 48.6-87.1/1000) was significantly higher than among the national population (146.9/1000 persons and 31.2/1000 persons, respectively), while asthma/COPD medication use was significantly lower (61.5/1000 persons [95% CI: 43.1-80/1000 persons] in the study population versus 97.6/1000 persons in the national population).

In the study population aged 65-74 years, total drug use was significantly lower (846.5/1000 persons [95% CI: 798.8-894.2/1000 persons]), when compared to the national population (881.8/1000 persons) (Table S.2.3). Only the use of anti-depressants was comparable between the study population and the national population, while all other drugs showed significant differences. In particular, the study population showed higher use of anti-hyperglycaemic, lipid lowering, and hypnotics/anxiolytics medications, yet had lower use of asthma/COPD medication, H2-receptor antagonists and PPIs.

Discussion

Random exclusion

We identified that drug use in the study population was similar to national data. However, differences in drug use were present in some drug classes and across age groups. In all groups, our results suggest that the use of anti-hyperglycaemic drugs and lipid lowering drugs was similar, while there are significant differences for the use of pulmonary medications and the use of hypnotics/anxiolytics between the study population and the national population.

The use of anti-hyperglycaemic and lipid lowering drugs was similar between the study population and the national population. This is reassuring as we randomly sampled the Maastricht Study population in order to create a study population with 6.5% and 16.1% T2DM patients aged 45-64 and 65-74, respectively. Furthermore, lipid lowering drugs are commonly prescribed to patients with T2DM[7,8]. Therefore, similar use of this co-prescribed drug class is to be expected.

In order to evaluate differences and similarities in drug use between a population-based study, such as the Maastricht Study, and the general population it is important to consider potential determinants for (non-)participation. Several factors that may be involved include the distance to research facility[9], medical history[10,11], age[11,12,13], sex[12,14], ethnicity[9,13], and education or income[9,10,15].

Previous studies have identified an underrepresentation of age extremes in studies that depend on active recruitment. It has been suggested that the time required to participate may be problematic for those at working age or those of advanced age[11,12,13]. In our study we identified an underrepresentation of participants in the oldest age category (70-74 years). Since older patients are more likely to use a higher number of drugs, this may have caused the lower total drug use identified among the participants aged 65-74 years[16].

Differential participation rates of patients with, and without, an extended medical history have been reported previously[10,11]. It is generally thought that an increased presence of comorbidities is associated with a decline in functional status, which may reduce participation rates[11]. Participation may be especially be problematic for patients with pulmonary morbidities. This is consistent with the results in this study.

The increased rates of hypnotic/anxiolytic drug use may be caused by a regional effect and by differences in health perception. The use of these drugs is estimated at 27.6/1000 inhabitants in the Zuid-Limburg area compared to 23.4/1000 persons in the national population[1]. However, this does not fully explain the more than doubled rates found in this study. It may, however, be associated with the assumption that a generally healthier, but care seeking population is more likely to participate in a study, such as the Maastricht Study[15]. Individuals from this population are concerned about their health and may therefore visit their general practitioner for unexplained complaints.

Sensitivity analyses that accounted for age distribution showed only minor differences

with the primary analyses. In the population aged 45-64 this procedure mainly resulted in the exclusion of a proportion of participants between 55-64 years. It was expected this would result in a reduction of drug utilisation compared to the primary analyses. Surprisingly the opposite was true. This may be explained by the fact that by reducing the proportion of participants, while retaining a population with 6.5% T2DM, predominantly healthier participants were excluded. This effect was less pronounced in the population aged 65-74 years. This is possibly due to smaller differences in drug utilisation between participants aged 65-69 and participants aged 70-74 years.

Random selection

In comparison with the random exclusion population, analyses using the randomly selected population resulted in more significant differences between the study population and the national population, especially in the population aged 65-74 years. This is most likely due to a larger sample size, consequently leading to smaller confidence intervals. However, this method may be less valid. By randomly selecting participants with replacement in the selection pool the study population will have less variation than expected when the same sample size is achieved by including new subjects in the study.

Strengths and limitations

The major strength of this study was the availability of detailed prescription data of the Maastricht Study participants, not only on the index date but also up to several years prior to index date. This enabled us to take drug prescriptions that were no longer active at index date into account.

A limitation of this study was the restricted availability of regional drug use data. Drug use in the Zuid-Limburg area is generally higher than the national drug utilisation[1]. However, in this study we identified drug use that is largely comparable to national rates. Consequently, there appeared to be an overall participation bias towards a relatively healthy or health-conscious study population. As described previously, this is a known phenomenon in studies such as the Maastricht Study[10,11]. The relatively low drug utilisation may also be explained by misclassification of participants with T2DM. In this study, they were classified based on an OGTT. However, T2DM is known to be undetected and untreated in a considerable proportion of the population. We may have therefore categorized participants as T2DM patients, while this may have been unknown to their general practitioner. Consequently, these patients did not receive pharmacological treatment as would have been expected for a T2DM patient. Arguably they should therefore have been classified as non-T2DM. However, in the population aged 45-64 approximately 0.4-1.0% was newly diagnosed based on the OGTT, and in the population aged 65-74 this was the case for 1.3-1.7%. We therefore expect this misclassification would not have affected the results. Due to limited availability of national drug use data we were only able to compare drug use in 2013. However, we

expect that results would have been comparable in other years, since recruitment methods were similar across the years. Furthermore, we were unable to compare other drug classes, such as drugs used for cardiovascular diseases. This would have been interesting, but not essential for the objective of this study. The statistical procedure used to compare the study populations may also have its limitations. The Z-test is partly affected by the absolute difference between the populations. Therefore, in the case of small numbers a 100% difference may result in a non-significant difference, whereas a 10% difference may trigger a significant difference in the case of higher numbers.

Conclusion

Drug use in the Maastricht Study appeared to be largely representative for drug use in the national population. However, due to the restricted availability of regional drug use data we were unable to assess representativeness compared to the Zuid-Limburg population. Since drug use in the Zuid-Limburg area is generally higher than the national drug utilisation, it is expected that there was an overall participation bias towards a relatively healthy or health-conscious study population. Nonetheless, data from this study could be used to assess drug utilisation or to determine the relative risk of specific outcomes associated with drug use. However, care should be taken when examining outcomes associated with the use of pulmonary drugs since functional impairment may have biased participation. In general, when conducting drug use studies using a cohort study, such as the Maastricht Study, it is important to assess representativeness of drug use and to be aware of deviating drug classes.

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TABLE S.2.1: Baseline characteristics of the Dutch national population and the study population. A representative study population was acquired by randomly selecting participants without T2DM, with replacement in the selection pool, from the Maastricht Study population. Categorized by age and year of inclusion.

		45-64 years			65-74 years		
Characteristic	Study population 2011-2013 n= 3,017 (%)	Study population randomly selected 2011-2013 n=7,291 (%)	Study population randomly selected 2013 n=2,707 (%)	National population 2013 n=4,693,909 (%)	Study population randomly selected 2011-2013 n=2,495 (%)	Study population randomly selected 2013 n=950 (%)	National population 2013 n=1,609,394 (%)
Number of females	1,449 (48.0)	4,098 (56.2)	1,566 (57.9)	2,336,655 (49.8)	1,070 (42.9)	457 (48.1)	822,596 (51.1)
Age (mean years, SD)	60.7 (7.3)	56.7 (5.4)	56.3 (5.4)	54.6	68.7 (2.8)	68.5 (2.7)	68.9
Age by category (years)							
45-49 years	263 (8.7)	1,028 (14.1)	425 (15.7)	1,292,024 (27.5)			
50-54 years	378 (12.5)	1,448 (19.9)	513 (19.0)	1,234,911 (26.3)			
55-59 years	624 (20.7)	2,252 (30.9)	867 (32.0)	1,115,177 (23.8)			
60-64 years	724 (24.0)	2,563 (35.2)	902 (33.3)	1,051,797 (22.4)			
65-69 years	655 (21.7)				1,662 (66.6)	623 (65.6)	941,814 (58.5)
70-74 years	373 (12.4)				833 (33.4)	327 (34.4)	667,580 (41.5)
Education							
Low	1,029 (34.1)	1,929 (26.5)	669 (24.8)	-	993 (39.8)	424 (44.6)	-
Medium	809 (26.8)	2,182 (29.9)	839 (31.1)	-	503 (20.2)	201 (21.2)	-
High	1,108 (36.7)	3,021 (41.4)	1,165 (43.1)	-	951 (38.1)	310 (32.6)	-
Missing	71 (2.4)	159 (2.2)	34 (1.3)	-	48 (1.9)	15 (1.6)	-
Alcohol use				-			-
Non	542 (18.0)	1,188 (16.3)	468 (17.3)	-	320 (12.8)	104 (10.9)	-
Low	1,631 (54.1)	4,088 (56.1)	1,676 (62.0)	-	1,364 (54.7)	540 (56.8)	-
High	780 (25.9)	1,888 (25.9)	563 (20.8)	-	765 (30.7)	303 (31.9)	-
Missing	64 (2.1)	127 (1.7)	11 (0.4)	-	46 (1.8)	3 (0.3)	-
Smoking status				-			-
Never	1,023 (33.9)	2,655 (36.4)	1,035 (38.3)	-	814 (32.6)	342 (36.0)	-
Former	1,557 (51.6)	3,519 (48.3)	1,302 (48.2)	-	1,441 (57.8)	544 (57.3)	-
Current	378 (12.5)	996 (13.7)	362 (13.4)	-	201 (8.1)	61 (6.4)	-
Missing	59 (2.0)	121 (1.7)	8 (0.3)	-	39 (1.6)	3 (0.3)	-
History of COPD	234 (7.8)	498 (6.8)	166 (6.1)	-	224 (9.0)	72 (7.6)	-
Missing	813 (26.9)	2,166 (29.7)	1,077 (39.9)	-	570 (22.8)	323 (34.0)	-
History of CVD	500 (16.6)	762 (10.5)	245 (9.1)	-	549 (22.0)	191 (20.1)	-
Missing	96 (3.2)	202 (2.8)	27 (1.0)	-	77 (3.1)	7 (0.7)	-

- Data not available. Abbreviations: COPD = chronic obstructive pulmonary disease, CVD = cardiovascular diseases, SD = standard deviation, T2DM = type 2 diabetes mellitus.

Table S.2.2: Drug use per 1000 inhabitants/participants aged 45-64 years. A representative study population was acquired by randomly selecting participants without T2DM, with replacement in the selection pool, from the Maastricht Study population.

Drug class	Dutch national population	Study population		
	2013	2011 (95% CI) [a]	2012 (95% CI) [a]	2013 (95% CI)
Total	718.8	755.0 (734.2-775.8)	760.7 (745.7-775.7)	699.0 (663.8-734.2)
H2-receptor antagonists and PPIs	144.5	184.3 (165.5-203.0)	189.4 (175.6-203.1)	147.2 (120.0-174.3)
Lipid lowering drugs	146.9	246.5 (225.7-267.4)	190.7 (176.9-204.5)	182.5 (152.8-212.1)*
Anti-hyperglycaemic drugs	58.6	64.7 (52.8-76.6)	53.9 (46.0-61.9)	68.7 (49.3-88.1)
Asthma/COPD treatment	97.6	95.3 (81.1-109.5)	74.6 (65.4-83.8)	61.5 (43.1-80.0)*
Antidepressants	89.5	97.7 (83.3-112.0)	78.7 (69.2-88.1)	77.0 (56.6-97.5)
Antipsychotics	21.4	14.0 (8.3-19.7)	10.0 (6.5-13.5)	7.7 (1.0-14.4)*
Hypnotics and anxiolytics	31.2	71.6 (59.2-84.1)	91.2 (81.1-101.4)	67.9 (48.6-87.1)*

[a] No data available for reference group/year, therefore not statistically tested. * Significantly different as compared to drug use in same year in the national population (p<0.05). Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, H2 = histamine 2, PPI = proton pump inhibitor, T2DM = type 2 diabetes mellitus.

Table S.2.3: Drug use per 1000 inhabitants/participants aged 65-74 years. A representative study population was acquired by randomly selecting participants without T2DM, with replacement in the selection pool, from the Maastricht Study population.

Drug class	Dutch national population	Study population		
	2013	2011 (95% CI) [a]	2012 (95% CI) [a]	2013 (95% CI)
Total	881.8	834.5 (804.6-864.4)	846.0 (823.0-869.0)	846.5 (798.8-894.2)*
H2-receptor antagonists and PPIs	282.6	274.0 (238.1-309.9)	233.6 (206.6-260.6)	216.0 (161.5-270.4)*
Lipid lowering drugs	374.3	445.4 (405.4-485.4)	409.9 (378.5-441.3)	423.7 (358.3-489.1)*
Anti-hyperglycaemic drugs	142.4	171.9 (141.5-202.2)	144.3 (121.9-166.7)	223.5 (168.3-278.6)*
Asthma/COPD treatment	141.0	123.1 (96.7-149.5)	75.4 (58.6-92.3)	104.7 (64.2-145.3)*
Antidepressants	83.9	47.6 (30.4-64.7)	70.6 (54.3-87.0)	64.3 (31.8-96.8)
Antipsychotics	18.5	4.0 (-1.1-9.2)	4.8 (0.4-9.2)	0.0 (0.0-0.0) *
Hypnotics and anxiolytics	36.3	104.2 (79.7-128.8)	98.4 (79.4-117.4)	90.1 (52.2-128.1)*

[a] No data available for reference group/year, therefore not statistically tested. * Significantly different as compared to drug use in same year in the national population (p<0.05). Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, H2 = histamine 2, PPI = proton pump inhibitor, T2DM = type 2 diabetes mellitus.

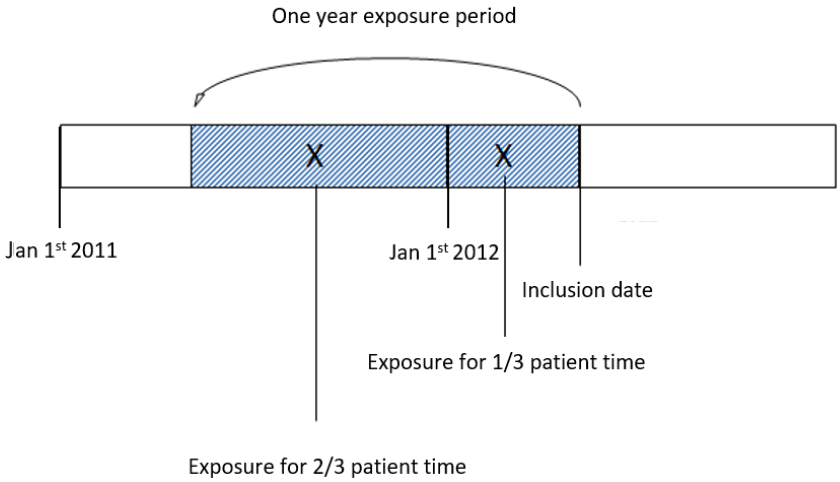

FIGURE S2.1: Exposure definition (X=dispensing)

Chapter 3

Association of type 2 diabetes mellitus with self-reported knee pain, and clinical knee osteoarthritis

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Submitted

Abstract

Background: Osteoarthritis (OA) is a disabling joint disease with a heterogeneous disease expression. Type 2 diabetes mellitus (T2DM) is suggested to be independently associated with knee OA. However, studies evaluating this association show inconsistent results and no data exist on whether the level of experienced pain differs among patients with or without T2DM.

Objective: To assess the association of T2DM with non-traumatic knee pain and knee OA, and to understand whether patients with and without T2DM express different levels of pain.

Methods: Participants of the Maastricht Study aged between 40 and 75 years, with complete data on all variables, were included. Logistic regression models were fitted to assess the association of T2DM with knee pain and clinical knee OA. A linear regression model was used to assess the difference in the level of pain between knee OA patients with and without T2DM.

Results: T2DM was associated with knee pain (OR=1.29 [95% CI=1.04-1.60]), and knee OA (OR=1.81 [95% CI: 1.42-2.30]), but associations were no longer statistically significant after adjustment for BMI (knee pain: OR=0.97 [95% CI=0.76-1.22]; knee OA: (OR=1.22 [95% CI=0.94-1.60]). Furthermore, among subjects with knee OA, there was no difference in the severity of knee pain between patients with or without T2DM.

Conclusion: T2DM does not seem to be independently associated with knee pain and knee OA. In view of the prominent role of BMI in this association and the clinical burden of OA, weight control should be further emphasized in the management of T2DM.

Introduction

Osteoarthritis (OA) of the knee is a progressive disabling joint disease, characterised by pain and functional limitations. Overall, OA is 13th on the list of causes of global years lived with a disease[1]. More specifically, the global age-standardised prevalence of knee OA in 2010 was estimated to be 3.8%, and was higher in females (4.8%) than in males (2.8%). There was no change in age-standardised prevalence between 1990 and 2010. However, disability-adjusted life years (DALYs) increased from 0.42% of total DALYs in 1990 to 0.69% of total DALYs in 2010[2]. One of the main challenges when trying to improve the management of patients with OA, is the large heterogeneity of the disease.

Several epidemiological studies have identified a strong association between type 2 diabetes mellitus (T2DM) and knee OA[3,4,5,6]. As both diseases share overweight and obesity as strong common risk factors, one of the main underlying mechanisms causing OA in T2DM patients is considered to be an increased mechanical load on the weight-bearing joints, especially the knee. However, the abovementioned studies have shown that T2DM may be an independent risk factor for OA, suggesting a co-existing metabolic causality[3,4,5,6]. Conversely, other studies have reported no independent association between T2DM and OA[7,8,9,10,11]. One of the challenges when interpreting the epidemiological literature regarding this topic can be found in different definitions used to identify OA cases and in heterogeneity in the severity of T2DM. To date, these aspects have been examined insufficiently.

From a bio-pathological point of view, there is an increasing body of evidence suggesting that hyperglycaemia and advanced glycation end products (AGEs) play an important role in the progression of OA[12,13,14]. First, an in vitro study using chondrocytes, isolated from human cartilage, concluded that OA chondrocytes exposed to high levels of glucose were unable to down-regulate glucose transporter-1 (GLUT-1). The inability to down-regulate GLUT-1 resulted in the intracellular accumulation of glucose and an increased production of reactive oxygen species (ROS), known for their deleterious effects in various celtypes[12]. Second, hyperglycaemic conditions stimulate formation of AGEs and subsequent accumulation and crosslinking of these products has been found to increase stiffness of the collagen network in articular cartilage[13,14]. Hyperglycaemia and AGEs may therefore be part of the mechanism promoting degenerative changes in the cartilage, possibly facilitating the onset as well as progression of OA. Particularly poorly controlled T2DM patients may be subjected to hyperglycaemic conditions regularly. It is therefore expected that these patients in particular are more likely to develop, or have a more severe course of OA.

Furthermore, underlying mechanisms of pain in knee OA are poorly understood. Currently, formation of neurovascular channels in the subchondral bone and the articular cartilage as mechanism of repair of subchondral cracks in early OA has been advocated as an important mechanism[15]. Additionally, the role of low grade inflammation in the synovium has been brought forward[16]. Perception of pain in patients with T2DM might be different, partly because of a different underlying bio-pathology, partly related to

diabetic neuropathy. Therefore, it is valuable to understand whether the level of knee pain experienced by patients with T2DM may be different compared to those without T2DM.

A better understanding of the association between T2DM and knee OA, may contribute to unravelling the different OA phenotypes. Moreover, findings might be influential for the management of T2DM. As we know that the presence of a musculoskeletal disorder amplifies the impact of diabetes on physical health[17], more evidence about which aspects of the multifaceted prevention or management of OA matter most in patients with T2DM may help to improve functional outcome of patients.

The primary aim of this study was to evaluate the association of T2DM with non-traumatic knee pain and knee OA. Secondly, we aimed to better understand whether patients with T2DM express different levels of pain compared to patients without T2DM.

Methods

Data sources

The Maastricht Study is an observational prospective population-based cohort study. The study focuses on the aetiology, pathophysiology, complications and comorbidities of T2DM and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. The present report includes cross-sectional data from the first 3,451 participants who completed the baseline survey between November 2010 and September 2013. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent[18]. Information regarding drug use was available from electronic dispensing records obtained from community pharmacies. Pharmacy data contained information, such as dose (e.g. 5 mg), frequency (e.g. once daily), and dispensed quantities (e.g. 30 tablets) on all drugs that were prescribed to an individual patient. Since this data is used for both medical record keeping and reimbursement purposes, it is expected to be highly accurate. We excluded participants who did not give consent for the collection of pharmacy data (n=163), had type 1 diabetes mellitus (T1DM; n=43), or had missing data for the outcome or any of the covariates (n=507) (remaining: n=2,738; Figure 3.1).

Exposure

Glucose metabolism status was defined according to the World Health Organization's 2006 criteria by a 2-hour oral glucose tolerance test (OGTT) after an overnight fast. For safety reasons, participants with a fasting glucose level >11.0 mmol/L, as determined by a finger

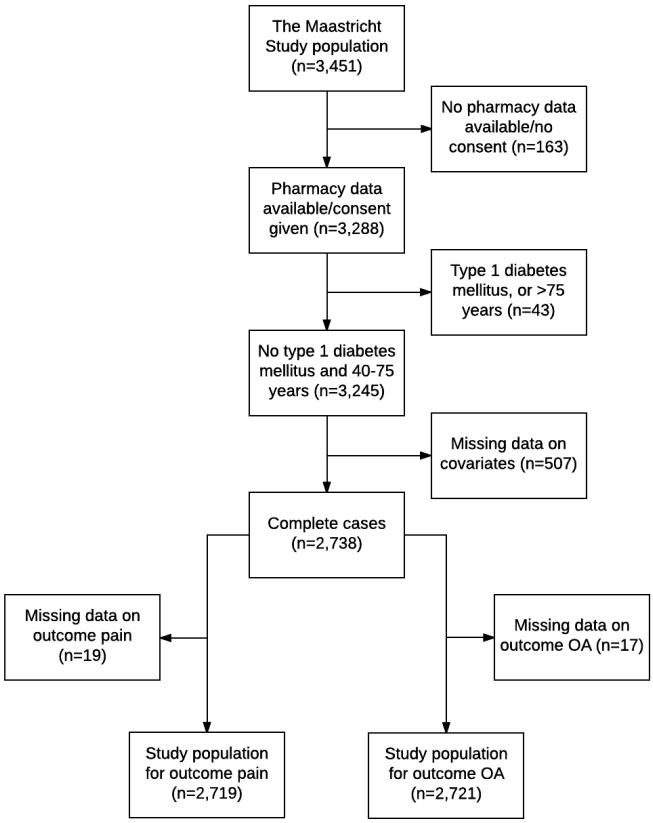

Figure 3.1: Inclusion flowchart

prick, did not undergo the OGTT. Participants were categorised as having a normal glucose metabolism (NGM), impaired fasting glucose (fasting plasma glucose 6.1–6.9 mmol/l and 2 h plasma glucose <7.8 mmol/l), impaired glucose tolerance (fasting plasma glucose <7.0 mmol/l and 2 h plasma glucose ≥ 7.0–11.1 mmol/l), or T2DM (fasting plasma glucose ≥ 7.0 mmol/l or 2 h plasma glucose ≥ 11.1 mmol/l). Prediabetes was defined as having either impaired fasting glucose and/or impaired glucose tolerance. Date of OGTT was used as the date of inclusion.

T2DM patients were stratified by metabolic control (i.e. HbA1c), and duration of drug treatment. First, metabolic control was classified into three HbA1c categories: ≤6.0%, 6.1-7.0%, and >7.0%. Second, within T2DM patients recent exposure to an anti-hyperglycaemic drug (AD) was defined. Use of biguanides, sulfonylureas, glitazones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, glinides, or insulin prior to the inclusion date was determined by reviewing drug dispensing (Anatomical Therapeutic Chemical (ATC) classification[19]: A10). Current users of these drugs comprised all patients with at least one recorded dispensing within the 90-day period before inclusion date. Recent users were those who had received an AD between 91 days and 180 days before

inclusion date, but without a dispensing in the 90-day period before the inclusion date. Past users were patients who had stopped using an AD more than 180 days before the inclusion date. Within current users, duration of use was defined as the time since the first recorded dispensing. Based on the distribution of duration of use, quartiles were defined.

Outcomes

The presence of knee pain was assessed by a single question asking participants 'whether knee pain, not due to an accident, was present during the previous 6 weeks for at least 4 weeks' (yes/no).

Clinical knee OA was defined based on modified versions of the American College of Rheumatology (ACR) guidelines (Table S.3.1)[20]. Trained researchers assessed all individual criteria of the ACR classification criteria for knee OA. However, as the criterion "crepitus" was only assessed in a limited number of participants, adapted versions of the ACR classification criteria were used. In the main analysis, the following definition was used: The participant should have experienced knee pain and at least three of the following criteria should apply: age>50 years; morning stiffness for less than 30 minutes; bony tenderness; bony distortion; no palpable warmth of the knee. Additionally, if the participant had a knee prosthesis he was classified as having knee OA. In a sensitivity analysis, another definition was evaluated: The participant should have experienced knee pain, and at least three of the following criteria should apply: age>50 years; morning stiffness for less than 30 minutes; bony tenderness; bony distortion. Additionally, if the participant had a knee prosthesis he was classified as having knee OA.

Severity of knee pain was scored on a visual analogue scale (VAS) ranging from 0-10, where 0 corresponds to "no pain" and 10 reflects "pain as bad as possibly could be". Subjects with missing data on one of the outcomes were excluded from analyses regarding that outcome (remaining: knee pain analyses: n=2,719; knee OA analyses: n=2,721; Figure 3.1).

Potential confounders

The following covariates were recorded at inclusion by the researcher: age, sex, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP), and alignment of knees (valgus/varus). Questionnaires were used to collect information on smoking status (never, former, current), level of education (low (no education, primary education not completed, primary education, lower vocational education), intermediate (intermediate vocational education, higher secondary education), high (higher professional education, university education)), alcohol use (non, low (≤7 glasses per week for women; ≤14 glasses per week for men), high (>7 glasses per week for women; >14 glasses per week for men)), history of cardiovascular diseases (CVD), previous knee surgery, previous sport related injury of the knee, presence of a physically intensive occupation, history of activities including running

and/or jumping, parents with a joint prosthesis, and presence of neuropathic pain (score of ≥3 on the Douleur Neuropathique 4 (DN4) questionnaire). Furthermore, the use of statins, diuretics, calcium channel blockers, beta-blockers, renin-angiotensin-aldosterone-system (RAAS) inhibitors, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, bisphosphonates, and systemic glucocorticoids in the six months prior to inclusion was determined.

Statistical analyses

Baseline characteristics of participants were described separately for participants with and without knee pain, and participants with and without knee OA. Age and sex standardised prevalence rates of OA per 100 persons with and without T2DM were calculated. Logistic regression models were fitted to test the association between T2DM and knee pain, and to test the association between T2DM and clinical knee OA. Odds ratios (OR) and 95% confidence intervals (CI) were first assessed in unadjusted models. Second, to evaluate the effect of BMI, we adjusted our analyses for BMI only. Third, we adjusted our analyses for age, sex, and BMI. Finally, in our fully adjusted models the following confounders were included: 1) at inclusion: age, sex, BMI, SBP, DBP, smoking status, level of education, alcohol use, presence of a physically intensive occupation, history of activities including running and/or jumping. 2) Drug use in the six months prior to inclusion: statins, diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, paracetamol, NSAIDs, opioids, bisphosphonates, and systemic corticoids. Patients with T2DM were subsequently stratified by HbA1c levels and duration of AD use.

The association of T2DM with the level of self-reported knee pain within patients with clinical knee OA was assessed using a linear regression model adjusting for the same confounders as the fully adjusted model previously mentioned, complemented with the following additional covariates: previous knee surgery, previous sport related injury of the knee, the presence of neuropathic pain, and the alignment of knees (valgus/varus). In this additional analysis prediabetic and NGM participants were combined into a non-T2DM group. Statistical significance was set at $p<0.05$. SAS version 9.4 was used for all analyses.

Results

From the base population of 3,451 participants, 2,719 (78.8%) and 2,721 (78.8%) complete cases were available for the knee pain and knee OA analyses respectively (Figure 3.1). For the knee pain analyses 549/2,719 (20.2%) fulfilled the case definition, and in the knee OA analyses 387/2,721 (14.2%) met the case definition (Table 3.1). Patients with knee pain (60.6 years) were approximately on average 1 year older as compared to patients without knee pain (59.8 years). On average, patients with knee OA were 62.3 years old and those without knee OA were 59.6 years. Patients with knee OA and those with knee pain had a higher BMI compared to those without knee OA or knee pain. The mean HbA1c and fasting

Table 3.1: Baseline characteristics

Characteristic	No knee pain n=2,170 (%)	Knee pain n=549 (%)	No knee OA n=2,334 (%)	Knee OA n=387 (%)
Male	1020 (47.0)	287 (52.3)	1086 (46.5)	221 (57.1)
BMI kg/m^2 (mean (SD))	26.7 (4.3)	28.1 (5.0)	26.7 (4.3)	28.9 (5.3)
Age years (mean (SD))	59.8 (8.3)	60.6 (7.5)	59.6 (8.3)	62.3 (6.5)
HbA1c % (mean (SD))	5.8 (0.8)	6.0 (1.0)	5.8 (0.8)	6.1 (1.1)
Fasting glucose mmol/L (mean (SD))	6.0 (1.5)	6.2 (1.9)	5.9 (1.5)	6.4 (2.1)
Systolic BP mmHg (mean(SD))	135.0 (18.2)	134.9 (17.6)	134.8 (17.9)	136.0 (18.7)
Diastolic BP mmHg (mean(SD))	76.4 (9.8)	76.4 (10.1)	76.4 (9.8)	76.1 (10.2)
Glucose metabolism status				
Normal glucose metabolism	1,267 (58.4)	297 (54.1)	1,383 (59.3)	182 (47.0)
Prediabetes	345 (15.9)	83 (15.1)	363 (15.6)	65 (16.8)
Type 2 Diabetes Mellitus	558 (25.7)	169 (30.8)	588 (25.2)	140 (36.2)
Alcohol use				
None	369 (17.0)	115 (20.9)	391 (16.8)	93 (24.0)
Low	1,225 (56.5)	300 (54.6)	1,327 (56.9)	200 (51.7)
High	576 (26.5)	134 (24.4)	616 (26.4)	94 (24.3)
Smoking status				
Never	771 (35.5)	189 (34.4)	835 (35.8)	126 (32.6)
Former	1,117 (51.5)	297 (54.1)	1,201 (51.5)	214 (55.3)
Current	282 (13.0)	63 (11.5)	298 (12.8)	47 (12.1)
Presence of ever before inclusion				
History of CVD	326 (15.0)	104 (18.9)	342 (14.7)	88 (22.7)
History of sports injury	491 (22.6)	199 (36.2)	541 (23.2)	149 (38.5)
History of knee surgery	350 (16.1)	187 (34.1)	370 (15.9)	169 (43.7)
Valgus or varus >2 degrees	2,083 (96.0)	527 (96.0)	2,242 (96.1)	370 (95.6)
History of physical job	1,402 (64.6)	408 (74.3)	1,519 (65.1)	293 (75.7)
Parents with prosthesis	325 (15.0)	101 (18.4)	352 (15.1)	74 (19.1)
History of sports activities	1,382 (63.7)	350 (63.8)	1,497 (64.1)	236 (61.0)
History of drug use within 6 months before inclusion				
Statins	693 (31.9)	200 (36.4)	726 (31.1)	168 (43.4)
Diuretics	332 (15.3)	109 (19.9)	345 (14.8)	97 (25.1)
Calcium channel blockers	172 (7.9)	53 (9.7)	179 (7.7)	47 (12.1)
Beta blockers	365 (16.8)	105 (19.1)	376 (16.1)	94 (24.3)
RAAS inhibitors	559 (25.8)	184 (33.5)	591 (25.3)	153 (39.5)
Paracetamol	43 (2.0)	26 (4.7)	46 (2.0)	23 (5.9)
NSAIDs	141 (6.5)	45 (8.2)	154 (6.6)	33 (8.5)
Opioids	154 (7.1)	46 (8.4)	164 (7.0)	37 (9.6)
Bisphosphonates	58 (2.7)	12 (2.2)	58 (2.5)	12 (3.1)
Systemic glucocorticoids	73 (3.4)	32 (5.8)	82 (3.5)	23 (5.9)

Abbreviations: BMI = body mass Index, BP = blood pressure, CVD = cardiovascular diseases, HbA1c = glycated haemoglobin, NSAID = non-steroidal anti-inflammatory drug, OA = osteoarthritis, RAAS = renin-aldosterone-angiotensin-system, SD = standard deviation, VAS = visual analogue scale.

glucose levels in patients with or without knee pain or knee OA were similar. Furthermore, patients with knee OA or knee pain had used more drugs in the six months prior to inclusion compared to those without knee OA or knee pain. The age and sex standardised rate of OA in T2DM patients was 21.5/100 persons, compared to 12.4/100 persons without T2DM. The age and sex distribution of the population without T2DM was used as reference population (results not shown).

Compared to NGM, T2DM (OR=1.29 [95% CI=1.04-1.60]), but not prediabetes (OR=1.03 [95% CI=0.78-1.35]), was associated with knee pain in the unadjusted model (Table 3.2). However, after adjustment for BMI, T2DM was no longer associated with knee pain (OR=0.97 [95% CI=0.76-1.22]). After subsequent adjustment for other relevant confounders the association did not change substantially (OR=0.89 [95% CI=0.67-1.19]). In the fully adjusted analyses, stratification of T2DM patients by HbA1c or duration of AD use resulted in increased

Table 3.2: Association of glucose metabolism status with self-reported knee pain stratified by HbA1c and duration of AD use

Exposure	No knee pain n=2,170 (%)	Knee pain n=549 (%)	OR (95% CI) Unadjusted	OR (95% CI) BMI adjusted	OR (95% CI) Age/sex/BMI adjusted	OR (95% CI) Fully adjusted [a]
Normal glucose metabolism	1,267 (58.4)	297 (54.1)	Reference	Reference	Reference	Reference
Prediabetes	345 (15.9)	83 (15.1)	1.03 (0.78-1.35)	0.87 (0.66-1.15)	0.85 (0.64-1.12)	0.87 (0.65-1.16)
Type 2 diabetes mellitus	558 (25.7)	169 (30.8)	1.29 (1.04-1.60)	0.97 (0.76-1.22)	0.96 (0.75-1.29)	0.89 (0.67-1.19)
By HbA1c						
≤6.0%	86 (15.4)	25 (14.8)	1.24 (0.78-1.97)	1.03 (0.64-1.65)	1.03 (0.64-1.65)	0.92 (0.56-1.52)
6.1- 7.0%	310 (55.6)	82 (48.5)	1.13 (0.86-1.48)	0.85 (0.64-1.14)	0.84 (0.62-1.13)	0.79 (0.56-1.10)
>7.0%	162 (29.0)	62 (36.7)	1.63 (1.19-2.25)	1.15 (0.82-1.63)	1.16 (0.81-1.65)	1.10 (0.74-1.62)
By AD use						
Never	142 (25.4)	44 (26.0)	1.32 (0.92-1.90)	1.00 (0.69-1.46)	0.96 (0.66-1.42)	0.95 (0.64-1.40)
Past	25 (4.5)	5 (3.0)	0.85 (0.32-2.25)	0.62 (0.23-1.64)	0.61 (0.23-1.65)	0.51 (0.19-1.41)
Recent	25 (4.5)	5 (3.0)	0.85 (0.32-2.25)	0.76 (0.29-2.01)	0.74 (0.28-1.97)	0.75 (0.28-2.04)
Current	366 (65.6)	115 (68.0)	1.34 (1.05-1.71)	0.99 (0.76-1.30)	0.99 (0.75-1.31)	0.91 (0.65-1.27)
By duration of use						
≤ 2.5 years	94 (25.7)	27 (23.5)	1.23 (0.78-1.91)	0.93 (0.59-1.47)	0.94 (0.59-1.50)	0.89 (0.54-1.47)
2.5-4.5 years	95 (26.0)	25 (21.7)	1.12 (0.71-1.78)	0.83 (0.52-1.33)	0.84 (0.52-1.36)	0.78 (0.47-1.31)
4.5-8.0 years	94 (25.7)	26 (22.6)	1.18 (0.75-1.85)	0.87 (0.55-1.40)	0.88 (0.55-1.42)	0.81 (0.48-1.37)
> 8.0 years	83 (22.7)	37 (32.2)	1.90 (1.27-2.86)	1.38 (0.90-2.11)	1.35 (0.87-2.10)	1.21 (0.74-1.96)

[a] Adjusted for: At inclusion date: age, sex, BMI, education level, smoking status, alcohol use, systolic and diastolic blood pressure, presence of a physically intensive occupation, history of activities including running and/or jumping. Drug use in the six months prior to inclusion date: statins, diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, paracetamol, NSAIDs, opioids, bisphosphonates, or systemic glucocorticoids. Abbreviations: AD = anti-hyperglycaemic drug, BMI = body mass index, CI = confidence interval, HbA1c = glycated haemoglobin, NSAID = non-steroidal anti-inflammatory drug, OR = odds ratio, RAAS = renin-aldosterone-angiotensin-system.

Table 3.3: Association of glucose metabolism status with knee OA* stratified by HbA1c and duration of AD use

Exposure	No knee OA n=2,334 (%)	Knee OA n=387 (%)	OR (95% CI) Unadjusted	OR (95% CI) BMI adjusted	OR (95% CI) Age/sex/ BMI adjusted	OR (95% CI) Fully adjusted [a]
Normal glucose metabolism	1383 (59.3)	182 (47.0)	Reference	Reference	Reference	Reference
Prediabetes	363 (15.6)	65 (16.8)	1.36 (0.99-1.85)	1.09 (0.80-1.49)	0.97 (0.70-1.35)	0.98 (0.70-1.37)
Type 2 diabetes mellitus	588 (25.2)	140 (36.2)	1.81 (1.42-2.30)	1.22 (0.94-1.60)	1.11 (0.84-1.48)	0.96 (0.69-1.33)
By HbA1c						
≤6.0%	94 (16.0)	17 (12.1)	1.37 (0.80-2.36)	1.07 (0.62-1.86)	1.00 (0.57-1.76)	0.84 (0.47-1.50)
6.1- 7.0%	324 (55.1)	68 (48.6)	1.59 (1.18-2.16)	1.10 (0.80-1.52)	0.97 (0.69-1.37)	0.86 (0.59-1.26)
>7.0%	170 (28.9)	55 (36.2)	2.46 (1.75-3.46)	1.55 (1.07-2.25)	1.47 (0.99-2.17)	1.28 (0.83-1.98)
By AD use						
Never	155 (26.4)	31 (22.1)	1.52 (1.00-2.30)	1.1 (0.67-1.60)	0.90 (0.57-1.40)	0.87 (0.55-1.38)
Past	24 (4.1)	6 (4.3)	1.90 (0.77-4.71)	1.2 (0.49-3.15)	1.10 (0.43-2.85)	0.95 (0.36-2.48)
Recent	25 (4.3)	5 (3.6)	1.52 (0.57-4.02)	1.3 (0.49-3.50)	1.16 (0.43-3.16)	1.04 (0.37-2.92)
Current	384 (65.3)	98 (70.0)	1.94 (1.48-2.54)	1.3 (0.96-1.74)	1.21 (0.88-1.66)	1.01 (0.70-1.47)
By duration of use						
≤ 2.5 years	101 (26.3)	20 (20.4)	1.50 (0.91-2.49)	1.0 (0.61-1.74)	1.01 (0.59-1.73)	0.87 (0.49-1.55)
2.5-4.5 years	97 (25.3)	23 (23.5)	1.80 (1.11-2.91)	1.2 (0.72-1.98)	1.13 (0.67-1.92)	0.99 (0.56-1.73)
4.5-8.0 years	96 (25.0)	25 (25.5)	1.98 (1.24-3.15)	1.3 (0.82-2.16)	1.26 (0.76-2.08)	1.05 (0.60-1.83)
> 8.0 years	90 (23.4)	30 (30.6)	2.53 (1.63-3.94)	1.6 (1.04-2.62)	1.45 (0.89-2.35)	1.17 (0.68-2.02)

[a] Adjusted for: At inclusion date: age, sex, BMI, education level, smoking status, alcohol use, systolic and diastolic blood pressure, presence of a physically intensive occupation, history of activities including running and/or jumping. Drug use in the six months prior to inclusion date: statins, diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, paracetamol, NSAIDs, opioids, bisphosphonates, or systemic glucocorticoids. * Adapted ACR criteria: The participant should have experienced knee pain during the last 6 weeks for at least 4 weeks and at least three of the following five criteria should apply: age>50 years; morning stiffness for less than 30 minutes; bony tenderness; bony distortions; no palpable warmth of the knee. Additionally, if the participant had a knee prosthesis he was classified as having knee OA. Abbreviations: AD = anti-hyperglycaemic drug, BMI = body mass index, CI = confidence interval, HbA1c = glycated haemoglobin, NSAID = non-steroidal anti-inflammatory drug, OR = odds ratio, RAAS = renin-aldosterone-angiotensin-system.

point estimates in the highest strata (HbA1c >7.0%: (OR=1.10 [95% CI=0.74-1.62]); duration of AD use >8 years: (OR=1.21 [95% CI=0.74-1.96])), but confidence intervals included the null value.

T2DM (OR=1.81 [95% CI=1.42-2.30]), but not prediabetes (OR=1.36 [95% CI=0.99-1.85]), was associated with knee OA in the unadjusted model (Table 3.3). However, T2DM was no longer associated with knee OA after adjustment for BMI (OR=1.22 [95% CI=0.94-1.60]). After subsequent adjustment for other relevant confounders this result did not materially change (T2DM: OR=0.96 [95% CI=0.69-1.33]). In the unadjusted model, further stratification by proxies for stage of T2DM resulted in a positive association in the highest strata of HbA1c (OR=2.46 [95% CI=1.75-3.46]) and duration of AD use (OR=2.53 [95% CI=1.63-3.94]). However, after adjustment for all relevant confounders, these associations were no longer statistically significant (HbA1c: OR=1.28 [95% CI=0.83-1.98]; duration of AD use >8 years: OR=1.17 [95% CI=0.68-2.02]). Sensitivity analyses using an alternative definition of knee OA showed similar results (Table S.3.2).

Severity of knee pain was rated by 327/387 (84.5%) patients with knee OA. Within these patients with knee OA, the severity of knee pain was 5.1 (standard deviation (SD): 2.0) and 4.8 (SD: 2.2) in patients with and without T2DM respectively. Additionally, T2DM did not contribute to the variance in the severity of knee pain in unadjusted (β:0.28; p=0.23) or adjusted (β:-0.04; p=0.88) models (Table 3.4).

Table 3.4: Association of T2DM with severity of knee pain within patients with knee OA.

	Knee OA			
Severity of knee pain	T2DM (n=120) *	No T2DM (n=207) *	Crude β	Adjusted β [a]
VAS (mean, SD)	5.1 (2.0)	4.8 (2.0)	0.28 (p=0.229)	-0.04 (p=0.884)

[a] Adjusted for: At inclusion date: age, sex, BMI, education level, smoking status, alcohol use, systolic and diastolic blood pressure, presence of a physically intensive occupation, history of activities including running and/or jumping, previous sport related injury of the knee, previous knee surgery, neuropathic pain, alignment of the knees (valgus/varus). Drug use in the six months prior to inclusion date: statins, diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, paracetamol, NSAIDs, opioids, bisphosphonates, or systemic glucocorticoids. * Numbers are lower compared to Table 3.1 and Table 3.3 due to exclusion of participants with missing data on severity of knee pain measurement (VAS-score). Abbreviations: BMI = body mass index, NSAID = non-steroidal anti-inflammatory drug, OA = osteoarthritis, RAAS = renin-aldosterone-angiotensin-system, SD = standard deviation, T2DM = type 2 diabetes mellitus, VAS = visual analogue scale.

Discussion

This study demonstrated that patients with T2DM were more likely to experience knee pain and clinical knee OA, with absolute age and sex standardised rates of OA that were markedly higher in T2DM patients compared to patients without T2DM. However, these associations were no longer present after adjusting for BMI, and did not materially change after adjusting for other confounders, reflecting the importance of overweight in the relationship between T2DM and knee pain or knee OA. Further stratification of patients with T2DM by metabolic control (i.e. HbA1c) and duration of AD use resulted in increased point estimates in the

highest strata of HbA1c and duration of AD use. However, after adjustment for relevant confounders, these associations were no longer present. Finally, within patients with knee OA, there was no difference in the severity of knee pain experienced by T2DM patients compared to those without T2DM.

The association of T2DM with knee pain reported in this study confirms previous studies[21,22]. Furthermore, the previously proposed impact of overweight on this association is confirmed by a strong confounding effect of BMI in this study. Additionally, the association of T2DM with knee OA was strongly affected by BMI, suggesting T2DM does not affect knee OA independently. Although in line with some studies[9,10,11] it is in contrast with our hypothesis and other previous studies and meta-analyses[3,4,5,6]. The inconsistency in these results may be due to methodological differences between these studies, such as variability in the definition of OA, and the difficulty to assess duration and date of onset of knee OA and T2DM. The known strong role of overweight in knee OA might overrule (small) metabolic effects. This may, however, be different for OA in other joints, such as the hand, where overweight is less likely to have an effect. Although it should be noted that two previous studies showed no association between diabetes and hand OA[10,11].

Stratification of T2DM patients by HbA1c and duration of AD use showed that the positive association of T2DM and knee pain and knee OA was especially pronounced in the highest strata of these factors. However, after adjustment for relevant confounders, these associations were no longer present. These results provide further evidence against the independent association of T2DM with knee OA as no association was found in T2DM patients with the poorest regulated glucose metabolism and the longest duration of the disease. However, it should be noted that, overall, the included population was relatively healthy, and, as reflected by relatively low HbA1c levels presented in Table 3.1, had generally well controlled glucose metabolism. Possibly, T2DM is associated with knee OA in a less healthy population, with more severely deregulated glucose metabolism.

Although T2DM patients experience knee pain more often than patients without T2DM, this study also shows that the experienced severity of knee pain, within patients with knee OA, is not different between T2DM patients and patients without T2DM. After adjustment for several factors, the estimate of the association was close to 0. Alternatively, this may be due to the fact that the included T2DM population is relatively healthy and glucose metabolism is relatively well controlled. Therefore, effects of underlying bio-pathological mechanisms (i.e. formation of neurovascular channels in the subchondral bone and articular cartilage, and low grade inflammation) or diabetic neuropathy may have been limited.

This study has several strengths. First, the Maastricht Study is characterised by an extensive phenotyping approach, resulting in the possibility to include a wide range of potential confounders. This provides the opportunity to better assess the independent association of T2DM and knee pain and knee OA. Second, as the Maastricht Study is focussed on T2DM and its comorbidities, glucose metabolism status was defined highly accurate.

Consequently, prediabetes and T2DM cases were well defined and risk of misclassification is low. Third, this is the first study providing insight into the difference in perception of severity of knee pain between patients with and without T2DM. However, there were some limitations as well. Due to the cross-sectional design of this study, causality cannot be assessed. Furthermore, as a measurement for crepitus on motion was missing, we were unable to use the original ACR definition of clinical knee OA. Adaptations of this method were used. These adaptations were stricter compared to the original method (3 out of 5 (and 3 out of 4 in sensitivity analysis) criteria were required, compared to 3 out of 6 criteria in the original definition). Consequently, some OA cases may have been misclassified as non-OA patients. It is expected that this misclassification was non-differential, resulting in a bias towards the null. Consequently, the effect of T2DM on OA may have been underestimated. Additionally, we had no data available on radiographic knee OA, which would have improved the specificity of our knee OA definition. However, we were able to include data regarding OA related knee prostheses, which has added to the specificity of our OA definition. Finally, as in most studies, duration of T2DM was difficult to assess. In this study, we have attempted to gain insight into this issue by stratifying T2DM patients by duration of AD use. Duration of knee pain or knee OA was not available and could therefore not be included in our analyses.

In conclusion, T2DM patients were more likely to experience knee pain or have knee OA compared to patients with a normal glucose metabolism. This seems, however, to be mainly associated with overweight rather than a metabolic effect, stressing the importance of weight reduction as an important element in the treatment and perhaps prevention of knee pain and knee OA. Furthermore, T2DM patients with knee OA do not experience knee pain differently than knee OA patients without T2DM.

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Supplementary material

Table S.3.1: OA criteria

Criterion	Original ACR criteria (pain + ≥3 out of 6)	Adapted ACR criteria 1 (pain + ≥3 out of 5) or knee prosthesis	Adapted ACR criteria 2 (pain + ≥3 out of 4) or knee prosthesis
Pain in the last 6 weeks, that was present for at least 4 weeks, and that was not due to an injury	X	X	X
Age >50 years	X	X	X
Crepitus	X		
Bony distortions	X	X	X
Bony tenderness	X	X	X
Lack of warmth	X	X	
Start pain/morning stiffness <30 minutes	X	X	X
Knee prosthesis		X	X

Abbreviations: ACR = American College of Rheumatology, OA = osteoarthritis.

Table S.3.2: Association of glucose metabolism status with knee OA* stratified by HbA1c and duration of AD use

Exposure	No knee OA n=2,501 (%)	Knee OA n=220 (%)	OR (95% CI) Unadjusted	OR (95% CI) BMI adjusted	OR (95% CI) Age/sex/BMI adjusted	OR (95% CI) Fully adjusted [a]
Normal glucose metabolism	1479 (59.1)	86 (39.1)	Reference	Reference	Reference	Reference
Prediabetes	384 (15.4)	44 (20.0)	1.97 (1.35-2.88)	1.53 (1.04-2.27)	1.40 (0.94-2.10)	1.51 (1.00-2.29)
Type 2 diabetes mellitus	638 (25.5)	90 (40.9)	2.43 (1.78-3.31)	1.55 (1.10-2.18)	1.47 (1.02-2.12)	1.34 (0.88-2.04)
By HbA1c						
≤6.0%	98 (15.4)	13 (14.4)	2.28 (1.23-4.23)	1.73 (0.92-3.24)	1.67 (0.88-3.12)	1.45 (0.74-2.85)
6.1- 7.0%	346 (54.2)	46 (51.1)	2.29 (1.57-3.33)	1.49 (0.99-2.22)	1.36 (0.89-2.09)	1.28 (0.80-2.07)
>7.0%	194 (30.4)	31 (34.4)	2.75 (1.78-4.25)	1.58 (0.98-2.54)	1.55 (0.94-2.55)	1.39 (0.80-2.43)
By AD use						
Never	165 (25.9)	21 (23.3)	2.19 (1.32-3.62)	1.41 (0.83-2.40)	1.25 (0.72-2.16)	1.27 (0.72-2.23)
Past	27 (4.2)	3 (3.3)	1.91 (0.57-6.42)	1.17 (0.34-4.03)	1.12 (0.32-3.96)	1.00 (0.28-3.63)
Recent	27 (4.2)	3 (3.3)	1.91 (0.57-6.42)	1.60 (0.47-5.45)	1.48 (0.43-5.10)	1.42 (0.40-5.10)
Current	419 (65.7)	63 (70.0)	2.59 (1.84-3.64)	1.63 (1.12-2.37)	1.58 (1.06-2.36)	1.42 (0.88-2.29)
By duration of use						
≤ 2.5 years	110 (26.3)	11 (17.5)	1.72 (0.89-3.32)	1.12 (0.57-2.20)	1.12 (0.56-2.25)	1.01 (0.47-2.14)
2.5-4.5 years	107 (25.5)	13 (20.6)	2.09 (1.13-3.87)	1.17 (0.68-2.46)	1.27 (0.65-2.50)	1.22 (0.59-2.49)
4.5-8.0 years	104 (24.8)	17 (27.0)	2.81 (1.61-4.91)	1.60 (1.00-3.20)	1.77 (0.97-3.22)	1.64 (0.84-3.22)
> 8.0 years	98 (23.4)	22 (34.9)	3.86 (2.32-6.44)	2.37 (1.38-4.07)	2.22 (1.25-3.92)	1.89 (0.99-3.61)

[a] Adjusted for: At inclusion date: age, sex, BMI, education level, smoking status, alcohol use, systolic and diastolic blood pressure, presence of a physically intensive occupation, history of activities including running and/or jumping. Drug use in the six months prior to inclusion date: statins, diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, paracetamol, NSAIDs, opioids, bisphosphonates, or systemic corticoids. * Adapted ACR criteria: The participant should have experienced knee pain, not due to an accident, during the last 6 weeks for at least 4 weeks and at least three of the following criteria should apply: age>50 years; morning stiffness for less than 30 minutes; bony tenderness; bony distortions. Additionally, if the participant had a knee prosthesis he was classified as having knee OA. Abbreviations: AD = anti-hyperglycaemic drug, BMI = body mass index, CI = confidence interval, HbA1c = glycated haemoglobin, NSAID = non-steroidal anti-inflammatory drug, OR = odds ratio, RAAS = renin-aldosterone-angiotensin-system.

Chapter 4

Severity of diabetes mellitus and risk of total hip or knee replacement: a population based case-control study

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Abstract

Background: It is generally thought that people with diabetes mellitus (DM) are more likely to suffer from osteoarthritis (OA) due to an increased body mass index (BMI), resulting in mechanical destruction of cartilage. However, previous studies have suggested a coexisting metabolic causality.

Objective: To evaluate the risk of hip or knee replacement, as a proxy for severe OA, in patients with DM. We additionally evaluated the risk of total joint replacement (TJR) with various proxies for increased DM severity.

Methods: A population-based case-control study was performed, using the Clinical Practice Research Datalink (CPRD). Cases (n=94,609) were defined as patients >18 years who had undergone TJR between 2000 and 2012. Controls were matched by age, gender, and general practice. Conditional logistic regression was used to estimate the risk of total knee (TKR) and total hip replacement (THR) surgery associated with use of anti-hyperglycaemic drugs (ADs). We additionally stratified current AD users by proxies for DM severity.

Results: Current AD use was significantly associated with a lower risk of TKR (OR=0.86 (95% CI =0.78–0.94)) and THR (OR = 0.90 (95% CI = 0.82 – 0.99)) compared to patients not using ADs. Moreover, risk of TKR and THR was decreased with increasing HbA1c.

Conclusion: This study does not support the theory that DM patients are more likely to suffer from severe OA as compared to patients without diabetes. Moreover, risk of severe OA necessitating TJR decreases with increasing DM severity. This is possibly due to dissimilarities in methodology, a decrease in eligibility for surgery, or variability of OA phenotypes.

Introduction

Osteoarthritis (OA) is the most common cause of pain and disability in the United Kingdom (UK)[1]. Approximately one-third of people aged 45 and over in the UK sought treatment for pain associated with OA[1]. Furthermore, between 1990 and 2010, disability due to OA has increased by 15%[2]. In patients with severe OA, total knee (TKR) and hip (THR) replacement are considered to improve the quality of life considerably[3].

Patients with OA are more likely to suffer from diabetes mellitus (DM). DM is characterized by several metabolic problems, such as impaired glucose metabolism and obesity. Until recently one of the mechanisms underlying OA was considered to be an increased mechanical load on the weight-bearing joints, especially the knee, of these patients. Previous studies have shown that DM is an independent risk factor for the non-weight-bearing types of OA, suggesting a metabolic causality[4–7]. In a cross-sectional study of 202 subjects, patients with DM had an increased risk of hand or knee OA compared to patients without DM (OR 2.18 (95% CI, 1.12–4.24))[4]. Furthermore, a population-based cohort study with a 20-year follow-up in a random sample of 927 subjects showed an increased risk of total joint replacement (TJR) in type 2 DM patients compared to non-DM subjects (OR 2.1 (95% CI, 1.1–3.8))[6]. According to the Ulm osteoarthritis study, bilateral hip and knee OA was more prevalent, although not statistically significantly, in patients with DM than in patients without DM (OR 2.21 (95% CI, 0.77–6.41))[7]. Despite this, other studies show no association between OA and DM[8,9].

From a biopathological point of view, there is an increasing body of evidence suggesting that hyperglycaemia and advanced glycation end products (AGEs) play an important role in the progression of OA[10–12]. An in vitro study using chondrocytes, isolated from human cartilage, has concluded that OA chondrocytes exposed to high levels of glucose were unable to down-regulate glucose transporter-1 (GLUT-1). The inability to down regulate GLUT-1 resulted in the accumulation of glucose and the production of reactive oxygen species (ROS), known for their deleterious effects in various celtypes[10]. Furthermore, AGEs have been linked to increased cartilage stiffness and a reduced capacity to repair articular cartilage[11,12]. These factors may be part of the mechanism promoting degenerative changes in the cartilage possibly facilitating the progression of OA.

Hyperglycaemia and increased levels of AGEs are likely to be found in diabetic patients. Particularly poorly controlled or severe diabetic patients may be subjected to these risk factors regularly. It is therefore expected that these patients in particular are more likely to develop, or have a more severe course of OA. Subsequent progression of OA may in time lead to pain, which in severe cases can be alleviated by elective joint replacement surgery.

To date, a limited number of studies have assessed the risk of OA in DM patients and showed inconsistent results. Moreover, none of these studies have determined the risk of OA needing TJR with increasing DM severity. The aim of this study was to evaluate the risk of TJR surgery with indicators of the severity of DM. Based on *in vitro*, *in vivo*, and

clinical studies we hypothesize that DM could be associated with an increased risk of OA. Furthermore, we expect to find a higher risk of OA with increased severity of DM.

Methods

This study protocol was approved by the Independent Scientific Advisory Committee (ISAC), protocol number: 14_054R.

Data Source

We performed a case-control study using the Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (GPRD). The CPRD is a large primary care database containing computerized medical records registered by over 625 general practitioners (GP) in the UK, thereby representing over 8% of the British population. This database provides information on a wide range of medical records, including diagnoses, prescriptions, referrals, and laboratory test results. We also used linked data on socio-economic status from the Index of Multiple Deprivation for descriptive purposes.

Study Population

All patients aged 18 years or older who had undergone a primary THR or TKR surgery from January 2000 until the 31st of October 2012 were selected as cases. Patients with a diagnosis of rheumatoid arthritis (RA) or hip/knee fractures preceding the TJR surgery were excluded from analyses. All cases were matched to one control patient without a record for TJR using incidence density sampling. Cases and controls were matched by year of birth, sex, and general practice. The index date for the patients was the date of TJR surgery. This date was imputed for the matched control patient. A patient that did not undergo TJR before and at the index date of a case, but was still at risk of undergoing TJR, was matched to this specific case.

Exposure

In order to evaluate the risk between TJR surgery and DM, we determined the most recent diagnosis of type 1 DM (T1DM) or type 2 DM (T2DM) before the index date. If type of DM was not specified, these patients were categorized as ''DM type unspecified.'' In addition, we determined the recency of exposure to anti-hyperglycaemic drugs (ADs): biguanides, sulfonylureas, glitazones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, glinides, and insulins, before the index date by reviewing prescriptions. Current users of these drugs comprised all patients with at least 1 recorded prescription within the 90-day period before the index date. Recent users were those with at least 1 prescription within the 180-day period before the index date, but who had stopped using these drugs 90 days before the index date. Past users were patients who had stopped using ADs more than 180 days before the index date.

Proxy indicators for the severity of DM were then defined using clinical information, lab test values, and exposure to drugs: clinical proxies of disease severity included a history of neuropathy or retinopathy 5 years before the index date and renal function. In addition, lab tests values including HbA1c and fasting glucose were also used to determine the risk of TJR with increased severity of DM. HbA1c was stratified into the following groups: <6.5%, 6.5% to 7.9%, 8.0% to 9.4%, ≥9.5%. Fasting plasma glucose was stratified into the following groups: <6 mmol/L, 6 to 7.4 mmol/L, 7.5 to 8.9 mmol/L, and ≥9.0 mmol/L. The most recent lab test value in the year before index date was used in this proxy. Lastly, we used proxy indicators of disease severity using longitudinal information on drug exposure according to the methods by Bazelier et al.[13]. This was done by stratification of current AD users, into four treatment stages ranging from mild (stage 1) to severe (stage 4): Stage 1 diabetics were current users of either a biguanide or a sulfonylurea. Stage 2 diabetics comprised all patients who used these drugs simultaneously. Stage 3 diabetics used one or more drugs from the following classes: thiazolidinediones (TZD), glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, or glinides, but were not on insulin treatment. Stage 4 diabetics were current users of insulin.

Covariates

We reviewed the literature to identify potential confounders for OA and TJR surgery. Factors including age, sex, socioeconomic status, body mass index (BMI), and smoking status were used as potential confounders[14–16]. A history of diseases such as angina pectoris, acute myocardial infarction (AMI), heart failure, haemorrhagic stroke, ischemic stroke, dementia, arrhythmia, peripheral vascular diseases, ulcers, and non-hip/femur fractures in the previous year were also included as potential confounders. Use of statins, loop diuretics, thiazides, NSAIDs, calcium channel blockers, beta-blockers, RAAS inhibitors, systemic glucocorticoids in the previous 6 months were also included as potential confounders[17]. In all analyses, potential confounders were included if they independently changed the beta-coefficient of the association between a DM diagnosis or current AD exposure and TKR or THR surgery by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature.

Statistical Analysis

Conditional logistic regression analysis was used to estimate the risk of TKR and THR surgery associated with a diagnosis of DM, and clinical proxies of disease severity (SAS version 9.3, PHREG procedure). In the analyses, risk was expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Furthermore, we estimated the risk of TKR and THR surgery associated with use of ADs. We additionally stratified current AD users by lab test and drug use proxies for disease severity. Missing data were classified as a separate category. Analyses assessing the association between prespecified treatment stages and

HbA1c levels have been conducted in order to determine whether these treatment stages reflect DM severity properly. These analyses have been conducted in a set of TKR and THR control patients using an AD.

Results

Baseline characteristics of TKR (n=44,768), THR patients (n=49,841), and their matched control subjects (n=94,609) are presented in Table 4.1. On average, the subjects were approximately 70 years of age and more than 55% of them were female. In general, TKR cases were more likely to have a DM diagnosis (n=5,118) compared to TKR controls (n=4,325). TKR cases were particularly more often diagnosed with T2DM compared to controls. In contrast, THR cases were less likely to have a DM diagnosis (n=4,075) compared to controls (n=4,591), regardless of type. On average, HbA1c values were lower in the cases compared to the controls in both TKR and THR subjects. The use of ADs was higher in the TKR cases compared to their controls. This was in contrast with the THR cases, where the use of ADs was lower compared to the controls. Socio-economic status and mean fasting glucose values were similar in cases and controls in both patient groups. Mean BMI, however, was higher in cases compared to their matched controls, especially in the TKR group.

The risk of TJR surgery was 13% to 15% reduced in patients with a diagnosis of DM versus non-diabetic patients, with an OR of 0.85 (95% CI=0.77-0.94) for TKR surgery and of 0.87 (95% CI = 0.82-0.93) for THR surgery. Risk reductions were on average more pronounced in patients with T1DM for TKR (OR=0.73 [95% CI=0.55-0.96]) but not for THR (OR=0.89 [95% CI=0.72-1.11]) surgery, as compared with non-DM patients. In T2DM patients the risk of TKR surgery (OR=0.85 [95% CI=0.76-0.94]) and THR surgery (OR=0.88 [95% CI = 0.83-0.94]) was slightly decreased compared to non-DM patients. Clinical proxies of the severity of DM were mostly not associated with risk of TJR. A diagnosis of retinopathy in the 5 years before TKR yielded an OR of 1.37 (95% CI=0.76-2.49) and an OR of 2.18 (95% CI=1.33-3.57) for THR surgery compared to patients without diabetes. We found no differences in risk of surgery in patients with a diagnosis of neuropathy in the 5 years before TKR or THR. Risk of TKR was increased in patients with a combined diagnosis of retinopathy and a neuropathy in the 5 years before surgery (OR = 2.20 [95% CI=1.04-4.66]), whereas no difference in risk of THR was found (OR=1.29 [95% CI=0.64-2.57]). Deterioration of renal function (eGFR 30-59 ml/min/1.73 m^2) was associated with a reduced risk of TKR and THR, yielding an OR of 0.69 (95% CI=0.60-0.79) and an OR of 0.79 (95% CI=0.71-0.87) respectively (Table 4.2).

The associations between current AD use and risk of TJR showed similar patterns as compared to the associations between diagnosis of DM and risk of TJR. Current AD use was significantly associated with a lower risk of TKR (OR=0.86 [95% CI =0.78-0.94]) and THR (OR=0.90 [95% CI=0.81-0.99]) compared to patients not using ADs. Moreover, risk of TKR and THR was decreased with increasing HbA1c in current AD users as compared to nonusers. More specifically, both TKR and THR patients using ADs with HbA1c values <6.5% were at

Table 4.1: Baseline characteristics of total knee and total hip replacement cases and controls

Characteristic	Total knee replacement n=89,536		Total hip replacement n=99,682	
	Cases n=44,768 (%)	Controls n=44,768 (%)	Cases n=49,841 (%)	Controls n=49,841 (%)
Number of females	24,912 (55.6)	24,912 (55.6)	29,724 (59.6)	29,724 (59.6)
Age at index date (years, (SD))	69.5 (9.5)	69.5 (9.5)	68.8 (11.5)	68.8 (11.5)
BMI, most recent value prior to index date (kg/m^2, mean (SD))	29.7 (5.2)	27.0 (5.1)	27.6 (5.0)	26.8 (5.0)
DM diagnosis, most recent diagnosis prior to index date				
DM regardless of type	5,118 (11.4)	4,325 (10.3)	4,075 (8.2)	4,591 (9.2)
Type I	149 (0.3)	211 (0.5)	189 (0.4)	243 (0.5)
Type II	4,636 (10.4)	4,077 (9.1)	3,579 (7.2)	3,979 (8.0)
Type unspecified	333 (0.7)	307 (0.7)	307 (0.6)	369 (0.7)
History of comorbidity 5 years before index date				
Retinopathy	884 (2.0)	911 (2.0)	643 (1.3)	850 (1.7)
Neuropathy	551 (1.2)	441 (1.0)	499 (1.0)	428 (0.9)
eGFR (ml/min/1,73 m^2, mean(SD))	71.9 (17.9)	70.8 (17.9)	71.9 (18.9)	70.4 (18.1)
HbA1c, most recent value within the year prior to index date				
HbA1c (%, mean (SD))	6.9 (1.2)	7.1 (1.4)	6.8 (1.2)	7.2 (1.4)
HbA1c, by category				
<6.5%	1,811 (4.0)	1,422 (3.2)	1,629 (3.3)	1,406 (2.8)
6.5-7.9%	2,331 (5.2)	1,976 (4.4)	1,623 (3.3)	1,837 (3.7)
8.0-9.4%	542 (1.2)	586 (1.3)	411 (0.8)	550 (1.1)
≥9.5%	189 (0.4)	299 (0.7)	133 (0.3)	310 (0.6)
Missing	39,895 (89.1)	40,485 (90.4)	46,045 (92.4)	45,738 (91.8)
Fasting glucose most recent value within the year prior to index date				
Fasting glucose (mean (SD))	5.7 (1.5)	5.7 (1.7)	5.6 (1.4)	5.7 (1.7)
Fasting glucose, by category				
<6.0 mmol/L	3,791 (8.5)	3,143 (7.0)	3,351 (6.7)	3,016 (6.1)
6.0-7.5 mmol/L	818 (1.8)	613 (1.4)	580 (1.2)	590 (1.2)
7.5-8.9 mmol/L	248 (0.6)	152 (0.3)	122 (0.2)	167 (0.3)
≥9.0 mmol/L	156 (0.3)	149 (0.3)	145 (0.3)	164 (0.3)
Missing	39,755 (88.8)	40,711 (90.9)	45,643 (91.6)	45,904 (92.1)
History of drug use within 6 months prior to index date				
All NIADs	3,430 (7.7)	3,075 (6.9)	2,511 (5.0)	3,037 (6.1)
Biguanides	2,780 (6.2)	2,406 (5.4)	1,995 (4.0)	2,388 (4.8)
Sulphonylureas	1,497 (3.3)	1,573 (3.5)	1,206 (2.4)	1,568 (3.1)
Thiazolidinediones	540 (1.2)	428 (1.0)	311 (0.6)	420 (0.8)
Glinides	38 (0.1)	28 (0.1)	18 (0.0)	26 (0.1)
GLP-1 analogues	53 (0.1)	28 (0.1)	27 (0.1)	17 (0.0)
DPP-4 inhibitors	93 (0.2)	89 (0.2)	62 (0.1)	60 (0.1)
Insulins	747 (1.7)	825 (1.8)	580 (1.2)	837 (1.7)
Socioeconomic status (IMD), by category				
Low	6,945 (15.5)	7,120 (15.9)	8,248 (16.5)	8,054 (16.2)
Low-medium	7,176 (16.0)	7,011 (15.7)	8,200 (16.5)	8,015 (16.1)
Medium	5,763 (12.9)	5,626 (12.6)	6,287 (12.6)	6,113 (12.3)
Medium-high	4,533 (10.1)	4,451 (9.9)	4,521 (9.1)	4,741 (9.5)
High	3,077 (6.9)	3,240 (7.2)	2,896 (5.8)	3,191 (6.4)
Missing	17,274 (38.6)	17,320 (38.7)	19,689 (39.5)	19,727 (39.6)
History of comorbidities before index date				
Angina pectoris	4,615 (10.3)	4,309 (9.6)	4,273 (8.6)	4,603 (9.2)
AMI	1,929 (4.3)	2,336 (5.2)	2,139 (4.3)	2,308 (4.6)
Ischemic stroke	332 (0.7)	468 (1.0)	347 (0.7)	483 (1.0)
Haemorrhagic stroke	191 (0.4)	261 (0.6)	239 (0.5)	275 (0.6)
Valve disorders	482 (1.1)	587 (1.3)	611 (1.2)	609 (1.2)
Peripheral vascular disorders	550 (1.2)	778 (1.7)	664 (1.3)	764 (1.5)
Ulcers	3,280 (7.3)	2,441 (5.5)	3,250 (6.5)	2,815 (5.6)
Non-hip/femur fractures in the year prior to index date	559 (1.2)	623 (1.4)	957 (1.9)	696 (1.4)

Abbreviations: AMI = acute myocardial infarction, BMI = body mass index, DM = diabetes mellitus, DPP-4 = dipeptidyl peptidase-4, eGFR = estimated glomerular filtration rate, GLP-1 = glucagon-like peptide-1, GP = general practitioner, HbA1c = glycated haemoglobin, IMD = index of multiple deprivation, NIAD = non-insulin anti-hyperglycaemic drug, SD = standard deviation.

Table 4.2: Risk of total knee replacement and total hip replacement in patients with diabetes mellitus, stratified by clinical proxies of the severity of DM

DM status	Total knee replacement n=89,536				Total hip replacement n=99,682			
	Cases n=44,768	Controls n=44,768	Crude OR (95% CI)	Fully adjusted OR (95% CI) [a]	Cases n=49,841	Controls n=49,841	Crude OR (95% CI)	Fully adjusted OR (95% CI) [b]
No	39,650	40,173	Reference	Reference	45,766	45,250	Reference	Reference
Yes	5,118	4,595	1.13 (1.08-1.18)	0.85 (0.77-0.94)	4,075	4,591	0.87 (0.84-0.91)	0.87 (0.82- 0.93)
By type of DM								
Type 1	149	211	0.71 (0.58-0.88)	0.73 (0.55-0.96)	189	243	0.77 (0.64-0.93)	0.89 (0.72-1.11)
Type 2	4,636	4,077	1.16 (1.10-1.21)	0.85 (0.76-0.94)	3,579	3,979	0.89 (0.85-0.93)	0.88 (0.83-0.94)
Type unspecified	333	307	1.10 (0.94-1.29)	0.89 (0.73-1.08)	307	369	0.82 (0.71-0.96)	0.79 (0.66-0.94)
By clinical proxies for DM severity								
No neuropathy or retinopathy	4,088	3,588	1.16 (1.10-1.21)	0.85 (0.77-0.94)	3,317	3,669	0.89 (0.85-0.94)	0.86 (0.81-0.92)
Neuropathy only	169	142	1.21 (0.97-1.51)	0.79 (0.56-1.11)	146	144	1.00 (0.80-1.26)	0.88 (0.64-1.22)
Retinopathy only	789	820	0.97 (0.88-1.08)	1.37 (0.76-2.49)	578	721	0.79 (0.70-0.88)	2.18 (1.33-3.57)
Retinopathy and neuropathy	72	45	1.60 (1.11-2.33)	2.20 (1.04-4.66)	34	57	0.58 (0.38-0.89)	1.29 (0.64-2.57)
By renal function (eGFR)								
≥90 ml/min/1,73m^2	787	568	1.42 (1.27-1.58)	1.11 (0.94-1.30)	624	553	1.12 (1.00-1.26)	1.14 (0.99-1.30)
60-89 ml/min/1,73m^2	2,602	2,212	1.20 (1.13-1.27)	0.87 (0.77-0.98)	1,901	2,135	0.88 (0.82-0.94)	0.90 (0.83-0.97)
30-59 ml/min/1,73m^2	1,298	1,376	0.95 (0.88-1.03)	0.69 (0.60-0.79)	1,092	1,322	0.81 (0.75-0.88)	0.79 (0.71-0.87)
15-29 ml/min/1,73m^2	51	96	0.54 (0.38-0.75)	0.43 (0.29-0.65)	63	88	0.70 (0.51-0.97)	0.75 (0.52-1.07)
<15 ml/min/1,73m^2	5	23	0.22 (0.08-0.59)	0.26 (0.08-0.78)	12	23	0.51 (0.25-1.03)	0.56 (0.27-1.19)
Missing	375	320	1.18 (1.02-1.38)	0.95 (0.79-1.14)	383	470	0.80 (0.70-0.92)	0.78 (0.66-0.92)

[a] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. History of comorbidity before index date: acute myocardial infarction, heart failure, cerebrovascular events, ulcers, and peripheral vascular disorders. Retinopathy or neuropathy in the 5 years prior to index date. Most recent value in year prior to index date: HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. [b] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. Retinopathy and neuropathy in the 5 years prior to index date. Most recent value in year prior to index date: fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. Abbreviations: BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HbA1c = glycated haemoglobin, NSAID= non-steroidal anti-inflammatory drug, OR = odds ratio, RAAS = renin-angiotensin-aldosterone system.

equal risk of surgery as compared to non-diabetic patients, but patients using ADs with HbA1c > 6.5 were at a lower risk of TJR. TKR (OR=0.53 [95% CI=0.42-0.66]) and THR (OR=0.44 [95% CI=0.34-0.56]) patients with HbA1c values ≥9.5% were approximately 50% less likely to undergo surgery. In contrast, fasting glucose levels were not associated with a change in risk of TJR. Lastly, treatment stages were generally not associated with risk of surgery. However, patients using both a biguanide and a sulfonylurea (stage 2) were less likely to undergo surgery as compared to non-diabetic patients, with an OR of 0.75 (95% CI=0.65–0.88) for TKR surgery and an OR of 0.80 (95% CI=0.69-0.93) for THR surgery (Table 4.3).

The proportion of control subjects currently using an AD with HbA1c levels ≥9.5% increased with every step up according to the prespecified treatment stages (Table 4.4). The proportion of subjects with HbA1c levels <6.5% decreased with every step up.

The inverse association between DM and TJR was no longer present when taking into account the average Hb1Ac level in the previous 5 years instead of the single most recent HbA1c level (Table S.4.1, Table S.4.2). However, risk of TKR and THR was still decreased with increasing HbA1c levels in current AD users as compared to non-users.

Discussion

In contrast to our hypothesis, the present population-based case-control study did not show a positive association between various proxy indicators of the severity of DM and the risk of TJR surgery. On the contrary, we found 13% to 15% reduced risks between a diagnosis of DM and TJR surgery, and up to a 46% reduction with clinical proxy indicators of disease severity of DM. The use of ADs was associated with a decreased risk of TKR (OR=0.86 [95% CI=0.78-0.94]) and THR (OR=0.90 [95% CI=0.81-0.99]). Moreover, increasing DM severity, according to HbA1c levels, was associated with a lower risk of undergoing TJR surgery. In fact, patients with HbA1c values ≥9.5% were approximately 50% less likely to undergo surgery. When taking into account the average Hb1Ac level in the previous 5 years instead of the single most recent HbA1c level, the inverse association between DM and TJR was no longer present. However, risk of TKR and THR was still decreased with increasing HbA1c levels in current AD users as compared to nonusers. Although this is probably the first study that evaluates the associations between DM as well as proxy indicators for DM severity with the risk of OA-related TJR surgery, it is not in line with previous studies that evaluated the association between (severity of) DM and OA[4,6,7]. This may be explained by mechanistic and methodological reasons.

A lacking differentiation of clinical phenotypes may explain the inverse association between AD use and OA. Previous work has suggested a division of the disease into 5 distinguishable clinical phenotypes[18]. First, a posttraumatic phenotype has been proposed. This phenotype is mainly caused by mechanical stress. Second, a metabolic phenotype, caused by mechanical stress, adipokines, hyperglycaemia, and hormonal imbalance, has been suggested. Third, the aging phenotype associated with AGEs and chondrocyte

TABLE 4.3: Risk of total knee replacement and total hip replacement in current anti-hyperglycaemic drug users, stratified by laboratory and drug use proxies for severity of DM.

AD use	Total knee replacement n=89,536				Total hip replacement n=99,682			
	Cases n= 44,768	Controls n= 44,768	Crude OR (95% CI)	Fully adjusted OR (95% CI) [a]	Cases n= 49,841	Controls n= 49,841	Crude OR (95% CI)	Fully adjusted OR (95% CI) [b]
Never	40,896	41,237	Reference	Reference	46,853	46,304	Reference	Reference
Past	176	179	0.99 (0.81-1.22)	0.96 (0.75-1.24)	166	169	0.96 (0.78-1.20)	0.97 (0.76-1.25)
Recent	73	100	0.74 (0.54-1.00)	0.74 (0.51-1.07)	74	96	0.76 (0.56-1.04)	0.84 (0.59-1.19)
Current	3,623	3,252	1.12 (1.07-1.18)	0.86 (0.78-0.94)	2,748	3,272	0.83 (0.79-0.87)	0.90 (0.81-0.99)
By HbA1c, most recent value in year prior to index date								
<6.5%	718	501	1.45 (1.29-1.63)	0.93 (0.81-1.07)	594	523	1.12 (0.99-1.26)	1.05 (0.92-1.21)
6.5-7.9%	1,771	1,489	1.20 (1.12-1.29)	0.87 (0.79-0.95)	1,205	1,401	0.85 (0.78-0.92)	0.88 (0.80-0.97)
8-9.4%	512	547	0.94 (0.83-1.07)	0.67 (0.58-0.78)	382	510	0.74 (0.65-0.84)	0.73 (0.63-0.86)
≥9.5%	176	280	0.63 (0.52-0.76)	0.53 (0.42-0.66)	123	293	0.41 (0.33-0.51)	0.44 (0.34-0.56)
Missing	446	435	1.03 (0.90-1.18)	0.75 (0.64-0.88)	444	545	0.80 (0.71-0.91)	0.81 (0.70-0.94)
By fasting glucose, most recent value in year prior to index date								
<6.0 mmol/L	95	83	1.16 (0.86-1.56)	0.89 (0.62-1.27)	89	91	0.96 (0.72-1.29)	0.97 (0.69-1.35)
6.0-7.4 mmol/L	163	128	1.29 (1.02-1.62)	0.88 (0.66-1.17)	105	101	1.02 (0.78-1.35)	1.15 (0.84-1.57)
7.5-8.9 mmol/L	169	90	1.91 (1.48-2.47)	1.22 (0.90-1.66)	78	103	0.75 (0.56-1.01)	0.83 (0.59-1.17)
≥9.0 mmol/L	133	133	1.01 (0.79-1.28)	0.79 (0.59-1.07)	117	139	0.83 (0.64-1.06)	0.98 (0.72-1.32)
Missing	3,063	2,818	1.10 (1.04-1.16)	0.83 (0.76-0.92)	2,359	2,838	0.82 (0.77-0.87)	0.89 (0.81-0.98)
By treatment stages								
Stage 1: current use of biguanides or sulfonylureas only	1,638	1,358	1.22 (1.13-1.31)	0.90 (0.80-1.01)	1,314	1,389	0.93 (0.86-1.01)	0.96 (0.86-1.08)
Stage 2: current use of biguanides and sulfonylureas, but no use of other ADs	650	674	0.97 (0.87-1.08)	0.75 (0.65-0.88)	536	672	0.79 (0.70-0.88)	0.80 (0.69-0.93)
Stage 3: current use of TZDs, GLP-1 analogues, DPP-4 inhibitors or glinides	618	466	1.34 (1.19-1.52)	0.89 (0.75-1.05)	356	445	0.79 (0.69-0.91)	0.84 (0.70-1.01)
Stage 4: current use of insulin	717	754	0.96 (0.86-1.06)	0.82 (0.70-0.95)	542	766	0.70 (0.62-0.78)	0.85 (0.73-1.00)

[a] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. History of comorbidity before index date: acute myocardial infarction, heart failure, cerebrovascular events, peripheral vascular disorders, ulcers. Retinopathy or neuropathy in the 5 years prior to index date. Most recent value in the year prior to index date: HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. [b] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. Retinopathy in the 5 years prior to index date. Most recent value in the year prior to index date: HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable.
Abbreviations: AD = anti-hyperglycaemic drug, BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, DM = diabetes mellitus, DPP-4 = dipeptidyl peptidase-4, GLP-1= glucagon-like peptide-1, HbA1c = glycated haemoglobin, NSAID= non-steroidal anti-inflammatory drug, OR = odds ratio, RAAS = renin-angiotensin-aldosterone system, TZD = thiazolidinedione.

Table 4.4: Proportion of HbA1c categories in controls (without total joint replacement). Current users of anti-hyperglycaemic drugs are stratified by treatment stages.

Treatment stages	HbA1c<6.5% n=(%)		HbA1c 6.5-7.9% n=(%)		HbA1c 8-9.4% n=(%)		HbA1c ≥9.5% n=(%)	
Stage 1: current use of biguanides or sulfonylureas only	612	(26.6)	1343	(58.4)	231	(10.0)	115	(5.0)
Stage 2: current use of biguanides and sulfonylureas, but no use of other ADs	194	(16.8)	618	(53.5)	244	(21.1)	99	(8.6)
Stage 3: current use of TZDs, GLP-1 analogues, DPP-4 inhibitors or glinides	134	(16.2)	449	(54.3)	150	(18.1)	94	(11.4)
Stage 4: current use of insulin	84	(6.7)	480	(38.1)	432	(34.3)	265	(21.0)

Abbreviations: DPP-4 = dipeptidyl peptidase-4, GLP-1= glucagon-like peptide-1, HbA1c = glycated haemoglobin, TZD = thiazolidinedione.

senescence has been mentioned. Fourth, a genetic phenotype has been proposed. Fifth, a pain related phenotype may also exist. According to this classification, if corrected for overweight, DM may primarily be associated with metabolic OA, whereas other phenotypes have other causative features. In this study, such a differentiation has not been made. We have, therefore, not exclusively included metabolic OA patients. This may explain the fact that we did not find an increased risk of TJR in DM patients compared to non-DM patients.

Dissimilarities in methodology, such as the definition of OA, between studies may be of interest. Other studies have determined OA by using the American College of Rheumatology classification criteria or by using radiographically determined Kellgren and Lawrence scores[4,7]. In this study we used TJR surgery to define severe OA. This may not reflect severity of OA as directly as Kellgren and Lawrence scores, for example, but in epidemiology it has been widely used in studies assessing risk factors for severe OA[6,19]. Remarkably, a study using a definition for severe OA similar to ours reported an increased risk of OA in DM patients compared to patients without DM[6]. Still, several dissimilarities exist between our study and that by Schett and colleagues. First, their population demographics, such as mean age and sex distribution, were different compared to those in our study. On average the population included by Schett et al. was younger than the patients in our study. A study by King et al.[20] reported increased rates of TJR at lower age. Therefore, this difference may have led to effect modification by age. After stratification by age we also found a decreased risk of surgery with increasing age.

It might be possible that, by missing out on the low risk older population, the analysis by Schett and colleagues resulted in an overall higher risk of surgery. Second, Schett and colleagues adjusted for age, sex, lifestyle factors, cholesterol and BMI, but no consideration was given toward covariates associated with hypertension. Since hypertension has also been considered to be an important component of the metabolic syndrome, possibly associated with metabolic OA, correction for this comorbidity is recommended[21]. However, when we estimated ORs without correcting for the use of antihypertensive drugs, similar ORs were found compared to analyses with adjustment for use of antihypertensive drugs (TKR: OR=0.86 [95% CI=0.81-0.91]; THR: OR=0.90 [95% CI=0.84-0.95]).

Although evidence is limited, a combination of these methodological differences may have resulted in our deviating finding. Although analyses were adjusted for BMI, drug use, and several comorbidities, other factors may have caused the inverse association between DM severity and the risk of OA. First, we should consider confounding by indication. Patients with DM, especially those with severe DM, are possibly less eligible for surgery due to an increased risk of surgical complications. For example, the risk of infection associated with surgery is higher in DM patients compared to patients who do not have DM[22]. More specifically, high HbA1c levels have been associated with more complications following TJR[23,24]. High HbA1c levels are particularly associated with more surgical site infections[25]. Furthermore, HbA1c levels have been associated with increased mortality rates in non-orthopaedic surgical procedures[26]. Based on these increased risks surgeons may be less tempted to operate on these patients. Also, patients with DM could have complications sufficiently serious to prevent surgery, regardless of risk. The duration of DM may also be of concern. Clinically, it is difficult to determine start of DM. Therefore, the time since the first AD prescription may be used to approximate this. Furthermore, DM is known to be underdiagnosed and undertreated[27]. Therefore, we assessed the risk of TJR with a DM diagnosis (Table 4.2) and with the use of an AD (Table 4.3). Second, high HbA1c levels are associated with a decreased adherence to medication[28]. The lack of adherence may suggest care evasive behaviour in general and, consequently, these patients may not be likely to visit their GPs and other healthcare providers on a regular basis. They are, therefore, less likely to undergo elective TJR. A combination of these factors may have resulted in a decreased risk of TJR in patients with increasing severity of DM compared to patients without DM.

Our study has several strengths. First, it was conducted using the world's largest primary care database, which is representative of the British population and consequently, we were able to assess the risk in a large population of >90,000 TJR patients. Second, to our knowledge this is the first study that stratifies risk of OA by disease severity, based on HbA1c values. Third, we had detailed information on both patients and their matched controls. Fourth, medical data were routinely recorded by GPs without the presence of a study hypothesis, minimizing the possibility of recall bias. Like most observational studies, our study is not without limitations. Despite attempts to adjust for several confounders, causal interpretation of the findings will be restricted and residual confounding must be considered when interpreting the results. Furthermore, because this study has focused on severe OA patients, other associations may be found in less severe diseased subjects. The quality of proxies of disease severity may also be of concern. HbA1c levels were generally well registered in the diabetic population that was analysed in this study (83–88%), most likely due to the introduction of the Quality and Outcomes Framework (QOF) indicators for DM in 2004. The impact of missing data on HbA1c in the diabetes population was therefore probably of minor concern. Fasting glucose levels, however, are not included as one of the QOF indicators and consequently have lower registration rates (13–15%). Based

on distribution of patients according to HbA1c levels, one might suggest that registration of fasting glucose is predominantly lacking in the lower fasting glucose categories (<6.0 mmol/L, 6.0-7.4 mmol/L, and 7.5-8.9 mmol/L). Considering the ORs calculated for the ''fasting glucose missing'' group, full registration of this test would probably lead in a reduction of risk in these categories. Misclassification of exposure may also be of concern. Use of ADs is based on prescription data registered in the CPRD. However, adherence is likely to be <100%. We may have therefore overestimated the number of patients using ADs. Assuming this is a non-differential misclassification, and the number of AD users would in fact be lower, this would have resulted in a dilution of the true effect. Consequently, this does not explain the inverse association presented in this study. Finally, TJR could be considered to be an inadequate definition for OA. However, in epidemiology it has been used in previous studies assessing risk factors for severe OA[6,19]. With this definition we are limited to severe cases of OA, missing possible beneficial effects in earlier stages of OA.

In conclusion, in contrast to previous reports, the present study does not indicate that patients with DM are more likely to suffer from severe OA as compared to those without DM. In fact, the risk of severe OA necessitating TJR even decreases with increasing DM severity, based on HbA1c values. This unexpected result may be caused by variability of OA phenotypes, dissimilarities in methodology, or a decrease in eligibility for surgery. Our results suggest more uniform work is still needed to determine the risk of OA in DM patients. Further research may also include differentiation of OA into relevant clinical phenotypes.

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TABLE S.4.1: Risk of total knee replacement and total hip replacement in patients with diabetes mellitus, stratified by clinical proxies of the severity of DM

DM status	Total knee replacement n=89,536				Total hip replacement n=99,682			
	Case n= 44,768	Control n= 44,768	Crude OR (95% CI)	Fully adjusted OR (95% CI) [a]	Case n= 49,841	Control n= 49,841	Crude OR (95% CI)	Fully adjusted OR (95% CI) [b]
No	39,650	40,173	Reference	Reference	45,766	45,250	Reference	Reference
Yes	5,118	4,595	1.13 (1.08-1.18)	1.01 (0.92-1.12)	4,075	4,591	0.87 (0.84-0.91)	0.87 (0.82- 0.93)
By type of DM								
Type 1	149	211	0.71 (0.58-0.88)	0.90 (0.68-1.19)	189	243	0.77 (0.64-0.93)	0.89 (0.72-1.11)
Type 2	4,636	4,077	1.16 (1.10-1.21)	1.02 (0.92-1.13)	3,579	3,979	0.89 (0.85-0.93)	0.88 (0.83-0.94)
Type unspecified	333	307	1.10 (0.94-1.29)	0.99 (0.82-1.21)	307	369	0.82 (0.71-0.96)	0.79 (0.66-0.94)
By clinical proxies for DM severity								
No neuropathy or retinopathy	4,088	3,588	1.16 (1.10-1.21)	1.01 (0.92-1.11)	3,317	3,669	0.89 (0.85-0.94)	0.86 (0.81-0.92)
Neuropathy only	169	142	1.21 (0.97-1.51)	0.95 (0.68-1.33)	146	144	1.00 (0.80-1.26)	0.88 (0.64-1.22)
Retinopathy only	789	820	0.97 (0.88-1.08)	1.55 (0.86-2.79)	578	721	0.79 (0.70-0.88)	2.18 (1.33-3.57)
Retinopathy and neuropathy	72	45	1.60 (1.11-2.33)	2.44 (1.16-5.15)	34	57	0.58 (0.38-0.89)	1.29 (0.64-2.57)
By renal function (eGFR)								
≥90 ml/min/1,73m^2	787	568	1.42 (1.27-1.58)	1.37 (1.16-1.60)	624	553	1.12 (1.00-1.26)	1.14 (0.99-1.30)
60-89 ml/min/1,73m^2	2,602	2,212	1.20 (1.13-1.27)	1.07 (0.96-1.20)	1,901	2,135	0.88 (0.82-0.94)	0.90 (0.83-0.97)
30-59 ml/min/1,73m^2	1,298	1,376	0.95 (0.88-1.03)	0.85 (0.75-0.97)	1,092	1,322	0.81 (0.75-0.88)	0.79 (0.71-0.87)
15-29 ml/min/1,73m^2	51	96	0.54 (0.38-0.75)	0.55 (0.37-0.82)	63	88	0.70 (0.51-0.97)	0.75 (0.52-1.07)
<15 ml/min/1,73m^2	5	23	0.22 (0.08-0.59)	0.29 (0.10-0.89)	12	23	0.51 (0.25-1.03)	0.56 (0.27-1.19)
Missing	375	320	1.18 (1.02-1.38)	0.99 (0.82-1.19)	383	470	0.80 (0.70-0.92)	0.78 (0.66-0.92)

[a] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. History of comorbidity before index date: acute myocardial infarction, heart failure, cerebrovascular events, ulcers, and peripheral vascular disorders. Retinopathy or neuropathy in the 5 years prior to index date. Most recent value in year prior to index date: fasting glucose. Average HbA1c in the 5 years prior to index date. Stratified variables were excluded as confounder in the analyses stratified by that variable. [b] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. Retinopathy and neuropathy in the 5 years prior to index date. Most recent value in the year prior to index date: fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. Abbreviations: BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HbA1c = glycated haemoglobin, NSAID= non-steroidal anti-inflammatory drug, OR = odds ratio, RAAS = renin-angiotensin-aldosterone system.

Table S.4.2: Risk of total knee replacement and total hip replacement in current anti-hyperglycaemic drug users, stratified by laboratory and drug use proxies for severity of DM

AD use	Total knee replacement n=89,536				Total hip replacement n=99,682			
	Case n=44,768	Control n=44,768	Crude OR (95% CI)	Fully adjusted OR (95% CI) [a]	Case n= 49,841	Control n= 49,841	Crude OR (95% CI)	Fully adjusted OR (95% CI) [b]
Never	40,896	41,237	Reference	Reference	46,853	46,304	Reference	Reference
Past	176	179	0.99 (0.81-1.22)	1.04 (0.81-1.34)	166	169	0.96 (0.78-1.20)	1.07 (0.83-1.37)
Recent	73	100	0.74 (0.54-1.00)	0.83 (0.57-1.21)	74	96	0.76 (0.56-1.04)	0.95 (0.67-1.35)
Current	3,623	3,252	1.12 (1.07-1.18)	1.01 (0.91-1.12)	2,748	3,272	0.83 (0.79-0.87)	1.03 (0.93-1.14)
By HbA1c, average value in the 5 years prior to index date								
<6.5%	465	375	1.25 (1.09-1.44)	0.82 (0.70-0.97)	388	365	1.05 (0.91-1.21)	1.02 (0.86-1.20)
6.5-7.9%	1,991	1,638	1.23 (1.15-1.31)	0.89 (0.82-0.97)	1,410	1,596	0.87 (0.81-0.94)	0.89 (0.82-0.98)
8-9.4%	721	744	0.98 (0.88-1.08)	0.71 (0.62-0.81)	542	713	0.75 (0.67-0.84)	0.74 (0.65-0.85)
≥9.5%	184	254	0.73 (0.60-0.88)	0.57 (0.45-0.72)	130	268	0.48 (0.39-0.59)	0.51 (0.40-0.65)
Missing	262	241	1.09 (0.91-1.31)	0.85 (0.68-1.05)	278	330	0.83 (0.71-0.98)	0.82 (0.68-1.00)
By fasting glucose, most recent value in the year prior to index date								
<6.0 mmol/L	95	83	1.16 (0.86-1.56)	1.05 (0.73-1.51)	89	91	0.96 (0.72-1.29)	1.13 (0.81-1.57)
6.0-7.4 mmol/L	163	128	1.29 (1.02-1.62)	1.06 (0.80-1.42)	105	101	1.02 (0.78-1.35)	1.33 (0.97-1.82)
7.5-8.9 mmol/L	169	90	1.91 (1.48-2.47)	1.45 (1.06-1.96)	78	103	0.75 (0.56-1.01)	0.95 (0.67-1.34)
≥9.0 mmol/L	133	133	1.01 (0.79-1.28)	0.94 (0.69-1.26)	117	139	0.83 (0.64-1.06)	1.08 (0.80-1.46)
Missing	3,063	2,818	1.10 (1.04-1.16)	0.99 (0.89-1.10)	2,359	2,838	0.82 (0.77-0.87)	1.01 (0.91-1.12)
By treatment stages								
Stage 1: current use of biguanide or sulfonylureas only	1,638	1,358	1.22 (1.13-1.31)	1.05 (0.93-1.17)	1,314	1,389	0.93 (0.86-1.01)	1.09 (0.98-1.22)
Stage 2: current use of biguanide and sulfonylureas, but no use of other ADs	650	674	0.97 (0.87-1.08)	0.89 (0.76-1.04)	536	672	0.79 (0.70-0.88)	0.91 (0.78-1.07)
Stage 3: current use of TZD, GLP-1 analogues, DPP-4 inhibitors or glinides	618	466	1.34 (1.19-1.52)	1.09 (0.92-1.29)	356	445	0.79 (0.69-0.91)	0.97 (0.80-1.17)
Stage 4: current use of insulin	717	754	0.96 (0.86-1.06)	0.99 (0.83-1.15)	542	766	0.70 (0.62-0.78)	0.97 (0.83-1.15)

[a] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. History of comorbidity before index date: acute myocardial infarction, heart failure, cerebrovascular events, peripheral vascular disorders, ulcers. Retinopathy or neuropathy in the 5 years prior to index date. Most recent value in the year prior to index date: fasting glucose. Average HbA1c in the 5 years prior to index date. Stratified variables were excluded as confounder in the analyses stratified by that variable. [b] Adjusted for: Smoking status and BMI. Drug use in the 6 months prior to index date: statins, thiazide diuretics, calcium channel blockers, beta-blockers, RAAS inhibitors, loop diuretics, non-selective NSAIDs, COX2-selective NSAIDs. Retinopathy in the 5 years prior to index date. Most recent value in the year prior to index date: fasting glucose. Average HbA1c in the 5 years prior to index date. Stratified variables were excluded as confounder in the analyses stratified by that variable. Abbreviations: AD = anti-hyperglycaemic drug, BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, DM = diabetes mellitus, DPP-4 = dipeptidyl peptidase-4, GLP-1= glucagon-like peptide-1, HbA1c = glycated haemoglobin, NSAID= non-steroidal anti-inflammatory drug, OR = odds ratio, RAAS = renin-angiotensin-aldosterone system, TZD = thiazolidinedione.

Chapter 5

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

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Submitted

Abstract

Background: 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 definition of osteoarthritis (OA) or misclassification of the onset of OA were raised as possible explanations.

Objective: To explore the effect of the definition of OA as outcome measure in the CPRD, 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. To determine the effect of the definition of the outcome, 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 20% lower than when OA diagnostic 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: The lower risk estimates found when using TJR as a proxy for OA compared to the use of diagnostic codes may possibly be the result of selection bias. Future studies should take this in to account, or use other proxies or validated diagnostic codes.

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 over[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[3,4,5,6]. 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 against relatively 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 regarding 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 properly. Consequently, the unexpected results obtained in our previous study may be the result of selection bias due to the use of TJR as a 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 order to evaluate the abovementioned 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.

Methods

Data source

A population-based cohort study was performed using the CPRD. 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.

Study population

In the CPRD database, all patients aged 18 years or older who received their first NIAD prescription between January 1987 and October 2012 were selected. Follow-up started at the date of the first NIAD prescription. Patients with a recorded diagnosis of rheumatoid arthritis (RA) or a hip/femur fracture 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 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 (Figure 5.1).

Exposure

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

Outcomes

For data analysis, two cohorts were created based on the outcome: TJR (total knee replacement (TKR) or total hip replacement (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 outcome of interest, whichever came first. Within these cohorts, five potential types of patients were considered (Figure 5.2). Type 1 patients had an OA diagnosis followed by a TJR later during follow-up. Type 2 patients only had an OA diagnosis during follow-up, and no TJR surgery.

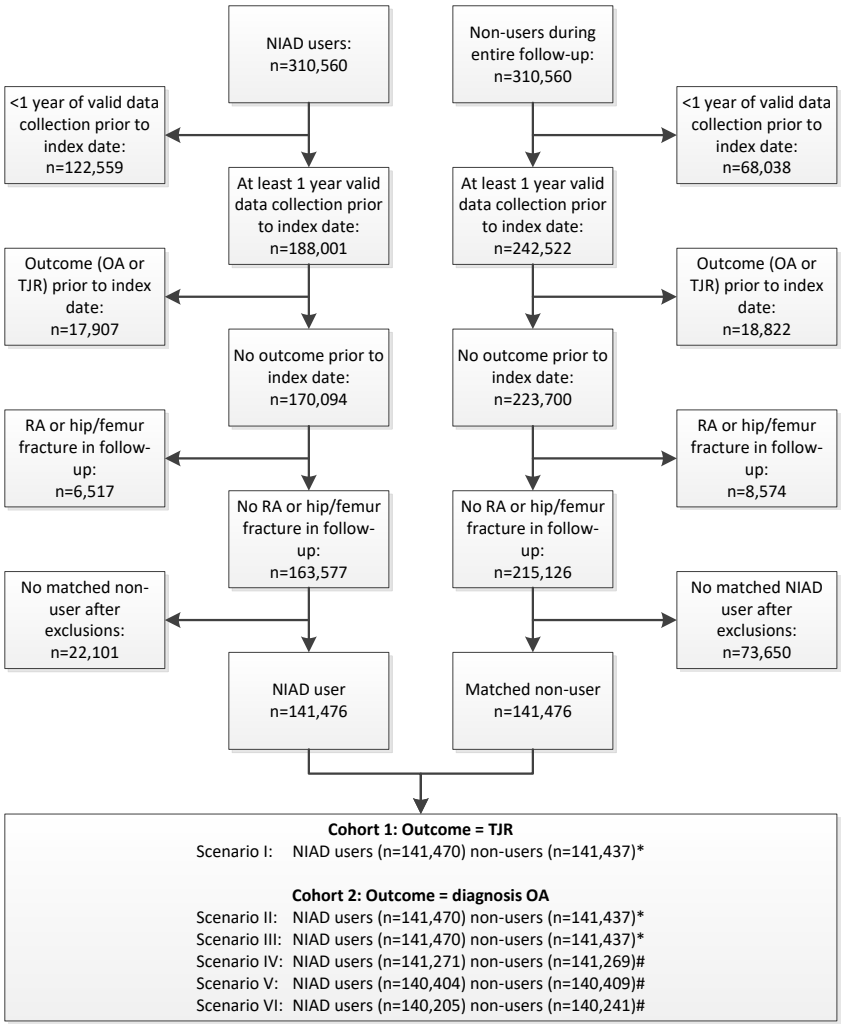

Figure 5.1: Exclusion flowchart. * Loss of patients due to lack of follow-up. # Additional loss of patients due to exclusion of specific patient types (Scenario IV: patient type 5 excluded; Scenario V: patient type 3 excluded; Scenario VI: patient type 3 and 5 excluded). Abbreviations: NIAD = non-insulin anti-hyperglycaemic drug, OA = osteoarthritis, RA = rheumatoid arthritis, TJR = total joint replacement.

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.

Potential confounders

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

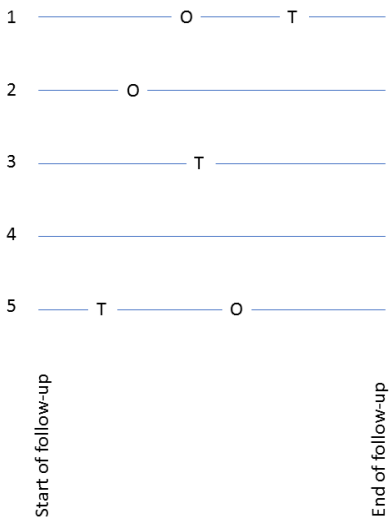

Figure 5.2: Potential patient types. Type 1 (n=3,133), type 2 (n=22,296), type 3 (n=2,094), type 4 (n=255,062), type 5 (n=367). O = osteoarthritis, T = total joint replacement surgery.

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 (Figure 5.2), six scenarios were analysed and are listed in detail in Table 5.1. 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 of interest.

In scenario I, the risk of TJR was assessed while ignoring a potential 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

Table 5.1: 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[7]. 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 was 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 occurs, - = in this patient type the outcome does not occur
Patient types (Figure S.5.1):
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 occurred during follow-up.
Type 5: In this patient type, first a TJR was registered, followed by an OA diagnosis.
Abbreviations: OA = osteoarthritis, TJR = total joint replacement.

same cohort as in scenario II, but now excluded patients with an OA diagnosis after TJR surgery (patient type 5). 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 (patient type 3). In scenario VI, the risk of an OA diagnosis was assessed while patients with a TJR surgery only (patient type 3), and patients with a TJR surgery prior to the OA diagnosis (patient type 5) were excluded (Table 5.1).

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

Results

Baseline characteristics of T2DM patients (n=141,476) and patients without T2DM (n=141,476) are presented in Table 5.2. 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 sustain either one of the outcomes (OA or TJR) during follow-up (10.4%), as compared to the patients without T2DM (9.3%) (Table 5.3).

The risk of TJR or OA for T2DM patients compared to patients without T2DM, determined in the various scenarios, is depicted in Table 5.4. 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 (Figure 5.3). Similar results were found when a latency period was added to the joint-specific subgroup analyses (Figures S.5.1, S.5.2, and S.5.3).

Table 5.2: Baseline characteristics

Characteristic	T2DM n=141,476 (%)	No T2DM n=141,476 (%)
Age (years, mean (SD))	58.3 (14.9)	58.3 (14.9)
<40 years	17,857 (12.6)	17,857 (12.6)
41-65 years	76,165 (53.8)	76,165 (53.8)
>65 years	47,454 (33.5)	47,454 (33.5)
BMI (kg/m^2, mean(SD))	31.4 (6.7)	26.7 (5.0)
≤20 kg/m^2	1,993 (1.4)	6,961 (4.9)
21-25 kg/m^2	18,442 (13.0)	42,895 (30.3)
26-30 kg/m^2	45,257 (32.0)	47,098 (33.3)
>30 kg/m^2	71,938 (50.8)	24,783 (17.5)
Missing	3,846 (2.7)	19,739 (14.0)
Number of females	63,860 (45.1)	63,860 (45.1)

Abbreviations: BMI = body mass index, SD = standard deviation, T2DM = type 2 diabetes mellitus

Table 5.3: Outcome during follow-up

Outcome during follow-up	T2DM n=141,476 (%)	No T2DM n=141,476 (%)
Any outcome	14,678 (10.4)	13,212 (9.3)
TJR only	1,066 (0.8)	1,028 (0.7)
OA only	11,975 (8.5)	10,321 (7.3)
TJR and OA	1,637 (1.2)	1,863 (1.3)

Abbreviations: OA = osteoarthritis, T2DM = type 2 diabetes mellitus, TJR = total joint replacement.

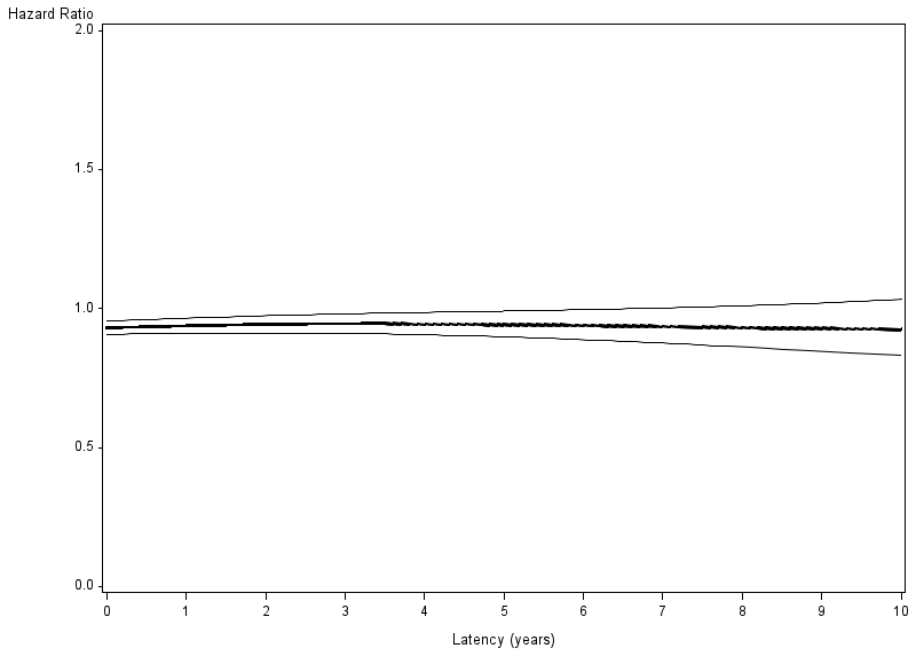

Figure 5.3: Risk (HR (bold line) and 95% CI) of OA in T2DM patients compared to patients without T2DM with varying latency period after start of follow-up. Analyses conducted in Scenario VI. Adjusted for: age, BMI, and sex. Abbreviations: BMI = body mass index, CI = confidence interval, HR = hazard ratio, OA = osteoarthritis, T2DM = type 2 diabetes mellitus.

Table 5.4: Primary, and subgroup analyses assessing risk of TJR or OA in T2DM patients compared to patients without T2DM.[a]

Diagnosis	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	Reference	Reference	Reference	Reference	Reference	Reference
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 or 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 or 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)

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

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 as the primary scenario (Scenario II). The results were 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 did 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 (odds ratio (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 potential relevant confounders that were included in the previous case-control study.

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 that the HR for the OA diagnosis. As suggested previously, this may have been caused by selection bias. Compared to patients without

T2DM, patients with T2DM may have a reduced eligibility to undergo elective joint surgery, due to the presence of contraindicating comorbidities or risk factors[12,13]. In contrast to TJR, this is unlikely to have affected the recording of an OA diagnosis.

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 subgroup 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 that is representative for the total 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 biopathological 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 relatively 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 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 misclassification 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. Possibly, 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.

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Supplementary material

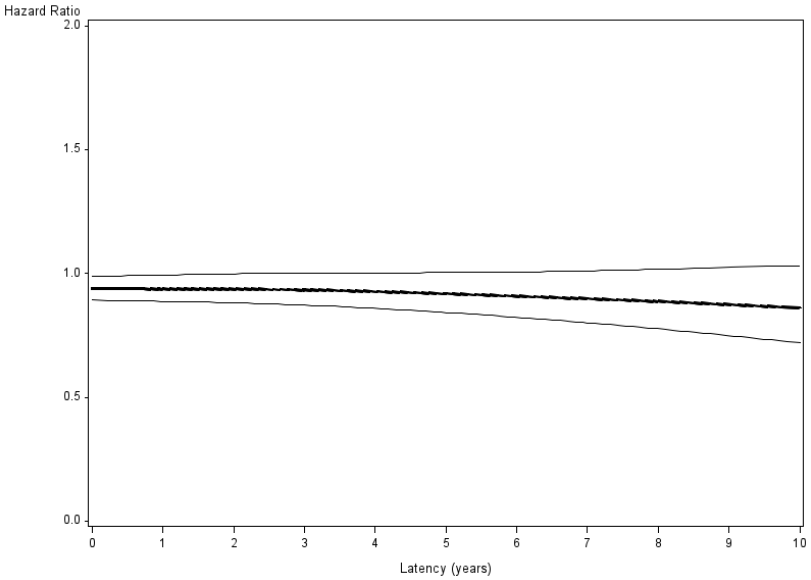

Figure S.5.1: Risk (HR (bold line) and 95% CI) of KOA in T2DM patients compared to patients without T2DM with varying latency period after start of follow-up. Analyses conducted in Scenario VI. Adjusted for: age, BMI, and sex. Abbreviations: BMI = body mass index, CI = confidence interval, HR = hazard ratio, KOA = knee osteoarthritis, T2DM = type 2 diabetes mellitus.

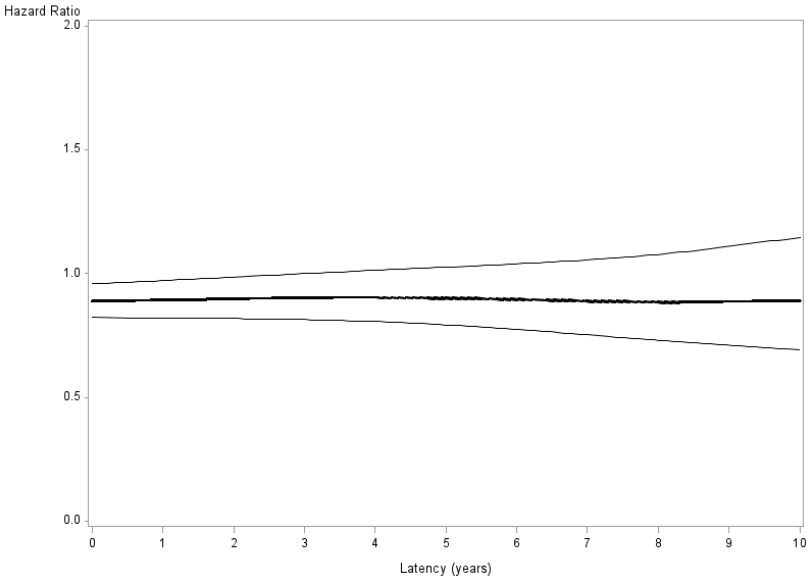

Figure S.5.2: Risk (HR (bold line) and 95% CI) of HOA in T2DM patients compared to patients without T2DM with varying latency period after start of follow-up. Analyses conducted in Scenario VI. Adjusted for: age, BMI, and sex. Abbreviations: BMI = body mass index, CI = confidence interval, HOA = hip osteoarthritis, HR = hazard ratio, T2DM = type 2 diabetes mellitus.

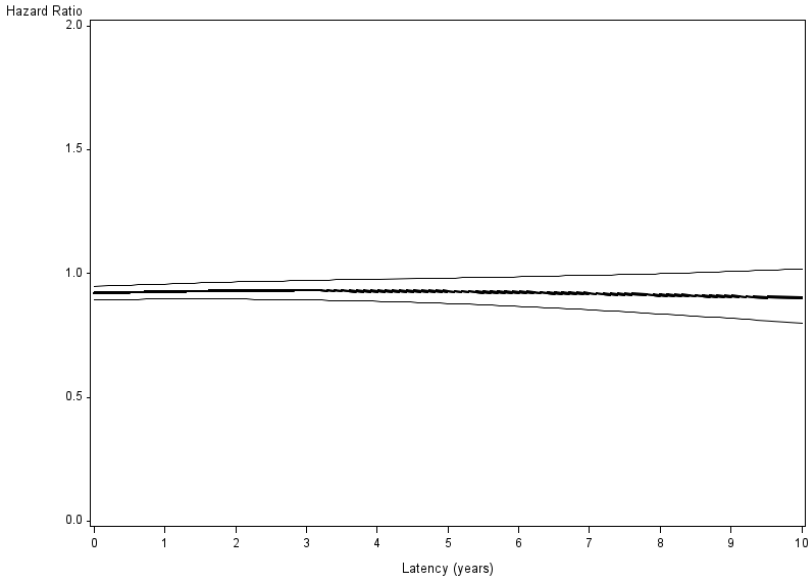

Figure S.5.3: Risk (HR (bold line) and 95% CI) of OA (other than HOA or KOA) in T2DM patients compared to patients without T2DM with varying latency period after start of follow-up. Analyses conducted in Scenario VI. Adjusted for: age, BMI, and sex. Abbreviations: BMI = body mass index, CI = confidence interval, HOA = hip osteoarthritis, HR = hazard ratio, KOA = knee osteoarthritis, OA = osteoarthritis, T2DM = type 2 diabetes mellitus.

Part 2

Effectiveness and safety outcomes associated with the treatment of osteoarthritis

Chapter 6

Use of parenteral glucocorticoids and the risk of new onset type 2 diabetes mellitus: a case-control study

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Submitted

Abstract

Background: Use of oral glucocorticoids (GCs) has been associated with hyperglycaemia and type 2 diabetes mellitus (T2DM). However, unlike oral GCs, there is minimal or no data on the effect of parenteral GC use on T2DM.

Objective: To assess the association between use of parenteral GCs and the risk of receiving a first prescription of a non-insulin anti-hyperglycaemic drug (NIAD) as a proxy for new onset of T2DM.

Methods: A population based case-control study was performed using the Clinical Practice Research Datalink (CPRD). Cases (n=177,154) were defined as patients >18 years of age who had their first ever NIAD prescription between January 1987 and October 2013. Controls were matched by age, gender and general practice. Conditional logistic regression analyses were used to estimate the risk of receiving a first NIAD prescription with the use of parenteral GCs. To determine the effect of prolonged GC use, we stratified current users by number of prescriptions. We also stratified current users by type of GC. Our analyses were statistically adjusted for lifestyle factors, comorbidities and concomitant drug use.

Results: Although this study confirmed that use of oral GCs increases the risk of receiving a first prescription of a NIAD (OR = 2.63 [95% CI = 2.53-2.73]), there was no association between the use of parenterally administered GCs and the risk of receiving a first prescription of a NIAD (OR = 0.88 [95% CI = 0.76-1.02]). The number of parenteral GC prescriptions was not associated with risk of new onset T2DM compared to no parenteral GCs use; neither was the type of GC.

Conclusion: Our study did not demonstrate an association between the use of parenteral GCs and the risk of new onset of T2DM.

Introduction

Glucocorticoids (GCs) are widely used as treatment for many diseases because of their anti-inflammatory and immunosuppressive properties. Despite their efficacy, their use has been associated with various side effects, including hyperglycaemia and induction of type 2 diabetes mellitus (T2DM)[1,2,3,4,5,6,7].

The risk of developing GC-induced diabetes has previously been described in multiple observational studies. A case-control study demonstrated that orally administered GCs may be associated with up to 2% of incident cases of diabetes in a primary care population[1]. Two other observational studies showed a two-fold increased risk of T2DM with oral GC use[3,6]. The main determinants of developing diabetes are the daily dose of GCs, type of GC, a longer duration of treatment, continuous use, an older age, a higher glycosylated haemoglobin (HbA1c) level at baseline and a higher body mass index (BMI)[5,7]. Multiple mechanisms have been suggested to be involved in the development of GC-induced T2DM, such as increased hepatic glucose production, inhibition of glucose uptake in muscles and adipose tissue, and decreased beta-cell function[7].

Similar to oral GCs, parenteral GCs are used mainly as pulse therapy in patients with rheumatoid arthritis and in patients with osteoarthritis. Previous studies have demonstrated that the use of parenteral GCs is associated with hyperglycaemia in non-diabetic patients[8,9]. However, unlike oral GCs, there is minimal or no data regarding the incidence of new onset of T2DM among parenteral GC users. Due to the different routes of administration and different dosing regimes, the risk of T2DM may differ from oral GCs. Therefore, the objective of this study was to assess the association between use of parenteral GCs and the risk of receiving a first prescription of a non-insulin anti-hyperglycaemic drug (NIAD) as a proxy for new onset T2DM.

Methods

Data sources

A case-control study was performed using the Clinical Practice Research Datalink (CPRD). The CPRD is a large primary care database containing medical records registered by over 625 general practitioners (GP) in the UK. It represents 8% of the total British population. In the UK, GPs play a key role in the healthcare system as they are responsible for primary care and specialist referrals. Consequently, this database provides information on a wide range of medical records, including diagnoses, prescriptions, specialist referrals, and laboratory test results[10].

Study population

All patients (>18 years of age), between January 1987 and October 2013, who had their first ever prescription record of a NIAD were defined as a case. The first prescription record of a NIAD was used as a proxy for new onset of T2DM. NIADs included metformin, sulphonylurea,

glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, thiazolidinediones, and acarbose. The index date was defined as the date of the first NIAD prescription. A minimum period of 12 months of follow-up before the index date was required to ensure new onset of T2DM. For each T2DM patient, one control patient without a NIAD or insulin prescription prior to the index date was selected and matched by year of birth, sex, and GP practice using incidence density sampling.

Exposure assessment

Use of oral and parenteral GCs was determined by reviewing prescriptions before the index date. Current users comprised all patients with at least one recorded prescription within the 90-day period before index date. Recent users were those who received a GC between 91 days and 180 days before index date, but without a prescription in the 90-day period before index date. Past users were defined as patients who had a last GC prescription more than 180 days before the index date.

Covariates

We reviewed the literature to identify risk factors for T2DM. Risk factors including BMI (most recent value prior to index date) and smoking status were used as potential confounders. Furthermore, a history of comorbidities such as heart failure, angina pectoris, acute myocardial infarction (AMI), hypertension, hypercholesterolemia, arrhythmias, cerebrovascular diseases, osteoarthritis, systemic lupus erythematosus, rheumatoid arthritis, transplants, retinopathy and neuropathy before index date were also included. Drugs which may induce hyperglycaemia[11], such as loop diuretics, beta-blockers, antipsychotics, protease inhibitor, other forms of GCs (nasal, topical, etc.) and other drugs such as calcium channel blockers, RAAS inhibitors, statins in the six months prior to index date were also considered as potential confounders.

Statistical analysis

Conditional logistic regression analyses (using SAS version 9.3, PHREG procedure) were used to assess the association between new onset of T2DM and use of oral and parenteral GCs, expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). In all analyses, covariates were included as confounders if they independently changed the beta-coefficient for current GC exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. To determine whether a duration-response relationship was present we stratified the current parenteral GC users by the number of prescriptions before index date (1-4, 5-8, >8 prescriptions). To determine whether there was a difference between the various parenteral GCs, current users were stratified by substance (triamcinolone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone).

Results

Between January 1987 and October 2013, 177,154 cases and 177,154 controls were identified. The characteristics of cases and controls are summarized in Table 6.1. Age, gender and smoking status distribution were similar among cases and controls. Cases had a higher average BMI (31.4kg/m^2 vs. 26.5 kg/m^2), average HbA1c (8.6 % vs. 6.3%), and average fasting glucose level (10.1 mmol/L vs. 5.3 mmol/L) compared to controls. Similarly, a history of comorbidities and drug use was found to be higher among the cases than among the controls.

Current use of oral GCs was associated with an increased risk of receiving a first NIAD prescription (OR=2.63 [95% CI=2.53-2.73]), Table 6.2. After adjusting for relevant confounders, the corresponding adjusted OR was 2.55 (95% CI=2.43-2.68).

Table 6.3 shows that there was an association between the use of parenteral GCs with receiving a first NIAD prescription (OR=1.29 [95% CI=1.15-1.44]). However, this association was no longer present after full statistical adjustment for confounders (OR=0.88 [95% CI=0.76-1.02]). There was no difference in the effect on risk of first NIAD prescription with increasing number of parenteral GC prescriptions compared to patients without parenteral GC use. Furthermore, there was no difference between the different parenteral GC substances (Table 6.4).

Discussion

This study found no association between the use of parenterally administered GCs and the risk of receiving a first prescription of a NIAD as a proxy for new onset T2DM. An increase in the number of GC prescriptions or the type of parenteral GC was not associated with risk of new onset T2DM compared to no parenteral GC use. However, in line with other observational studies, we found an increased risk of GC-induced diabetes among oral GC users compared to non-users[1,3,6]. This provides evidence for the 'assay sensitivity' of our data source, study design and definitions of exposure and outcome.

We did not find an association between the use of parenteral GCs and new onset of T2DM. First, this may be explained by the short duration and intermittent use of parenteral GCs. The effect of GCs is usually transient and reversible. As GC doses are reduced, their effect on endocrine metabolism returns to baseline and drug induced diabetes is expected to resolve[8]. Among oral GC users, a continuous GC scheme and long duration have been described as predictors for T2DM[5,7]. Blackburn et al. showed that the incidence of T2DM increased with longer duration of oral GC use. The incidence of T2DM increased after >3 months of GC use among oral GC users compared with the reference group. The numbers needed to harm for continuous use of oral GCs over 1, 2 and 3 years were 41, 23 and 16 respectively[3]. In our study, approximately 85% of the cases currently using a GC had 1-4 prescriptions prior to index date. This duration of parenteral GC use may be too short to affect the development of T2DM. Furthermore, the risk of new onset of T2DM within current

Table 6.1: Baseline characteristics of cases (NIAD users) and controls (non-NIAD users)

Characteristic	Cases n=177,154 (%)	Controls n=177,154 (%)
Mean age at index date (years, (SD))	60.8 (15.0)	60.8 (15.0)
Number of females	83,359 (47.1)	83,359 (47.1)
Smoking status, by category		
Never	71,544 (40.4)	77,842 (43.9)
Current	32,667 (18.4)	34,349 (19.4)
Ex	64,476 (36.4)	45,412 (25.6)
Missing	8,467 (4.8)	19,551 (11.0)
BMI, most recent value prior to index date		
BMI (kg/m^2, mean (SD))	31.4 (6.6)	26.5 (4.9)
BMI, by category		
<25.0 kg/m^2	22,597 (12.8)	58,027 (32.8)
25-29.9 kg/m^2	53,338 (30.1)	54,671 (30.9)
30-34.9 kg/m^2	46,940 (26.5)	20,258 (11.4)
≥ 35.0 kg/m^2	40,473 (22.8)	7,757 (4.4)
Missing	13,806 (7.8)	36,441 (20.6)
HbA1c most recent value within the year prior to index date		
HbA1c (%, mean (SD))	8.6 (1.8)	6.3 (1.2)
HbA1c, by category		
<6.5%	5,138 (2.9)	2,334 (1.3)
6.5-7.9%	37,484 (21.2)	712 (0.4)
8.0-9.4%	27,313 (15.4)	216 (0.1)
≥9.5	24,119 (13.6)	86 (0.0)
Missing	83,100 (46.9)	173,806 (98.1)
Fasting glucose most recent value within the year prior to index date		
Fasting glucose (mmol/L, mean (SD))	10.1 (4.0)	5.3 (0.8)
Fasting glucose, by category		
<6.0 mmol/L	2,075 (1.2)	8,748 (4.9)
6.0-7.4 mmol/L	8,329 (4.7)	1,181 (0.7)
7.5-8.9 mmol/L	9,080 (5.1)	98 (0.1)
≥9.0 mmol/L	17,814 (10.1)	39 (0.0)
Missing	139,856 (78.9)	167,088 (94.3)
History of comorbidities before index date		
Type 2 diabetes mellitus	133,069 (75.1)	1,955 (1.1)
Retinopathy	9,161 (5.2)	902 (0.5)
Neuropathy	3,528 (2.0)	1,258 (0.7)
Angina pectoris	20,290 (11.5)	11,193 (6.3)
Acute myocardial infarction	11,880 (6.7)	6,186 (3.5)
Heart failure	8,528 (4.8)	4,173 (2.4)
Hypercholesterolemia	16,572 (9.4)	9,025 (5.1)
Hypertension	82,665 (46.7)	44,686 (25.2)
Arrhythmias	12,919 (7.3)	8,403 (4.7)
Cerebrovascular diseases	12,489 (7.0)	8,115 (4.6)
Osteoarthritis	35,440 (20.0)	28,248 (15.9)
Rheumatoid arthritis	2,919 (1.6)	2,549 (1.4)
Transplants	412 (0.2)	210 (0.1)
History of drug use within 6 months before index date		
Loop diuretics	21,481 (12.1)	9,178 (5.2)
Calcium channel blockers	38,179 (21.6)	19,204 (10.8)
Beta-blockers	35,116 (19.8)	17,922 (10.1)
RAAS inhibitors	65,994 (37.3)	25,596 (14.4)
Statins	76,753 (43.3)	25,241 (14.2)
Antipsychotics	4,367 (2.5)	2,404 (1.4)
Other administration forms of GCs (oral, topical, nasal etc.)	30,073 (17.0)	16,787 (9.5)

Abbreviations: BMI = body mass index, GC = glucocorticoid, HbA1c = glycated haemoglobin, RAAS = renin-angiotensin-aldosterone-system, SD = standard deviation.

Table 6.2: Use of oral GCs and risk of first NIAD prescription

Oral GC use	Cases (n=177,154)	Controls (n=177,154)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)
Never	146,700	156,679	Reference	Reference
Past	18,988	15,104	1.37 (1.34-1.40)	1.04 (1.01-1.07)
Recent	1,946	1,426	1.48 (1.38-1.59)	1.14 (1.04-1.25)
Current	9,520	3,945	2.63 (2.53-2.73)	2.55 (2.43-2.68)

[a] Adjusted for: BMI and smoking status. History of disease ever before index date: angina pectoris, heart failure, hypertension, neuropathy, osteoarthritis. Drug use in 6 months prior to index date: loop diuretics, RAAS-inhibitors, statins, calcium channel blockers. Abbreviations: BMI = body mass index, CI = confidence interval, GCs = glucocorticoids, OR = odds ratio, RAAS = renin-angiotensin-aldosterone-system.

Table 6.3: Use of parenteral GCs and risk of first NIAD prescription, stratified by number of parenteral GC prescriptions.

Parenteral GC use	Cases (n=177,154)	Controls (n=177,154)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)
Never	164,615	167,423	Reference	Reference
Past	11,191	8,656	1.34 (1.30-1.38)	1.02 (0.98-1.06)
Recent	639	503	1.32 (1.18-1.49)	0.91 (0.77-1.06)
Current	709	572	1.29 (1.15-1.44)	0.88 (0.76-1.02)
By number of prescriptions ever before index date				
1 – 4	601	507	1.23 (1.09-1.38)	0.87 (0.74-1.03)
5 – 8	76	46	1.73 (1.20-2.50)	0.76 (0.48-1.23)
>8	32	19	1.76 (0.99-3.10)	1.55 (0.70-3.43)

[a] Adjusted for: BMI and smoking status. History of disease ever before index date: angina pectoris, heart failure, hypertension, neuropathy, osteoarthritis. Drug use in 6 months prior to index date: loop diuretics, RAAS-inhibitors, statins, calcium channel blockers, other glucocorticoids. Abbreviations: BMI = body mass index, CI = confidence interval, GCs = glucocorticoids, NIAD = non-insulin anti-hyperglycaemic drug, OR = odds ratio, RAAS = renin-angiotensin-aldosterone-system.

Table 6.4: Use of parenteral GCs and risk of first NIAD prescription, stratified by substance.

Parenteral GC use	Cases (n=177,154)	Controls (n=177,154)	Crude OR (95% CI)	Adjusted OR [a] (95% CI)
Never	164,615	16,7423	Reference	Reference
Past	111,91	8,656	1.34 (1.30-1.38)	1.02 (0.98-1.06)
Recent	639	503	1.32 (1.18-1.49)	0.91 (0.77-1.06)
Current	709	572	1.29 (1.15-1.44)	0.88 (0.76-1.02)
By substance, most recent prior to index date				
Triamcinolone	175	140	1.29 (1.03-1.61)	0.87 (0.65-1.18)
Prednisolone	18	8	2.33 (1.01-5.37)	2.28 (0.79-6.60)
Methylprednisolone	462	370	1.30 (1.13-1.49)	0.86 (0.72-1.04)
Hydrocortisone	54	54	1.04 (0.72-1.52)	0.83 (0.50-1.38)
Dexamethasone	0	0	-	-

[a] Adjusted for: BMI and smoking status. History of disease ever before index date: angina pectoris, heart failure, hypertension, neuropathy, osteoarthritis. Drug use in 6 months prior to index date: loop diuretics, RAAS-inhibitors, statins, calcium channel blockers, other glucocorticoids. Abbreviations: BMI = body mass index, CI = confidence interval, GC = glucocorticoid, NIAD = non-insulin anti-hyperglycaemic drug, OR = odds ratio, RAAS = renin-angiotensin-aldosterone-system.

GC users with >8 prescriptions was increased (OR=1.55 [95% CI=0.70-3.43]). This effect, however, was not statistically significant, possibly due to a small sample size. Secondly, most of the parenteral GCs are locally administered. Of the parenteral GCs, methylprednisolone was mostly used in both cases and controls (about 65%). In general, this GC is used intra-articularly or intramuscularly. A previous study showed that intra-articularly administered GCs influence glucose concentrations in patients with controlled diabetes[12]. However, when using GCs locally the time exposed to sufficiently high concentrations may be too short to have systemic effects and to develop T2DM. After administration of methylprednisolone intra-articularly peak levels were observed after 2-12 hours and complete clearance from the blood after 5 days[13,14,15].

Our study has several strengths and limitations. To our knowledge, this is the first study that evaluated the association between use of parenteral GCs and new onset of T2DM. It was conducted using the world's largest primary care database which is representative for 8% of the British population. This enabled us to assess the risk of T2DM in 12,539 users of parenteral GCs. Third, we have evaluated the effect of duration of parenteral GC use and risk of T2DM by stratifying our analyses by number of prescriptions.

A limitation of this study is that the causal interpretation of the findings will be restricted. Although we corrected for relevant covariates, confounding remains a considerable concern in observational studies. Due to limited availability of data we were unable to control for some factors, such as ethnicity, and genetic factors. This may have influenced the results, since ethnicity and genetic factors are important risk factors for developing T2DM. In the United Kingdom, South Asian and Black communities are two to four times more likely to develop T2DM than those with a Caucasian background[16,17]. Since the majority of the British population includes Caucasians, lack of data on ethnicity is not likely to be an important limitation in our study. Confounding by indication may be another concern in observational studies. GCs are mostly prescribed in patients with rheumatoid arthritis, systemic lupus erythematosus and other inflammatory disease. These patients are at increased risk of developing cardiovascular disease and T2DM because of their pathological background. Based on this knowledge, GC users are, due to their co-morbidity, more likely to develop T2DM[18]. However, these factors did not change the beta-coefficient of current GC use with >5% compared to the crude analysis. Therefore, they were not included as relevant confounders. Misclassification of exposure may also be of concern. Prescription data were used to determine exposure. However, the nature of this data does not allow us to confirm compliance of medication. Furthermore, since the CPRD database does not contain prescription data from hospitals or day care clinics, we were not able to include parenteral GC administrations from these settings. These factors may have led to underestimation of the exposure. However, since most locally used parenteral GCs are administered by nurses or GPs in the primary care setting, this is unlikely to have substantially influenced the results. A dose-response relationship could not be accurately ascertained given

the limitations in data availability regarding the different routes of administration and different dose regimens of parenteral GCs. A first NIAD prescription could be considered an inadequate definition of new onset of T2DM. The earlier stages of T2DM are usually either undetected or treated with non-pharmacological methods. Therefore, at the time of the first prescription, the disease has likely been present for some time. However, a first NIAD prescription provides a clear date at which a stage of the disease that requires pharmacological treatment is reached. Fasting glucose or HbA1c levels do not provide such a clear and unambiguous cut-off. Furthermore, NIAD use has been previously used in CPRD studies to define T2DM[19,20]. Since anti-hyperglycaemic drugs are relatively specific for the treatment of diabetes, the possibility of misclassifying non-diseased subjects as diseased subjects is minimal. Finally, we were not able to determine the effect of intravenous use of GCs on T2DM. Since intravenous GCs are administered in hospitals and hospital data is limited in the CPRD database [21], we only focused on locally used parenteral GCs in the primary care line setting.

In conclusion, our study did not demonstrate a significant increase in the risk of new onset of T2DM among current users of parenteral GCs compared to non-users. This is in contrast to our findings that demonstrated an association between oral GC use and the risk of T2DM. Since this was the first observational study assessing the effects of parenteral use of GCs on onset of TD2M, more studies are necessary to confirm the absence of possible metabolic side effects of parenteral GCs.

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Chapter 7

Disease burden of knee osteoarthritis patients with joint replacement compared to matched controls: a population-based analysis of a Dutch medical claims database

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Abstract

Background: Knee osteoarthritis (OA) is associated with joint pain and decreased functioning. In severe cases, knee prostheses (KPs) can improve health-related quality of life. In the Netherlands, the incidence of KPs and surgical revisions has increased. But health care costs related to these procedures over time and their determinants are unknown.

Objective: To provide estimates of age and sex-specific incidence of KPs, revision KPs, and prosthesis complications in Dutch patients with knee OA and to determine health care costs associated with these outcomes compared with matched controls.

Methods: All KPs in OA patients in the Achmea Health Database were identified as well as up to four controls. Incidence rates of KPs, revisions of KPs, and their complications (per 1000 persons per year) from 2006-2013 were determined. Annual health care cost and excess costs (over matched controls) preceding, during, and after surgery were calculated and their determinants were evaluated.

Results: The incidence of KPs, revision KPs, and complications increased over time. This increase was strongest in the younger age categories and in men. The annual health care costs of patients with a KP slightly increased up to the year of surgery, with high costs in the year of surgery. After surgery, costs reached similar or higher levels as compared to the costs prior to surgery. High post-surgery care costs were mainly associated with subsequent KPs.

Conclusion: These results underscore the increasing burden and medical need associated with end-stage OA, especially in younger age categories. Improvement of guidelines aimed at avoiding complications and revisions is required to counteract this increasing burden.

Introduction

Osteoarthritis (OA) is a progressive disease generally associated with joint pain and decreased functioning. Based on general practitioner (GP) registries, it is estimated that in 2011 approximately 1.2 million people in the Netherlands had (a history of) an OA diagnosis, making it one of the most common musculoskeletal conditions in the Dutch population[1]. In the same year, the incidence of this disease was estimated at 9.9/1000 persons. OA is generally more prevalent in women (88.5/1000 persons) compared to men (53.8/1000 persons)[1]. In newly diagnosed patients, the knee is most frequently affected (32%)[1]. In severe cases of knee OA a knee prosthesis (KP) is considered to be an effective procedure to improve functioning, reduce pain, and consequently improve health-related quality of life[2].

In the Netherlands, the incidence of KPs has increased from 20,559 in 2010 to 26,754 in 2014, and the number of revision surgeries from 1,619 in 2010 to 2,541 in 2014[3]. Similarly, in the United States (US) the prevalence of total KPs has increased over the years[4]. Moreover, there appears to be a shift towards undergoing this surgical procedure at a younger age[4]. However, there is limited research on health care costs associated with KPs. Previous studies have suggested an increase in mean health care costs in the years prior to the surgery, followed by a peak in the first year after surgery. From the second year onwards, health care costs appear to stabilize after a marked reduction compared to the first year after surgery[5,6]. Health care costs preceding and following a KP in OA patients in the Netherlands, however, are unknown. Furthermore, it is unclear which patient characteristics are likely to influence these costs and how these costs relate to health care costs in the general population. Knowledge of these determinants may provide insight into current clinical practice and may be relevant for future budget allocation.

Therefore, the aim of this study was to provide estimates of the age and sex-specific incidence of KPs, revision KPs, and prosthesis complications in patients with knee OA over calendar time in the Netherlands. Furthermore, we aimed to determine health care costs over calendar time, distinguishing costs preceding, during, and following arthroplasties. Different cost categories, overall as well as excess costs compared with age- and sex-matched controls, and determinants of high excess cost were evaluated.

Methods

Data source

The Netherlands has a singular healthcare system. All residents are fully insured for medical care regardless of income or socioeconomic status, although a deductible (which has ranged between €150 and €385 per annum over the past decade) applies to adults. All health insurance companies in the Netherlands have the same basic health insurance package which covers most medical services, including KPs. Supplementary insurance packages may be added by each individual.

The Achmea Health Database (AHD), previously known as the Agis Health Database,

records claims for medical care provided to 5 million people who have health insurance policies with Achmea Insurance Company. These records include information on patients, health care professionals, and the provided health service. The first two pertain to demographic data. The latter includes information regarding health services provided by general practitioners (GP), drug prescriptions (ATC-coding), and information regarding hospital care based on the diagnosis related groups (DRG) coding system as well as care with other health care providers that is insured. Achmea is the main health insurance company in the central part of the Netherlands and its insured population is representative for the Dutch urban population[7].

STUDY POPULATION

All patients ≥16 years who had a KP (Table S.7.1; DRG coding: specialty code 05, diagnostic code 1801 or 1803 and treatment code 008, 019, 036, 051, 103, 104, 223, or 226) between 2006-2013 were included in the study. Up to four population controls from AHD were matched to each patient by age, sex, and region (first two digits of postal code). Controls were not allowed to have had a KP within the study period. Patients and controls with a diagnosis of rheumatoid arthritis (RA), monoarthritis, oligoarthritis, or polyarthritis, during the study period were excluded (DRG coding: specialty code 24, and diagnostic code 0101, 0115, 0116, 0117).

STATISTICAL ANALYSES

Baseline characteristics of KP cases and matched controls were described. Age and gender specific incidences (per 1000 persons per year) of all KPs and complications (DRG diagnostic code 1803 without treatment code 008, 019, 036, 051, 223 or 226) associated with end-stage OA were calculated for every year between 2006 and 2013. All KPs included initial/non-revision KPs (diagnostic code 1801 and treatment code 103, 104, 223 or 226) and revision KPs (DRG diagnostic code 1803 and treatment code 008, 019, 036, 051, 223 or 226). The denominator for calculating incidences was the age and gender-specific population size in the AHD database per calendar year.

In all cost-analyses, health care costs were presented as total costs and stratified by four cost-categories: GP; pharmaceutical; hospital; and other costs. First, average annual health care costs per patient in the year of their first KP were calculated by calendar year. Second, average annual health care costs per patient over the observation period were calculated and stratified by year of the first KP. Third, average annual health care costs per patient were calculated relative in time to the surgical procedure. Inherent to the structure of the data, for a patient who had a KP in 2013, we were able to calculate annual health care costs during and up to 7 years prior to surgery, whereas for a patient who had a KP surgery in 2006, we were able to calculate costs during and up to 7 years after surgery. As all costs were calculated using a similar approach for the matched controls (i.e. taking the

date of KP for the matched OA patient as reference date for cost comparison), excess costs associated with KP surgery in OA patients could be calculated. Fourth, the presentation of excess costs was performed separately for patients with a subsequent KP (revision or subsequent KP in contralateral knee) and patients without a subsequent KP in follow-up, as these were considered to be two distinct groups with regards to economic burden. Fifth, to determine characteristics associated with excess costs, patient characteristics (age category, gender, number of years insured with Achmea, the occurrence of a subsequent revision KP, a subsequent non-revision KP, and complications) were described and stratified by the average annual excess cost of patients over follow-up using quartiles (Q1 being the lowest excess costs, and Q4 the highest). Kruskal-Wallis tests were conducted in order to assess differences in median values for the previously mentioned characteristics between quartiles. Sixth, the association of possible predictive variables (age, gender, number of years insured, socioeconomic status (SES; tertiles), and time-varying variables: the year relative to first KP, calendar year, and the occurrence of a subsequent revision KP, non-revision KP, and/or complication,) with high average yearly excess health care costs over time was examined using longitudinal logistic regression analyses (using the genmod procedure in SAS 9.4). High annual excess health care costs were defined per year as costs higher than the median excess costs over the total observation period. These associations were expressed as odds ratios (OR) with 95% confidence intervals (95% CI), with p-values. Health care costs were expressed as non-indexed euros (€). Analyses were conducted using SAS 9.4.

Results

Baseline characteristics of all KP cases and matched controls are depicted in Table 7.1. Distribution of age, gender, and year of inclusion per definition was comparable in cases and controls due to matching. The average number of years insured by Achmea was also similar in cases compared to controls (7.4 and 7.2 years respectively). Eighteen percent of the cases underwent subsequent KP surgery in the study period. The first subsequent KP was mostly (79.5%) a non-revision type KP. Furthermore, less than 1.5% of the cases had a second or third subsequent KP in the study period. The second and third subsequent KPs were mostly revisions (71.6% and 87.3% respectively). Approximately 14% of the cases had a prosthesis complication that did not require surgery. Detailed information regarding the type of subsequent KPs in the study period is depicted in Figure S.7.1.

The incidence rates of all KPs, revisions, and complications were higher in women than in men. Furthermore, the incidence rates of all KPs, revisions, and complications were highest in the population aged 60-85 years. The relative increase in incidence rates of all KPs, revision, and complications from 2006 to 2013 was strongest in men, and in younger age categories (<60 years). The relative increase over time was strongest for complications not requiring surgery (Figure 7.1, Table 7.2).

Table 7.1: Baseline characteristics of all KP cases and their controls.

Characteristic	Cases n=26,963 (%)	Controls n=84,786 (%)
Age, by category (years)		
16-20 years	6 (0.0)	13 (0.0)
21-30 years	20 (0.1)	57 (0.1)
31-40 years	160 (0.6)	515 (0.6)
41-50 years	1,190 (4.4)	4,107 (4.8)
51-60 years	5,059 (18.8)	17,372 (20.5)
61-70 years	9,022 (33.5)	28,838 (34.0)
71-80 years	8,466 (31.4)	25,113 (29.6)
81-85 years	2,323 (8.6)	6,697 (7.9)
>85 years	717 (2.7)	2,074 (2.4)
Number of females	17,876 (66.3)	55,270 (65.2)
Socioeconomic status, by category		
Low	8,918 (33.1)	28,019 (33.0)
Medium	8,912 (33.1)	27,236 (32.1)
High	8,896 (33.0)	28,800 (34.0)
Missing	237 (0.9)	731 (0.9)
Year of inclusion		
2006	23,479 (87.1)	76,262 (89.9)
2007	834 (3.1)	2,580 (3.0)
2008	176 (0.7)	483 (0.6)
2009	1,763 (6.5)	4,269 (5.0)
2010	175 (0.6)	350 (0.4)
2011	191 (0.7)	310 (0.4)
2012	207 (0.8)	299 (0.4)
2013	138 (0.5)	233 (0.3)
Years insured with Achmea in study period (mean, SD)	7.4 (1.4)	7.2 (1.7)
First subsequent KP in study period	4,746 (17.6)	- -
Revision	975 (20.5) *	- -
Second subsequent KP in study period	345 (1.3)	- -
Revision	247 (71.6) *	- -
Third subsequent KP in study period	55 (0.2)	- -
Revision	48 (87.3) *	- -
Fourth subsequent KP in study period	11 (0.0)	- -
Revision	10 (90.9) *	- -
Fifth subsequent KP in study period	3 (0.0)	- -
Revision	3 (100.0) *	- -
Complications other than revision	3,877 (14.4)	- -

* Percentage of patients for whom subsequent KP in study period was a revision. Detailed information regarding type of subsequent KPs in follow-up is depicted in Figure S.7.1. Abbreviations: KP = knee prosthesis, SD = standard deviation.

The average annual health care costs and excess costs during the year of surgery were stable between 2006 and 2012 (Figure 7.2a) and increased in 2013 by approximately €10,000. The average annual health care costs and excess health care cost for cases over the patient observation period decreased between 2006 (€11,837 and €6,021 respectively) and 2012 (€9,417 and €5,070 respectively). In 2013, the average annual health care costs and excess health care cost for cases over the observed period (€11,347 and €7,074 respectively) increased compared to previous years (Figure 7.2b).

The average annual health care costs and excess costs in cases slightly increased up to the year of surgery and were highest in the year of surgery (€29,211 and €24,353 respectively). Excess costs in the year of surgery were largely attributable to increased hospital costs. Health care costs subsequently decreased in the first year after surgery, but excess costs did not reach the level of the years prior to KP. In the years following KP, health care costs

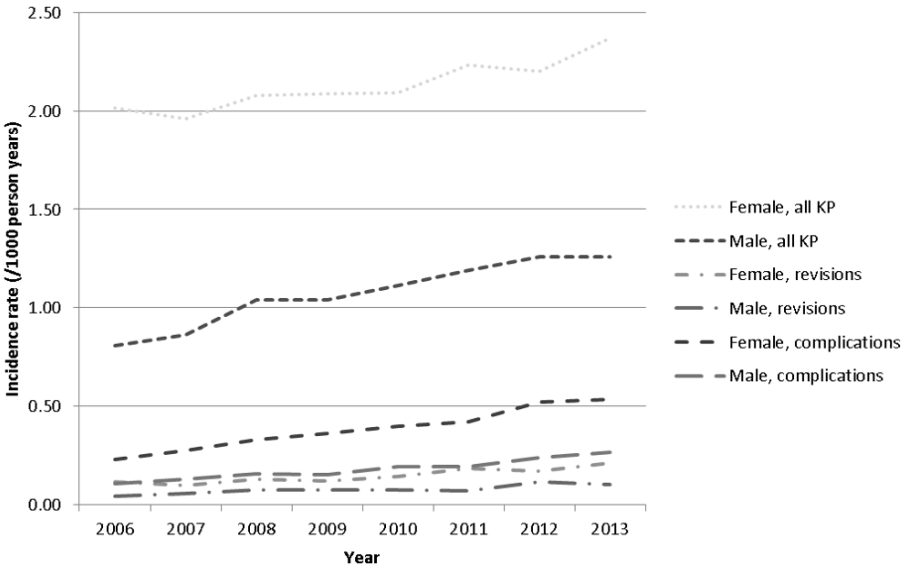

FIGURE 7.1: Incidence rates of all KPs, revision KPs, and complications. Abbreviation: KP = knee prosthesis.

and excess costs stabilized at a level higher than the years prior to surgery. However, from the sixth year after KP onwards, the health care costs and excess cost gradually increased (Figure 7.3a). Excess costs of cases without a subsequent KP (either revision or new primary KP) in the study period returned to a level comparable (or only slightly higher) to the years prior to surgery (Figure 7.3b).

The percentage of patients in lower age categories, who were female, with revision KPs, with subsequent non-revision KPs, and with complications increased with increasing excess cost quartiles. The average number of years insured with Achmea during follow-up was lower in higher excess cost quartiles. These differences were statistically significant based on Kruskal-Wallis tests ($p<0.05$) (Table S.7.2). Over time, revisions, other subsequent KPs, and complications were significantly associated with high average annual excess health care costs. Male gender, SES, and the number of years insured, were associated with low average annual excess costs. Lower age categories were associated with significantly increased excess health care costs. Prior to the KP the years towards the year of surgery were increasingly associated with higher excess health care costs. There was no clear trend for calendar year, except 2013, which was associated with high excess annual health care costs (Table 7.3).

Table 7.2: Age and sex-specific incidence rates (per 1,000 person years) of all KPs, revisions, and complications associated with OA within the study period.

		2006		2007		2008		2009		2010		2011		2012		2013	
	Age group	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR
All KPs																	
Male	≤40	6	0.01	8	0.02	12	0.03	11	0.02	24	0.05	25	0.05	13	0.03	12	0.02
	41-50	32	0.16	35	0.17	52	0.25	83	0.33	88	0.35	85	0.35	113	0.45	111	0.44
	51-60	198	1.05	221	1.17	249	1.34	314	1.46	366	1.71	344	1.62	403	1.85	432	1.94
	61-70	281	2.15	335	2.36	417	2.79	478	2.77	487	2.76	582	3.29	646	3.54	637	3.38
	71-80	286	3.41	290	3.31	336	3.80	368	3.78	380	3.83	393	3.92	376	3.66	411	3.85
	81-85	67	2.80	67	2.64	86	3.37	76	2.75	81	2.86	72	2.49	78	2.62	64	2.08
	>85	22	1.53	17	1.08	25	1.51	23	1.24	13	0.67	23	1.15	21	1.00	15	0.68
	all	892	0.81	973	0.86	1,177	1.04	1,353	1.04	1,439	1.11	1,524	1.19	1,650	1.26	1,682	1.26
Female	≤40	8	0.02	6	0.01	9	0.02	15	0.03	16	0.03	20	0.04	19	0.04	20	0.04
	41-50	48	0.25	57	0.29	75	0.38	111	0.47	114	0.49	141	0.61	143	0.60	169	0.70
	51-60	339	1.88	343	1.91	374	2.11	444	2.23	459	2.32	566	2.88	579	2.85	620	2.98
	61-70	655	4.97	648	4.54	756	5.07	884	5.24	934	5.44	961	5.58	1,053	5.95	1,139	6.28
	71-80	886	8.44	870	8.05	852	7.93	911	7.93	872	7.54	878	7.61	838	7.17	976	8.17
	81-85	279	6.73	275	6.50	267	6.35	277	6.25	246	5.56	229	5.16	225	5.02	216	4.75
	>85	86	2.29	80	2.01	84	2.04	93	2.10	85	1.87	79	1.70	51	1.08	53	1.10
	all	2,301	2.01	2,279	1.96	2,417	2.08	2,735	2.09	2,726	2.09	2,874	2.23	2,908	2.20	3,193	2.37
Total		3,193	2.82	3,252	2.82	3,594	3.12	4,088	3.13	4,165	3.20	4,398	3.42	4,558	3.46	4,875	3.62
Revision KPs																	
Male	≤40	1	0.00	0	0.00	1	0.00	1	0.00	0	0.00	1	0.00	1	0.00	4	0.01
	41-50	5	0.02	7	0.03	8	0.04	11	0.04	5	0.02	7	0.03	16	0.06	15	0.06
	51-60	10	0.05	18	0.10	25	0.13	30	0.14	36	0.17	26	0.12	54	0.25	40	0.18
	61-70	13	0.10	14	0.10	28	0.19	32	0.19	35	0.20	34	0.19	53	0.29	51	0.27
	71-80	15	0.18	20	0.23	19	0.22	17	0.17	17	0.17	17	0.17	25	0.24	21	0.20
	81-85	1	0.04	3	0.12	4	0.16	6	0.22	2	0.07	2	0.07	3	0.10	5	0.16
	>85	3	0.21	1	0.06	1	0.06	0	0.00	1	0.05	4	0.20	2	0.10	1	0.05
	all	48	0.04	63	0.06	86	0.08	97	0.07	96	0.07	91	0.07	154	0.12	137	0.10
Female	≤40	1	0.00	1	0.00	4	0.01	1	0.00	2	0.00	3	0.01	7	0.01	2	0.00
	41-50	5	0.03	2	0.01	10	0.05	11	0.05	14	0.06	19	0.08	18	0.08	23	0.10
	51-60	21	0.12	31	0.17	27	0.15	30	0.15	36	0.18	63	0.32	47	0.23	78	0.38
	61-70	42	0.32	31	0.22	50	0.34	61	0.36	65	0.38	88	0.51	76	0.43	91	0.50
	71-80	48	0.46	34	0.31	36	0.33	39	0.34	45	0.39	55	0.48	58	0.50	71	0.59
	81-85	15	0.36	12	0.28	15	0.36	15	0.34	22	0.50	8	0.18	15	0.33	14	0.31
	>85	2	0.05	5	0.13	12	0.29	5	0.11	3	0.07	2	0.04	7	0.15	7	0.15
	all	134	0.12	116	0.10	154	0.13	162	0.12	187	0.14	238	0.18	228	0.17	286	0.21
Total		182	0.16	179	0.16	240	0.21	259	0.20	283	0.22	329	0.26	382	0.29	423	0.31

Table 7.2 (continued): Age and sex-specific incidence rates (per 1,000 person years) of all KPs, revisions, and complications associated with OA within the study period.

		2006		2007		2008		2009		2010		2011		2012		2013	
	Age group	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR
Complications																	
Male	≤40	3	0.01	3	0.01	3	0.01	4	0.01	1	0.00	2	0.00	5	0.01	6	0.01
	41-50	14	0.07	16	0.08	18	0.09	14	0.06	23	0.09	30	0.12	24	0.10	39	0.16
	51-60	26	0.14	34	0.18	40	0.21	53	0.25	57	0.27	73	0.34	90	0.41	104	0.47
	61-70	16	0.12	42	0.30	50	0.33	71	0.41	89	0.50	77	0.44	107	0.59	113	0.60
	71-80	43	0.51	43	0.49	49	0.55	43	0.44	60	0.61	58	0.58	65	0.63	74	0.69
	81-85	12	0.50	10	0.39	10	0.39	10	0.36	16	0.56	6	0.21	19	0.64	20	0.65
	>85	6	0.42	1	0.06	8	0.48	6	0.32	4	0.21	5	0.25	6	0.29	3	0.14
	all	120	0.11	149	0.13	178	0.16	201	0.15	250	0.19	251	0.20	316	0.24	359	0.27
Female	≤40	2	0.00	3	0.01	5	0.01	9	0.02	10	0.02	7	0.01	8	0.02	9	0.02
	41-50	5	0.03	12	0.06	18	0.09	21	0.09	36	0.15	35	0.15	38	0.16	56	0.23
	51-60	39	0.22	55	0.31	63	0.36	76	0.38	104	0.52	105	0.53	142	0.70	159	0.76
	61-70	87	0.66	99	0.69	113	0.76	130	0.77	154	0.90	164	0.95	245	1.38	280	1.54
	71-80	79	0.75	90	0.83	125	1.16	159	1.38	140	1.21	157	1.36	182	1.56	163	1.36
	81-85	37	0.89	40	0.95	38	0.90	55	1.24	51	1.15	53	1.20	52	1.16	34	0.75
	>85	17	0.45	21	0.53	22	0.54	26	0.59	23	0.51	23	0.50	24	0.51	19	0.39
	all	266	0.23	320	0.28	384	0.33	476	0.36	518	0.40	544	0.42	691	0.52	720	0.53
Total		386	0.34	469	0.41	562	0.49	677	0.52	768	0.59	795	0.62	1,007	0.76	1,079	0.80

Abbreviations: IR = incidence rate, KP = knee prosthesis, No. = number

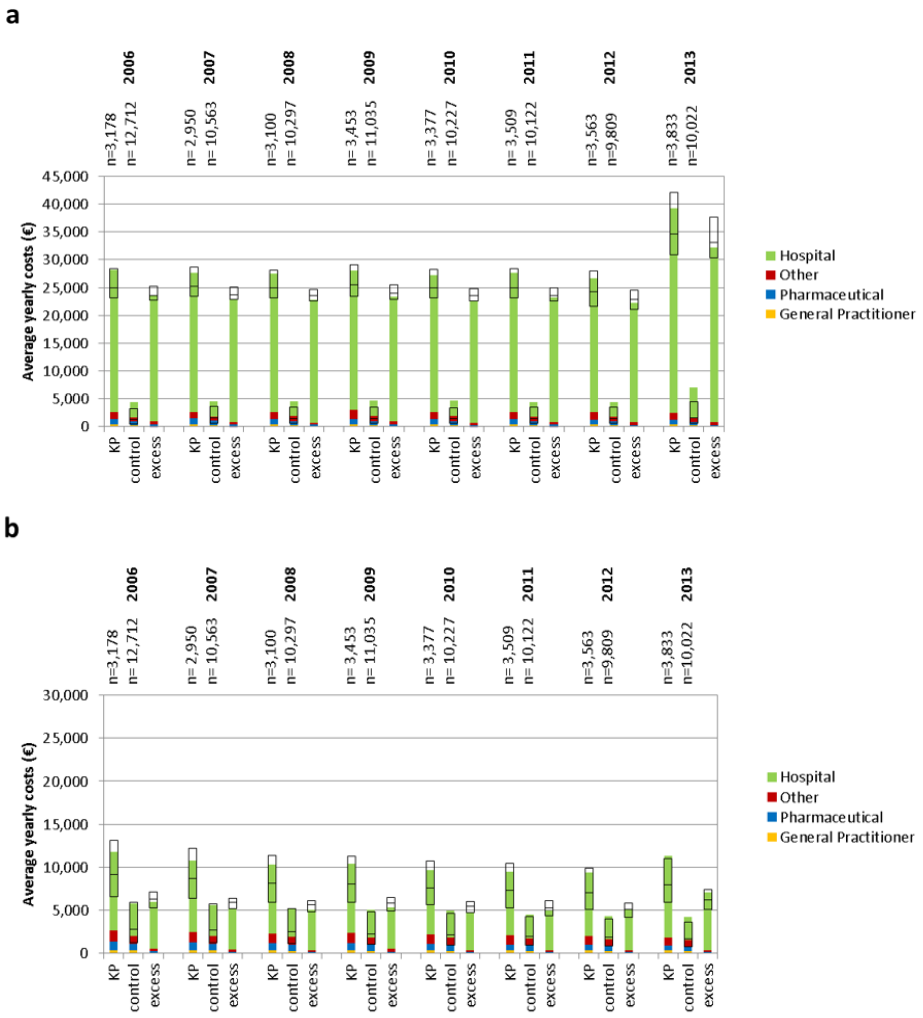

FIGURE 7.2: a) Average health care costs in the year of first surgery per calendar year, categorized by cost category. b) Average yearly health care costs over the observation period stratified by year of first surgery, categorized by cost category. Box plots show Q1, median, and Q3 values of total yearly costs. Abbreviation: KP = knee prosthesis.

Table 7.3: Odds of exceeding the median (€4,656) average yearly excess health care cost in years around first KP for potential predictors of high costs based on a multivariate longitudinal logistic regression model.

Variable	OR (95% CI)	p-value
Intercept	0.04 (0.01-0.12)	<0.0001
Male	0.92 (0.89-0.97)	<0.0001
Years insured	0.93 (0.92-0.95)	<0.0001
Revision in follow-up	114.33 (83.06-157.37)	<0.0001
Non-revision KP in follow-up	234.78 (179.08-307.81)	<0.0001
Complication in follow-up	2.65 (2.43-2.88)	<0.0001
Age category (years) (overall significance p<0.0001)		
<20 years	Reference	
21-30 years	16.88 (5.04-56.52)	<0.0001
31-40 years	8.38 (2.87-24.43)	<0.0001
41-50 years	6.88 (2.42-19.60)	<0.0001
51-60 years	5.57 (1.96-15.81)	0.001
61-70 years	5.38 (1.89-15.26)	0.002
71-80 years	5.90 (2.08-16.76)	0.001
81-85 years	5.79 (2.04-16.48)	0.001
>85 years	5.93 (2.08-16.92)	0.001
Socioeconomic status, by category (overall significance p<0.0001)		
Low	Reference	
Medium	0.90 (0.86-0.94)	<0.0001
High	0.86 (0.82-0.90)	<0.0001
Year relative to year of first KP (overall significance p<0.0001)		
7 years prior to first KP	Reference	
6 years prior to first KP	1.02 (0.89-1.17)	0.729
5 years prior to first KP	1.15 (1.00-1.31)	0.043
4 years prior to first KP	1.20 (1.04-1.37)	0. 010
3 years prior to first KP	1.38 (1.21-1.58)	<0.0001
2 years prior to first KP	1.43 (1.24-1.64)	<0.0001
1 year prior to first KP	1.71 (1.48-1.95)	<0.0001
Year of first KP	465.24 (390.76-553.90)	<0.0001
1 year after first KP	1.96 (1.69-2.27)	<0.0001
2 years after first KP	1.75 (1.50-2.04)	<0.0001
3 years after first KP	1.81 (1.55-2.12)	<0.0001
4 years after first KP	1.93 (1.64-2.26)	<0.0001
5 years after first KP	1.96 (1.66-2.32)	<0.0001
6 years after first KP	2.06 (1.73-2.45)	<0.0001
7 years after first KP	2.21 (1.84-2.66)	<0.0001
Calendar year (overall significance p<0.0001)		
2006	Reference	
2007	1.00 (0.95-1.05)	0.974
2008	1.03 (0.97-1.09)	0.350
2009	1.07 (1.01-1.13)	0.031
2010	1.04 (0.98-1.11)	0.234
2011	1.09 (1.02-1.17)	0.013
2012	1.05 (0.98-1.13)	0.188
2013	1.47 (1.36-1.60)	<0.0001

Abbreviations: CI = confidence interval; KP = knee prosthesis

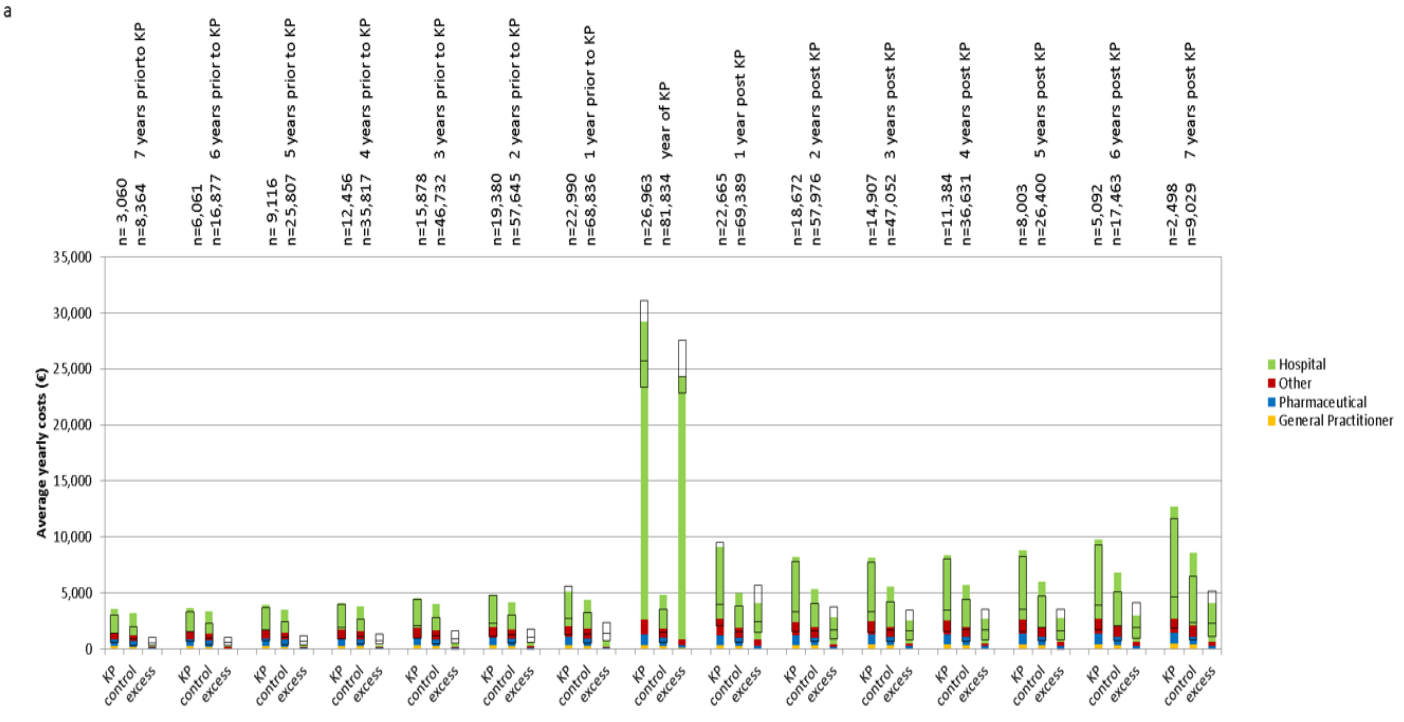

FIGURE 7.3a: Average yearly health care costs of all cases and controls and excess costs per year per patient categorized by type. Plots show Q1, median, and Q3 values of total yearly costs. Year of KP is year of first KP. Abbreviation: KP = knee prosthesis.

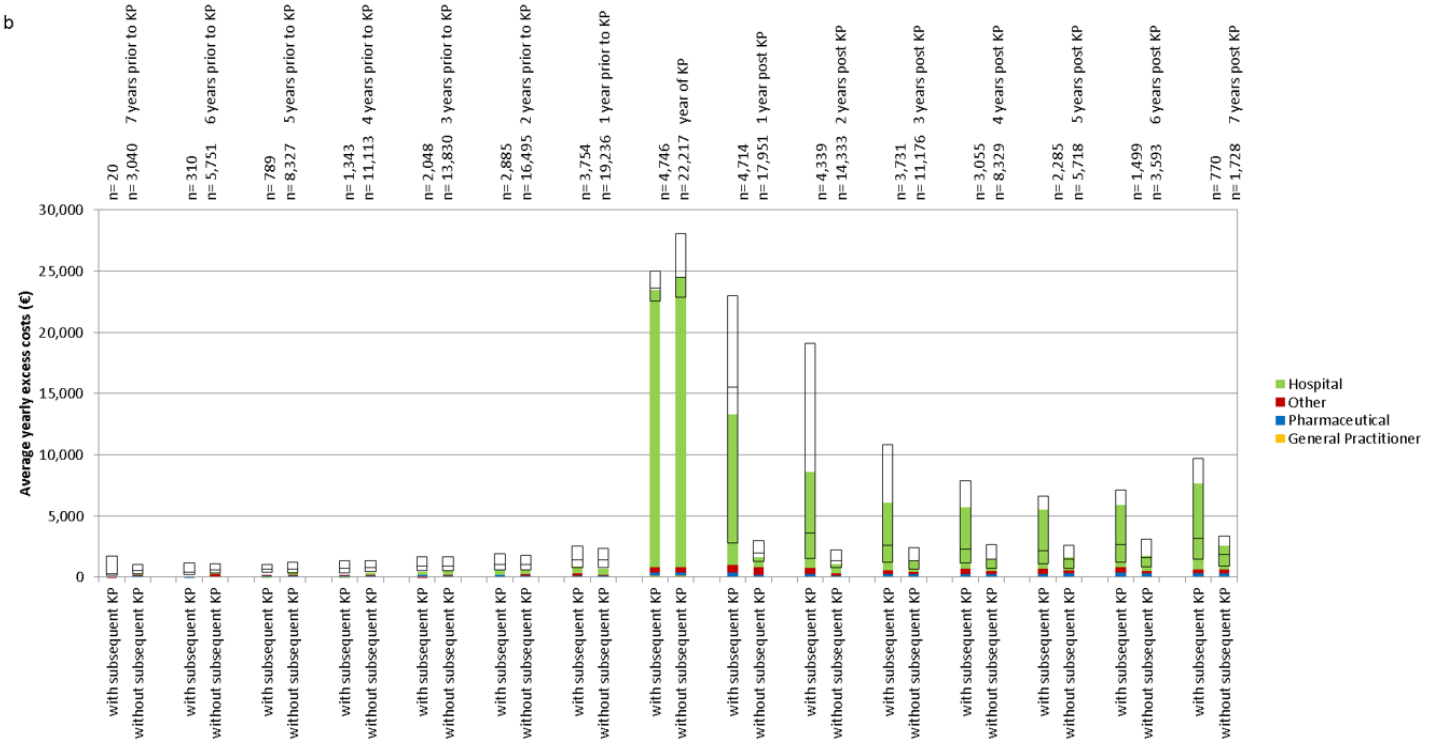

FIGURE 7.3b: Average yearly excess health care costs of cases with or without a subsequent KP per year relative to year of first KP categorized by type. Plots show Q1, median, and Q3 values of total yearly costs. Year of KP is year of first KP. Abbreviation: KP = knee prosthesis.

Discussion

In the present study, we evaluated the age and sex-specific incidence of KPs, revision KPs, and prosthesis complications in patients with knee OA over calendar time. Furthermore, we determined health care costs and excess health care costs associated with these procedures. We showed that the incidence of KPs, revision KPs, and complications increased over time. The strongest relative increase was seen for complications. There was an increased incidence of these procedures at a younger age, and a stronger increase in men compared to women. Higher excess health care costs were associated with subsequent KPs, revision KPs, complications, younger age, and the year relative to surgery. Although these excess costs were mainly related to hospital costs, which may be a direct result of these operations, excess costs increased in other cost categories as well. Low costs were associated with male gender and the number of years insured by Achmea.

In this study, we found incidence rates of KPs and revisions that were more than twice as high as previously reported national rates reported by the Dutch Arthroplasty Register (in Dutch: Landelijke Registratie Orthopedische Implantaten (LROI)). In their report, the number of KPs had increased from 20,558 in 2010 to 26,754 in 2014[3]. This corresponds with an incidence rate of 1.24/1000 persons in 2010 to 1.59/1000 persons in 2014 (based on 16.6 and 16.8 million inhabitants in 2010 and 2014 respectively[8]). The number of revisions had increased from 1,619 in 2010 to 2,541 in 2014, corresponding to an incidence rate of 0.10/1000 persons in 2010 to 0.15/1000 persons in 2014[3]. Several aspects should be accounted for when comparing the figures. First, our definition of all KPs included total, unicondylar, patellofemoral, and revision KPs, whereas revisions were excluded from the LROI definition of a KP. However, after subtracting these, incidence rates of the first recorded KP were still twice as high as compared to the LROI data. Second, the LROI included only primary KPs. Any change (insertion, replacement and / or removal) of one or more components of a KP was registered as a revision, whereas this could have been classified as a non-revision KP in our analyses. For instance, if an unicondylar prosthesis was replaced by a total KP. While this could explain the higher rate of KPs in our study, it would inherently result in higher revision rates in the LROI study compared to ours. However, the opposite was the case. This is most likely due to the fact that any surgical procedure that is associated with the revision of a single primary KP was registered as one revision in the LROI study, whereas this was registered as multiple revision surgeries in our study. Third, the lower number of KPs or revisions in the LROI report may be due to the fact that not all medical facilities performing KP surgeries were included, especially in the years prior to 2012. It is expected that approximately 10% of all KPs in 2010 was not included in the LROI report[9]. In 2014 this was expected to be 3% of all KPs. Furthermore, the LROI report shows an increased incidence rate of approximately 22% and 50% for KPs and revisions respectively from 2010 to 2014. In our study the incidence rate of KPs and revisions increased by 14% and 35% respectively from 2009 to 2013. The degree of under-registration in the LROI report in 2010

(10%) compared to 2014 (3%) may explain the stronger relative increase in the LROI report compared to our study. Lastly, the hospitals that were included in our study may differ from those in the LROI study. The AHD is representative for an urban population, whereas the LROI included (90-97% of the) hospitals nationwide. Similar to other studies, KPs were mostly conducted in females and in the population aged >60 years, while the incidence rates show a stronger increase in men and patients at a younger age[3,4]. Overall, our study shows the same trends compared to existing reports. However, absolute numbers may be different due to the use of different definitions.

The average annual health care costs and excess costs during year of surgery were stable between 2006 and 2012, and increased in 2013 with approximately €10,000. This substantial increase may be due to a reallocation budget of health care from the 'Algemene Wet Bijzondere Ziektekosten' to the 'Zorgverzekeringswet' in 2013 where e.g. some rehabilitation related care is now part of ensured care and thus registered in AHD[10]. Average annual cost over the observation period ranged between €11,837-€9,417, which is in line with previous studies reported in a recent review on the economic consequences of lower-limb OA[11].

Trends in health care costs relative to year of surgery found in this study were largely comparable to two previous studies. In those studies, there was an increase of annual health care cost towards year of surgery and costs stabilized after the year of surgery[5,6]. Due to a relative short follow-up, the increase from the sixth year onwards that was observed in the present study, was not reported in previous studies[5,6]. A study from the United States (US) from 2010 by Graver et al. reported the highest cost in first year after surgery, whereas in our study health care costs were highest in the year of surgery. This difference was due to the fact that in the study by Graver et al. the surgical costs were categorized in the first year after surgery rather than the year of surgery itself[6]. In our study, the excess costs after the year of surgery did not reach the level of the years prior to KP. However, in patients without a subsequent KP costs returned to a level that was comparable to the level prior to surgery. Therefore, a subsequent KP is a strong determinant for high health care costs following surgery. Similar to our study, a Canadian study from 2009 by Hawker et al. showed no difference in total costs in the post-surgery period compared to the pre-surgery period in patients without a subsequent KP[12].

High annual health care costs were associated with a younger age, female gender, a subsequent (revision or non-revision) KP during follow-up, or a complication during follow-up. Due to additional surgical or less invasive additional procedures, it was expected that subsequent KPs and complications during follow-up would have resulted in higher costs. A younger age was an independent determinant of excess costs, possibly because controls in these age categories are healthier compared to the controls in older age categories. Moreover, patients in the older population are more likely to have a comorbidity that is contraindicated with KP surgery. The presence of these contraindicating comorbidities

could lead to a control population that has relatively high health care costs. Furthermore, functionality levels set or expected by health care professionals as well as patients may be higher in younger age categories compared to older patients. Additional care needed to achieve these levels could result in higher health care costs. The inverse association between number of years insured and health care costs may indicate that patients with stable health (and consequently less costs) are more likely to be satisfied with their insurer and therefore less likely to switch to another insurance company.

This study has several strengths. To the best of our knowledge, it is the first study looking at excess costs and factors influencing these costs in OA patients preceding, during, and after KP surgery. Furthermore, misclassification of surgical procedures could have a substantial impact on hospital budgets. In the case of primary KP surgery associated with OA it is required to register the code for the underlying disease along with the code for surgery. It is therefore expected that classification of OA (based on DRG code 1801) as underlying indication for a non-revision KP is highly accurate. There were some limitations as well. First, the definition of revisions and complications based on DRG could have resulted in an overestimation of revisions and complications due to OA. Revisions and complications were based on code DRG code 1803. In contrast to code 1801, this code does not specify the primary underlying disease for KP surgery. If an RA-like disease was the primary underlying disease for KP, additional (e.g. pharmaceutical) costs associated with this disease could have affected the analysis. In order to limit this misclassification, we excluded patients with a diagnosis of RA, monoarthritis, oligoarthritis, or polyarthritis during the entire study period. Second, this study is based on claims data from one health insurance company in the Netherlands. The population insured by this company is representative for the Dutch urban population only, limiting the generalizability of these results.[7] Furthermore, costs were expressed as non-indexed euro's, therefore inflation has not been taken into account. Lastly, we were unable to adjust for comorbidities in our regression analysis, resulting in residual confounding.

The results of this study show that in The Netherlands, the incidence of KPs, revision KPs, and complications has markedly increased over the period 2006-2013. Similar to other studies there was an increased incidence of these procedures at a younger age, and a stronger increase in men as compared to women. In patients without a subsequent KP, the annual health care costs after surgery reached similar levels compared to the period prior to surgery, suggesting the public health gain associated with KPs is in quality of life and participation rather than in costs. High health care costs were mainly associated with subsequent KPs and revision KPs. Complications not leading to surgical intervention, female gender, and a lower age were also associated with high health care cost, but to a lesser extent. These results underscore the high, increasing burden and medical need associated with end-stage OA, especially in younger age categories. Furthermore, public awareness of OA risk factors and improvement of research and clinical guidelines aimed at indications for

surgery and avoiding complications and revisions are required to counteract this increasing burden. The increasing incidence of KPs and associated costs in younger age categories warrants further research into the reasons for these trends.

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Supplementary material

Table S.7.1: Diagnosis related group codes

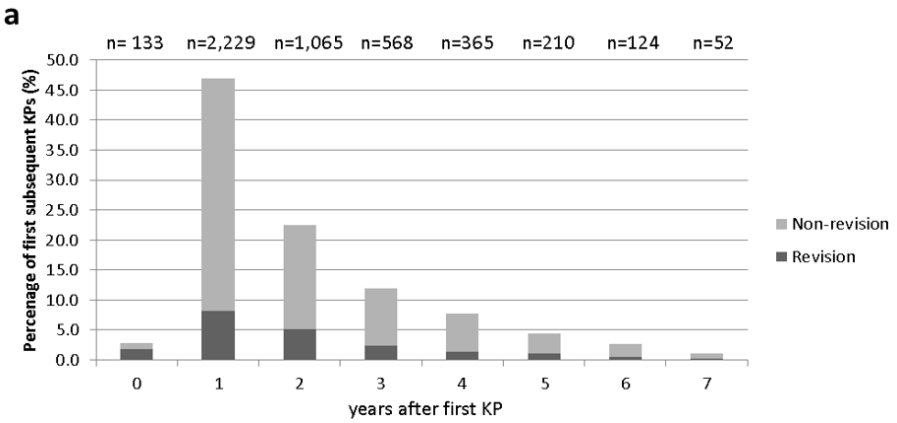
Description	DRG code for diagnosis	DRG code for treatment
Orthopaedics (specialty code = 05)		
Knee Osteoarthritis	1801	
Complications (loosening/infection/malposition) knee prosthesis	1803	
Operation with clinical episode(s) associated with joint prosthesis		223 or 226 (Prior to 2012) 103 or 104 (2012 and later)
Removal and replacement of knee prosthesis		008 (2012 and later)
Surgery without removal of knee prosthesis		019 or 051 (2012 and later)
Removal without replacement of knee prosthesis		036 (2012 and later)
Rheumatology (speciality code = 24)		
Rheumatoid arthritis	0101	
Mono arthritis	0115	
Oligo arthritis	0116	
Polyarthritis	0117	

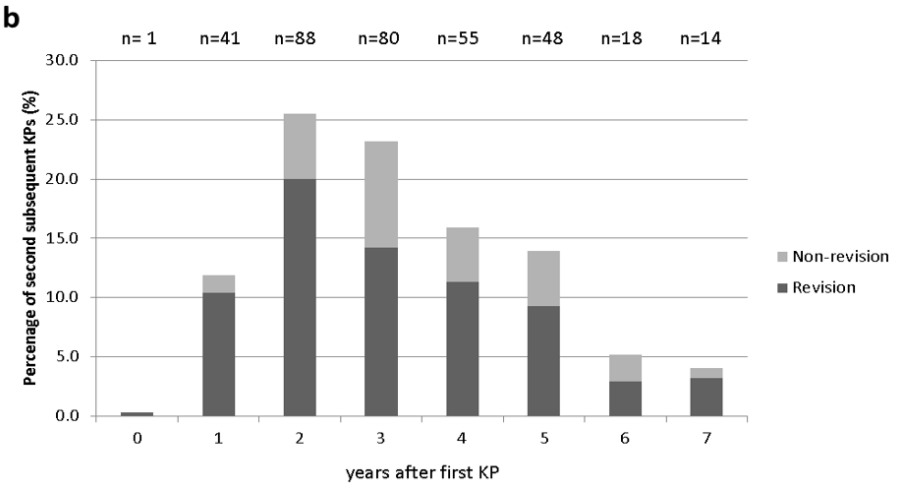
Prior to 2012:
All KP = specialty code 05; diagnostic code 1801 or 1803 and treatment code 223 or 226
Non-revision KP = specialty code 05; diagnostic code 1801 and treatment code 223 or 226
Revision KP = specialty code 05; diagnostic code 1803 and treatment code 223 or 226
Prosthesis complication = specialty code 05; diagnostic code 1803 without treatment code 223 or 226
2012 and later:
All KP = specialty code 05; diagnostic code 1801 or 1803 and treatment code 008, 019, 036, 051, 103, or 104
Non-revision KP = specialty code 05; diagnostic code 1801 and treatment code 103 or 104
Revision KP = specialty code 05; diagnostic code 1803 and treatment code 008, 019, 036, or 051
Prosthesis complication = specialty code 05; diagnostic code 1803 without treatment code 008, 019, 036, or 051
Abbreviations: DRG = diagnosis related group, KP = knee prosthesis

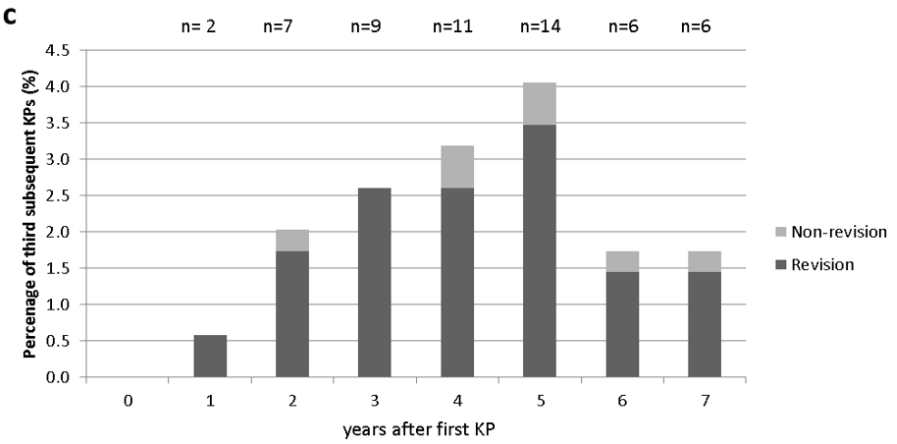
Table S.7.2: Characteristics of KP patients stratified by increasing (quartiles of) average yearly excess cost during the observation period.

Characteristic	Q1 (<€2,148) n=6,625 (%)	Q2 (€2,148-€4,656) n=6,625 (%)	Q3 (€4,656-€8,037) n=6,626 (%)	Q4 (>€8,037) n=6,625 (%)
Age category (years)*				
≤40 years	8 (0.1)	46 (0.7)	61 (0.9)	70 (1.1)
41-50 years	112 (1.7)	310 (4.7)	345 (5.2)	409 (6.2)
51-60 years	847 (12.8)	1,383 (20.9)	1,418 (21.4)	1,360 (20.5)
61-70 years	2,128 (32.1)	2,308 (34.8)	2,305 (34.8)	2,159 (32.6)
71-80 years	2,542 (38.4)	1,934 (29.2)	1,845 (27.8)	1,960 (29.6)
81-85 years	777 (11.7)	489 (7.4)	479 (7.2)	506 (7.6)
>85 years	211 (3.2)	155 (2.3)	173 (2.6)	161 (2.4)
Number of females *	4,212 (63.6)	4,414 (66.6)	4,495 (67.8)	4,426 (66.8)
Revision KP in follow-up *	39 (0.6)	58 (0.9)	195 (2.9)	731 (11.0)
Non-revision KP in follow-up *	449 (6.8)	626 (9.4)	1,263 (19.1)	1,375 (20.8)
Complication in follow-up *	270 (4.1)	300 (4.5)	514 (7.8)	989 (14.9)
Years in dataset (mean, SD) *	7.7 (0.9)	7.6 (1.0)	7.4 (1.2)	6.7 (2.0)

* Statistically significant difference between quartiles based on Kruskal-Wallis test (p<0.05)
Abbreviations: KP = knee prosthesis, SD = standard deviation


a
n= 133
n=2,229
n=1,065
n=568
n=365
n=210
n=124
n=52
Percenage of first subsequent KPs (%)
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0
1
2
3
4
5
6
7
years after first KP
Non-revision
Revision


b
n= 1
n=41
n=88
n=80
n=55
n=48
n=18
n=14
Percenage of second subsequent KPs (%)
30.0
25.0
20.0
15.0
10.0
5.0
0.0
0
1
2
3
4
5
6
7
years after first KP
Non-revision
Revision


c
n= 2
n=7
n=9
n=11
n=14
n=6
n=6
Percenage of third subsequent KPs (%)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
years after first KP
Non-revision
Revision

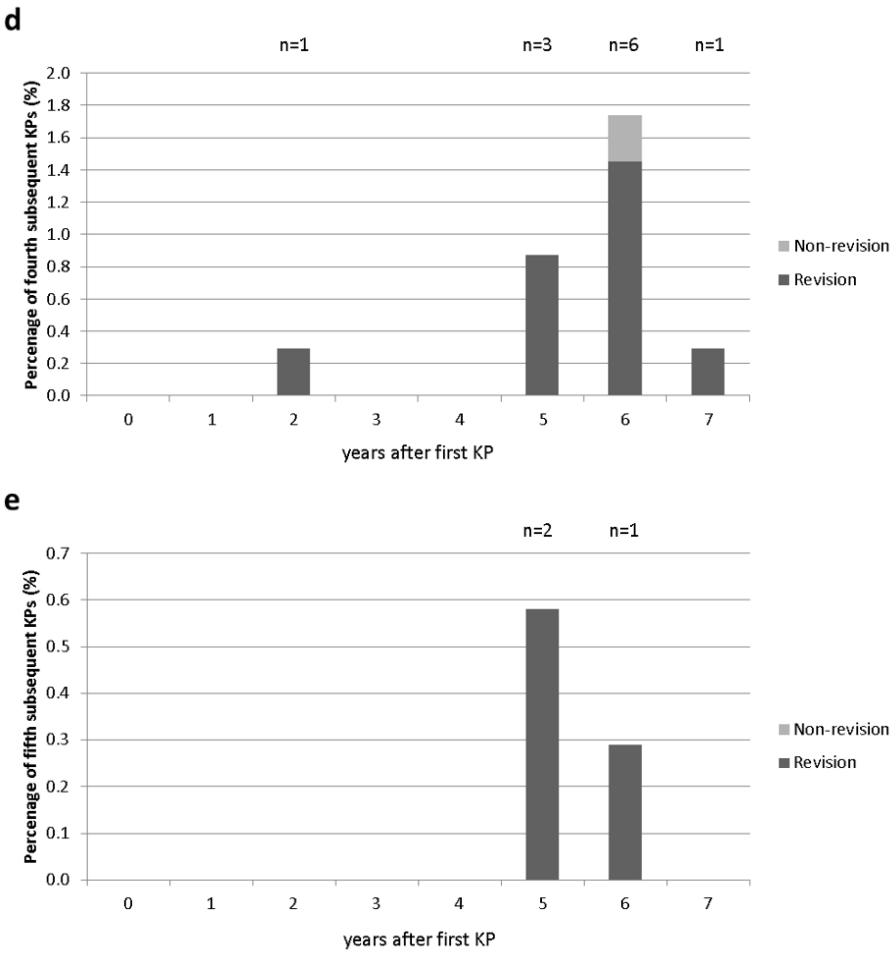


Figure S.7.1: Timing of first (a), second (b), third (c), fourth (d), and fifth (e) subsequent KP, stratified by reason for surgery. Abbreviation: KP = knee prosthesis.

Chapter 8

Identification of antithrombotic drugs related to total joint replacement using anonymised free text notes: a validation study in the Clinical Practice Research Datalink

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BMJ Open. 2015; 5 (11): e009017

Abstract

Objectives: We aimed to design and test a method to extract information on antithrombotic therapy from anonymised free text notes in the Clinical Practice Research Datalink (CPRD).

Setting: General practice database, representative of the total UK population.

Participants: All patients undergoing total hip replacement (THR) (n=25,898) or total knee replacement (TKR) (n=22,231) between January 2008 and October 2012 were included. Antithrombotic drug use related to THR or TKR was identified using anonymised free text and prescription data.

Primary and secondary outcome measures: Internal validity of our newly designed method was determined by calculating positive predictive values (PPVs) of hits for predefined keywords in a random sample of anonymised free text notes. In order to determine potential detection bias, total joint replacement (TJR) patient characteristics were compared as per their status of exposure to antithrombotics.

Results: PPVs ranging between 97% and 99% for new oral anticoagulants (NOAC) or low-molecular-weight heparins (LMWHs) exposure related to TJR were obtained with our method. Our search strategy increased detection rates by 57%, yielding a total proportion of 18.5% of all THR and 18.6% of all TKR surgeries. Identified users of NOACs and LMWHs were largely similar with regards to age, sex, lifestyle, disease, and drug history compared to patients without identified drug use.

Conclusions: We have developed a useful method to identify additional exposure to NOACs or LMWHs with TJR surgery.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal condition in older people in the UK[1]. Based on 7-year consultation prevalence in British general practice, an estimated 8.75 million people have been treated for OA. This constitutes one-third of the people aged 45 years and over in the UK[1] Total joint replacements (TJR), such as total hip replacement (THR) or total knee replacement (TKR), substantially improve quality of life in these patients[2]. However, risk of potentially fatal venous thromboembolic events, such as deepvein thrombosis (DVT), is increased up to 14-fold following these surgical procedures when no drug for thromboprophylaxis is given[3]. Intensive antithrombotic treatment up to 35 days is, therefore, recommended and has resulted in a reduced risk of asymptomatic DVT in a meta-analysis of randomised trials (relative risk (RR)=0.51 [95% confidence interval (CI)=0.45-0.59])[4,5].

There has been much debate about the risk/benefit ratio of antithrombotic agents following THR or TKR surgery[6,7,8]. Low-molecular-weight heparins (LMWHs) have gained popularity over the past decade, but can only be administered subcutaneously. The recently introduced orally administered direct thrombin inhibitors and direct factor Xa inhibitors (e.g. dabigatran and rivaroxaban) seem to combine both advantages of vitamin-K antagonists (VKAs) and LMWHs. Their risk/benefit profile has been suggested to outperform VKAs in patients with atrial fibrillation[9]. To further understand the risk/benefit profile of these antithrombotic drugs in real life use, data form large databases, such as the Clinical Practice Research Datalink (CPRD), could contribute largely. However, some antithrombotic therapies are 'red-listed' and therefore, predominantly dispensed during inpatient hospitalisations and the period post-discharge. Consequently, patients do not have to visit a public pharmacy to repeat their prescription. Unfortunately, hospital pharmacy data is often lacking in general practitioner (GP) databases. Therefore, there are limitations in using these databases to conduct drug utilisation or drug effect studies. However, Martinez et al.[10] have found a feasible approach to overcome some of these restrictions. They identified a total of 754 rivaroxaban users by combining information from prescription files and electronic search of anonymised free text in the CPRD between October 2008 and January 2012. Approximately 66% of these users were identified by anonymised free text only, thereby tripling the information on exposure to rivaroxaban. Unfortunately, details of the electronic search method used were lacking in this study and it focused only on one drug (rivaroxaban).

In order to assess safety and efficacy of the new oral anticoagulants (NOACs), new methods are needed to efficiently extract the additional information from anonymised free text notes. In some fields this has already been done. For example, Shah et al. designed an algorithm that identifies dosage instructions for a variety of drugs in anonymised free text. Their algorithm converted unstructured data from these notes to structured, usable data. They subsequently validated their structured data by manually checking a random

sample of these records. Their algorithm identified correct dosage information in 99% of the analysed anonymised free text[11]. Since hospital pharmacy data are not included in most primary care databases, we aimed to design and test a method to extract additional information on antithrombotic therapy in patients undergoing TJR surgery from anonymised free text notes in the CPRD.

Methods

Data source

This study was conducted using the CPRD, formally known as the General Practice Research Database (GPRD). The CPRD is a GP database currently containing approximately 8% of the UK population. GPs play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals. Consequently, medical information from GPs, referrals, and hospitalisation data are recorded in the CPRD[12]. Most data are recorded using CPRD's therapy files, but some data, such as hospital discharge summaries, are collected as anonymised free text. CPRD has been used to study outcomes after TJR surgery[13,14].

Study population

The study population comprised all patients who underwent a primary THR or TKR surgery from January 2008 to October 2012. This time frame was chosen because NOACs have been registered for antithrombotic therapy after TKR and THR in Europe since 2008 (dabigatran, 18 March 2008; rivaroxaban, 13 September 2008).

Selection of comparison groups

We determined the exposure to antithrombotics using CPRD product codes and analysis of anonymised free text. Use of product codes of NOACs (dabigatran and rivaroxaban), LMWHs (bemiparin, certoparin, reviparin, enoxaparin, tinzaparin, dalteparin), and aspirin during the 10 days before and 10 days after surgery were included. Based on the annual reports of the National Joint Registry (NJR), VKAs were used for thromboprophylaxis in <1% of the TJR surgeries. They were, therefore, not included in the analyses. The procedure of the anonymised free text analysis (Figure 8.1) was based on methods used in a previous study that identified rivaroxaban use and a study that restructured dosage instructions[10,11]. For the anonymised free text analysis, we first ran our search strategy on the study population to determine the use of NOACs, LMWHs and aspirin. This search strategy searched for specific keywords in the anonymised free text notes of TJR patients. Keywords included abbreviations, misspelled variations, and actual names of both the generic and the brand products (Table S.8.1). Anonymised free text notes between 10 days before and 10 days after date of surgery were included in the analysis. This time window was based on the mean duration of hospital stays after TJRs, as reported in the National Registry of Hospitalisations of England (2008–2013)[15].

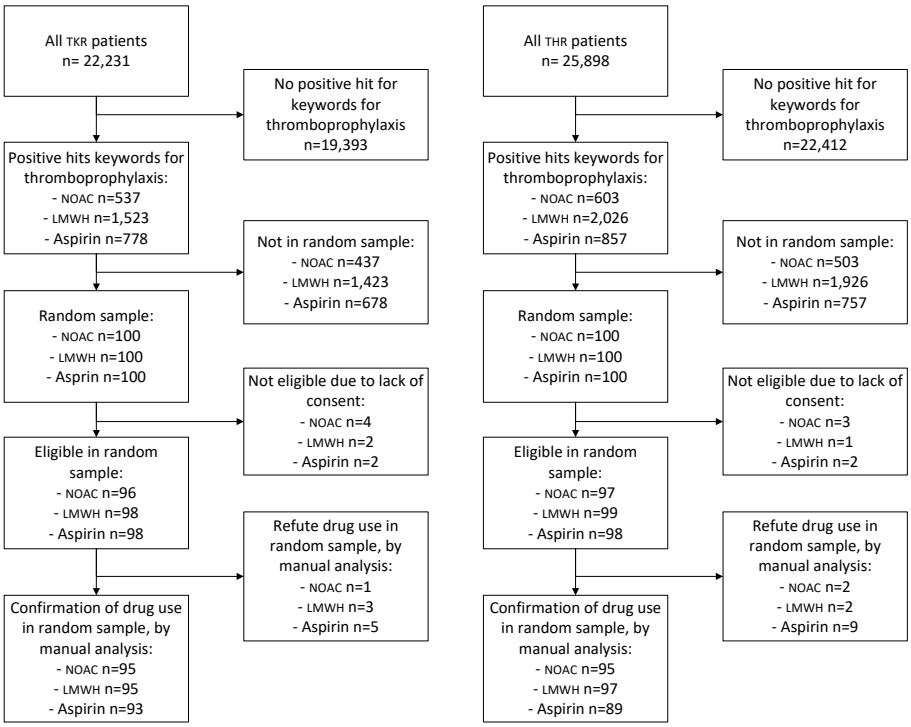

FIGURE 8.1: Study flowchart. Abbreviations: LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant, THR = total hip replacement, TKR = total knee replacement.

Patients with a positive hit for these keywords were further analysed to determine the validity of this positive response. From both THR and TKR patients, we randomly selected 100 patients with at least one positive NOAC hit, 100 patients with at least one positive LMWH hit, and 100 patients with at least one positive aspirin hit. This resulted in a total of 300 THR patients and 300 TKR patients. Additionally, anonymised free text notes of these randomly selected patients were analysed. The additional analysis consisted of anonymising of the free text surrounding the positive hit in each record. By anonymising 20 words before and after the positive hit, we either confirmed or refuted the drug use. In the following examples drug use was confirmed (1) or refuted (2), respectively:

1. …still on dabigatran…
2. …aspirin was stopped in …

Within the anonymised free text, we manually searched for negating or confirming terms. Two pharmacists (JTHN and FdV) then independently decided whether a patient had been exposed or unexposed to antithrombotic drugs. In case of disagreement, the participant was discussed until an agreement was reached.

Subsequently, we determined exposure to antithrombotics in the entire study population by combining drug use based on a positive response in the anonymised free

text analysis and drug use based on product codes. Concomitant use of NOACs and aspirin were categorised as NOAC use. Concomitant use of LMWHs and aspirin were categorised as LMWH use. This classification was chosen because it is more likely that in these cases the exposure to NOACs or LMWHs is associated with TJR. Patients without identified drug use were categorised as unknown users. Exposure to a NOAC and a LMWH is highly unlikely. Therefore, concomitant use of these drugs was also classified as unknown use.

Data analysis

Positive predictive values (PPVs) of the positive hits by free text search were calculated by dividing the number of positive hits, confirmed by manual analysis of surrounding free text, by the total number of positive hits. PPVs can range between 0% and 100%, where 100% corresponds with perfect predictive value of positive hits. We were unable to calculate false or true negatives because we did not analyse the free text notes without a positive hit. As a result, we could not determine the specificity and sensitivity of our method. In order to assess the additional detection rate by using our free text search, we determined the distribution of cases within a drug category according to the identification method. Cases were categorised according to type of surgery and the previously described user categories. To gain insight into the external validity of the method, we first compared the proportion of NOAC and LMWH use in the CPRD to the proportion reported by the National Joint Registry (NJR)[13] by means of the $\chi 2$ statistic for independent samples ($p<0.05$). Second, we compared the characteristics of the different user groups (NOACs, LMWHs and aspirin) to patients without identified drug use by means of the $\chi 2$ or t-test statistic ($p<0.05$). We used SAS 9.3 software for statistical testing and randomisation. This study protocol was approved by the Independent Scientific Advisory Committee (ISAC), protocol number: 14_026R.

Results

A total of 22,231 TKR patients and 25,898 THR patients were included in our study. From all patients (n=6,324) with a positive hit for antithrombotic drug use, 600 patients were randomly selected for anonymization of the free text surrounding a keyword. However, 14 patients did not give consent for this analysis. The remaining 586 patients were further analysed to determine actual drug use (Figure 8.1). On an average, TKR patients were younger than THR patients. They also had a higher BMI and used more drugs, such as statins, nonsteroidal anti-inflammatory drugs (NSAIDs), and antihypertensive drugs (Table 8.1).

PPVs of drugs used for thromboprophylaxis related to TJR ranged between 97% and 99% for NOAC and LMWH use, and between 91% and 95% for aspirin use. Overall, 96.2% of the hits were true positives and 3.8% of the hits were false positives. By combining exposure according to positive anonymised free text hits with exposure according to product codes identification of drug use was increased by 57% compared to product codes only. Ultimately, drug use was identified in a total proportion of 18.5% of all THR and 18.6% of all

Table 8.1: Baseline characteristics of total knee replacement and total hip replacement cases.

Characteristic	Total knee replacement n=22,231 (%)	Total hip replacement n=25,898 (%)
Number of females	12,576 (56.6)	16,036 (61.9)
Age (years, (SD))	68.9 (9.9)	70.1 (12.3)
18-49 years	637 (2.9)	1,491 (5.8)
50-69 years	10,665 (48.0)	10,036 (38.8)
≥70 years	10,929 (49.2)	14,371 (55.5)
Socioeconomic status (IMD), by category		
Low	3,519 (15.8)	4,214 (16.3)
Low-medium	3,581 (16.1)	4,158 (16.1)
Medium	2,810 (12.6)	3,143 (12.1)
Medium-high	2,170 (9.8)	2,295 (8.9)
High	1,481 (6.7)	1,561 (6.0)
Missing	8,670 (39.0)	10,527 (40.6)
Region		
England	17,371 (78.1)	19,746 (76.2)
Northern-Ireland	480 (2.2)	795 (3.1)
Scotland	2,016 (9.1)	2,944 (11.4)
Wales	2,364 (10.6)	2,413 (9.3)
BMI, most recent value before index date		
BMI (kg/m^2, mean(SD))	30.0 (5.4)	27.4 (5.2)
History of comorbidity before index date		
Angina pectoris	2,068 (9.3)	2,214 (8.5)
AMI	871 (3.9)	1,190 (4.6)
Haemorrhagic stroke	110 (0.5)	177 (0.7)
Ischemic stroke	174 (0.8)	324 (1.3)
Heart failure	581 (2.6)	885 (3.4)
Cancer	1,352 (6.1)	1,838 (7.1)
IBD*	320 (1.4)	315 (1.2)
Varicose veins	3,744 (16.8)	3,957 V
GI ulcer	1,068 (4.8)	1,174 (4.5)
Atrial fibrillation	985 (4.4)	1,441 (5.6)
VTE event	1,074 (4.8)	1,183 (4.6)
History of drug use within 6 months before index date		
Statins	8,471 (38.1)	8,293 (32.0)
Systemic glucocorticoids	1,227 (5.5)	1,413 (5.5)
Any NSAID	8,708 (39.2)	9,027 (34.9)
COX-2 selective NSAIDs	685 (3.1)	663 (2.6)
Non-selective NSAIDs	8,148 (36.7)	8,506 (32.8)
Antibiotics	6,764 (30.4)	7,587 (29.3)
Antihypertensive drugs	12,948 (58.2)	13,553 (52.3)

* IBD: Crohn's disease or ulcerative colitis. Abbreviations: AMI = acute myocardial infarction, BMI = body mass index, COX = cyclooxygenase, GI = gastrointestinal, IBD = inflammatory bowel disease, IMD = index of multiple deprivation, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation, VTE = venous thromboembolic.

TKR surgeries. Antithrombotic drug use was determined by free text analysis only in 65–70% of the LMWHs group and >80% of the NOACs group; which threefold to fivefold increased the detection rates of these drugs compared to detection by product codes. In the aspirin group, drug use was mostly (~90%) determined by coded prescription data (Figure 8.2 and Table S.8.2). Use of NOACs was higher with our method in CPRD as compared to the NJR reports in both THR and TKR patients when ratio of NOAC and LMWH use was compared. NOAC/LMWH ratio was only statistically significantly different in TKR patients in 2009 and 2010. All other groups were not statistically significantly different (Table 8.2). Given the lower PPV and the substantial difference of baseline characteristics, and the limited role of thromboprophylaxis as related to TJR, we did not further focus on comparing our aspirin data with those from the NJR.

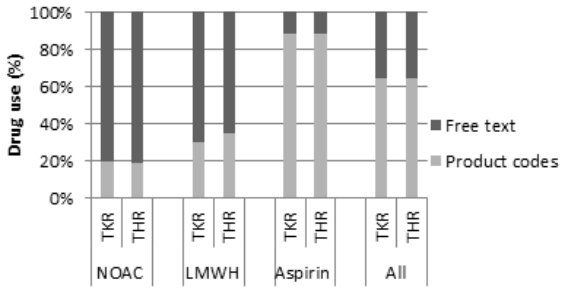

Figure 8.2: Drug use according to identification method Abbreviations: LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant, THR = total hip replacement, TKR = total knee replacement.

Table 8.2: Difference in NOAC/LMWH ratio found in the CPRD and the NJR

		Total knee replacement				Total hip replacement			
Year	Source	NOAC (%)	LMWH (%)	Ratio	p-value	NOAC (%)	LMWH (%)	Ratio	p-value
2008	CPRD	3.7	96.3	0.04	0.56	3.1	96.9	0.03	0.29
	NJR	2.3	97.7	0.02		1.0	99.0	0.01	
2009	CPRD	22.7	77.4	0.29	0.01	17.5	82.5	0.21	0.10
	NJR	9.5	90.6	0.10		9.5	90.5	0.10	
2010	CPRD	37.4	62.6	0.60	0.02	33.2	66.8	0.50	0.11
	NJR	22.7	77.3	0.29		22.9	77.1	0.30	
2011	CPRD	36.5	63.6	0.57	0.07	30.7	69.3	0.44	0.39
	NJR	24.6	75.4	0.33		25.2	74.8	0.34	

Abbreviations: CPRD = Clinical Practice Research Datalink, LMWH = low-molecular-weight heparin, NJR = National Joint Registry, NOAC = new oral anticoagulant.

Table 8.3 shows that TKR and THR patients using NOACs or LMWHs were largely similar with regard to distribution by age, sex, comorbidities and drug use as compared to patients with unknown drug use. Aspirin users, however, were different as compared to unknown users particularly with regard to a history of ischaemic heart disease. Compared to unknown use, prescription of antithrombotic drugs was higher in the highest socioeconomic status (SES) quintile and lower in the lowest SES quintile (except for THR patients using NOACs). Compared to unknown users, all other groups showed a different distribution across the four major regions. Moreover, only one NOAC prescription was identified in Northern Ireland. Furthermore, THR patients using NOACs or LMWHs had a higher BMI as compared to unknown users.

Discussion

We have developed a useful method to identify exposure to NOACs or LMWHs related to TJR surgery. Our search method identified NOAC and LMWH use with PPVs between 97% and 99%. Aspirin use yielded PPVs ranging from 91% to 95%. When combining our anonymised

Table 8.3: Characteristics of user groups identified by free text analysis and product codes after total joint replacement

Characteristic	Total knee replacement n=22,231 (%)				Total hip replacement n=25,898 (%)			
	NOAC n=450	LMWH n=1,164	Aspirin n=2,519	Unknown n=18,098	NOAC n=488	LMWH n=1,534	Aspirin n=2,770	Unknown n=21,106
Number of females	268 (59.6)	659 (56.6)	1,281 (50.9)[a]	10,368 (57.3)	287 (58.8)	943 (61.5)	1,602 (57.8)[a]	13,204 (62.6)
Age (years, (SD))	68.5 (9.0)	69.0 (9.5)	71.8 (8.7)[a]	68.5 (10.0)	68.2 (10.7)[a]	69.5 (11.4)	73.7 (10.9)[a]	69.7 (12.5)
Socioeconomic status (IMD), by category								
Low	75 (16.7)[a]	169 (14.5)[a]	305 (12.1)[a]	2,970 (16.4)	78 (16.0)	244 (15.9)[a]	344 (12.4)[a]	3,548 (16.8)
Low-medium	81 (18.0)[a]	191 (16.4)[a]	381 (15.1)[a]	2,928 (16.2)	81 (16.6)	263 (17.1)[a]	377 (13.6)[a]	3,437 (16.3)
Medium	64 (14.2)[a]	179 (15.4)[a]	280 (11.1)[a]	2,287 (12.6)	54 (11.1)	226 (14.7)[a]	316 (11.4)[a]	2,547 (12.1)
Medium-high	29 (6.4)[a]	106 (9.1)[a]	232 (9.2)[a]	1,803 (10.0)	42 (8.6)	150 (9.8)[a]	231 (8.3)[a]	1,872 (8.9)
High	39 (8.7)[a]	114 (9.8)[a]	171 (6.8)[a]	1,157 (6.4)	31 (6.4)	142 (9.3)[a]	160 (5.8)[a]	1,228 (5.8)
Missing	162 (36.0)[a]	405 (34.8)[a]	1,150 (45.7)[a]	6,953 (38.4)	202 (41.4)	509 (33.2)[a]	1,342 (48.4)[a]	8,474 (40.1)
Region								
England	388 (86.2)[a]	963 (82.7)[a]	1,735 (68.9)[a]	14,285 (78.9)	386 (79.1)[a]	1,267 (82.6)[a]	1,795 (64.8)[a]	16,298 (77.2)
Northern-Ireland	0 (0.0)[a]	43 (3.7)[a]	145 (5.8)[a]	292 (1.6)	1 (0.2)[a]	56 (3.7)[a]	242 (8.7)[a]	496 (2.4)
Scotland	42 (9.3)[a]	83 (7.1)[a]	313 (12.9)[a]	1,565 (8.6)	60 (12.3)[a]	137 (8.9)[a]	405 (14.6)[a]	2,342 (11.1)
Wales	20 (4.4)[a]	75 (6.4)[a]	326 (12.4)[a]	1,956 (10.8)	41 (8.4)[a]	74 (4.8)[a]	328 (11.8)[a]	1,970 (9.3)
BMI, most recent value before index date								
BMI (kg/m^2, mean(SD))	30.0 (5.5)	30.2 (5.5)	29.9 (5.2)	30.0 (5.4)	28.4 (5.4)[a]	27.8 (5.3)[a]	27.6 (5.3)[a]	27.4 (5.2)
History of comorbidity before index date								
Angina pectoris	33 (7.3)	110 (9.5)[a]	611 (24.3)[a]	1,314 (7.3)	34 (7.0)	112 (7.3)	628 (22.7)[a]	1,440 (6.8)
AMI	9 (2.0)	62 (5.3)[a]	269 (10.7)[a]	531 (2.9)	20 (4.1)	65 (4.2)	358 (12.9)[a]	747 (3.5)
Haemorrhagic stroke	6 (1.3)[a]	7 (0.6)	10 (0.4)	87 (0.5)	2 (0.4)	13 (0.8)	15 (0.5)	147 (0.7)
Ischemic stroke	2 (0.4)[a]	6 (0.5)	56 (2.2)[a]	110 (0.6)	0 (0.0)[a]	21 (1.4)	80 (2.9)[a]	223 (1.1)
Heart failure	8 (1.8)	36 (3.1)	110 (4.4)[a]	427 (2.4)	10 (2.0)	53 (3.5)	167 (6.0)[a]	655 (3.1)
Cancer	29 (6.4)	77 (6.6)	176 (7.0)[a]	1,070 (5.9)	32 (6.6)	111 (7.2)	204 (7.4)	1,491 (7.1)
IBD*	8 (1.8)	22 (1.9)	44 (1.7)	246 (1.4)	11 (2.3)[a]	17 (1.1)	38 (1.4)	249 (1.2)
Varicose veins	75 (16.7)	215 (18.5)	449 (17.8)	3,005 (16.6)	79 (16.2)	252 (16.4)	440 (15.9)	3,186 (15.1)
GI ulcer	23 (5.1)	75 (6.4)[a]	136 (5.4)	834 (4.6)	20 (4.1)	70 (4.6)	149 (5.4)[a]	935 (4.4)
Atrial fibrillation	9 (2.0)[a]	84 (7.2)	137 (5.4)[a]	755 (4.2)	20 (4.1)	116 (7.6)[a]	237 (8.6)[a]	1,068 (5.1)
VTE event	26 (5.8)	96 (8.2)[a]	113 (4.5)	839 (4.6)	12 (2.5)[a]	119 (7.8)[a]	122 (4.4)	930 (4.4)
History of drug use within 6 months before index date								
Statins	172 (38.2)	482 (41.4)[a]	1,644 (65.3)[a]	6,173 (34.1)	168 (34.4)[a]	515 (33.6)[a]	1,639 (59.2)[a]	5,971 (28.3)
Systemic glucocorticoids	25 (5.6)	76 (6.5)	124 (4.9)	1,002 (5.5)	26 (5.3)	86 (5.6)	150 (5.4)	1,151 (5.5)
Any NSAID	171 (38.0)	450 (38.7)	867 (34.4)[a]	7,220 (39.9)	190 (38.9)	569 (37.1)	837 (30.2)[a]	7,431 (35.2)
COX-2 selective NSAIDs	20 (4.4)	41 (3.5)	62 (2.5)	562 (3.1)	11 (2.3)	42 (2.7)	65 (2.3)	545 (2.6)
Non-selective NSAIDs	153 (34.0)	419 (36.0)	818 (32.5)[a]	6,758 (37.3)	182 (37.3)	543 (35.4)	784 (28.3)[a]	6,997 (33.2)
Antibiotics	145 (32.2)	394 (33.8)[a]	770 (30.6)	5,455 (30.1)	133 (27.3)	481 (31.4)[a]	968 (34.9)[a]	6,005 (28.5)
Antihypertensive drugs	261 (58.0)	704 (60.5)[a]	1,972 (78.3)[a]	10,011 (55.3)	259 (53.1)	803 (52.3)[a]	2,036 (73.5)[a]	10,455 (49.5)

[a] Different as compared to patients with unknown chemical thromboprophylaxis ($p<0.05$).* IBD: Crohn's disease or ulcerative colitis. Abbreviations: AMI = acute myocardial infarction, BMI = body mass index, COX = cyclooxygenase, GI = gastrointestinal, IBD = inflammatory bowel disease, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation, VTE = venous thromboembolic.

free text method with a traditional method using CPRD product codes, the identification of drug use increased by 57% on average. Moreover, the identification of NOAC use showed a fivefold increase and the exposure to LMWHs a more than threefold increase as compared to identification by product codes. Users of NOACs or LMWHs were largely similar to patients with unknown thromboprophylaxis related to TJR surgery with regards to age, sex, comorbidities and use of other drugs. As expected, aspirin users were different and had, for example, more often a history of ischaemic heart disease.

To our knowledge, anonymised free text has only been used once to identify antithrombotic drug use in the CPRD.[10] However, details of the electronic search method used in this study are unclear and results were restricted to rivaroxaban use only. In this paper, we present an effective and highly efficient approach to additionally identify exposure to multiple antithrombotic drug classes, using a predefined set of keywords. Positive hits using the selected keywords in anonymised free text notes were highly associated with actual use, especially the use of NOACs and LMWHs. Thus, we believe that our free text search method is a valid method for the additional identification of drug use in the CPRD. When combining our anonymised free text method with a traditional method using CPRD product codes, identification of drug use is increased by 57% compared to the identification based on product codes. This increase of NOAC identification is somewhat higher than the threefold increase of rivaroxaban use presented by Martinez et al.[10]. This difference could be caused by an overestimation in our method due to false positive responses. However, previously described PPVs indicate this can only account for 1–3% overestimation. It could also be due to the fact that we determined both rivaroxaban and dabigatran use, whereas Martinez and colleagues only measured rivaroxaban use. An alternative explanation is that Martinez et al. underestimated the drug utilisation. Our method could be more sensitive due to the wider variety of keywords used in our electronic search.

While we found a method to increase the detection rate of drug use, the question that arises is whether there is a reason why drug use was identified in these specific patients (i.e., are these patients different compared to the patients without identified drug use, and could this difference be the reason why drug use was identified in the former group and not in the latter). In order to determine whether we were dealing with a deviating group of patients and to confirm external validity, we first compared use of NOACs and LMWHs with annual NJR reports. We did not include aspirin use in this analysis because of expected differences based on the fact that aspirin is indicated for various other cardiovascular diseases. The ratio of NOAC and LMWH use in our CPRD analysis appeared to be different compared to the NJR reports in TKR patients in 2009 and 2010 only. This could be due to the fact that a NOAC prescription is considered to be new and therefore more likely to be mentioned in the free text notes as compared to LMWH use. To further investigate this, we also compared comorbidities and history of drug use of NOACs, LMWHs or aspirin among patients with unknown drug exposure status.

Only minor differences in characteristics were found between NOAC or LMWH users and patients with an unknown exposure status associated with TJR surgery (Table 8.3). This suggests that these groups are comparable and that there is no apparent reason for a detection bias of NOAC or LMWH use in these specific patients. This is reassuring when long-term effects and side effects of the different drugs are compared in further research. As expected, aspirin users were very different compared to unknown users with regard to comorbidities and drug use (Table 8.3). This is most likely due to the fact that aspirin is indicated for multiple other conditions such as angina pectoris, the prevention of myocardial infarction and other types of ischaemic heart disease. Therefore, our method seems to have limited usability for the identification of aspirin use in chemical thromboprophylaxis related to TJR. Differences in drug use according to region may be caused by use of regional guidelines. NICE guidance is predominantly designed for use in England and Wales. The Health and Social Care (HSC) and the Scottish Intercollegiate Guidelines Network (SIGN) are responsible for guidance in Northern Ireland and Scotland, respectively. However, linkage with NICE guidelines for implementation in Northern Ireland has been available since 2006.

Our study had various strengths. To the best of our knowledge, this is the first study reporting an effective method to identify antithrombotic drug use from anonymised free text in a large population-based GP database in a peer-reviewed scientific journal. Moreover, our method can be implemented at relatively low costs, since actual anonymization of free text is not required. This will then allow us to use the wealth of data in the world's largest primary care database to study, for example, the potential side effects of thromboprophylaxis associated with TJR. Our study also had limitations. We were unable to calculate false or true negatives. As a result, we were unable to determine the specificity and sensitivity of our method. In order to evaluate whether documentation of the exposure was differential between patients with a positive hit and patients without a hit, we applied two methods. First, we assessed distribution of NOAC and LMWH use from an external source, the NJR. Second, we assessed differences in baseline characteristics of the various exposure groups to the group without a hit. With these surrogate measurements, we have generated information concerning the potential differential detection of drug use exposure. Another limitation was that we were able to identify thromboprophylaxis related to TJR for only 18% of our patients, whereas actual thromboprophylaxis is likely to be close to 100%. This is probably the result of under-reporting of thromboprophylaxis by either hospitals, the GP or simply because discharge letters were sent to GPs as scanned PDF files rather than searchable free text. Nevertheless, we were still able to substantially increase identification using anonymised free text compared to identification based on product codes only. In the future, this may be further enhanced by linking to other data sources such as the hospital prescribing data, or by making the existing linkage between the NJR and CPRD available to researchers without any restrictions.

In conclusion, we have developed a useful method to identify exposure to NOACs or

LMWHs associated with TJR surgery. We can conclude that positive hits using the selected keywords in anonymised free text notes are strongly associated with actual use and that by using this method, identification of drug use has increased fivefold. Furthermore, identified users of NOACs and LMWH users appear to be reasonably similar to patients without identified drug use (Table 8.3). In contrast, aspirin users were very different as compared to patients without identified drug use, possibly due to the fact that aspirin is prescribed for various other health problems. Identification of drugs used for a specific post-surgery health ailment can be substantially enhanced by using our method; similar methods may be used for the identification of drugs prescribed for other diseases or hospital-specific medications such as biologicals and blood products. Our method is a useful tool to identify exposure to NOACs or LMWHs related to total TKR or THR surgery in the CPRD, and increases statistical power to evaluate potential side effects of these drugs in pharmacoepidemiological studies.

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Supplementary material

Table S.8.1: Keywords

Drug group	Keywords
NOACs	dabigatran, pradaxa, abigatra, dabagatran, dabegatran, dibagatran, ibegatran, dibigatran, debegatran, debigatran, debagatran, dabigetran, dabegetran, dabagetran, debigetran, debagetran, debegetran, dibigetran, dibagetran, dibegetran, rivaroxaban, xarelto, rivarox, aroxab, riveroxaban, rivoroxaban, riviroxaban, revaroxaban, reviroxaban, reveroxaban, revoroxaban, raviroxaban, raveroxaban, ravaroxaban, ravoroxaban, raviroxeban, raveroxeban, ravaroxeban, ravoroxeban, rivaroxeban, riveroxeban, rivoroxeban, riviroxeban, revaroxeban, reviroxeban, reveroxeban, revoroxeban, xaretlo, xaralto, xaratlo, xirelto, apixaban, eliquis, apixeban, apixiban, apixoban, apaxiban, apaxeban, apaxaban, apaxoban, apexiban, apexaban, apexoban, apoxaban, apoxeban, apoxiban, apoxoban, eliquies, elicquis, rivarocaban, reberoxeran, rivavonabam
Heparins	heparin, monoparin, unihep, calciparine, hepsal, canusal, multiparin, minihep, unfractionated heparin, ufh, heperin, hepirin, haparin, hapirin, hiparin, hiperin, hipirin, monopar, calcipar, multipar, bemiparin, zibor, bemip,mipa bemiprin, bemeparin, bemaparin, bemoparin, bimeparin, bamiparin, bameparin, bemiparine, zibro, certoparin, alphaparin, topari, certoprin, certeparin, certaparin, certiparin, cartoparin, certoparine, cetroparin, alfaparin, alphaprin, alphap, phapa, dalteparin, fragmin, tepari, dalteprin, daltoparin, daltaparin, daltiparin, delteparin, deltiparin, deltoparin,dilteparin, diltaparin, dolteparin, doltaparin, doltiparin, dalteparine, fragmine, fragmi, framgin, enoxaparin, clexane, noxapa, enoxaprin, xapar, enoxiparin, enoxeparin, enaxaparin, enaxeparin, enaxiparin, enaxoparin, enoxaparine, claxane, clexa, lexan, reviparin, clivarine, revipa, reviprin, reveparin, revaparin, raviparin, reviparine, clivarin, clivar, ivari, tinzaparin, innohep, tinza, zapar, tinzaprin, tinzeparin, tinziparin, tinzoparin, tanziparin, tanzeparin, tanzaparin, tanzoparin, tenzoparin, tenzaparin, tenziparin, tinzaparine, inohep, enoxoparin, fondaparinux, arixtra, fondap, dapari, parinux, fondaprinux, fondapinux, fondeparinux, fondaparinyx, fondaparinix, fondeparinyx, fondeparinix, arixt, arextra
Aspirin	acetylsalicylic acid, aspirin, micropirin, nu-seals, aspro, caprin, angettes, acetyl salicylic acid, acetylsal, acetylsalycilic acid, acetylsalycylic acid, acetylsalycylyc acid, acetylsalycilyc acid, acatylsalicylic acid, acatylsalicylyc acid, acatylsalycylyc acid, acatylsalycylic acid, acetylsalisylic acid, aspirn, asprin, aspirine, asperin, pirin, micropirine, microperin, micropirrin, microperrin, nuseals, nu-saels, nusaels, micropi, ropiri, apsro, asrpo, angett

Abbreviation: NOACs = new oral anticoagulants

Table S.8.2: Drug use according to identification method

	TKR		THR	
Drug use	Free text (%)	Product codes (%)	Free text (%)	Product codes (%)
All	36	64	36	64
NOAC	81	19	82	18
LMWH	70	30	66	34
Aspirin	12	88	12	88

Abbreviations: LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant, THR = total hip replacement, TKR = total knee replacement.

Chapter 9

Safety and efficacy of new oral anti-coagulants, and low molecular weight heparins compared to aspirin associated with total knee and hip replacement

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Abstract

Background: There has been much debate recently on the best type of thromboprophylaxis following elective total joint replacement surgery.

Objective: This study aims to compare rates of venous thromboembolism (VTE), gastrointestinal (GI) bleeding and mortality events, with use of new oral anticoagulants (NOACs) or low-molecular-weight heparins (LMWHs) compared with aspirin in patients undergoing total joint replacement.

Methods: A population-based retrospective cohort study was performed using the Clinical Practice Research Datalink. Patients ≥18 years of age who had undergone total knee (TKR (n=3,261)) or hip replacement (THR (n=4,016)) between 2008 and 2012 were included. Within this population, three cohorts were selected, based on their first prescription within the 35-day period after surgery: use of NOACs only, LMWHs only, or aspirin only. Incidence rates were calculated, and Cox proportional hazard models were fitted to estimate the risk of VTE, GI bleeding, or all-cause mortality with the use of NOACs and LMWHs compared with aspirin use after TKR and THR. We statistically adjusted our analyses for lifestyle factors, comorbidities, and concomitant drug use.

Results: TKR and THR patients currently on LMWHs had higher risk of VTE (hazard ratio (HR)=17.2 [95% confidence interval (CI)=6.9-43.0] and HR=39.5 [95% CI=18.0-87.0] respectively), GI bleeding (HR=20.9 [95% CI=1.9-232.3] and HR=2.0 [95% CI=0.2-17.2] respectively) and all-cause mortality (HR=4.3 [95% CI=1.7-12.4] and HR=4.0 [95% CI=2.4-6.7] respectively). NOAC use was associated with an increased risk of GI bleeding in patients undergoing THR surgery.

Conclusions: In contrast to previous studies, we found an increased risk of VTE, GI bleeding, and all-cause mortality with the use of LMWHs compared with aspirin. Risk of GI bleeding was increased with the use of NOACs compared with aspirin use after THR surgery.

Introduction

Osteoarthritis (OA) is the most prominent cause of pain and disability in the UK[1]. Based on 7-year consultation prevalence in general practice, an estimated 8.75 million people have sought treatment for pain associated with OA. This is one-third of the people aged 45 years and over in the UK[1]. Between 1990 and 2010, in the UK, the prevalence of disability due to OA increased by 15%[2]. Total joint replacement (TJR) surgeries, such as total hip replacement (THR) or total knee replacement (TKR), substantially improve quality of life in these patients[3]. However, potentially fatal venous thromboembolic (VTE) events may occur in up to 4.3% following this drastic surgical procedure[4]. Intensive antithrombotic treatment up to 35 days has therefore been suggested, but this may in turn result into life-threatening major bleedings such as gastrointestinal (GI) bleeding and haemorrhagic stroke[4]. Clinical trials have reported a major bleeding incidence of approximately 2% following THR or TKR surgery[5].

There has been much debate recently on the best type of thromboprophylaxis following THR or TKR surgery, in particular in terms of bleeding risk[6,7,8,9]. Low-molecular-weight heparins (LMWHs) have gained popularity over the past decades but can only be administered subcutaneously. The recently introduced direct thrombin inhibitors and direct factor Xa inhibitors (e.g. dabigatran and rivaroxaban) combine advantages of vitamin K antagonists, aspirin (a platelet aggregation inhibitor), and LMWHs. They can be orally administered and do not require international normalised ratio (INR) monitoring. Several randomised controlled trials (RCT), studying the safety and efficacy profiles of these new oral anticoagulants (NOACs) compared with LMWHs have been conducted. However, there is limited information on the safety profile of NOAC and LMWH use compared with aspirin in real practice, despite the fact that, on average, aspirin is used as antithrombotic therapy in 14% of TJR surgeries[10]. Currently, clinicians cannot evaluate an individual patient's risk of major bleeding when they undergo THR or TKR surgery. It is therefore important to address long-term safety in a population-based setting.

The aim of this study was to compare rates of VTE events, GI bleeding events, and mortality, with the use of NOACs or LMWHs compared with aspirin in patients undergoing THR or TKR surgery. We hypothesised that NOAC and LMWH use would be associated with more bleeding, but less thrombotic events.

Methods

The study protocol was approved by the Independent Scientific Advisory Committee, protocol number: 13_218R.

Data source

A population-based retrospective cohort study was performed using the Clinical Practice Research Datalink (CPRD). CPRD collates the computerised medical records of general

practitioners (GP). GPs play a key role in the UK healthcare system, as they are responsible for primary healthcare and specialist referrals. Patients are semi-permanently affiliated with a practice that centralises the medical information from the GPs, specialist referrals and hospitalisations. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major outcomes.

STUDY POPULATION

The study population comprised all patients aged 18 years or older who underwent a primary THR or TKR surgery between January 2008 and 31 October 2012. This time frame was chosen because NOACs have been registered for anticoagulant therapy after TKR and THR in Europe since 2008. The date of THR or TKR surgery was selected as index date. Each patient was then followed until the end of valid data collection (a patient's transfer out of practice or 1 November 2012), the date of death, or when an outcome of interest occurred, whichever came first. When death was considered an outcome of interest, it was not part of the definition of censoring. Patients with documented pregnancy in the year prior to surgery were excluded from analysis (Figure 9.1).

EXPOSURE

Three cohorts were selected, based on their first prescription within the 35-day period after surgery: use of NOACs (direct thrombin inhibitors/direct factor Xa inhibitors) only,

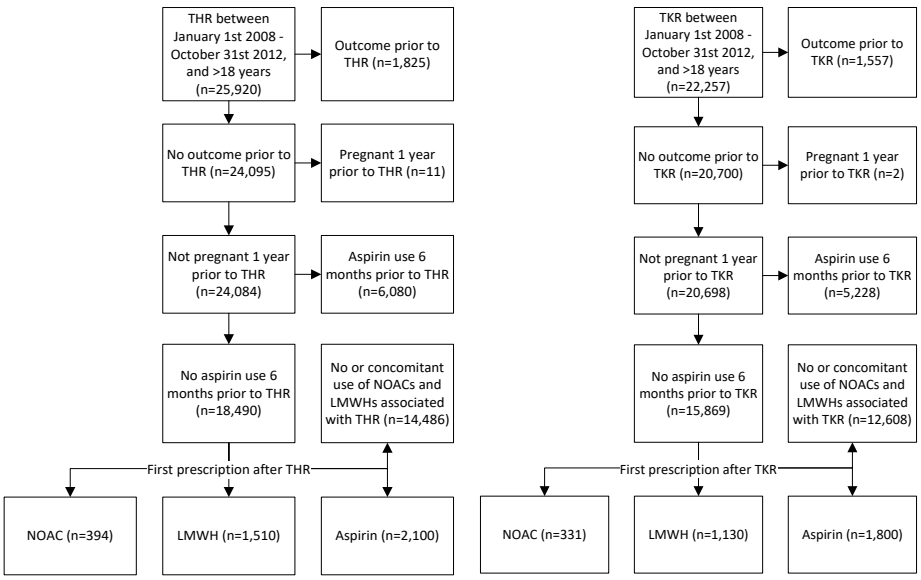

FIGURE 9.1: Flowchart depicting the selection of the study population. LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant, THR = total hip replacement, TKR = total knee replacement

LMWHs only and aspirin only. Patients without identified drug use, due to missing data on thromboprophylaxis, were excluded. Concomitant use of NOACs and aspirin was categorised as NOAC use. Concomitant use of LMWHs and aspirin was categorised as LMWH use. This classification was chosen because it is more likely that in these cases, the exposure to NOACs or LMWHs is associated with TJR, whereas the aspirin prescription was either additional or for another indication. Exposure to both a NOAC and a LMWH is highly unlikely. Therefore, patients with concomitant use of these drugs any time during follow-up were excluded. Patients with a NOAC, LMWH or an aspirin prescription in the 6 months prior to TJR were also excluded (Figure 9.1). In addition to product codes, we used anonymised free text recordings during the 10 days before/after surgery. This time window was based on the mean duration of hospital stays after TJRs, as reported in the National Registry of Hospitalisations of England (2008–2013)[11]. Use of anonymised free text has previously proven to be an effective method to increase detection rate of exposure to hospital-prescribed medications[12]. We expected that the duration of initial thromboprophylaxis would take either 14 days (TKR) or 35 days (THR) based on the summary of product characteristics (SPC). Exposure was classified as a time-dependent variable, that is, it could vary over follow-up. At the start of each 7-day period, exposure to a thromboprophylactic drug in the 14 days (TKR) or 35 days (THR) prior to this period was assessed. Exposure within this period was classified as current use. When the prescription was not renewed within 7 days after its estimated date of cessation, a patient became a past user. When a new prescription was received, a past user became a current user again.

Outcomes

All patients were followed up until the occurrence of GI bleeding (Table S.9.1), VTE (Table S.9.2), or all-cause mortality. Patients with a documented history of these outcomes, except all-cause mortality, were excluded from analysis (Figure 9.1).

Covariates

Risk factors for each outcome were identified based on literature and used as potential confounders. Potential confounders were assessed in a time-dependent manner, with the exception of smoking status, body mass index (BMI), socioeconomic status (SES), and alcohol use. We divided total follow-up into 7-day intervals. Information on time-dependent potential confounders was determined at the start of each time interval. All variables were treated as categorical variables (with the exception of age), and we used dummy indicator variables to account for missing data.

Potential confounders per outcome

The following potential confounders were included in the analyses assessing risk of GI bleeding: age and sex at index date; presence of GI ulcers, gastritis, duodenitis, oesophagitis,

oesophageal and gastric varices, and atrial fibrillation before index date; and use of antithrombotic agents (vitamin K antagonists and antiplatelet drugs), use of nonsteroidal anti-inflammatory drugs, use of systemic glucocorticoids, use of selective serotonin reuptake inhibitors, use of antihypertensive drugs, use of statins, use of anti-hyperglycaemic drugs and use of acid suppressants (proton pump inhibitors (PPI) or histamine 2 (H2)-receptor antagonists) in the 6 months prior to index date.

The following potential confounders were included in the analyses assessing risk of VTE: age, sex, SES, smoking status, and BMI at index date; presence of varicose veins, inflammatory bowel disease, fractures, heart failure, ischemic stroke, cerebrovascular diseases, atrial fibrillation, cancer, and chronic obstructive pulmonary disease (COPD) before index date; and use of hormone replacement therapy, use of tamoxifen, use of anticoagulants (vitamin K antagonists, antiplatelet drugs, use of non-steroidal anti-inflammatory drugs, and use of contraceptives in the 6 months prior to index date.

The following potential confounders were included in the analyses assessing risk of all-cause mortality: age, sex, SES, BMI, smoking status, and alcohol use at index date; presence of cancer, COPD, pneumonia, cardiovascular disease, and cerebrovascular disease before index date; and use of anti-hyperglycaemic drugs, use of statins, use of antihypertensive drugs and use of antibiotics in the 6 months prior to index date.

Statistical analysis

Person-years (PYs) of follow-up were calculated by adding all person-time from the start date to either the date of outcome or to the date of censoring, if no outcome had occurred. The incidence rates (IRs) of the outcomes were estimated as the number of events per 1,000 PY. In case of sufficient amount of events, time-varying Cox proportional hazard models were used to estimate the hazard ratios (HRs) for outcomes with past or current use of LMWHs, and NOACs compared with current aspirin use. HRs were adjusted, in a time-dependent manner, for age, sex and potential confounders, as specified per outcome in the previous section, which showed a >5% change in the beta-coefficient of current use, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. In the case of insufficient number of events, categories were combined (e.g. past NOAC users were combined with current NOAC users). In the case of insufficient number of events, we were unable to conduct analyses adjusted by more than two confounders (age and sex). Sensitivity analyses were conducted taking into account VTE events occurring >30 days after surgery only.

Results

Baseline characteristics of THR (NOAC: n=385; LMWH: n=1,429; aspirin: n=2,096) and TKR patients (NOAC: n=328; LMWH: n=1,072; aspirin: n=1,791) are presented in Table 9.1. NOACs were prescribed to relatively young patients, whereas aspirin was prescribed to a relatively

Table 9.1: Baseline characteristics of patients using NOACs, LMWHs, or aspirin associated with total hip and knee replacement.

Characteristic	Total hip replacement			Total knee replacement		
	NOAC n=385 (%)	LMWH n=1,429 (%)	Aspirin n=2,096 (%)	NOAC n=328 (%)	LMWH n=1,072 (%)	Aspirin n=1,791 (%)
Follow up (mean, years (SD))	1.6 (1.1)	2.2 (1.3)	2.7 (1.3)	1.7 (1.0)	2.3 (1.4)	2.9 (1.3)
Age (mean, years (SD))	66.7 (11.3)	68.5 (11.6)	70.9 (11.7)	68.0 (9.3)	67.9 (10.0)	69.6 (9.6)
Number of females	241 (62.6)	893 (62.5)	1,300 (62.0)	202 (61.6)	653 (60.9)	990 (55.3)
Socioeconomic status (IMD), by category						
Low	66 (17.1)	233 (16.3)	274 (13.1)	61 (18.6)	182 (17.0)	212 (11.8)
Low-medium	61 (15.8)	253 (17.7)	266 (12.7)	65 (19.8)	188 (17.5)	235 (13.1)
Medium	45 (11.7)	212 (14.8)	196 (9.4)	43 (13.1)	188 (17.5)	189 (10.6)
Medium-high	30 (7.8)	141 (9.9)	143 (6.8)	17 (5.2)	87 (8.1)	158 (8.8)
High	22 (5.7)	111 (7.8)	90 (4.3)	22 (6.7)	70 (6.5)	105 (5.9)
Missing	161 (41.8)	479 (33.5)	1,127 (53.8)	120 (36.6)	357 (33.3)	892 (49.8)
BMI, most recent value prior to index date						
BMI (kg/m^2, mean (SD))	28.2 (5.7)	27.6 (5.4)	27.1 (5.1)	29.8 (5.4)	30.1 (5.7)	29.8 (5.4)
<20.0 kg/m^2	108 (28.1)	449 (31.4)	699 (33.3)	55 (16.8)	183 (17.1)	328 (18.3)
20.0 – 24.9 kg/m^2	120 (31.2)	496 (34.7)	752 (35.9)	120 (36.6)	380 (35.4)	647 (36.1)
25.0 – 29.9 kg/m^2	97 (25.2)	266 (18.6)	391 (18.7)	89 (27.1)	257 (24.0)	478 (26.7)
>30.0 kg/m^2	37 (9.6)	127 (8.9)	140 (6.7)	51 (15.5)	214 (20.0)	277 (15.5)
Missing	23 (6.0)	91 (6.4)	114 (5.4)	13 (4.0)	38 (3.5)	61 (3.4)
Alcohol consumption						
Yes	285 (74.0)	1,087 (76.1)	1,485 (70.8)	264 (80.5)	794 (74.1)	1,295 (72.3)
No	74 (19.2)	225 (15.7)	475 (22.7)	51 (15.5)	224 (20.9)	402 (22.4)
Unknown	26 (6.8)	117 (8.2)	136 (6.5)	13 (4.0)	54 (5.0)	94 (5.2)
Smoking status						
Never	159 (41.3)	698 (48.8)	951 (45.4)	159 (48.5)	490 (45.7)	804 (44.9)
Former	165 (42.9)	544 (38.1)	907 (43.3)	149 (45.4)	477 (44.5)	811 (45.3)
Current	61 (15.8)	185 (12.9)	237 (11.3)	20 (6.1)	104 (9.7)	176 (9.8)
Unknown	0 (0.0)	2 (0.1)	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Drug use in the 6 months prior to index date						
VKA	5 (1.3)	130 (9.1)	87 (4.2)	6 (1.8)	106 (9.9)	65 (3.6)
Antiplatelet (excluding aspirin)	5 (1.3)	32 (2.2)	188 (9.0)	7 (2.1)	29 (2.7)	146 (8.2)
Antihypertensive drugs	173 (44.9)	635 (44.4)	1,205 (57.5)	153 (46.6)	555 (51.8)	1,105 (61.7)
Statins	86 (22.3)	321 (22.5)	764 (36.5)	92 (28.0)	316 (29.5)	733 (40.9)
Anti-hyperglycaemic drugs	21 (5.5)	77 (5.4)	123 (5.9)	18 (5.5)	81 (7.6)	136 (7.6)
PPI	131 (34.0)	483 (33.8)	915 (43.7)	131 (39.9)	423 (39.5)	840 (46.9)
H2-receptor antagonist	11 (2.9)	41 (2.9)	93 (4.4)	9 (2.7)	43 (4.0)	71 (4.0)
Tamoxifen	4 (1.0)	5 (0.3)	4 (0.2)	4 (1.2)	9 (0.8)	5 (0.3)
SSRIs	30 (7.8)	108 (7.6)	185 (8.8)	23 (7.0)	80 (7.5)	160 (8.9)
Systemic corticosteroids	21 (5.5)	92 (6.4)	126 (6.0)	16 (4.9)	73 (6.8)	121 (6.8)
NSAIDs	159 (41.3)	570 (39.9)	755 (36.0)	138 (42.1)	472 (44.0)	718 (40.1)
NSAIDs COX-selective	13 (3.4)	51 (3.6)	73 (3.5)	15 (4.6)	45 (4.2)	66 (3.7)
NSAIDs non-selective	151 (39.2)	537 (37.6)	699 (33.3)	123 (37.5)	439 (41.0)	669 (37.4)
Antibiotics	102 (26.5)	482 (33.7)	693 (33.1)	112 (34.1)	429 (40.0)	603 (33.7)
Contraceptives	1 (0.3)	9 (0.6)	3 (0.1)	0 (0.0)	3 (0.3)	1 (0.1)
Hormone replacement therapy	12 (3.1)	30 (2.1)	31 (1.5)	3 (0.9)	40 (3.7)	28 (1.6)
Comorbidities before index date						
Cancer	1 (0.3)	21 (1.5)	15 (0.7)	0 (0.0)	6 (0.6)	15 (0.8)
GI ulcers	11 (2.9)	55 (3.8)	97 (4.6)	16 (4.9)	64 (6.0)	98 (5.5)
Gastric and oesophageal varices	1 (0.3)	1 (0.1)	2 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)
Oesophagitis	35 (9.1)	129 (9.0)	169 (8.1)	37 (11.3)	113 (10.5)	186 (10.4)
Gastritis/duodenitis	31 (8.1)	85 (5.9)	148 (7.1)	25 (7.6)	79 (7.4)	143 (8.0)
Varicose veins	65 (16.9)	220 (15.4)	331 (15.8)	55 (16.8)	202 (18.8)	315 (17.6)
IBD*	11 (2.9)	18 (1.3)	24 (1.1)	3 (0.9)	19 (1.8)	21 (1.2)
Fractures	115 (29.9)	463 (32.4)	812 (38.7)	77 (23.5)	317 (29.6)	477 (26.6)
Atrial fibrillation	13 (3.4)	83 (5.8)	186 (8.9)	7 (2.1)	65 (6.1)	128 (7.1)
Heart failure	5 (1.3)	30 (2.1)	62 (3.0)	2 (0.6)	25 (2.3)	62 (3.5)
Ischemic stroke	0 (0.0)	7 (0.5)	34 (1.6)	1 (0.3)	5 (0.5)	22 (1.2)
Cerebrovascular diseases	8 (2.1)	49 (3.4)	199 (9.5)	9 (2.7)	36 (3.4)	136 (7.6)
COPD	18 (4.7)	96 (6.7)	110 (5.2)	11 (3.4)	66 (6.2)	111 (6.2)
Pneumonia	11 (2.9)	45 (3.1)	84 (4.0)	13 (4.0)	27 (2.5)	62 (3.5)

* IBD: Crohn's disease or ulcerative colitis. Abbreviations: BMI = body mass index, COPD = chronic obstructive pulmonary disease, COX = cyclooxygenase, H2 = histamine 2, IMD = index of multiple deprivation, IBD = inflammatory bowel disease, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, VKA = vitamin K antagonist.

older group. Between 62.0% and 62.6% of the THR patients and between 55.3% and 61.6% of the TKR were women. In both the TKR and the THR patients, aspirin users were more likely to have been diagnosed with previous comorbidities and consequently used more drugs.

GI bleeding occurred more often in patients currently on thromboprophylaxis when compared with patients who had stopped using thromboprophylaxis or patients without documented use of thromboprophylaxis (Table 9.2). IRs of GI bleeding in THR and TKR patients currently on thromboprophylaxis were 4.6 and 4.5 per 1,000 PY, respectively. In the THR group, GI bleeding mostly occurred with the use of NOACs (IR=22.1/1,000 PY; HR=9.4 [95% confidence interval (CI)=1.1-82.0]). In the TKR patients, events mostly occurred with the use of LMWHs (IR=31.9/1,000 PY; HR=20.9 [95% CI=1.9-232.3]). In past users, the differences were not statistically significant.

VTE events occurred more often in patients currently on thromboprophylaxis when compared with patients who had stopped using thromboprophylaxis (Table 9.3). IRs of VTE events in THR and TKR patients currently on thromboprophylaxis were 31.1 and 45.4 per 1,000 PY, respectively. In the THR group, these VTE events mostly occurred with the use of LMWHs (IR=260.2/1,000 PY; HR=39.5 [95% CI=18.0-87.0]). In the TKR patients, VTE events mostly occurred with the use of LMWHs (IR=402.9/1,000 PY; HR=17.2 [95% CI=6.9-43.0]). Sensitivity analyses only taking VTE events occurring >30 days after surgery into account revealed similar results when compared with the primary analyses (Table S.9.3) in THR patients. In THR patients, the IR of VTE events with current use of LMWHs was 187.5/1,000 PY, and the adjusted HR was 30.6 (95% CI=13.3-70.4). In the TKR patients, the IR of VTE events with current use of LMWHs was 548.2/1,000 PY, and the adjusted HR was 51.2 (95% CI=13.1-200.4).

Patients currently on thromboprophylaxis died more often when compared with patients who had stopped using thromboprophylaxis (Table 9.4). The IRs of all-cause mortality in THR and TKR patients currently on thromboprophylaxis were 47.1 and 32.9 per 1,000 PY, respectively. In the THR group, all-cause mortality mostly occurred with the current use of LMWHs (IR=106.7/1,000 PY; HR=4.0 [95% CI=2.4-6.7]). In the TKR patients, all-cause mortality mostly occurred with the use of LMWHs (IR =79.3/1,000 PY; HR=4.5 [95% CI=1.7-12.4]).

Discussion

This study shows that TKR and THR patients currently on LMWHs had higher IRs of VTE events and all-cause mortality compared with current aspirin users. Moreover, risk of VTE events and all-cause mortality was significantly higher in current users compared with current aspirin users. TKR patients currently on LMWHs had a higher risk of GI bleedings compared with patients currently on aspirin, whereas THR patients currently on LMWHs had a similar risk compared with patients currently on aspirin. THR patients currently on NOACs had a higher risk of GI bleedings, but a similar risk of VTE events compared with current aspirin users.

Table 9.2: Risk of GI bleeding following thromboprophylaxis after total hip and knee replacement surgery.

Exposure	Total hip replacement			Total knee replacement		
	GI bleeding IR (/1,000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)	GI bleeding IR (/1,000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)
No thromboprophylaxis	1.9	0.6 (0.1-2.7)	-	3.6	1.5 (0.2-12.9)	-
Past thromboprophylaxis	1.6	0.6 (0.2-1.8)	-	3.8	2.3 (0.3-17.1)	-
By type of thromboprophylaxis						
NOAC	1.7	1.0 (0.1-8.9)	-	7.3	5.7 (0.6-51.6)*	-
LMWH	2.0	0.7 (0.2-2.6)	-	2.4	1.6 (0.2-13.2)	-
Aspirin	1.3	0.5 (0.1-1.8)	-	4.2	2.4 (0.3-17.8)	-
Current thromboprophylaxis	4.6	-	-	4.5	-	-
By type of thromboprophylaxis						
NOAC	22.1	9.4 (1.1-82.0)	-	0.0	-	-
LMWH	5.3	2.0 (0.2-17.2)	-	31.9	20.9 (1.9-232.3)	-
Aspirin	3.9	Reference	-	1.7	Reference	-

* Includes person time of current NOAC users due to lack of events in current NOAC group.- No full confounder adjustment due to limited number of events. Abbreviations: CI = confidence interval, GI = gastrointestinal, HR = hazard ratio, IR = incidence rate, LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant.

Table 9.3: Risk of VTE following thromboprophylaxis after total hip and knee replacement surgery.

Exposure	Total hip replacement			Total knee replacement		
	VTE IR (/1000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[a]	VTE IR (/1000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[b]
No thromboprophylaxis	56.7	9.3 (4.5-19.5)	10.1 (4.8-21.5)	53.3	3.6 (1.6-7.8)	3.5 (1.6-7.6)
Past thromboprophylaxis	9.4	1.5 (0.7-3.1)	1.5 (0.7-3.3)	13.0	0.9 (0.4-2.0)	0.9 (0.4-2.0)
By type of thromboprophylaxis						
NOAC	1.7	0.3 (0.0-2.7)	0.4 (0.0-3.0)	3.6	0.3 (0.1-1.5)*	0.3 (0.1-1.4)*
LMWH	11.4	1.5 (0.7-3.4)	1.6 (0.7-3.6)	15.1	1.1 (0.5-2.5)	1.0 (0.4-2.3)
Aspirin	9.1	1.6 (0.7-3.4)	1.6 (0.7-3.6)	13.1	0.9 (0.4-2.1)	1.0 (0.4-2.2)
Current thromboprophylaxis	31.1	-	-	45.4	-	-
By type of thromboprophylaxis						
NOAC	22.1	4.4 (0.6-35.5)	4.7 (0.6-37.9)	0.0	-	-
LMWH	260.2	39.2 (18.0-85.0)	39.5 (18.0-87.0)	402.9	18.9 (7.6-46.9)	17.2 (6.9-43.0)
Aspirin	6.0	Reference	Reference	12.3	Reference	Reference

[a] Adjusted for: age and sex; drug use in 6 months prior to index date: vitamin-K antagonists. [b] Adjusted for: age, sex, and socioeconomic status; drug use in 6 months prior to index date: vitamin-K antagonists, antiplatelet drugs. * Includes person time of current NOAC users due to lack of events in current NOAC group. Abbreviations: CI = confidence interval, HR = hazard ratio, IR = incidence rate, LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant, VTE = venous thromboembolism.

Table 9.4: Risk of all-cause mortality following thromboprophylaxis after total hip and knee replacement surgery.

	Total hip replacement			Total knee replacement		
Exposure	All-cause mortality IR (/1000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI) [a]	All-cause mortality IR (/1000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI) [b]
No thromboprophylaxis	0.0	-	-	0.0	-	-
Past thromboprophylaxis	19.5	0.7 (0.5-1.0)	0.8 (0.6-1.1)	13.1	0.5 (0.3-0.9)	0.6 (0.3-1.0)
By type of thromboprophylaxis						
NOAC*	6.7	0.3 (0.1-0.7)	0.3 (0.1-0.8)	7.2	0.3 (0.1-0.8)	0.3 (0.1-0.9)
LMWH	17.9	0.7 (0.5-1.0)	0.7 (0.5-1.1)	14.6	0.6 (0.3-1.1)	0.7 (0.4-1.2)
Aspirin	22.6	0.8 (0.6-1.1)	0.9 (0.6-1.2)	13.0	0.5 (0.3-0.9)	0.6 (0.3-1.0)
Current thromboprophylaxis	47.1	-	-	32.9	-	-
By type of thromboprophylaxis						
NOAC	0.0	-	-	0.0	-	-
LMWH	106.7	4.0 (2.4-6.6)	4.0 (2.4-6.7)	79.3	4.3 (1.6-11.7)	4.5 (1.7-12.4)
Aspirin	41.1	Reference	Reference	28.9	Reference	Reference

[a] Adjusted for: age, sex, BMI, socioeconomic status, smoking, and alcohol use; drug use in the 6 months prior to index date: antihypertensive drugs, and antibiotics; history of comorbidity before index date: cancer, pneumonia, atrial fibrillation, heart failure, and cerebrovascular events. [b] Adjusted for: age, sex, smoking, and alcohol use; drug use in the 6 months prior to index date: antihypertensive drugs, statins, and antibiotics; history of comorbidity ever before: atrial fibrillation, heart failure, cancer. * Includes person time of current NOAC users due to lack of events in current NOAC group (for HR calculations only). Abbreviations: BMI = body mass index, HR = hazard ratio, IR = incidence rate, LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant.

To our knowledge, safety and efficacy of NOACs and LMWHs compared with aspirin after TJR have previously been assessed in three studies. One observational study (n=258) and two (n=120 and n=324) RCTs have been reported on this subject. No significant differences in the incidence of VTE events or major bleeding were found in the studies by Jiang et al.[13], and Sindali et al.[14]. A lower incidence of deep venous thrombosis with the use of rivaroxaban compared with LMWH or aspirin use was reported in the study by Zou et al.[15]. Traditional meta-analyses and indirect network meta-analyses of RCTs addressing the safety and efficacy of NOACs compared with LMWHs generally presented similar or better safety and efficacy of NOACs compared with LMWHs[16,1718]. However, it should be mentioned that low-dose (150mg daily) dabigatran was associated with an increased risk of VTE events compared with enoxaparin[16] and rivaroxaban was associated with an increased risk of bleeding[17]. Finally, mortality rates were similar in NOAC users compared with LMWH users[16,17,18].

The present study has several strengths. This is the first study addressing the safety and efficacy of NOACs and LMWHs compared with aspirin use in a large population-based database. This enabled us to assess the risk of VTE events, GI bleeding and all-cause mortality associated with NOAC and LMWH use compared with aspirin use in 4,016 THR and 3,261 TKR patients. Granted we were unable to accurately assess these risks, the generated data may be of use in future studies. Data from multiple studies, such as the present, with limited follow-up time and few events should be collected and combined in future meta-analyses. These meta-analyses will eventually be of sufficient power to generate clinically relevant results, limiting the need to conduct expensive trials.

The risks presented in this study are different when compared with previous research. In contrast to the previously reported similar or better safety and efficacy profile of NOACs and LMHWs compared with aspirin, we found a similar or increased risk of VTE events, GI bleeding and all-cause mortality. The difference between our study and previous work is probably due to some limitations in our study. First, because of a relatively low detection rate of drug exposure, we were unable to capture sufficient outcome events to properly compare safety and efficacy of NOACs and LMWHs compared with aspirin. The CPRD is a GP-based database; therefore, hospital-prescribed drugs, without the need of a repeat prescription by a GP, are likely to be under registered. Efforts were made to increase detection rate by including data from anonymised free text notes. Using this approach, we were able to increase the detection of exposure by 57% on average. Furthermore, exposure may be differentially reported in patients who did experience some kind of adverse event compared with those who did not. Second, our study showed unexpectedly high IRs of VTE events with the use of LMWHs, which is unexpected because LMWHs are also indicated for the treatment of acute VTE events such as deep venous thrombosis and pulmonary embolism. This would suggest that our results may have been influenced by reverse causality, that is, the incidence of VTE events is not likely to be the result of LMWH use, but rather LMWH use is the result of

the occurrence of a VTE event. In other words, timing of registration of the VTE event and registration of LMWH prescription may have been distorted. Possibly, the registration of the VTE event was delayed relative to the LMWH prescription. This type of information bias may especially occur in the case of acute events. We therefore conducted sensitivity analyses only taking VTE events occurring >30 days after surgery into account. These analyses revealed similar results when compared with the primary analyses. This was expected because the initial problem regarding reverse causality still remains. Third, although we made an effort to correct for relevant covariates, confounding is of considerable concern in an observational study. However, because of limited number of events, we were inherently limited in the inclusion of potential confounders when analysing the risk of GI bleeding. Time-varying propensity score adjusted methods, such as marginal structural models, could have been used to overcome this limitation. However, the assumptions associated with these models may not all be met and consequently result in the introduction of bias. Fourth, we categorised concomitant use of a NOAC (or a LMWH) and aspirin as NOAC (or LMWH) use. We did not differentiate between combined users and NOAC (or LMWH) only users because of low number of events. In future, larger studies, this may be an interesting topic to assess.

In contrast to previous studies, we found an increased risk of VTE events, GI bleeding and all-cause mortality with the use of LMWHs compared with aspirin. Risk of GI bleeding was increased with the use of NOACs compared with aspirin use after THR surgery. However, we would like to stress that these results should be interpreted with great care. Based on the results presented in this study, comparison of the safety and efficacy of NOACs and LMWHs after TKR or THR cannot be made accurately. However, the data generated could contribute to future studies and meta-analyses addressing these topics.

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Supplementary material

Table S.9.1: CPRD medical codes gastrointestinal bleeding

medcode	Read term
1188	Haematemesis
397	Melaena
1642	GIB- Gastrointestinal bleeding
3097	Gastrointestinal haemorrhage
4354	Upper gastrointestinal haemorrhage
2814	Unspecified duodenal ulcer with haemorrhage
4636	Gastrointestinal tract haemorrhage NOS
15517	Gastric haemorrhage NOS
18001	Acute duodenal ulcer with haemorrhage
12471	Gastrointestinal haemorrhage unspecified
2150	Intestinal haemorrhage NOS
18625	Bleeding chronic duodenal ulcer
11124	Bleeding acute gastric ulcer
30054	Acute gastric ulcer with haemorrhage
48951	Chronic duodenal ulcer with haemorrhage
37299	Melaena- O/E of faeces
63582	Chronic gastric ulcer with haemorrhage
36583	Bleeding chronic gastric ulcer
23813	Gastrotomy and ligation of bleeding point of stomach
57958	Unspecified gastric ulcer with haemorrhage
48730	Acute duodenal ulcer with haemorrhage and perforation
94397	Unspec gastric ulcer; unspec haemorrhage and/or perforation
71403	Acute gastric ulcer with haemorrhage and perforation
28366	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
71897	Chronic gastric ulcer with haemorrhage and perforation
71881	Chronic duodenal ulcer with haemorrhage and perforation
93436	Unspecified duodenal ulcer with haemorrhage and perforation

Table S.9.2: CPRD medical codes venous thromboembolism

medcode	Read term
824	Deep vein thrombosis
1266	Pulmonary embolism
3576	Deep vein phlebitis and thrombophlebitis of the leg
9701	Pulmonary embolus
3392	DVT- Deep vein thrombosis
607	Creation of ileostomy
22038	Deep vein thrombosis of lower limb
1224	Post-operative deep vein thrombosis
32002	Deep vein thrombophlebitis of the leg unspecified
18121	Post-operative pulmonary embolus
27284	Deep vein phlebitis and thrombophlebitis of the leg NOS
15382	Thrombophlebitis of the femoral vein
25478	Deep vein thrombosis, leg
18830	DVT- deep venous thrombosis, postnatal
7174	Obstetric pulmonary embolism
23667	Antenatal deep vein thrombosis
42506	Deep vein thrombosis of leg related to air travel
48920	Deep vein thrombosis of leg related to intravenous drug use
61204	Postnatal deep vein thrombosis NOS
44192	Amniotic fluid pulmonary embolism
61203	Antenatal deep vein thrombosis NOS
23588	Postnatal deep vein thrombosis with postnatal complication
65725	Antenatal deep vein thrombosis unspecified
44404	Obstetric pulmonary embolism NOS with postnatal complication
31313	Obstetric air pulmonary embolism
69921	Postnatal deep vein thrombosis unspecified
67006	Pulmonary embolism following abortive pregnancy
73569	Obstetric pulmonary embolism NOS
49269	Obstetric blood-clot pulmonary embolism
73624	Amniotic fluid pulmonary embolism- delivered
94405	Antenatal deep vein thrombosis- delivered
97367	Obstetric pulmonary embolism NOS- delivered

Table S.9.3: Risk of VTE following thromboprophylaxis after total hip and knee replacement surgery, restricted to VTE events that occurred >30 days after surgery.

Exposure	Total Hip Replacement			Total Knee Replacement		
	VTE IR (/1000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI) [a]	VTE IR (/1000PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR (95% CI)[b]
No thromboprophylaxis	1.3	0.3 (0.1-1.3)	0.3 (0.1-1.3)	1.9	0.4 (0.1-2.0)	0.3 (0.1-1.8)
Past thromboprophylaxis	5.7	0.9 (0.4-2.1)	0.9 (0.4-2.0)	8.4	1.3 (0.4-4.2)	1.1 (0.3-3.6)
By type of thromboprophylaxis						
NOAC	2.3	0.5 (0.1-4.2)	0.5 (0.1-4.2)	0.0	-	-
LMWH	11.3	1.6 (0.7-3.8)	1.5 (0.6-3.6)	25.2	3.9 (1.1-13.6)	3.0 (0.9-10.7)
Aspirin	2.5	0.5 (0.2-1.4)	0.5 (0.2-1.3)	4.0	0.6 (0.2-2.2)	0.5 (0.1-2.0)
Current thromboprophylaxis	21.7	-	-	27.8	-	-
By type of thromboprophylaxis						
NOAC	29.0	6.7 (0.8-54.1)	6.3 (0.8-50.8)	0.0	-	-
LMWH	187.5	32.9 (14.4-75.2)	30.6 (13.3-70.4)	548.2	67.1 (17.5-257.4)	51.2 (13.1-200.4)
Aspirin	5.4	Reference	Reference	5.5	Reference	Reference

[a] Adjusted for: Age, and sex. Drug use in previous 6 months: Vitamin-K antagonists. [b] Adjusted for: Age, sex, and socioeconomic status. Drug use in previous 6 months: Vitamin-K antagonists, antiplatelets. Abbreviations: CI = confidence interval, HR = hazard ratio, IR = incidence rate, LMWH = low-molecular-weight heparin, NOAC = new oral anticoagulant, VTE = venous thromboembolism

Chapter 10

Use of thiazolidinediones and the risk of elective hip or knee replacement: a population based case-control study

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Abstract

Aims: Osteoarthritis (OA) is the most common musculoskeletal condition in the elderly population. However, no disease modifying drug exists for this disease. *In vivo* animal studies have suggested that thiazolidinediones (TZD) may be used as disease modifying osteoarthritis drugs (DMOADs). To our knowledge, this has not yet been examined in humans before. The aim was to determine the risk of total joint replacement (TJR) in patients using TZDs compared with diabetic patients using other anti-hyperglycaemic drugs (ADs).

Methods: A population based case-control study was performed using the Clinical Practice Research Datalink (CPRD). Cases (n=94,609) were defined as patients >18 years of age who had undergone total knee (TKR) or hip replacement (THR) between 2000 and 2012. Controls were matched by age, gender and practice. Conditional logistic regression analyses were used to estimate the risk of TKR and THR with the use of TZDs in patients currently using one or more ADs. In order to determine effect with prolonged use, we also stratified TZD users by total number of prescriptions prior to surgery. We statistically adjusted our analyses for lifestyle factors, comorbidities, and concomitant drug use.

Results: There was no difference in risk of TKR (OR=1.09 [95% confidence interval (CI)=0.93-1.27]) and THR (OR=0.92 [95% CI=0.76-1.10]) when TZD users were compared with other AD users. Furthermore, we did not find an association with prolonged use of TZDs and TJR.

Conclusion: Despite promising results from animal in vivo studies, this study did not find any evidence for a disease modifying osteoarthritic effect of TZDs.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal condition in elderly people in the United Kingdom (UK). Based on 7 year consultation prevalence in general practice, it is estimated that approximately 8.8 million people, aged 45 years and over, in the UK have sought treatment for OA[1]. This progressive disease affects the joints, causing them to become painful and thereby limiting a patient's functioning and health. Total joint replacement surgery (TJR), such as total hip replacement (THR) or total knee replacement (TKR), can substantially improve the quality of life in these patients[2].

Patients with diabetes mellitus (DM) are more likely to suffer from OA[3]. Until recently this was related to increased prevalence of overweight in persons with DM and with the increased mechanical load on the weight-bearing joints of these patients. However, DM is also preceded by metabolic problems, such as impaired glucose metabolism. Several recent studies support the hypothesis that DM may be an independent risk factor for OA, possibly related to these and other metabolic features[4,5,6,7]. On this line, research suggests that hyperglycaemia and advanced glycation end products (AGEs) play an important role in the progression of OA[8,9,10]. Other factors may include dyslipidaemia and adipose tissue inflammation[11]. Dyslipidaemia may link DM to OA trough low concentrations of high density lipoprotein cholesterol[12], and increased concentrations of oxidized low density lipoprotein[13]. Adipose tissue inflammation may link DM to OA through elevated (pro-inflammatory) cytokine secretion[14] and increased adipokine concentrations[15,16].

Peroxisome proliferator-activated receptor gamma (PPARγ) is primarily involved in the regulation of glucose and lipid metabolism. It has been associated with several conditions, such as cardiovascular diseases and DM. Additionally, previous studies have suggested that PPARγ may also play an important role in the pathogenesis of osteoarthritis[17,18,19]. It has been reported that PPARγ expression of chondrocytes is down regulated *in vitro*, in human OA cartilage compared with normal cartilage[11]. Furthermore, *in vivo* animal models have shown that PPARγ-deficiency is associated with an increased occurrence of a spontaneous OA phenotype[13]. Therefore, activation of PPARγ may result in a reduction of development and progression of OA. Several mechanisms have been suggested for this effect. Activation of PPARγ has been associated with a reduction of (pro) inflammatory cytokines, such as tumour necrosis factor alpha, interleukin-6, interleukin-1β and matrix metalloproteinases[20]. Interestingly, PPARγ can be activated by various therapeutic compounds, including the antidiabetic thiazolidinediones (TZD), such as rosiglitazone (withdrawn from the European market in 2010, due to an association with increased risk of myocardial infarction and death from cardiovascular causes[21]) and pioglitazone[22].The effect of TZDs on PPARγ has been assessed in several *in vivo* animal studies. In a study using a guinea pig OA model, four treatment groups were compared: normal animals, OA animals given placebo, OA animals given a low dose (2 mg kg^{-1} day^{-1}) of pioglitazone, and OA animals given a high dose (20 mg kg^{-1} day^{-1}) pioglitazone. The high dosed guinea pigs showed a significant

decrease in size and depth of macroscopic cartilage lesions compared with the OA placebo group[23]. In a similar canine model, high dose (30 mg day^{-1}) pioglitazone was also associated with a reduced development of cartilage lesions[24]. Currently, TZDs are only indicated for the treatment of DM. They can be used alone or in combination with metformin or with a sulfonylurea (SU).

To date, no disease modifying osteoarthritic drugs (DMOADs) exist. Therefore, it seemed attractive to further investigate PPARγ activation. To our knowledge, the possible disease modifying osteoarthritic effect of PPARγ activating drugs, such as TZDs, has not been studied in humans yet. Based on existing *in vitro* and *in vivo* studies, we hypothesize that patients using TZDs may have a reduced risk of severe OA and consequently have less TJRs. Furthermore, we expect to see a decreased risk of surgery with a longer duration of TZD use. Therefore, the aim of this study was to determine the risk of TJR in patients using TZDs compared with diabetic patients using other antidiabetic drugs.

Methods

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research, protocol number: 14_054R. The ISAC is an expert advisory body established to provide advice on research related requests to access data provided by the Clinical Practice Research Datalink (CPRD). This body is based in London, the UK.

Data source

A case-control study was performed using the CPRD, previously known as the General Practice Research Database (GPRD). The CPRD is a large primary care database containing medical records registered by over 625 general practitioners (GP) in the UK. It represents >8% of the British population. In the UK, GPs play a key role in the healthcare system as they are responsible for primary care and specialist referrals. Consequently, this database provides information on a wide range of medical records, including diagnoses, prescriptions, referrals, laboratory test results and socioeconomic status (Index of Multiple Deprivation).

Study population

All patients aged 18 years or older who had undergone a primary THR or TKR surgery between January 2000 and the 31 October 2012 were selected as cases. This time frame was chosen because TZDs have been registered in Europe since 2000. Patients with a diagnosis of rheumatoid arthritis (RA) or hip/knee fractures preceding the TJR surgery were excluded from the analyses. All cases were matched to one control patient without a record for TJR using incidence density sampling. Cases and controls were matched by year of birth, gender, and practice. The index date for the patients was the date of TJR surgery. This date was imputed for the matched control patient.

Exposure definitions

The use of TZDs and other anti-hyperglycaemic drugs (ADs) prior to TJR surgery was determined by reviewing dispensing information before the index date. Other ADs include all other ADs such as biguanides, SUs, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, glinides, and insulin. Current users of these drugs comprised all patients with at least one recorded prescription within the 90 day period before the index date. To determine whether duration of use would affect the risk of TJR, we stratified the risk of TJR in current TZD users by the number of TZD prescriptions ever before surgery. Group 1 consisted of patients with 1-4 prescriptions, group 2 with 5-8 prescriptions, group 3 with 9-14 prescriptions, group 4 with 15-29 prescriptions, and group 5 with ≥30 prescriptions[25]. On average one prescription corresponds with 4 weeks of drug use. Consequently, four and eight prescriptions will, on average, cover a duration of approximately 16 and 32 weeks respectively. More than 30 prescriptions will correspond with, on average, more than 2 years and 16 weeks of drug use.

Selection of covariates

We reviewed the literature to identify potential confounders for OA and TJR surgery. Factors including age, gender, socioeconomic status (SES), the number of GP consultations, body mass index (BMI), glomerular filtration rate (GFR), and smoking status were used as potential confounders[26,27,28]. A history of diseases such as angina pectoris, acute myocardial infarction (AMI), heart failure, arrhythmia, hypertension, haemorrhagic stroke, ischaemic stroke, retinopathy, and neuropathy were also included. Non-hip/femur fractures in the previous year were also included as potential confounders. Use of loop diuretics, thiazides, non-steroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers, β-adrenoceptor blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, systemic glucocorticoids in the previous 6 months, and the most recent laboratory test value for glycosylated haemoglobin (HbA1c) and fasting glucose in the previous year were also considered as potential confounders[29]. In all analyses potential confounders were included if they independently changed the beta-coefficient for current TZD exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from the literature.

Statistical analysis

Conditional logistic regression analyses were used to estimate the risk of TKR and THR surgery associated with severe OA with the use of TZDs in patients currently using one or more ADs. Risk of surgery was compared within all diabetic patients because the underlying disease may influence the outcome. We additionally stratified current TZD users by BMI, HbA1c and fasting glucose. BMI was stratified into the following groups: <25.0 kg m^{-2}, 25-29.9 kg m^{-2}, 30–34.9 kg m^{-2}, ≥ 35.0 kg m^{-2} according to the BMI classification of the World

Health Organization (WHO). HbA1c was stratified into the following groups: <6.5%, 6.5-7.9%, 8-9.4%, ≥9.5%. Fasting plasma glucose was stratified into the following groups: <5 mmol l^{-1}, 5–5.9 mmol l^{-1}, 6-6.9 mmol l^{-1}, 7-7.9 mmol l^{-1}, 8-8.9 mmol l^{-1}, ≥9.0 mmol l^{-1}. To determine whether an effect with duration of use was present we determined the risk of TKR and THR in current TZD users stratified by number of TZD prescriptions ever before surgery. Sensitively analyses were performed to address the effect of missing key data such as HbA1c and fasting glucose. In order to determine this effect, conditional logistic regression analyses were performed excluding these variables from our statistical models. In order to address the duration of drug use we performed sensitivity analyses in which the risk of surgery was estimated with at least nine prescriptions. All analyses were conducted using SAS statistical software version 9.3.

Results

Between January 2000 and October 2012 a total of 44,768 TKR patients and 49,841 THR patients were identified (Table 10.1). The subjects were approximately 70 years old and 55%-60% of them were female. Both TKR and THR cases visited their GPs approximately 30% more often than their matched controls in the year prior to TJR. Furthermore, a total of 17,512 (39.1%) TKR and 12,424 (24.9%) THR cases were defined as obese (BMI ≥ 30 kg m^{-2}) compared with 9,068 (20.2%) TKR and 9,419 (18.9%) THR controls. Socioeconomic status distribution was similar in both TKR and THR cases and controls. Mean estimated GFR (eGFR) and laboratory test values (HbA1c and fasting glucose) were comparable in the cases and the controls. In the TKR group there were 3,623 cases and 3,252 controls currently using an AD, whereas there were 2,749 cases and 3,272 controls in the THR group (Table 10.2).

TZD use was not associated with risk of TKR (odds ratio (OR)=1.03 [95% confidence interval (CI)=0.88-1.22]) or THR (OR=0.90 [95% CI=0.75-1.08]) compared with patients using an AD other than a TZD (Table 10.2). Patients with a BMI ranging from 30 to 34.9 kg m^{-2} (OR=1.32 [95% CI=1.02-1.71]) and those with a BMI >35 kg m^{-2} (OR=1.25 [95% CI=0.95-1.64]) using TZDs showed a tendency towards an increased risk of TKR compared with patients using other ADs. This BMI effect was not observed for the risk of THR. Furthermore, there was no tendency for risk of THR and TKR with increasing HbA1c levels in TZD users compared with non-users. In fact, TZD users with HbA1c levels ≥9.5% had significantly lower risks of TKR (OR=0.42 [95% CI=0.20-0.86]) and THR (OR=0.34 [95% CI=0.18-0.64]) compared with patients using other ADs. No tendency for risk of THR and TKR with increasing fasting glucose concentrations was found in TZD users compared with patients using other ADs. Moreover, there was no effect on risk of THR or TKR with increasing number of TZD prescriptions compared with patients using other ADs (Table 10.3). Patients who received up to four prescriptions of TZDs were, however, at lower risk of THR compared with patients receiving other ADs but who had never used a TZD (OR=0.32 [95% CI=0.16-0.63]).

Table 10.1: Baseline characteristics of total knee and total hip replacement surgery cases and controls

Characteristic	Total knee replacement n=89,536		Total hip replacement n=99,682	
	Cases (%) n=44,768	Controls (%) n=44,768	Cases (%) n=49,841	Controls (%) n=49,841
Number of females	24,912 (55.6)	24,912 (55.6)	29,724 (59.6)	29,724 (59.6)
No of GP consultations in the year prior to index date (mean (SD))	41.3 (25.7)	28.9 (26.2)	40.2 (27.0)	28.0 (26.1)
Age at index date (years, (SD))	69.5 (9.5)	69.5 (9.5)	68.8 (11.5)	68.8 (11.5)
Socioeconomic status (IMD), by category				
Low	6,945 (15.5)	7,120 (15.9)	8,248 (16.5)	8,054 (16.2)
Low-medium	7,176 (16.0)	7,011 (15.7)	8,200 (16.5)	8,015 (16.1)
Medium	5,763 (12.9)	5,626 (12.6)	6,287 (12.6)	6,113 (12.3)
Medium-high	4,533 (10.1)	4,451 (9.9)	4,521 (9.1)	4,741 (9.5)
High	3,077 (6.9)	3,240 (7.2)	2,896 (5.8)	3,191 (6.4)
Missing	17,274 (38.6)	17,320 (38.7)	19,689 (39.5)	19,727 (39.6)
BMI, most recent value prior to index date				
BMI (kg/m^2, mean (SD))	29.7 (5.2)	27.0 (5.1)	27.6 (5.0)	26.8 (5.0)
BMI, by category				
<25.0 kg/m^2	7,248 (16.2)	14,415 (32.2)	13,789 (27.7)	16,495 (33.1)
25.0-29.9 kg/m^2	16,245 (36.3)	15,243 (34.0)	17,982 (36.1)	16,524 (33.2)
30.0-34.9 kg/m^2	11,258 (25.1)	6,464 (14.4)	8,839 (17.7)	6,647 (13.3)
≥35.0 kg/m^2	6,254 (14.0)	2,604 (5.8)	3,585 (7.2)	2,772 (5.6)
Missing	3,763 (8.4)	6,042 (13.5)	5,646 (11.3)	7,403 (14.9)
HbA1c, most recent value within the year prior to index date				
HbA1c (%, mean (SD))	6.9 (1.2)	7.1 (1.4)	6.8 (1.2)	7.2 (1.4)
HbA1c, by category				
<6.5%	1,811 (4.0)	1,422 (3.2)	1,629 (3.3)	1,406 (2.8)
6.5-7.9%	2,331 (5.2)	1,976 (4.4)	1,623 (3.3)	1,837 (3.7)
8.0-9.4%	542 (1.2)	586 (1.3)	411 (0.8)	550 (1.1)
≥9.5%	189 (0.4)	299 (0.7)	133 (0.3)	310 (0.6)
Missing	39,895 (89.1)	40,485 (90.4)	46,045 (92.4)	45,738 (91.8)
Fasting glucose, most recent value within the year prior to index date				
Fasting glucose (mmol/L, mean (SD))	5.7 (1.5)	5.7 (1.7)	5.6 (1.4)	5.7 (1.7)
Fasting glucose, by category				
<6.0 mmol/L	3,791 (8.5)	3,143 (7.0)	3,351 (6.7)	3,016 (6.1)
6.0-7.5 mmol/L	818 (1.8)	613 (1.4)	580 (1.2)	590 (1.2)
7.5-8.9 mmol/L	248 (0.6)	152 (0.3)	122 (0.2)	167 (0.3)
≥9.0 mmol/L	156 (0.3)	149 (0.3)	145 (0.3)	164 (0.3)
Missing	39,755 (88.8)	40,711 (90.9)	45,643 (91.6)	45,904 (92.1)
eGFR, most recent value within the year prior to index date				
eGFR (mL/min/1.73m², mean (SD))	71.9 (17.9)	70.8 (17.9)	71.9 (18.9)	70.4 (18.1)
eGFR, by category				
≥ 90 mL/min/1.73m²	4,720 (10.5)	3,464 (7.7)	4,998 (10.0)	3,654 (7.3)
60-89 mL/min/1.73m²	19,900 (44.5)	16,953 (37.9)	19,389 (38.9)	17,082 (34.3)
30-59 mL/min/1.73m²	8,366 (18.7)	7,398 (16.5)	8,504 (17.1)	8,028 (16.1)
15-29 mL/min/1.73m²	171 (0.4)	272 (0.6)	280 (0.6)	283 (0.6)
<15 mL/min/1.73m²	23 (0.1)	53 (0.1)	49 (0.1)	71 (0.1)
Missing	11,588 (25.9)	16,628 (37.1)	16,621 (33.3)	20,723 (41.6)
History of comorbidity before index date				
Angina pectoris	4,615 (10.3)	4,309 (9.6)	4,273 (8.6)	4,603 (9.2)
AMI	1,929 (4.3)	2,336 (5.2)	2,139 (4.3)	2,308 (4.6)
Ischemic stroke	332 (0.7)	468 (1.0)	347 (0.7)	483 (1.0)
Haemorrhagic stroke	191 (0.4)	261 (0.6)	239 (0.5)	275 (0.6)
Valve disorders	482 (1.1)	587 (1.3)	611 (1.2)	609 (1.2)
Peripheral vascular disorders	550 (1.2)	778 (1.7)	664 (1.3)	764 (1.5)
Ulcers	3,280 (7.3)	2,441 (5.5)	3,250 (6.5)	2,815 (5.6)
Non-hip/femur fractures in the year prior to index date	559 (1.2)	623 (1.4)	957 (1.9)	696 (1.4)
History of comorbidity 5 years before index date				
Retinopathy	884 (2.0)	911 (2.0)	643 (1.3)	850 (1.7)
Neuropathy	551 (1.2)	441 (1.0)	499 (1.0)	428 (0.9)
History of drug use within 6 months prior to index date				
NSAIDs	19,522 (43.6)	5,773 (12.9)	22,467 (45.1)	6,259 (12.6)
All NIADs	3,430 (7.7)	3,075 (6.9)	2,511 (5.0)	3,037 (6.1)
Biguanides	2,780 (6.2)	2,406 (5.4)	1,995 (4.0)	2,388 (4.8)
Sulphonylureas	1,497 (3.3)	1,573 (3.5)	1,206 (2.4)	1,568 (3.1)
Thiazolidinediones	540 (1.2)	428 (1.0)	311 (0.6)	420 (0.8)
Glinides	38 (0.1)	28 (0.1)	18 (0.0)	26 (0.1)
GLP-1 analogues	53 (0.1)	28 (0.1)	27 (0.1)	17 (0.0)
DPP-4 inhibitors	93 (0.2)	89 (0.2)	62 (0.1)	60 (0.1)
Insulins	747 (1.7)	825 (1.8)	580 (1.2)	837 (1.7)

Abbreviations: AMI = acute myocardial infarction, BMI = body mass index, DPP-4 = dipeptidyl peptidase-4, eGFR = estimated glomerular filtration rate, GLP-1 = glucagon-like peptide-1, GP = general practitioner, HbA1c = glycated haemoglobin, IMD = index of multiple deprivation, NIAD = non-insulin anti-hyperglycaemic drug, NSAID = non-steroidal anti-inflammatory drugs, SD = standard deviation.

TABLE 10.2: Use of thiazolidinediones and risk of total knee or total hip replacement in current users of antidiabetic drugs, stratified by BMI, HbA1c and fasting glucose levels.

	TKR n=89,536				THR n=99,682			
AD use*	Cases n= 44,768	Control n= 44,768	Crude OR (95% CI)	Fully adjusted OR[a] (95% CI)	Cases n= 49,841	Control n=49,841	Crude OR (95%CI)	Fully adjusted OR[b] (95%CI)
Current AD use	3,623	3,252			2,748	3,272		
AD use excl. TZD	3,111	2,861	Reference	Reference	2,461	2,889	Reference	Reference
TZD use	512	391	1.21 (1.05- 1.39)	1.03 (0.88-1.22)	287	383	0.88 (0.75- 1.04)	0.90 (0.75-1.08)
By BMI, most recent								
<25 kg/m^2	18	32	0.52 (0.29-0.93)	0.56 (0.29-1.06)	21	38	0.65 (0.38-1.12)	0.73 (0.41-1.30)
25-29.9 kg/m^2	114	128	0.82 (0.63-1.06)	0.92 (0.69-1.23)	78	119	0.77 (0.58-1.03)	0.83 (0.60-1.14)
30-34.9 kg/m^2	196	122	1.50 (1.18-1.89)	1.32 (1.02-1.71)	102	121	0.99 (0.76-1.30)	1.05 (0.78-1.43)
≥35 kg/m^2	182	106	1.58 (1.23- 2.01)	1.25 (0.95-1.64)	85	101	0.99 (0.74-1.34)	0.97 (0.69-1.36)
Missing	2	3	0.61 (0.10-3.64)	0.72 (0.12-4.43)	1	4	0.30 (0.03-2.68)	0.23 (0.02-2.92)
By HbA1c, most recent in previous year								
<6.5 %	116	65	1.65 (1.21-2.24)	1.26 (0.88-1.79)	59	60	1.16 (0.81-1.67)	1.13 (0.75-1.71)
6.5-7.9 %	263	192	1.26 (1.04-1.53)	1.04 (0.83-1.29)	131	191	0.81 (0.64-1.01)	0.80 (0.62-1.03)
8.0-9.4 %	86	58	1.38 (0.98-1.93)	1.40 (0.95-2.06)	54	52	1.22 (0.83-1.80)	1.23 (0.80-1.89)
≥9.5 %	15	35	0.39 (0.21-0.72)	0.42 (0.20-0.86)	17	49	0.39 (0.22-0.69)	0.34 (0.18-0.64)
Missing	32	41	0.72 (0.45-1.15)	0.61 (0.35-1.07)	26	31	0.98 (0.58-1.66)	1.17 (0.64-2.14)
By fasting glucose, most recent in previous year								
<6.0 mmol/L	16	15	0.98 (0.48-1.98)	0.94 (0.41- .19)	11	16	0.81 (0.37-1.75)	0.78 (0.33-1.86)
6.0-7.4 mmol/L	25	18	1.28 (0.69-2.34)	1.08 (0.54-2.18)	16	15	1.27 (0.63-2.57)	1.36 (0.61-3.05)
7.5-8.9 mmol/L	33	11	2.92 (1.43-5.95)	2.07 (0.95-4.51)	16	14	1.35 (0.66-2.76)	1.67 (0.74-3.77)
≥9.0 mmol/L	16	17	0.87 (0.44-1.72)	0.75 (0.33-1.68)	14	19	0.84 (0.41-1.71)	0.97 (0.43-2.22)
Missing	422	330	1.18 (1.01-1.38)	1.01 (0.85-1.21)	230	319	0.85 (0.71-1.01)	0.85 (0.69-1.04)

a) Adjusted for: smoking status and BMI. Drug use in previous 6 months: statins, RAAS inhibitors, non-selective NSAIDs. Most recent value in previous year for HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. b) Adjusted for: BMI. Drug use in previous 6 months: non-selective NSAIDs and COX2-selective NSAIDs. History of retinopathy in 5 years prior to TJR. Most recent value in previous year for HbA1c. Stratified variables were excluded as confounder in the analyses stratified by that variable. * Numbers may not add up, as patients not using anti-hyperglycaemic drugs are not shown, but were included in the analyses. Abbreviations: AD= anti-hyperglycaemic drug, BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, HbA1c = glycated haemoglobin, OR = odds ratio, RAAS = renin-angiotensin-aldosterone system, THR = total hip replacement, TJR = total joint replacement, TKR = total knee replacement, TZD = thiazolidinedione.

Table 10.3: Use of thiazolidinediones and risk of total knee or total hip replacement in current users of antidiabetic drugs, stratified by number of TZD prescription before surgery.

	TKR (n=89,536)				THR (n=99,682)			
AD use*	Case n= 44,768	Control n= 44,768	Crude OR (95% CI)	Fully adjusted OR [a] (95% CI)	Case n= 49,841	Control n=49,841	Crude OR (95% CI)	Fully adjusted OR [b] (95% CI)
Current AD use	3,623	3,252			2,748	3,272		
AD use excl. TZD	3,111	2,861	Reference	Reference	2,461	2,889	Reference	Reference
TZD use	512	391	1.21 (1.05-1.39)	1.03 (0.88-1.22)	287	383	0.88 (0.75-1.04)	0.90 (0.75-1.08)
By number of TZD prescriptions ever before TJR surgery								
1-4	45	47	0.88 (0.58-1.33)	1.04 (0.65-1.69)	15	51	0.35 (0.20-0.62)	0.32 (0.16-0.63)
5-8	48	29	1.53 (0.96-2.43)	1.45 (0.86-2.46)	38	43	1.04 (0.67-1.62)	1.30 (0.78-2.16)
9-14	68	50	1.25 (0.86-1.81)	1.36 (0.87-2.11)	34	47	0.85 (0.55-1.33)	0.78 (0.47-1.28)
15-29	157	113	1.28 (1.00-1.63)	1.00 (0.75-1.33)	90	97	1.09 (0.81-1.46)	1.04 (0.75-1.45)
≥30	194	152	1.18 (0.95-1.48)	0.90 (0.70-1.15)	110	145	0.89 (0.69-1.15)	0.93 (0.70-1.23)

a) Adjusted for: Smoking status and BMI. Drug use in previous 6 months: statins, RAAS inhibitors, non-selective NSAIDs. Most recent value in previous year for HbA1c and fasting glucose. Stratified variables were excluded as confounder in the analyses stratified by that variable. b) Adjusted for: BMI. Drug use in previous 6 months: non-selective NSAIDs and COX2-selective NSAIDs. History of retinopathy in 5 years prior to TJR. Most recent value in previous year for HbA1c. Stratified variables were excluded as confounder in the analyses stratified by that variable. * Numbers may not add up, as patients not using anti-hyperglycaemic drugs are not shown, but were included in the analyses. Abbreviations: AD= anti-hyperglycaemic drug, BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, HbA1c = glycated haemoglobin, OR = odds ratio, RAAS = renin-angiotensin-aldosterone system, THR = total hip replacement, TJR = total joint replacement, TKR = total knee replacement, TZD = thiazolidinedione.

Sensitivity analyses excluding HbA1c resulted in an OR of 0.88 (95% CI=0.73-1.05) and an OR of 1.04 (95% CI=0.88-1.22) for THR and TKR respectively. Sensitivity analyses excluding fasting glucose resulted in an OR of 1.04 (95% CI=0.88-1.22) for TKR. Sensitivity analyses estimating the risk of surgery with at least nine prescriptions resulted in ORs of 0.94 (95% CI=0.77-1.16) and 1.01 (95% CI=0.84-1.20) for THR and TKR surgery, respectively.

Discussion

The present study showed that there was no difference in risk of TJR, associated with severe OA, when comparing TZD use to use of other ADs. Furthermore, no association with THR or TKR was found with stratification of TZD users by BMI and fasting glucose. High HbA1c levels (≥9.5%) were associated with a decreased risk of surgery. Furthermore, an increase in number of TZD prescriptions was not associated with risk of TJR compared with DM patients using other ADs. Finally, sensitivity analyses excluding HbA1c and fasting glucose showed similar results compared with the analyses including HbA1c and fasting glucose as a confounder. Sensitivity analyses estimating the risk of surgery with at least nine prescription showed similar results compared with analyses including all current TZD users.

The suggested protective effect of TZDs on the development and progression of OA, based on animal *in vivo* studies, was not present in humans when we determined the risk of TKR or THR in TZD users compared with patients using other ADs. Species differences could have contributed to the deviated findings. Despite the fact that the experimental dog model has been used extensively and successfully in previous OA studies, it is unknown whether it is possible to extrapolate data from this animal model to clinical observations[30,31,32,33,34,35]. Furthermore, in a clinical setting pioglitazone is usually prescribed in doses ranging from 15 to 45 mg day^{-1}, which is comparable with the high doses used in the canine model. Unfortunately, pharmacokinetic (PK) parameters of pioglitazone were not examined in the canine study. Therefore, comparison of dose and effect between the species is challenging. A separate study presented a PK profile of pioglitazone in dogs including a time to maximal concentration (t_{max}) of 0.5 hours and a half-life ($t_{½}$) of 2.1 hours, which are both lower than the parameters in humans (t_{max} = 2 hours, $t_{½}$ = 5–6 hours)[36]. This suggests that the dogs would be exposed to the drug for a shorter period of time if the same dosage was given. However, other PK and pharmacodynamic parameters may also affect the dose-effect relationship. Consequently, limitations regarding species comparison remain present.

There was no difference in risk of surgery when comparing TZD use with the use of other ADs. TZDs are predominantly prescribed to patients unable to control their glucose metabolism sufficiently with use of metformin or SUs only. The TZD users may therefore be relatively severe DM patients. This may potentially result in confounding by disease severity, masking a pharmacological effect of TZDs. Additionally, severe OA patients have a reduced mobility[37], potentially resulting in a decreased ability to control their diabetes. As a result of this, severe OA patients are more likely to be prescribed a third AD, such as a TZD. Since DM

has previously been associated with an increased risk of OA, the effect of this underlying disease should be taken into account. Our finding could be the result of fact that DM as such already increases the risk for OA and TZDs were not able to counteract this effect through PPARγ activation. Stratification by HbA1c and fasting glucose, however, did not reveal an association with risk of surgery and an increasing severity of DM. In fact, patients with HbA1c values >9.5% were at lower risk of surgery. This suggests that TZDs reduce the risk of surgery in this poorly controlled diabetic population. However, it seems more likely that other factors are responsible for the reduced eligibility of surgery in patients with high HbA1c. Finally, an increase in number of TZD prescriptions was not associated with risk of TJR compared with DM patients using other ADs. These results suggest that there is no protective effect through PPARγ activation of TZD on the progression of OA.

Our study has several strengths and limitations. To the best of our knowledge this is the first study investigating the risk of OA with use of TZDs in a human population. We were, therefore, able to investigate the possible disease modifying osteoarthritic effect of TZDs, which has only been reported in pre-clinical studies. Furthermore, it was conducted using the world's largest primary care database representing >8% of the British population. This enabled us to assess the risk of TJR associated with TZD use in 94,609 TJR patients. A limitation of this study is that the causal interpretation of the findings will be restricted. Although we made an effort to correct for relevant covariates, confounding is of considerable concern in an observational study. Due to limited availability of data we were unable to control for several factors, such as valgus/varus deformity, or a history of meniscus surgery or anterior cruciate ligament rupture. Furthermore, TJR could be considered to be an inadequate definition for OA. However, in epidemiology it has been widely used in previous studies assessing risk factors for severe OA[6,38]. With this definition we are limited to severe cases of OA, missing possible beneficial effects in earlier stages of OA. Additionally, the severity of OA in the *in vivo* animal studies could be characterized as mild to moderate, limiting the comparability with the cases in our study. Finally, adherence is a concern when using large databases, such as the CPRD. Misclassification of exposure is therefore of concern[39]. Adherence to ADs is estimated to be approximately 70%[40]. The possible effect of TZDs may therefore be underestimated. Compensating for an underestimation would result in an OR closer to 1.0 in the case of TKR surgery and a potentially significantly lower risk of THR associated with TZD use.

In summary, we did not find any evidence supporting the hypothesis that TZDs could be used as disease modifying osteoarthritic drugs. There is no difference in risk of THR or TKR when TZD users are compared with other AD users. Finally, no duration of use effect was found with an increasing number of prescriptions. When these results will be confirmed in other observational studies, we would not recommend further clinical studies on the disease modifying osteoarthritic effect of TZDs.

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Chapter 11

General discussion

The overall objective of this thesis was to assess the association between diabetes mellitus (DM) and osteoarthritis (OA) of the knee and hip, and to gain insight into outcomes associated with a broad spectrum of treatment strategies for knee and hip OA. In this final chapter, the main findings from the studies included in this thesis will be evaluated, followed by some methodological considerations. This chapter will conclude with a discussion on the implications of the results and future recommendations.

Main findings

The objective of part one of this thesis was to improve our knowledge about the association between DM and OA of the knee and hip. To evaluate this association in the Maastricht Study, we first assessed the representativeness of the population participating in this study by comparing drug dispensing data with national reimbursement data in Chapter 2. Total drug use of the Maastricht Study population was comparable with the national population. However, for some classes of medications, drug utilization in the Maastricht Study was lower as compared to national data. Participants who used respiratory drugs were especially underrepresented in the study population. It has been suggested this may reflect issues related to functional status, as it may be more difficult for people with a respiratory morbidity to participate in a study such as the Maastricht Study as compared to those without a respiratory illness[1]. Conversely, the use of hypnotics and anxiolytics was higher as compared to national rates, especially in the population aged 65-74 years. This may suggest that the included participants were concerned about their health, and therefore participated in the study. Because drug use in the Zuid-Limburg region is higher as compared to the national population[2], a generally healthy population seems to have been included in the Maastricht Study. Altogether, the included population is likely to be relatively healthy, health-conscious, and possibly health-concerned. Consequently, data from the Maastricht Study can be used to address a wide range of research questions, provided that general health status of the included population is of no concern. However, if this may be the case, the potential effect on the results should be weighed and use of the data should be reconsidered.

The association between DM and OA was evaluated in the Maastricht Study (Chapter 3) and in the Clinical Practice Research Datalink (CPRD) (Chapter 4). In the Maastricht Study, age and sex standardised rates of clinical knee OA and knee pain were higher in patients with type 2 DM (T2DM) compared to those without T2DM. However, after adjustment for BMI, there were no differences in the risk of knee pain or clinical knee OA, between patients with or without T2DM. Furthermore, there was no association between T2DM and knee pain or clinical knee OA with increasing severity of T2DM. Similarly, in the CPRD, there was no difference in the risk of total knee (TKR) or total hip replacement (THR) surgery between patients with or without DM. In fact, the risk of TKR or THR was reduced with increasing severity of DM. Overall, these results do not support the hypothesis that DM is an

independent risk factor for OA as suggested in two meta-analyses of observational studies[3,4]. It should be noted, however, that the included studies had considerable heterogeneity, as reflected by a high I^2 statistic[3,4]. The heterogeneity of the included studies and discrepancies with our studies may have been caused by the use of different definitions of OA, and the fact that date of onset of OA is generally difficult to determine.

When evaluating the association between DM and OA, the use of total joint replacement (TJR) as proxy for OA may have led to bias, as DM-related factors may have been involved preventing DM patients from undergoing surgery. Furthermore, as the date of onset of OA is difficult to determine, misclassification of timing of onset may also affect this association. Therefore, the effect of the choice of the definition of OA and the timing of its onset relative to the start of pharmacological DM treatment on the association between DM and OA was assessed in Chapter 5. This study showed that there was a difference between the use of a surgical proxy for the outcome (i.e. TJR) or the diagnosis as recorded by the general practitioner (GP). More specifically, when using TJR as a proxy for OA the risk estimate was approximately 20% lower than when the diagnosis was used. This supports the hypothesis that the association may be affected by bias when using TJR as proxy for OA. Furthermore, addition of a latency period of up to ten years after start of follow-up did not affect the association. Consequently, temporality related issues did not appear to affect the association.

The objective of part two was to evaluate the effectiveness and safety outcomes associated with a broad spectrum of treatment strategies for knee and hip OA. In this thesis, a selection of preventive, surgical, and pharmacological options were evaluated. Given the possibility that DM is an independent risk factor for OA, and as intra-articular glucocorticoids (GCs) injections can be given to treat inflammatory episodes of OA, the use of orally and parenterally administered GCs and the risk of onset of DM was evaluated in Chapter 6. In this chapter we confirmed previous findings suggesting that the use of oral GCs may result in an increased risk of DM[5,6,7]. Furthermore, local injections of GCs have been associated with transient changes in glucose levels in both diabetic and non-diabetic patients[8]. However, in this chapter, the use of parenterally administered GCs was not associated with an increased risk of new onset of DM. This may be explained by the generally short and intermittent use of these GCs resulting in a limited effect on glucose metabolism and, consequently, onset of DM.

With regards to surgical treatment strategies, we determined the age and sex specific incidence rates of knee prostheses (KPs) and health care costs associated with these procedures compared to matched controls in Chapter 7. We found an increase of KPs, revision KPs, and complications over time, which is largely in line with results published by the Dutch Arthroplasty Register (Dutch: Landelijke Registratie Orthopedische Implantaten (LROI))[9]. Furthermore, in line with a previous study from the United States, the prevalence of surgeries is particularly increasing in younger age categories[10]. Additionally, excess costs of

patients with a KP compared to controls were mainly associated with (multiple) subsequent surgeries, post-operative complications, younger age, and female gender.

TJR surgery has been associated with an increased risk of venous thromboembolic (VTE) events[11], for which various preventive treatment options are available[12]. However, recently there has been much discussion about the risk-benefit profiles of the pharmacological treatment options following TJR. Therefore, in Chapter 8, we first designed a search strategy that improved the detection rate of antithrombotic drug use, using anonymised free text notes, in the CPRD. Subsequently, we applied this method to compare safety and effectiveness outcomes of low molecular weight heparins (LMWHs), and new (or direct) oral anticoagulants (DOACs/NOACs), with aspirin use in Chapter 9. We found that the use of a NOAC or a LMWH following TJR carried similar risk of GI bleeding, and all-cause mortality compared to the use of aspirin. However, LMWH use was associated with an increased risk of VTE events compared to aspirin use, which was in contrast with previous studies that compared these drugs[13,14]. This unexpected result may have been caused by reverse causality as LMWHs were probably prescribed to treat a VTE event. Due to a low detection rate and some potential methodological limitations it should be noted that the results from this study should be interpreted with care.

With regards to pharmacological treatment strategies we evaluated the potential disease modifying properties of thiazolidinediones (TZDs), used to treat T2DM, that have been proposed in pre-clinical studies[15,16]. In Chapter 10 of this thesis, we found no difference in risk of TKR or THR surgery when TZD users were compared to DM patients using other anti-hyperglycaemic drugs. This has provided no additional evidence for TZDs being a potential disease modifying osteoarthritic drug (DMOAD).

Methodological considerations

The studies presented in this thesis all had their own specific strengths and limitations. However, some methodological issues may have broader implications and are therefore discussed in more detail in this section. For instance, different types of bias may cause deviation from accurate and precise estimates of associations in observation research. According to the Dictionary of Epidemiology, bias can be defined as "an error in either the conception and design of a study, or in the collection, analysis, interpretation, reporting, publication, or review of data, leading to results or conclusions that are systematically, as opposed to randomly, different from truth"[17]. Generally, bias can be classified as information bias, selection bias, or confounding. Information bias can be described as "a flaw in measuring exposure, covariate, or outcome variables that results in different quality of information between comparison groups"[17]. Selection bias is defined as "an error in the estimated association or effect of an exposure on an outcome that arises from the procedures used to select individuals into the study or the analysis"[17]. Confounding can be defined as "the distortion of a measure of the effect of an exposure on an outcome

due to the association of the exposure with other factors that influence the occurrence of the outcome"[17]. In this section, various types of information bias, selection bias, and confounding, often encountered in pharmacoepidemiological studies, and their effect on the studies in this thesis will be discussed (Figure 11.1).

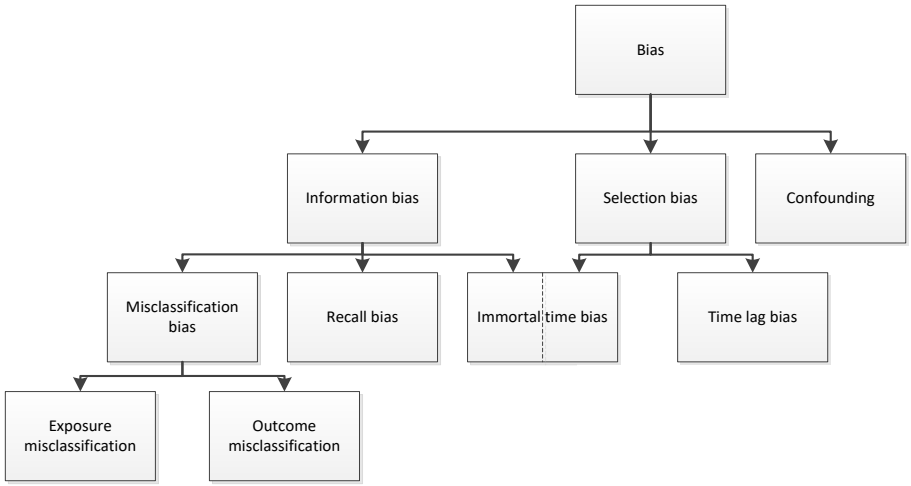

Figure 11.1: Types of bias discussed in this chapter

Information bias

Misclassification bias

Misclassification has been described as "the erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned"[17]. According to the Dictionary of Epidemiology misclassification bias is a type of information bias[17], whereas others use misclassification bias and information bias interchangeably[18]. As will become clear in this section, various types of information bias may result in misclassification, possibly contributing to the equivocal use of these definitions. If misclassification is more likely to occur in one of the comparison groups compared to the other, i.e. when it is differential, this may lead to either an over- or an underestimation of the association. If the misclassification is non-differential this can lead to a bias towards the null[19,20]. In this section misclassification of exposure and misclassification of the outcome will be discussed.

Drug exposure may be misclassified as a result of medication non-adherence or due to underrecording. First, misclassification of drug exposure due to medication non-adherence results from the fact that prescribed drugs are not necessarily dispensed, let alone ingested or administered[18]. It is estimated that medication adherence for the treatment of chronic

diseases is 50% on average[21], but it may vary from 0% to more than 100%[22]. Consequently, when using the CPRD, which does not include data on drug dispensing or intake, to evaluate a pharmacological effect, potential misclassification of drug exposure should be considered (Chapters 6, 9, and 10). In Chapter 6, the effect of parenteral GCs on the onset of DM was evaluated. Because GCs are usually administered by a health care professional, it is unlikely that misclassification of exposure due to non-adherence will have affected the results in this chapter. In Chapter 9, safety and effectiveness outcomes with the use of antithrombotic drugs after TKR and THR were evaluated. On average, patients remain in the hospital for 7 days after these surgical interventions[23]. During the period in this relatively controlled environment, misclassification due to non-adherence is unlikely to occur. However, after discharge, patients using a LMWH may be less adherent, compared to NOAC or aspirin users, as they have to administer the drug by subcutaneous injection. Therefore, misclassification of the exposure may have been differential and could have affected the results in this chapter. More specifically, in LMWH users the risk of adverse outcomes, such as GI bleeding, may have been underestimated. In Chapter 10 the risk of TKR and THR with the use of TZDs compared to other anti-hyperglycaemic drugs was evaluated. A previous study has shown that adherence to metformin, sulfonylurea, and pioglitazone was comparable[24]. Consequently, it is expected that the potential misclassification of exposure was non-differential and that in this chapter the results may have been biased towards the null. Without this potential distortion, the risk estimates of TZD use with THR (OR=0.90 [95% CI=0.75-1.08]) and TKR (OR=1.03 [95% CI=0.88-1.22]) may have been lower and higher respectively.

Second, misclassification of exposure may be the result of underrecording. Some drugs are not usually prescribed in the primary care setting, but for instance in a hospital. Consequently, when using a GP-database such as the CPRD, patients who were classified as unexposed, may actually have been exposed if the prescription was not recorded by the GP. In Chapter 6, parenteral GC injections may have been underrecorded for this reason. As this underrecording is expected to be non-differential, the results may have been biased towards the null. Consequently, the risk estimate (OR=0.88 [95% CI=0.76-1.02]) may have been lower without this potential bias. In Chapter 9, we have tried to reduce misclassification of exposure by including additional information from anonymised free text notes. Although we only had access to flat text notes, but not to discharge letters in PDF format, we were able to substantially increase detection rate of drug exposure. Despite this attempt, misclassification may still have been present, as we managed to identify drug use for approximately 20% of the patients, where close to 100% was expected. However, as it is expected that this misclassification will apply to all exposure categories (NOACs, LMWHs, and aspirin) equally the misclassification will not have affected the results substantially.

In this thesis, knee and hip OA are the main outcomes of interest. The way these outcomes have been (mis)classified in the studies presented in this thesis and in other

studies evaluating the association between DM and knee or hip OA may explain the difference in results regarding this association. In some studies, the definition of OA was based on radiographic abnormalities only, whereas others applied the clinical (Chapter 3) or radiological criteria determined by the American College of Rheumatology (ACR)[25] which require presence of knee pain, self-reported or physician reported diagnoses, or TJR surgery (Chapter 4). Inherently, these criteria reflect a different stage of the disease. For instance, TJR is likely to occur at a late stage of the disease, where pharmacological treatment is no longer sufficient, while the ACR criteria may reflect an earlier symptomatic stage. The studies in this thesis that used the clinical ACR definition (Chapter 3) or TJR as proxy for OA (Chapter 4) both showed that DM was not associated with an increased risk of OA. Therefore, misclassification due to the stage of OA that is reflected by the proxy does not seem to affect the results substantially. However, confounding by disease severity, due to the selected definition of OA, may have affected the results in Chapter 4. This issue will be discussed in a later section of this methodological discussion.

Additionally, as the onset of OA is difficult to determine, misclassification of timing of onset of OA may have affected the results in this thesis (Chapter 4). The registration of an OA diagnosis or a proxy for OA may not reflect the actual date of onset of the disease. In fact, the date of OA diagnosis probably reflects the actual date of onset of the disease with an average delay of 7.7 years[26]. Therefore, including a registration of OA shortly after the start of T2DM could result in biased estimates. However, as discussed in Chapter 5, this potential misclassification does not seem to affect the association substantially.

Furthermore, misclassification of the outcome may have occurred due to the sensitivity and specificity of the selected definition. For instance, the clinical ACR criteria applied in Chapter 3 have a sensitivity of 95% and a specificity of 69%[25]. Consequently, in this chapter there may have been a considerable amount of patients falsely classified as having OA. This potential misclassification may have been differential as DM patients are more likely to experience knee pain[27,28], which is the first criterion for the clinical ACR definition of knee OA. Consequently, the risk of OA in DM patients may have been overestimated and the observed risk estimate could have been lower.

Recall bias

Recall bias occurs when there is "a difference in the accuracy or completeness of recall to memory of past events or experiences"[17]. For instance, mothers of children with congenital malformations recall various exposure factors differentially than mothers of children without these malformations[29]. This type of bias is unlikely to have occurred in the studies using the CPRD or the AHD as the main outcomes and covariates used in these studies were not based on self-reported variables. The Maastricht Study, on the other hand, contains various self-reported variables and consequently the studies in this thesis using data from the Maastricht Study may have been affected by this type of bias (Chapters 2 and 3). As

the study described in Chapter 2 only includes drug utilisation data from pharmacies, it is unlikely to be affected by recall bias. In Chapter 3, self-reported presence and severity of knee pain were used as outcomes and consequently recall bias may have affected the results in this chapter. Possibly, participants with a disease are more likely to address other health related issues. Consequently, the presence of knee pain may be "recalled" more often by patients with DM. This may have led to an overestimation of knee pain and knee OA in patients with DM compared to patients without DM and the found risk estimates could have been lower. This possible differential misclassification may have resulted in overestimation of the risk of knee OA or knee pain in patients with DM.

IMMORTAL TIME BIAS

Immortal time refers to "a period of cohort follow-up time during which death (or an outcome that determines end of follow-up) cannot occur"[30]. Immortal time bias can either be classified as information bias or selection bias (Figure 11.2)[31]. Immortal time bias classified as information bias will be discussed in this section, and the variant leading to selection bias will be discussed in the following section. Misclassification of immortal time (e.g. when classified as exposed instead of unexposed) may lead to distorted estimates[31]. For example, a study assessing the association between use of inhaled corticosteroids (ICS) and death in a COPD population used a cohort design that classified complete person time (from cohort entry until end of follow-up) as exposed if a ICS was dispensed in the 90 days after cohort entry[32]. In this case the time between cohort entry and the first ICS prescription was misclassified immortal time. Typically, this type of immortal time bias might result in a lower estimation of the effect of the studied drug and can be solved by classifying person time time-dependently[31]. By definition, this type of bias can only occur in cohort studies. This thesis includes two cohort studies (Chapters 5 and 9). In the first study, we did not assess the effects of drug exposure on an outcome (Chapter 5), and in the second study, person time was assessed in a time-dependant manner (Chapter 9). Therefore, this type of bias is not likely to have affected the results in this thesis.

SELECTION BIAS

IMMORTAL TIME BIAS

In addition to misclassified immortal time leading to information bias, immortal time can also be excluded (Figure 11.2)[31]. As this affects the inclusion of persons or person time into the study it is classified as selection bias. For example, a study assessing the risk of rehospitalisation or death with the use of ICS included only those who were exposed on date of entry, and those without exposure during entire follow-up. Consequently, patients who were initially unexposed but became exposed at some point during follow-up were excluded[33]. As a result, the risk estimate was strongly underestimated[34]. This type of bias can be prevented by not taking future information into account when selecting the study

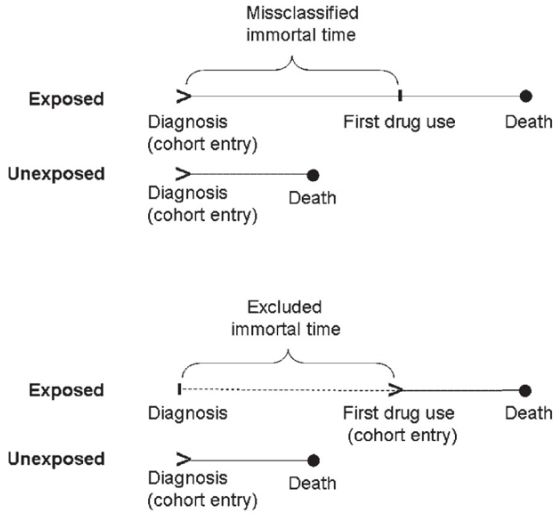

Figure 11.2: Misclassified immortal time (information bias) and excluded immortal time (selection bias)[31].

population (when conducting time-fixed analyses) or by conducting time-dependent analyses. Similar to misclassified immortal time bias, this type of bias can only occur in cohort studies. This thesis includes two cohort studies (Chapters 5 and 9). In the first study, we did not assess the effect of drug exposure on an outcome (Chapter 5), and in the second study time-dependent analyses were conducted (Chapter 9). Therefore, this type of bias is not likely to have affected the results in this thesis.

Time lag bias

Time lag bias can occur when patients with a certain disease, that intrinsically may affect the outcome, are compared to patients with a different duration or severity of the same disease[35]. For instance, a study comparing the risk of cancer with second and third line treatment strategies to first line treatment, reported an increased risk of cancer with the use of the second and third line treatment strategies[36]. Instead of a pharmacological effect, the increased risk may have been caused by a longer duration of the underlying disease. Additionally, the effect of potential previous exposure to first line drugs is not taken into account. Matching on disease duration is suggested to avoid this type of bias[35]. In this thesis, the study presented in Chapter 10 may have been affect by time lag bias. In this chapter TZD users are compared with patient with DM using other anti-hyperglycaemic drugs. As TZDs are generally prescribed in a more advanced stage of DM, comparison with earlier stages may lead to biased results. Specifically, it should be considered that a potential protective effect of the TZDs on the development or progression of OA may have been masked by the effect of a longer duration of DM in the TZD users.

Confounding

Confounding occurs when "the apparent effect of the exposure of interest is distorted because the effect of extraneous factors is mistaken for, or mixed with, the actual exposure effect"[20]. The extraneous factor is referred to as a confounder. Typically, three characteristics are required for a true confounder: 1) a confounder must be an extraneous risk factor for the disease; 2) a confounder must be associated with the exposure; 3) a confounder must not be an intermediate step in the causal pathway between the exposure and the disease. When considering the association of DM with knee and hip OA, age, sex, and BMI are considered to be important confounders we were able to adjust for (**Chapter 3**, **4**, and **10**). In **Chapter 3**, the importance of BMI is specifically reflected by the fact that the elevated crude estimate was markedly attenuated after adjustment for BMI only, and subsequent adjustment for other covariates barely changed the association.

Even if effort is put into the prevention of confounding by matching, stratification, and multivariate adjustment for known available factors, there is risk of residual confounding in all observational studies. First, there may be residual confounding when data on known confounders are partially, or completely unavailable in the used dataset. For example, previous studies have shown that (a history of) sport activities are associated with an increased risk of OA[37,38]. However, in the CPRD, information on these factors is largely missing, which may have led to residual confounding in **Chapter 4**. As these factors were available in the Maastricht Study, we were able to take them into account in **Chapter 3**. Since the results from the studies in **Chapters 3** and **4** were similar, it is expected that the effect of residual confounding was probably limited in **Chapter 4**. Second, residual confounding may be present if the number of events occurring in the included population is low. As a rule of thumb, it is suggested to include a maximum of one independent variable per ten events[39,40]. Consequently, due to a low number of events in **Chapter 9**, we were unable to include all relevant covariates in some of the statistical models. Propensity score-adjusted models could have been used to address this issue[41]. However, as propensity scores cannot account for unmeasured covariates, and as we were able to include the most relevant measured confounders, we think that additional adjustment would not have changed the results of this chapter substantially.

When data regarding a confounder are (partly) missing, bias may be introduced by the way these missing data are handled[42,43,44]. In this thesis, two methods have been applied to address missing data on confounders: complete cases analyses (**Chapter 3**), and the missing-indicator method (**Chapters 4**, **5**, **6**, **9**, and **10**). Complete case analyses will lead to unbiased estimates if the data are missing completely at random (MCAR), i.e. data being missing is unrelated to any of the variables involved in the analysis[44]. However, it is unlikely that the covariate data in **Chapter 3** were MCAR and consequently this may have led to distorted estimates. The direction of and the extent to which this bias has affected the results is unclear. However, the following possibilities may be considered. If T2DM patients

have a higher likelihood of having missing covariate data compared to participants without T2DM, the association may have been underestimated. Alternatively, a lower likelihood of having missing covariate data in patients with T2DM may lead to an overestimation of the association. Furthermore, it is suggested that when using the missing-indicator method to account for missing data, in non-randomized studies the estimates are likely to be biased[42,43,44]. As the direction and magnitude of the potential bias caused by implementation of this method are unpredictable[45], replication of these studies in sources without missing data is suggested.

Implications and recommendations for future studies and clinical care

Although knee pain, and knee OA are more common in T2DM patients, DM does not appear to be an independent risk factor for knee or hip OA. However, with reflection on literature, and in light of some potential methodological inferences, it is not possible to rule out that there may be specific subgroups of OA that are influenced by DM and its physiologic characteristics.

Nevertheless, in patients with DM, overweight seems to be a prominent determinant for OA of the weight-bearing joints, particularly the knee, as reflected by a strong confounding effect of BMI. Regarding the management of OA, therapy should therefore focus on weight reduction to prevent and halt progression of OA. As this is already a cornerstone in the treatment of DM and other cardiovascular diseases, increased guidance from health care professionals supported by policy makers and raised public awareness may be required to effectively counteract the increasing prevalence of this disabling disease.

In the past decades, the physiological mechanisms involved in the association between DM and OA are better understood. The wear-an-tear theory has been replaced by a more complex concept of interplaying mechanical, metabolic, and inflammatory factors. However, further unravelling this complex interplay and providing targets for therapy should still be subject for future studies. In light of the suggested differentiation of OA into specific phenotypes, future studies may focus on identifying risk factors for specific types of OA[46].

With an expected continuation of the increase in prevalence of OA over the next decades[47], the medical and societal need for new effective prevention and treatment strategies for this disease will become increasingly important. Currently, it is unclear whether the use of intra-articular GCs results in clinically important benefits in patients with knee OA[48]. Although we did not evaluate the association for OA patients specifically, it was reassuring that parenteral GC use did not induce DM. Ultimately, in patients with end stage knee or hip OA, surgical procedures are the last effective treatment options available.

In the Netherlands, in parallel with the rise in incidence of knee OA, the prevalence of knee replacement surgeries, and with this the improved mobility of thousands of patients each year, has increased over time, especially in patients <60 years of age. However, it should be emphasized that this trend was accompanied by an increase in complications, such as

infections, leading to increased prevalence of morbidity and mortality[49,50]. Furthermore, excess costs of patients with a KP compared to controls were mainly associated with (multiple) subsequent surgeries, and post-operative complications. These results indicate that there is an increasing medical and societal burden that requires improvement of guidelines aimed at avoiding complications and revision surgeries. Development, validation, and evaluation of efficacy of clinical scores predicting which patients will benefit from surgery or improvement of surgical techniques resulting in less chance of complications and revision surgeries might contribute to this issue.

The safety and effectiveness of antithrombotic and anticoagulation therapy following TJR surgery has been the subject of discussion in the past years. In this thesis, we have shown that the use of a NOAC or a LMWH following TJR had a similar risk of GI bleeding, and all-cause mortality compared to the use of aspirin. However, LMWH use was associated with an increased risk of VTE events compared to aspirin use. It should be noted that, due to lack of hospital prescription data, the detection rate of drug use was low and results may be affected by reverse causality. Therefore, results should be interpreted with care and more observational studies are required. Future studies should be conducted using data sources that contain, or are linked to hospital prescription data. In order to provide definitive answers, with implications for clinical practice, the results from the study presented in this thesis and future observational studies may be combined into meta-analyses. Furthermore, in the first years after the introduction of the NOACs there was some hesitancy due to the fact that, in contrast to other treatment options, there were no antidotes available that could be administered in case of a major bleeding event. Nowadays, idarucizumab is available as an antidote in the case of bleeding after dagbigatran use and andexanet alfa is being studied as antidote for rivaroxaban related bleeding. These developments should be taken into account when assessing the risk-benefit profiles of the available therapies in the future.

As reflected by the burden associated with joint replacement, and the lack of available disease modifying drugs, new treatment options are warranted. Based on this thesis, there is no indication that TZDs may act as a DMOAD. Future research should therefore focus on other potential candidates. New entities targeting cartilage metabolism, such as bone morphogenetic protein-7 (BMP-7)[51] and fibroblast growth factor-18 (FGF-18, also known as sprifermin)[52], have shown positive results in phase I trials and are now being studied in phase II trials. Existing drugs targeting subchondral bone, such as zoledronic acid[53] and strontium ranelate[54], have been associated with potential DMOAD properties. Furthermore, drugs targeting the inflammatory component of OA, such as adalimumab[55], and anakinra[56] have shown mixed results and overall effectiveness seems limited. However, besides effectiveness, unwanted side effects of these drugs should be considered in light of the benefits of preventing joint surgery. Altogether, it is likely that future OA treatment will be multifactorial, aimed at treating the various aspects of the complex underlying pathophysiology, and tailored to the specific needs for the individual patient.

Conclusion

The objective of part one of this thesis was to improve our knowledge about the association between DM and OA of the knee and hip. Based on the studies presented in this thesis DM does not appear to be an independent risk factor for knee or hip OA, but there may be, yet unidentified, specific types of OA that are affected by DM independently. These types might be joint specific, or rather share a similar clinical or molecular phenotype. Cluster analyses that include a wide range of demographic, clinical, and physiological parameters, may contribute to better identifying these specific types of OA.

The objective of part two was to evaluate effectiveness and safety outcomes associated with a broad spectrum of treatment strategies for knee and hip OA. In view of the fact that the prevalence of knee and hip OA is rising, and in combination with our finding that the incidence rates of KPs, revision KPs, and complications are increasing, there is an increasing medical and societal need for effective treatment strategies. Currently, in patients with end stage knee or hip OA, surgical procedures are the last effective means of providing improvement of mobility, symptom relief, and quality of life. However, as these surgical procedures are not without risk, new treatment options are needed. With the increasing knowledge on the complex underlying pathophysiology and the associated multifactorial approach in finding DMOADs, future treatment is likely to contain a broad spectrum of therapeutic options tailored to the patient-specific needs.

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Appendices

Abbreviations

Abbreviations

ACR	American College of Rheumatology
AD	Anti-hyperglycaemic drug
AGE	Advanced glycation end product
AHD	Achmea Health Database
AMI	Acute myocardial infarction
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BMP	Bone morphogenetic protein
BP	Blood pressure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DBP	Diastolic blood pressure
DDD	Defined daily dose
DM	Diabetes mellitus
DMOAD	Disease modifying osteoarthritic drug
DN-4	Douleur Neuropathique-4
DOAC	Direct oral anticoagulant
DPP-4	Dipeptidyl peptidase 4
DRG	Diagnosis related group
DVT	Deep venous thrombosis
eGFR	Estimated glomerular filtration rate
FGF	Fibroblast growth factor
GC	Glucocorticoid
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIP	Genees- en hulpmiddelen Informatie Project
GLP-1	Glucagon-like peptide 1
GLUT	Glucose transporter
GP	General practitioner
GPRD	General Practice Research Database
H2	Histamine 2
HbA1c	Glycated haemoglobin type A1c
HOA	Hip osteoarthritis
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICS	Inhaled corticosteroid
IL	Interleukin
IMD	Index of multiple deprivation
INR	International normalised ratio
IR	Incidence rate
ISAC	Independent Scientific Advisory Committee
KOA	Knee osteoathritis
KP	Knee prosthesis

LMWH	Low-molecular-weight heparin
LROI	Landelijke Registratie Orthopedische Implantaten
MCAR	Missing completely at random
MHRA	Medicines and Healthcare products Regulatory Agency
MMP	Matrix metalloproteinase
NGM	Normal glucose metabolism
NIAD	Non-insulin anti-hyperglycaemic drug
NICE	National Institute for Health and Care Excellence
NJR	National Joint Registry
NOAC	New oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OGTT	Oral glucose tolerance test
OR	Odds ratio
OTC	Over the counter
PE	Pulmonary embolism
PGE2	Prostaglandin E_2
PK	Pharmacokinetic
PPAR-γ	Peroxisome proliferator-activated receptor-γ
PPI	Proton pump inhibitor
PPV	Positive predictive value
PY	Person years
QOF	Quality of outcomes framework
RA	Rheumatoid arthritis
RAAS	Renin-angiotensin-aldosterone system
RAGE	Receptor for AGE
RCT	Randomized controlled trial
ROS	Reactive oxygen species
RR	Relative risk
SBP	Systolic blood pressure
SES	Socioeconomic status
SD	Standard deviation
SPC	Summary of product characteristics
SSRI	Selective serotonin reuptake inhibitor
SU	Sulphonylurea
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
THR	Total hip replacement
TJR	Total joint replacement
TKR	Total knee replacement
TNF	Tumour necrosis factor
TZD	Thiazolidinedione
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WHO	World Health Organisation

Summary

Summary

General introduction

Osteoarthritis (OA) is one of the most common chronic diseases worldwide and with the global increase of life expectancy and the strong relationship with obesity, the prevalence of this painful disease is likely to increase in the next decades. OA is considered to be a complex disease involving degradation of cartilage, bone remodelling, and inflammation of the synovium. In clinical research regarding knee or hip OA different classification criteria are used. The Kellgren and Lawrence score defines OA based on radiographic characteristics, and it can be used to classify the severity of OA based on these characteristics. However, clinical symptoms associated with OA are not necessarily captured with this method. These symptoms are included in the criteria provided by The American College of Rheumatology. Known risk factors for OA of the hip and knee are age, sex, overweight, physical activity, and genetic elements. Furthermore, metabolic factors may play a role in the development and progression of knee and hip OA. The treatment of knee and hip OA is mainly focussed on pain relief and optimizing functioning. Conservative treatment options include education, exercise, weight loss, and supportive devices. Pharmacological therapies, including analgesics and anti-inflammatory drugs, focus on pain relief, as disease modifying drugs are lacking. In severe cases of OA with inadequate response to pharmacological treatment, surgical therapy may be considered.

The relationship between diabetes mellitus (DM) and OA has been subject of research for decades. As a shared risk factor, overweight has been suggested to be the main feature causing OA in patients with DM. However, recent studies have suggested that DM might be an independent risk factor for OA. Despite the existing evidence and plausible underlying metabolic pathways, other studies have shown no association between DM and OA. Consequently, the heterogeneity in the available literature suggest more research is required.

Recently, in the clinical and scientific field the attention regarding the different treatment options for knee and hip OA has increased. Consequently, it has become clear that the effectiveness and safety outcomes of some of these therapies are unknown. For instance, intra-articular glucocorticoid (GC) injections are used for the treatment of OA. However, it is unknown whether they increase the risk of hyperglycaemia and DM as is the case with oral GCs. Additionally, among patients with severe OA, surgical therapy including joint replacement procedures may be considered. However, the incidence and associated costs of these procedures are largely unknown. Furthermore, these procedures are not without risk. On the one hand, risk of bleeding may increase following total joint replacement (TJR) surgery. On the other hand, risk of venous thromboembolic (VTE) events may increase after TJR. These VTE events can be prevented with a variety of medicines, including aspirin, coumarins, heparins, and the recently introduced new (or direct) oral anticoagulants

(NOAC/DOAC). However, there has been much discussion on the risk-benefit profiles of these agents and large post-marketing studies comparing safety and effectiveness of these drugs are scarce.

In order to address some of the abovementioned knowledge gaps three data sources were used in this thesis: The Maastricht Study, the Clinical Practice Research Datalink (CPRD), and the Achmea Health Database (AHD). The Maastricht Study is a prospective population-based cohort study assessing the aetiology, pathophysiology, complications and comorbidities of type 2 DM (T2DM). Currently, cross-sectional data from the first 3,451 participants are available. The CPRD is world's largest primary care database and is representative of the population of the United Kingdom (UK). The AHD is a medical claims database representative of the Dutch urban population.

The overall objective of this thesis was to assess the association between DM and OA of the knee and hip, and to gain insight into outcomes associated with the treatment of knee and hip OA. In part one we aimed to improve our knowledge about the association between DM and OA of the knee and hip. In part two we aimed to assess effectiveness and safety outcomes associated with a broad spectrum of treatment strategies for knee and hip OA.

Part 1: the association between diabetes mellitus and osteoarthritis

In order to assess the association between DM and OA of the knee and hip in The Maastricht Study, we first assessed the representativeness of the population participating in this study by comparing drug dispensing data with national reimbursement data in Chapter 2. Total drug use of The Maastricht Study population was largely comparable with the national population. However, for some classes of medications, such as respiratory drugs, utilisation in The Maastricht Study was lower as compared to national data. Conversely, the use of hypnotics and anxiolytics was higher as compared to national rates, especially in the population aged 65-74 years. Altogether, we concluded that the population included in The Maastricht Study is largely comparable to the Dutch population.

In Chapter 3 the association between DM, and knee pain and clinical knee OA was assessed in The Maastricht Study. Age- and sex standardised rates of clinical knee OA and knee pain were higher in patients with T2DM compared to those without T2DM. However, after adjusting for differences in BMI between groups, there were no differences in the risk of knee pain or clinical knee OA between patients with or without T2DM. Furthermore, within patients with clinical knee OA there was no difference in pain perception between patients with or without T2DM.

In the CPRD (Chapter 4) the association between DM and TJR, as a proxy for severe OA, was assessed. There was no increased risk of total knee (TKR) or total hip replacement (THR) surgeries between patients with or without DM. In fact, the risk of TKR or THR was reduced with increasing severity of DM. In conclusion, the results from Chapters 3 and 4 indicated that DM is not an independent risk factor for knee or hip OA.

When assessing the association between DM and OA, the use of TJR as proxy for OA in Chapter 4 may have led to bias, as other factors may have been involved preventing DM patients from undergoing surgery. Furthermore, as the date of onset of OA is difficult to determine, misclassification of timing of onset may also affect this association. Therefore, the effect of the choice of the definition of OA and the timing of its onset relative to the start of pharmacological DM treatment on the association between DM and OA was assessed in Chapter 5. This study showed that when using a surgical proxy for the outcome (i.e. TJR) the risk estimate was approximately 20% lower than when the diagnosis was used. In conclusion, the association may be affected by bias when using TJR as proxy for OA. Furthermore, as addition of a latency period of up to ten years after start of follow-up did not affect the association temporality related issues did not appear to affect the association.

PART 2: EFFECTIVENESS AND SAFETY OUTCOMES ASSOCIATED WITH THE TREATMENT OF OSTEOARTHRITIS

Intra-articular glucocorticoid (GC) injections can be given to treat inflammatory episodes of OA. As the use of oral GCs has been associated with an increased risk of hyperglycaemia and DM, we assessed the risk of onset of DM with the use of orally and parenterally administered GCs in Chapter 6. In this chapter, we confirmed previous findings suggesting that the use of oral GCs may result in an increased risk of DM. However, the use of parenterally administered GCs was not associated with an increased risk of new onset of DM. This may be explained by the generally short and intermittent use of these GCs resulting in a limited effect on glucose metabolism and, consequently, onset of DM.

With regards to surgical treatment strategies, we determined the age- and sex specific incidence rates of knee prostheses (KPs) and health care costs associated with these procedures compared to matched controls in Chapter 7. We found an increase of KPs, revision KPs, and complications over time, especially in younger age categories. Additionally, excess costs of patients with a KP compared to controls were mainly associated with (multiple) subsequent knee surgeries, post-operative complications, younger age, and female gender.

TJR surgery has been associated with an increased risk of VTE events, for which various preventive treatment strategies are available. Recently, there has been much discussion about the risk-benefit profiles of the available pharmacological treatment options following TJR, including low molecular weight heparins (LMWHs), NOACs, and aspirin. However, these drugs are usually prescribed in the hospital setting and hospital pharmacy data are largely lacking in the CPRD. Therefore, the use of the CPRD may be limited when assessing safety and effectiveness outcomes of these drugs. Therefore, in Chapter 8, we first designed a search strategy that improved the detection rate of antithrombotic drug use, by using anonymised free-text notes, in the CPRD. With this strategy, we increased detection rates by 57% on average, yielding a total proportion of 18.5% of all THR and 18.6% of all TKR surgeries.

Subsequently, we applied the abovementioned method to compare safety and effectiveness outcomes of LMWHs, and NOACs with aspirin use in Chapter 9. We found that the use of a NOAC or a LMWH following TJR resulted in a similar risk of gastrointestinal (GI) bleeding, and all-cause mortality compared to the use of aspirin. However, LMWH use was associated with an increased risk of VTE events compared to aspirin use. This unexpected result may have been caused by reverse causality as LMWHs were probably prescribed to treat a VTE event.

With regards to pharmacological treatment strategies of OA we assessed the potential disease modifying properties of the anti-hyperglycaemic thiazolidinediones (TZDs) that have been proposed in pre-clinical studies. In Chapter 10, we found no difference in risk of TKR or THR surgery when TZD users were compared to DM patients using other anti-hyperglycaemic drugs. This has provided no additional evidence for TZDs being a potential disease modifying osteoarthritic drug (DMOAD).

General discussion

In Chapter 11 the main results of the aforementioned studies were combined and discussed in light of potential methodological issues, including various types of bias and confounding. Additionally, a discussion on implications, and recommendations for future studies and clinical care were presented in this chapter.

In conclusion, based on the studies presented in this thesis DM does not appear to be an independent risk factor for knee or hip OA, but there may be, yet unidentified, specific types of OA that are affected by DM independently. These types might be joint specific, or rather share a similar clinical or molecular phenotype.

Furthermore, we can conclude that, in view of the fact that the prevalence of knee and hip OA is rising, in combination with increasing incidence rates of joint replacement surgeries, there is an increasing medical and societal need for new effective treatment strategies. With the increasing knowledge on the complex underlying pathophysiology and the associated multifactorial approach in finding DMOADs, future treatment is likely to contain a broad spectrum of therapeutic options tailored to the patient-specific needs.

Samenvatting

Samenvatting

Algemene introductie

Artrose is een van de meest voorkomende chronische aandoeningen wereldwijd. Door de mondiale toename van de levensverwachting en de sterke relatie met obesitas zal de prevalentie van deze pijnlijke aandoening in de komende decennia waarschijnlijk toenemen. Artrose wordt beschouwd als een complexe ziekte die zich kenmerkt door afbraak van kraakbeen, vervorming van het bot en ontsteking van het synovium (slijmvlies in de gewrichten). In klinisch onderzoek naar knie- of heupartrose worden verschillende classificatiecriteria voor artrose toegepast. De Kellgren en Lawrence score definieert artrose op basis van radiologische kenmerken en kan daarnaast gebruikt worden om de ernst van radiologische afwijkingen te classificeren. Deze score houdt echter geen rekening met klinische manifestaties passend bij artrose. Deze symptomen zijn echter wel opgenomen in de criteria die opgesteld zijn door The American College of Rheumatology. Bekende risicofactoren voor artrose van de heup en knie zijn leeftijd, geslacht, overgewicht, lichamelijke activiteit en genetische elementen. Daarnaast spelen metabole factoren mogelijk ook een rol in de ontwikkeling en progressie van knie- en heupartrose. De behandeling van knie- en heupartrose is voornamelijk gericht op pijnvermindering en optimalisatie van het functioneren. Conservatieve behandelingsopties zijn onder andere educatie, lichaamsbeweging, gewichtsverlies en ondersteunende hulpmiddelen. Medicamenteuze behandelingen, waaronder pijnstillers en anti-inflammatoire geneesmiddelen, richten zich op pijnvermindering, omdat geneesmiddelen die het ziekteproces onderbreken of remmen niet bestaan. In ernstige gevallen van artrose, waarbij medicamenteuze behandeling onvoldoende effect heeft, kan chirurgische therapie overwogen worden.

De relatie tussen diabetes mellitus en artrose wordt al tientallen jaren onderzocht. Overgewicht wordt, als een gedeelde risicofactor, gezien als de belangrijkste oorzaak voor het ontwikkelen van artrose bij patiënten met diabetes. Resultaten van recente studies suggereren echter dat diabetes een onafhankelijke risicofactor voor artrose is. Ondanks deze bewijzen en aannemelijke onderliggende fysiologische processen (biologische werkingsmechanismen), tonen andere studies aan dat er geen verband is tussen diabetes en artrose. Vanwege de heterogeniteit in de beschikbare literatuur is er meer onderzoek nodig.

De aandacht voor de verschillende behandelingsopties van knie- en heupartrose is de afgelopen jaren op klinisch en wetenschappelijk gebied toegenomen. Daarbij is gebleken dat de effectiviteit en veiligheid van sommige van deze behandelingen, zoals het intra-articulair (injecties in het gewricht) toedienen van glucocorticoïden (GCs), niet volledig bekend zijn. Het is bijvoorbeeld onbekend of deze GC's het risico op hyperglycemie (te hoog glucosegehalte in het bloed) en diabetes verhogen, zoals het geval is bij orale GC's. Daarnaast kunnen totale gewrichtsvervangende operaties (total joint replacement, TJR) overwogen

worden bij patiënten met ernstige artrose. De incidentie en bijbehorende kosten van deze operaties zijn echter grotendeels onbekend. Bovendien zijn deze procedures niet zonder risico. Enerzijds kan het risico op bloedingen toenemen na deze TJR-operaties. Anderzijds kan het risico op een veneuze trombo-embolie na deze operaties toenemen. Deze veneuze trombo-embolieën kunnen voorkomen worden met verschillende geneesmiddelen, zoals aspirine, coumarines, heparines, en de recent geïntroduceerde nieuwe (of directe) orale anticoagulantia (NOAC/DOAC). Er is echter veel discussie over de risico- en voordeelprofielen van deze middelen en grote observationele studies die de veiligheid en effectiviteit van deze geneesmiddelen vergelijken ontbreken.

Om een aantal leemtes zoals hierboven benoemd te kunnen beantwoorden, werden in dit proefschrift drie databases gebruikt: De Maastricht Studie, de Clinical Practice Research Datalink (CPRD) en de Achmea Health Database (AHD). De Maastricht Studie is een prospectieve cohortstudie waarbij de etiologie, pathofysiologie, complicaties en comorbiditeiten van type 2 diabetes worden onderzocht. Momenteel zijn cross-sectionele gegevens van de eerste 3451 deelnemers beschikbaar. De CPRD is 's werelds grootste eerstelijnsdatabase en is representatief voor de bevolking van het Verenigd Koninkrijk. De AHD is een zorgverzekeraarsdatabase met declaratiegegevens die representatief zijn voor de Nederlandse stedelijke bevolking.

Het algemene doel van dit proefschrift was om de associatie tussen diabetes en artrose van de knie en heup te onderzoeken en inzicht te krijgen in veiligheids- en effectiviteitsuitkomsten van de behandeling van knie- en heupartrose. Deel 1 is gericht op het vergroten van onze kennis over de associatie tussen diabetes en artrose van de knie en de heup. In Deel 2 hebben we de veiligheids- en effectiviteitsuitkomsten van een breed spectrum aan behandelingen van knie- en heupartrose onderzocht.

Deel 1: de associatie tussen diabetes mellitus en artrose

Om de associatie tussen diabetes en artrose van de knie en heup in De Maastricht Studie te onderzoeken, hebben we in Hoofdstuk 2 de representativiteit van de studiepopulatie beoordeeld door geneesmiddelgebruik van deze populatie te vergelijken met nationale gegevens. Het totale geneesmiddelgebruik van de populatie in De Maastricht Studie was grotendeels vergelijkbaar met dat van de nationale bevolking. Echter voor sommige medicijngroepen, zoals respiratoire geneesmiddelen, was het gebruik in De Maastricht Studie lager dan in de nationale bevolking. Omgekeerd was het gebruik van hypnotica (slaapmiddelen) en anxiolytica (kalmerende middelen) hoger dan in de nationale populatie, vooral in de groep van 65-74 jaar. Al met al hebben we geconcludeerd dat de populatie in De Maastricht Studie in het algemeen vergelijkbaar is met de Nederlandse bevolking.

In Hoofdstuk 3 is de associatie tussen diabetes en kniepijn en klinische knieartrose onderzocht in De Maastricht Studie. Klinische knieartrose en kniepijn kwamen, na correctie voor leeftijd en geslacht, vaker voor bij patiënten met diabetes dan bij patiënten zonder

diabetes. Echter, rekening houdend met verschillen in BMI tussen beide patiëntengroepen, waren er geen verschillen in het risico op kniepijn of klinische knieartrose tussen patiënten met of zonder diabetes. Bovendien was er binnen patiënten met klinische knieartrose geen verschil in de mate van zelf-gerapporteerde pijn tussen patiënten met of zonder diabetes.

In de CPRD (Hoofdstuk 4) werd de associatie tussen diabetes en TJR, als indicator voor ernstige artrose, onderzocht. Er was geen verhoogd risico op totale knie- (total knee replacement, TKR) of totale heupvervangende (total hip replacement, THR) operaties tussen patiënten met of zonder diabetes. Het risico op TKR of THR verminderde zelfs met toenemende ernst van diabetes. Concluderend bleek uit de resultaten van Hoofdstukken 3 en 4 dat diabetes geen onafhankelijke risicofactor is voor knie- en heupartrose.

Bij het onderzoeken van de associatie tussen diabetes en artrose kan het gebruik van TJR als indicator voor artrose in Hoofdstuk 4 hebben geleid tot bias, aangezien er mogelijk andere factoren kunnen zijn geweest die ervoor zorgen dat diabetespatiënten geen operatie ondergaan. Bovendien kan misclassificatie van het moment waarop artrose ontstaat ook invloed hebben gehad op deze associatie. Dit moment is immers moeilijk vast te stellen. In Hoofdstuk 5 onderzochten we daarom zowel het effect van de keuze van de definitie van artrose als de timing van het moment van het ontstaan ervan op de associatie tussen diabetes en artrose. Deze studie toonde aan dat bij het gebruik van een chirurgische indicator voor de uitkomst (d.w.z. TJR) de risicoschatting ongeveer 20% lager was dan bij de diagnose. Het gebruik van TJR als indicator voor artrose kan dus leiden tot bias wat betreft de associatie tussen diabetes en artrose. Problemen met tijdsvolgorde lijken geen effect te hebben gehad op de associatie, aangezien de toevoeging van een latentietijd van maximaal tien jaar na de start van follow-up de associatie niet heeft beïnvloed.

Deel 2: effectiviteits- en veiligheidsuitkomsten geassocieerd met de behandeling van artrose

Intra-articulaire glucocorticoïden (GC's) kunnen gegeven worden om inflammatoire episodes van artrose te behandelen. Omdat het gebruik van orale GC's geassocieerd is met een verhoogd risico op hyperglycemie (te hoog glucosegehalte in het bloed) en diabetes, is het risico op het ontwikkelen van diabetes bij gebruik van orale en geïnjecteerde GC's in Hoofdstuk 6 onderzocht. In dit hoofdstuk bevestigden we eerdere bevindingen die suggereren dat het gebruik van orale GC's kan leiden tot een verhoogd risico op diabetes. Het gebruik van geïnjecteerde GC's was echter niet geassocieerd met een verhoogd risico op het ontwikkelen van diabetes. Dit kan mogelijk worden verklaard door het feit dat deze GC's in het algemeen voor korte periodes en met tussenpozen worden gebruikt, waardoor deze slechts een beperkt effect hebben op het glucosemetabolisme en derhalve op het ontstaan van diabetes.

In het kader van chirurgische behandelstrategieën hebben we in Hoofdstuk 7 de leeftijds- en geslacht specifieke incidentie van knieprothesen (KP's) bepaald. Daarnaast hebben

we in dit hoofdstuk de zorgkosten van deze procedures bepaald in vergelijking met een controlegroep. We vonden een toename van het aantal KP's, revisie operaties (vervanging van de prothese) en complicaties over de tijd, vooral in de jongere leeftijdscategorieën. Daarnaast waren de extra kosten van patiënten met een KP, vergeleken met controles, hoofdzakelijk geassocieerd met (meerdere) opvolgende knieoperaties, postoperatieve complicaties, jongere leeftijd en het vrouwelijk geslacht.

Na een TJR-operatie is er een verhoogd risico op een veneuze trombo-embolie, waarvoor diverse preventieve behandelingsstrategieën beschikbaar zijn. Recentelijk is er veel discussie over de risico- en voordeelprofielen van de beschikbare farmacologische behandelingsopties na een TJR-operatie, waaronder laagmoleculairgewicht heparines (LMWH's), NOAC's en aspirine. Deze medicijnen worden voor deze indicatie echter voornamelijk voorgeschreven in het ziekenhuis en aangezien deze gegevens grotendeels ontbreken in de CPRD, kan deze database slechts beperkt gebruikt worden bij het beoordelen van de effectiviteits- en veiligheidsuitkomsten van deze geneesmiddelen. Daarom hebben we in Hoofdstuk 8 eerst een zoekstrategie ontwikkeld die de detectie van het gebruik van dergelijke middelen verbeterde door gebruik te maken van geanonimiseerde vrije-tekst notities. Met deze strategie hebben we de detectiegraad met gemiddeld 57% verhoogd, waardoor er geneesmiddelgebruik bij 18,5% van alle THR en 18,6% van alle TKR-operaties gevonden werd.

Vervolgens hebben we de bovengenoemde methode toegepast om de effectiviteits- en veiligheidsuitkomsten van LMWH- en NOAC-gebruik te vergelijken met het gebruik van aspirine in Hoofdstuk 9. We vonden dat het gebruik van een NOAC of een LMWH resulteerde in een risico op gastro-intestinale bloedingen en mortaliteit dat vergelijkbaar was met het gebruik van aspirine. LMWH-gebruik was echter geassocieerd met een verhoogd risico op veneuze trombo-embolieën in vergelijking met aspirinegebruik. Dit onverwachte resultaat kan mogelijk verklaard worden door "omgekeerde causaliteit" (*reverse causality*), aangezien LMWH's waarschijnlijk werden voorgeschreven om een veneuze trombo-embolie te behandelen.

Met betrekking tot farmacologische behandelingsstrategieën voor artrose hebben we de mogelijke ziekte-modificerende eigenschappen van de anti-hyperglycemische thiazolidinedionen (TZD's) onderzocht die in preklinische studies zijn voorgesteld. In Hoofdstuk 10 vonden we echter geen verhoogd risico op een TKR- of THR-operatie wanneer TZD-gebruikers werden vergeleken met diabetespatiënten die andere anti-hyperglycemische geneesmiddelen gebruikten. Er lijkt dus geen aanvullend bewijs te zijn dat TZD's mogelijk geneesmiddelen zijn die het ziekteproces van artrose kunnen beïnvloeden.

Algemene discussie

In Hoofdstuk 11 werden de belangrijkste resultaten van de bovenstaande studies gecombineerd en werden mogelijke methodologische problemen, waaronder diverse

vormen van bias bediscussieerd. Daarnaast is er een discussie over implicaties en aanbevelingen voor toekomstige studies en klinische zorg in dit hoofdstuk opgenomen.

Concluderend lijkt, op basis van de studies die in dit proefschrift worden gepresenteerd, diabetes geen onafhankelijke risicofactor voor knie- of heupartrose te zijn, maar mogelijk zijn er nog onbekende typen artrose die wel onafhankelijk door diabetes beïnvloed worden. Deze typen kunnen gewrichtspecifiek zijn, of mogelijk een vergelijkbaar klinisch of moleculair fenotype delen. Verder kunnen we concluderen dat, aangezien de prevalentie van knie- en heupartrose stijgt, in combinatie met toenemende incidentie van gewrichtsvervangende operaties, er een steeds grotere medische en maatschappelijke behoefte is aan nieuwe behandelingsstrategieën. Met de toenemende kennis over de complexe onderliggende pathofysiologie en de bijbehorende multifactoriële aanpak bij het vinden van geneesmiddelen die het ziekteproces van artrose kunnen veranderen, zal de toekomstige behandeling waarschijnlijk een breed spectrum aan therapeutische opties bevatten die zijn afgestemd op de patiënt specifieke behoeften.

Valorisation

Valorisation addendum

Valorisation of research is defined as "the process of creating value from knowledge, by making this knowledge available and suitable for economic and social exploitation and to translate this knowledge into products, services, processes, and new business."[1]. In other words, how can society benefit from the knowledge acquired with research? In this addendum, the possibilities for valorisation of the results presented in this thesis are described.

Osteoarthritis (OA) is one of the most common musculoskeletal diseases worldwide[2,3,4]. In 2015 the prevalence of OA in the Netherlands was approximately 7%, making it the most prevalent disease in the coutry[5]. Furthermore, OA is 13th on the list of causes of global years lived with a disease[6]. The high number of years lived with OA reflect the strong impact of this disease not only on individual patients, but also on society in general. By gaining knowledge on risk factors of this disease, evaluating current treatment strategies, and exploring possible new therapies, the studies in this thesis provide value for society.

Society may benefit from new knowledge on risk factors of OA by means of improvement of guidelines and strategies aimed at identifying groups at risk. Diabetes mellitus (DM) has been suggested to be an independent risk factor for OA, but results regarding this association are heterogeneous and inconclusive. Therefore, in part 1 of this thesis we studied the association between DM and knee and hip OA. The studies presented in this part have shown that knee and hip OA are more common in patients with DM. However, DM does not seem to be an independent risk factor for knee and hip OA. In fact, the increased presence of knee and hip OA in patients with DM appeared to be mainly caused by an overall higher body mass index in these patients. Consequently, when aiming to reduce the occurrence of knee and hip OA, society may gain the most by focussing on prevention of overweight, which is already a cornerstone in the treatment of DM.

In part 2 of this thesis we assessed effectiveness and safety outcomes associated with a broad spectrum of treatment strategies for knee and hip OA. We described an increasing incidence of knee prostheses, revision surgeries, and complications over time. By undergoing these surgeries, mobility, quality of life, productivity, and participation of these patients is likely to increase, which could be considered beneficial for society. However, these interventions are expensive and health care cost post-surgery never reach the level of costs prior to surgery, potentially because joint replacement surgery is not beneficial for all patients with clinical symptoms associated with OA. Possibly improvement in prosthetic materials or techniques for joint replacement can ameliorate outcomes of surgery. Also, patients with nociceptive pain not caused by cartilage damage or patients with neuropathic pain are unlikely to benefit from joint replacement surgery. Consequently, by better understanding the cause of pain in the individual patient may help to determine whether patients should undergo joint replacement surgery or not. Altogether, these results suggest

that in order to maintain a healthy and productive population, while keeping treatment affordable, new, patient-specific, non-invasive, disease modifying therapies, are needed.

As there are currently no disease-modifying osteoarthritic drugs, exploring potential candidates, such as the anti-hyperglycaemic thiazolidinediones, may improve treatment. However, in this thesis we found no additional evidence supporting the suggestion that thiazolidinediones could be disease-modifying osteoarthritic drugs. Future research should therefore focus on other potential candidates, such bone morphogenetic protein-7[7] and fibroblast growth factor-18, also known as sprifermin[8]. Existing drugs targeting subchondral bone, such as zoledronic acid[9] and strontium ranelate[10], have also been associated with potential disease-modifying properties. Unfortunately, drugs targeting the inflammatory component of OA, such as adalimumab[11], and anakinra[12] have shown mixed results and overall effectiveness seems limited. Altogether, it is likely that future OA treatment will aim at treating the various aspects of the complex underlying pathophysiology of the disease, and will be tailored to the specific needs for the individual patient.

Society may also benefit indirectly from improvement of research methodologies. We designed and successfully tested a search strategy aimed at increasing the detection rate of hospital prescribed drugs in a primary care database, the Clinical Practice Research Datalink (CPRD). By using anonymised free text notes, we were able to increase detection rate of antithrombotic drugs with approximately 60%, thereby reducing misclassification of exposure. In future research assessing the association of other outcomes with these drugs, the same strategy may be used. Furthermore, a similar process could be used to increase detection rate of other types of drugs or perhaps it could be applied to different data sources. Currently, this process is relatively time-consuming and the development of automated algorithms capable of analysing text notes in a short period of time may further increase the usability of free text notes in observational research. However, the CPRD no longer allows the use of free text notes due to privacy concerns. While privacy may be better ensured, this causes research aimed at improving public health to be limited in its potentials. Alternatively, if database registration and linkage possibilities would improve, free text mining may become obsolete altogether.

In addition, epidemiological research regarding OA is likely to benefit from development of a uniform operational definition of this disease. Currently, multiple definitions of OA are used interchangeably, limiting the comparability of study results, which may ultimately result inefficient use of resources. Development of an operational definition of OA, including a date of onset that is approximated with sufficient validity, is likely to improve efficiency of epidemiological OA research.

In conclusion, DM does not appear to be an independent risk factor for OA of the hip or knee, and society will benefit most from OA prevention by targeting obesity. Furthermore, in order to maintain a healthy and productive population, while keeping treatment affordable, new disease modifying therapies are needed. With regard to these

therapies, thiazolidinediones do not appear to be disease-modifying osteoarthritic drugs and research should focus on other potential candidates. Finally, we developed an effective search strategy that can be easily applied to other observational studies, but observational research may possibly benefit the most from development of automated text-mining algorithms, and improvement of database registration and linkage possibilities.

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List of Publications

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Dankwoord

Dankwoord

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