Population-based Study on the Epidemiology of Gout

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The Introduction of the Gout, a painting by George Cruikshank (1818)

Lots of things are mysteries.
But that doesn't mean there isn't an answer to them.
It's just that scientists haven't found the answer yet.

Mark Haddon, The Curious Incident of the Dog in the Night-Time

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Being clever was when you looked at how things were and used the evidence to work out something new.

Mark Haddon, The Curious Incident of the Dog in the Night-Time

CONTENTS

SUMMARY

Pharmacoepidemiology enables researchers to assess the effects of drugs on outcomes, such as diseases, in large study populations. Furthermore, pharmacoepidemiology is gaining importance in the premarketing phase of the drug development process to provide information on the natural history of the disease the respective drug is being tested for.

Gout is a common, excruciatingly painful, long-known and widely spread inflammatory arthritis characterized by increased serum uric acid levels, and uric acid crystals in the joints (typically in the metatarsophalangeal joint, called *podagra*). Even though the disease has been long-known and affects about 1.4% to 2.5% of the United Kingdom (UK) population, evidence on many risk factors is lacking. Studies that closely describe the affected population and strengthen existing evidence on risk factors such as drug use are needed to improve treatment and care of affected patients.

The aim of this thesis was to increase the knowledge of gout by providing new information and complementing existing data, and by precisely describing the epidemiology of gout and demographic characteristics, comorbidities, and comedication of the affected population. Furthermore, the goal was to assess the impact of long-known and accepted risk factors in a population-based setting.

The gout project consisted of an epidemiological cohort study, a nested case-control study, and three case-control studies, using data from the Clinical Practice Research Datalink (CPRD). The CPRD is a UK-based general practitioner database containing primary-care records directly entered by general practitioners who do not have any study hypothesis in mind when they

record the data. The CPRD population is representative of the UK population in terms of age, sex, geographic distribution, and annual turnover rate. The CPRD is a very useful tool to conduct pharmacoepidemiological research due to its large size, the population-based character of the data, and the opportunity for researchers to gain access to original medical records. However, data on some important confounders such as dietary habits are missing.

All case-control populations of the different gout projects were matched on age, sex, general practice, index date, and history on the CPRD. The overall incidence rate of diagnosed gout in the UK per 10,000 person-years (PYs) was 18.0 (95% CI 17.9-18.1), 29.0 (95% CI 28.8-29.2) in men, and 8.6 (95% CI 8.5-8.8) in women; we further stratified by age, calendar time, region, and seasonality. The nested case-control part of the first project described the study population in terms of demographic characteristics, comorbidities, and comedication. The second project assessed the association between different diuretic drug classes and incident gout. Current use of loop diuretics, thiazide diuretics, and thiazide-like diuretics was associated with a substantially increased risk of incident gout. In the third project, the association between different antidiabetic drug classes, diabetes duration, and diabetes severity and the risk of incident gout was investigated. Increasing glycosylated haemoglobin (A1C) levels were associated with a markedly decreased risk of incident gout in patients with type 2 diabetes mellitus. Neither use of insulin, metformin, nor sulfonylureas was associated with an altered risk of incident gout. The fourth project assessed the association of hormone replacement therapy with gout, and the effect of timing, duration, and route of administration. Current use of oral opposed oestrogens, but not unopposed oestrogens, was associated with a decreased risk of incident gout in patients without renal failure and was more pronounced in patients with hypertension. The observed risk decrease for gout in users of opposed oestrogens may be explained by the progesterone rather than the oestrogen component.

In summary, these large observational studies of this thesis analysed existing hypotheses and contributed to the evidence of different risk factors for gout such as diuretic drug classes, antidiabetic drugs, diabetes duration and severity, and hormone replacement therapy. Furthermore, several interesting ideas developed in the context of this thesis might be studied in association with gout within the CPRD in near future, to further increase evidence on risk factors associated with the disease, and to improve patient care.

ABBREVIATIONS

BCDSP	Boston Collaborative Drug Surveillance Program
BHPR	British Health Professionals in Rheumatology
BSR	British Society for Rheumatology
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
EULAR	European League Against Rheumatism Recommendations
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
IR	Incidence Rate
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PY	Person-Year
UK	United Kingdom
VAMP	Value Added Medical Products

Part I

INTRODUCTION

1. PHARMACOEPIDEMIOLOGY

1.1 Definition

Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people (1).

1.2 Development

After the thalidomide disaster, where children of mothers who used this drug during pregnancy were born with limb deformations, the awareness of serious adverse drug effects increased rapidly and in the 1960s several developments have prompted the beginning of the science *Pharmacoepidemiology* (1). Post-marketing drug surveillance was first initiated with spontaneous reporting systems in the United States and Europe in which suspected adverse drug events were captured and centred. The focus lay on the assessment of drug effects that were difficult to capture in preclinical randomized controlled trials due to limited numbers of participants, rather short duration, and non representative patient populations (1). With the composition of databases the quantitative assessment of drug hazards in post-marketing drug surveillance became feasible.

2. THE DATABASE: CLINICAL PRACTICE RESEARCH DATALINK

Databases are a very important source for pharmacoepidemiological studies. One of the largest and most detailed computerised databases is the Clinical Practice Research Datalink (CPRD).

2.1 History of the CPRD

The CPRD contains population-based data from the United Kingdom (UK) and was first established in 1987 (2, 3). Back in the 1980s, a company developed a computer system called Value Added Medical Products (VAMP) which enabled enrolled general practitioners to record electronically their patient information (2, 4). The general practitioners who participated provided anonymised data to the centralized database and were trained in data quality (2, 4, 5). The VAMP database was donated to the UK department of Health in 1994 and renamed into General Practice Research Database (GPRD) (5). In April 2012 the database was linked to several datasets and again was renamed into the *Clinical Practice Research Datalink (CPRD)*. The Boston Collaborative Drug Surveillance Program (BCDSP) conducted a broad range of studies to evaluate the quality and completeness of the recorded data for research purposes, especially drug safety studies (2, 4, 5). Since 1991 most practices have been providing data of required quality and completeness for pharmacoepidemiological studies (6). However, for a limited number of practices data have been available since 1987 (2, 5). Since 1994 the CPRD has belonged to the UK department of Health and is currently managed by the UK Medicines and Healthcare products Regulatory Agency (MHRA) (6). To date, the CPRD

has been validated extensively and the individuals enrolled in the database are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate (6–10).

2.2 Data in the CPRD

All information available from the CPRD is anonymised for research purposes (2, 4–6). The general practitioner provides extensive information on medical symptoms and diagnoses using Read medical codes, therapy (medication prescriptions, vaccines, medical devices), patient demographics (including age and sex), lifestyle factors (including height, weight, smoking status, and alcohol consumption), laboratory tests, pathology results, treatment outcomes, events leading to withdrawal of a treatment, patient registration, practice, and consultation details (6). In addition, information on hospital discharge letters, outpatient diagnoses, and referrals to second care or specialists are also provided, since within the National Health Service (NHS) all consultants are required to forward the information to the general practitioner who represents the primary care giver (6). The database has been described in detail (3, 11) and has been validated extensively (2, 4, 5, 9, 10, 12). A systematic review supported a high validity of recorded diagnoses in the CPRD (13). To date, the CPRD comprises more than 40 million patient-years from more than 600 participating practices (9, 14).

2.2.1 Read codes

Within the CPRD, diagnoses and symptoms are coded with Read medical codes (15). Read codes are a coded thesaurus of clinical terms which facilitate efficient modern electronic communication and support patient records, public health and activity reporting, payments, audit, research, and the automation of repetitive manual tasks (15, 16). Read codes are the standard clinical terminology system used in general practice in the UK (16, 17). It supports detailed

clinical encoding of multiple patient phenomena, such as clinical signs, symptoms and observations, laboratory tests and results, diagnoses, and diagnostic, therapeutic or surgical procedures performed (15, 17).

2.2.2 Prescribing codes

Until recently the prescribing codes were based on the Multilex drug terminology which included clinical and commercial information on more than 75,000 pharmaceutical products and packs and provides active clinical decision support and referential medicines information for all healthcare professionals. The Multilex drug knowledge base is widely used throughout the UK and is integrated into clinical systems across the whole healthcare community. In 2013 the CPRD introduced a new coding system called Gemscript (18).

2.2.3 Hospital Episode Statistics

The Hospital Episode Statistics (HES) contains details on all admissions, outpatient appointments, and accident and emergency attendances at NHS hospitals in England. It is a records-based system that covers all NHS trusts in England, including acute hospitals, primary care trusts, and mental health trusts. HES data provide several benefits for epidemiological studies, for example, it enables the assessment of effective delivery of care (19).

2.3 Gout diagnosis within the CPRD

Many studies suggest high validity of data within the CPRD in general (2, 4, 5, 10, 12). Additionally, a systematic review suggested a high validity of recorded diagnoses stating that on average 89% of recorded diagnoses were confirmed (13).

The gout diagnosis was evaluated through profile reviewing and was reported to be highly valid in 1997 (20). Other studies used similar patient definitions for the diagnosis of gout as those used in this thesis (7, 21–23).

2.4 Ethical approval

Study protocols have to be approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

3. EPIDEMIOLOGIC STUDY DESIGNS

Clinical research is either experimental or observational, based on whether the investigator assigns the exposures or not (24, 25). Observational studies can be either descriptive or analytical (24). Descriptive studies describe the occurrence of outcome while analytical studies measure the association between exposure and outcome but only analytical studies include a comparison or control group (24, 25). Pharmacoepidemiology aims at describing the association between exposures and outcomes. Hypotheses can be tested to some extent, but no causal relationship can be proven (26, 27).

3.1 Descriptive studies

Descriptive studies either deal with individuals (case reports, case-series reports, cross-sectional studies, and surveillance studies) or relate to populations (ecological correlational studies), and describe the occurrence of outcome (28). Even if descriptive studies do not have a comparison group and therefore cannot measure association, they can be used to generate hypotheses that can be tested in analytical studies (28).

3.2 Cohort studies

Cohort studies track groups forward in time from exposure to outcome and can be carried out prospectively or retrospectively (24, 29). A cohort study is the best way to identify incidence and natural history of a disease and can be used to examine multiple outcomes after a single exposure (29).

Confounding factors, which can lead to spurious findings, need to be mea-

sured and controlled for (29). Loss to follow-up, which occurs when patients who at one point in time were actively participating, e.g. in a clinical research trial, have become lost either by error in a computer tracking system or by being unreachable in the point of follow-up in the trial, is a challenge (29). The measure of association is the relative risk (29).

For this thesis, a cohort design was used to calculate incidence rates (IRs) with 95% confidence intervals (CIs) of incident gout within the overall CPRD population.

3.3 Case-control studies

Case-control studies include cases with the outcome of interest, e.g. incident gout, and controls without the respective outcome (24, 30). In contrast to cohort studies, case-control studies are carried out retrospectively (30).

To yield good validity of the data, some important points should be considered (24, 30): The researcher should define precise eligibility criteria for the selection of a case. The same eligibility criteria should be applied for the selection of controls, except they are not allowed to have the outcome of interest. Controls should be from the same population and the selection criteria should be independent of exposure. Case-control status should be blinded and exposure has to be assessed in the same way in cases and controls. Confounding should be addressed either in designing the study, i.e. in matching controls to cases, or in using analytical techniques.

Ideally, the only difference between cases and controls should be the outcome status. Prevalence of an exposure is compared between the case and the respective control and the measure of association is the odds ratio (30).

For this thesis, a case-control design was used to calculate odds ratios (ORs) with 95% CIs of incident gout in association with use of diuretics, antidiabetic drugs, diabetes duration and severity, and use of hormone replacement therapy.

3.4 Nested case-control studies

A case-control study is nested when the study population stems from a well-defined cohort, but almost any case-control study can be thought of as nested within some source population (26, 31, 32). A nested case-control study is more efficient if more information on exposure is needed than is readily available from records and if it would be too expensive to seek this information for the whole cohort (26).

4. BIAS

An observed relation may be either true or caused by chance or by an erroneous analysis (1). An error can either be at random or systematic; a bias is generally any systematic error in an epidemiological study due to the incorrect assessment of the association between an exposure and an effect or the lack of internal validity (33). The most important biases are those related to the definition and selection of the study population called selection bias, to the data collection called information bias, or to the association between different determinants of an effect in the population called confounding (33, 34). It is important to consider the different types of biases, and the likely direction and size of the resulting effect (1).

4.1 Selection bias

The term *selection bias* includes various biases, such as inappropriate selection of controls in case-control studies, or informative censoring in cohort studies (35, 36). A selection bias occurs when the study population is different to the target population, therefore not representative (33). This bias can be introduced at several stages, either by defining poor eligibility criteria, inaccurate sampling frame, or unequal diagnostic procedures between the study population and the target population (33).

A further bias is called healthy user bias where cases differ with regard to their adherence to preventive treatments and those with a good compliance may be systematically healthier (37, 38). In addition, prevalent user bias can occur in cohort studies which compare prevalent users of a drug to non-users

of the respective drug due to the fact that prevalent users have by definition survived under treatment (39). Selection bias should be addressed at the stage of study design by matching (33, 40).

4.2 Information bias

Information bias is related to the accuracy of information, arises during data collection, and can be divided into random misclassification or non-random misclassification. Non-random misclassification can be further divided into recall bias or observer bias (26). The three main types of information bias are misclassification bias, ecological fallacy, and regression to the mean (26).

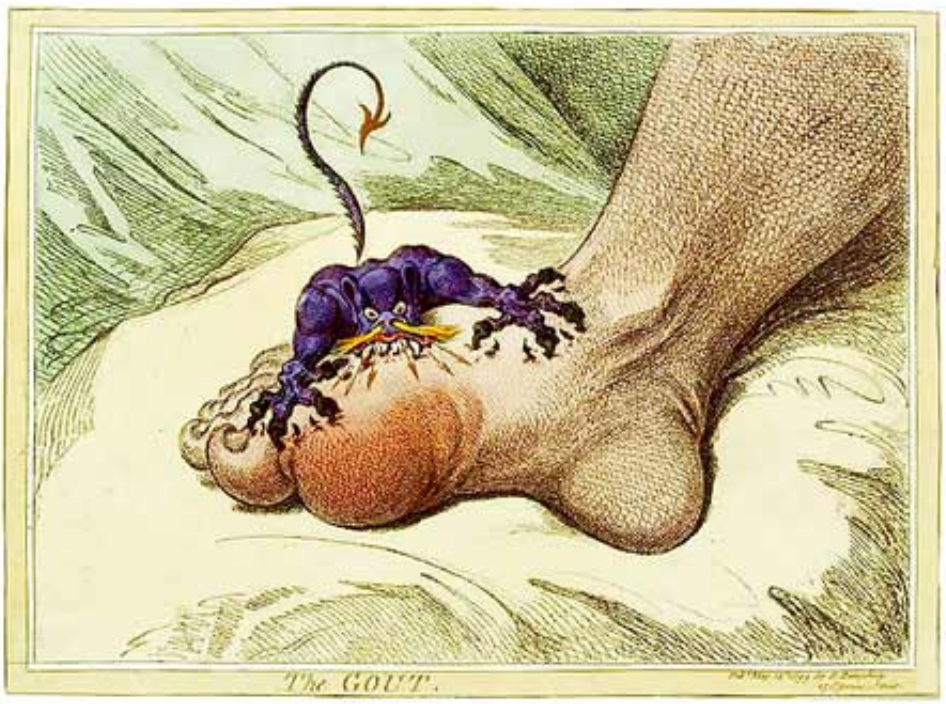
4.3 Confounding

Confounding is a mixing of effects, meaning that the effect of the exposure is mixed with the effect of another variable, leading to a bias (26). A confounder must be associated with the disease, either as a cause or as a proxy for a cause, but not as an effect of it. Additionally, it must be associated with the exposure without being an effect of it (26). The effect of confounders can be reduced by matching for some factors, such as age, gender, location of residence etc., or by a random selection of cases and controls from a study population (25). In the analysis, confounding can be controlled for by adjusting for the presence or absence of multiple confounding factors (25).

A special occurrence of confounding is confounding by indication. It is sometimes encountered in observational studies of drug effects because the allocation of treatment is not randomized and the indication for treatment may be related to the risk of future health outcomes (41). However, this bias often occurs in studies of drugs that are not widely prescribed, if indication for their use is narrow and not likely to be present in the comparison group (41).

4.4 Interaction

Interaction in epidemiology, also called effect modification or effect measure modification, refers to the common situation in which a measure of effect changes over values of some other variable (26). Calculation of stratum-specific effects is necessary to show the influence of the effect modifier on the association between the exposure and the outcome (42).



The Gout, caricature by James Gillray (1799)

Die böse Gicht

Starker Schmerz in Hand und Bein,
lässt schließen auf das Zipperlein,
wenn die Zehe teuflisch sticht,
dann vergesse man es nicht:
zuviel an Fleisch, zuwenig Fisch
kommt in der Regel auf dem Tisch.
Ist man dem Weine zugetan,
oder Äthanol und Ethylen
fängt das Spiel genauso an,
dann muss dich auch der Doktor seh'n.
Zuviel der Säure in dem Harn,
wird die Schmerzen nicht erspar'n,
lieber etwas leiser treten,
mit Alkohol und mit den Fetten,
kann eine Linderung bedeuten,
was manche Gichtler nicht bereuten.

von Franz Christian Hörschläger

5. GOUT

5.1 Definition

Gout is an acute, excruciatingly painful, inflammatory arthritis that occurs suddenly with a maximal severity within 12 to 24 hours and resolves spontaneously and completely, even without treatment, within a few days to several weeks (43–45). Gout is a consequence of hyperuricaemia, an extracellular elevation of uric acid levels, which is defined as urate levels >6.8 mg/dl (≥360mmol/l) (45, 46); if saturation threshold is reached, uric acid can crystallize, and the monosodium urate crystals, called tophi, can deposit in joints, tendons, bone, cartilage, skin, surrounding tissues, and seldom in parenchymal organs, with a chronic inflammatory response as a general tissue reaction (45, 46). The solubility of monosodium urate depends on temperature and falls rapidly with decreasing temperature (47). Most often a single joint is involved, and it is called *podagra*, when acute gout involves the base of the great toe, with a red, tender, hot, swollen metatarsophalangeal joint. Hyperuricaemia can occur by impaired renal excretion, overproduction of uric acid, or by overconsumption of purine-rich foods that are metabolized to urate (48–50). Even if hyperuricaemia is a necessary predisposing factor, its presence does not always lead to the onset of gout (51–53).

The three stages in natural history of gout are acute gouty arthritis, intercritical gout, and chronic recurrent and tophaceous gout (54).

5.2 History

Gout is one of the oldest known diseases and has first been identified by the Egyptians. Hippocrates, an ancient Greek physician, referred to it as *the unwalkable disease* in the fifth century (55). Some of Hippocrates aphorisms are still more or less valuable today, as e.g. „a women does not take the gout, unless her menses be stopped"or „in gouty affections, inflammation subsides within 40 days"(55). Hippocrates noted the link between the disease and an intemperate lifestyle, referring to *podagra*, as the *arthritis of the rich* or the *arthritis of kings*, how it was called throughout history since in the past only affluent people could afford such a lifestyle (55). Later, Galen, a prominent Greek physician, surgeon and philosopher in the Roman empire, was the first to describe gouty *tophi*, the crystallized monosodium urate deposits, and associated gout with debauchery and intemperance, and recognized a hereditary trait that had previously been referred to by Seneca, a Roman philosopher and statesman (55).

The Dominican monk Randolphus of Bocking was the first person to use the word *gout* to describe *podagra* in the 13^{th} century: *„gutta quam podagram vel artiticam vocant"* – „the gout that is called podagra or arthritis"(55). The term *gout* is derived from the Latin word *gutta* which means *drop*. This was at a time when current knowledge was the belief that an excess of one of the four *humours of Hippocratic medicine* – which in equilibrium were thought to maintain health – would flow or drop into a joint causing pain and inflammation (55).

Der Hencker und die Gicht

Der Hencker und die Gicht verschaffen gleiche Pein;
Nur er macht kleine lang, sie lange Leute klein.

von Friedrich von Logau

5.3 Diagnosis and management

The diagnosis focuses on the fundamental pathophysiologic events defining the clinical state with tissue deposition of urate crystals and the accompanying inflammation and potentially destructive consequences. The visualization of monosodium urate crystals by experienced examiners in a sample of fluid aspirated from an affected joint or tophi is the gold standard for the diagnosis of gout, but in daily practice it is sometimes impossible to perform (especially in primary care); thus, the diagnosis is mostly based on clinical judgement, including patient history, physical examination, appropriate laboratory tests, and increasingly imaging studies (56, 57).

In 1963 the Rome criteria, in 1968 the New York criteria, and in 1977 the American Rheumatism Association diagnostic criteria (58) guidelines for the diagnosis of acute gout were published (59). The American College of Rheumatology formulated criteria in order to classify gout without identification of monosodium urate (58). The criteria were not developed with reference to monosodium urate crystals, nor were they tested properly afterwards against this gold standard, and therefore have shown limited validity (56, 57). However, the criteria can provide support for a diagnosis or exclusion of gout, but crystal identification should remain the gold standard (56, 57).

The most recent European criteria recommendations from the European League Against Rheumatism Recommendations (EULAR) have been developed on clinical practice and the best available evidence in 2006 (59). Ten key recommendations regarding clinical features of gout, biochemical examinations, urate crystals, radiographs, risk factors, and comorbidities have been evaluated (59). Furthermore, most recent guidelines by the British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) released in 2007 contain patient-focused, evidence-based recommendations for the management of gout for primary care and hospital practice in the UK (54).

Differential diagnoses include septic arthritis, osteoarthritis, rheumatoid arthritis, hemochromatosis, trauma, or calcium pyrophosphate deposition (pseudogout).

5.4 Epidemiology

Gout is an inflammatory, painful arthritis with acute onset (60, 61) with a reported prevalence in the UK population of about 1.4% between 1999 and 2005 (7, 46) and about 2.5% in 2012 (23). The incidence was reported to be 17.7 per 10,000 PYs in 2012 (23) and appears to be rising (62, 63).

Die Gicht

Die Gicht verbeut den Wein zu trincken,
Sonst mustu liegen oder hincken.
Mich dünckt, es sey ein groß Verdruß,
Wann über Maul regirt der Fuß.

von Friedrich von Logau

5.4.1 Risk factors

Hyperuricaemia is the most important risk factor for gout (43, 64). Increasing age, male gender (7), obesity (65, 66), and alcohol intake, especially beer and spirits (66, 67), are other important risk factors. In addition, high levels of purine-rich food, fructose-containing sugars, dehydration, trauma or surgery, ingestion of drugs affecting serum urate concentrations, e.g. allopurinol, uricosuric agents, thiazide or loop diuretics, and low-dose acetylsalicylic acid may

promote gouty attacks (48, 50, 66, 68). Furthermore, comorbidities such as hypertension and cardiovascular diseases are associated with gout (7, 66, 69). On the other hand, higher coffee consumption was associated with a lower risk of gout (70, 71).

5.4.2 Gender differences

Gout has long been considered a male disease, while during the time of the Roman Empire Seneca, a Roman Stoic philosopher, was the first to observe that women suffered from gout only at older ages (55). Previous studies reported gender differences, especially that women were older at onset of gouty arthritis (43, 44, 72). Since today people grow older, gout has become increasingly more frequent in women, particularly after menopause (73, 74).

In addition, women with gout have a higher prevalence of comorbidities such as hypertension or renal insufficiency, and more frequently used diuretics (44, 72). However, women with gout are less likely to drink alcohol, suffer less often from *podagra* but more often have involvement of other joints such as finger or ankle, have less frequent recurrent attacks, and receive different treatment patterns compared to men (44, 72). Atypical locations may cause a delay in the diagnosis in women due to unfamiliarity of physicians or due to the severity of coexisting diseases (44).

5.4.3 Regional differences

The lifestyle in Western countries predisposes individuals to hyperuricaemia and gout: an excess of dietary purines derived from meat, seafood, and beer increases the incidence and prevalence of gout. Asian cultures relatively rarely suffer from gout due to their nutrition based on rice and vegetables, which are low in purines (48, 50). However, even within the UK some regional differences have been shown based on the assumption of differences in socioeconomic status, lifestyle, and nutrition (75).

5.4.4 Seasonal differences

Seasonal differences have been known for a long time. One of Hippocrates aphorism was: „Gouty affections become active in spring and in autumn“(55). In contrast, a study reported increased incidence during the summer period, late April to mid-September (76).

5.5 Treatment

Treatment goals in an acute gout attack are to (54):

- Exclude a diagnosis of septic arthritis.
- Terminate the attack and improve symptoms as promptly as possible using non-pharmacological and pharmacological treatments.
- Seek, assess, and control associated diseases, such as diabetes mellitus, hypertension, hyperlipidaemia and cardiovascular disease.

Current guidelines by the British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) (54) and the EULAR (77), both relating to the management of gout in primary care, are similar and propose non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroid as initial treatment. After four to six weeks patients should be reviewed and lifestyle factors, blood pressure, serum urate levels, renal function, and glucose should be assessed (54).

The current guidelines (54, 77) encourage urate-lowering therapy if patients had two or more attacks of acute gout, or have other risk factors that would make further attacks likely. The initiation of urate-lowering therapy can precipitate an acute gouty attack; therefore a prophylaxis is usually given to prevent this complication. However, the urate-lowering therapy should not be interrupted in patients on such therapy at the time of an acute attack (54, 77).

With effective therapies, progression of gout to the chronic tophaceous

stage is now less frequent among the compliant patients with primary gout and among most patients with secondary gout (54, 77). In general, treatments for gout are well tolerated, although they are associated with the potential for drug interaction which can be influenced by patient comorbidities and concomitant medication (78).

During the last decades advances in the understanding, causes and pathophysiology of hyperuricaemia and gout have led to the development of effective therapies (55). In addition, patients with renal impairment or continuing acute gout attacks are now considered in the guideline (54). However, challenges remain in treating patients with renal impairment (78).

Artzney wider Gicht

Wer Gicht auffs Alter nicht wil leiden,
Der mag sich jung bald lassen schneiden.

von Friedrich von Logau

5.5.1 Diet

Purine-rich food has long been known to be a major risk factor for hyperuricaemia and gout, and the knowledge that gout could be controlled by lowering the intake of purine-rich food have been long known (48, 50). However, dietary restrictions or modifications as a means of controlling gout has so far largely been neglected (55), even though, in the current British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) guideline recommendations for diet, lifestyle modifications and non-pharmacological modalities are included (54).

5.5.2 Initial treatment of acute gouty attacks

Several classes of anti-inflammatory agents are effective for the treatment of acute gout, including NSAIDs, colchicine, and systemic and intra-articular glucocorticoids (77). Nowadays, NSAIDs with or without proton pump inhibitors are the drugs of choice (43, 54). Furthermore, colchicine and (systemic) corticosteroids are recommended but used less frequently due to relative contraindications (54).

There is evidence that colchicine was used 2000 years ago, while its use against gout has been reported for the first time in the 6th century (55). Since Thomas Sydenham, an English physician who lived in the 17^{th} century, rejected all medications that were purgatives as being too toxic for use, colchicine was not used for the treatment of gout for about 150 years. It was not until 250 years ago that it was rediscovered in 1763 (55). Colchicine has been long known to cause dose-dependent gastrointestinal side effects, to have a narrow therapeutic index, and to induce drug interactions (78).

A set of general principles is important in the effective management of acute gout, regardless of the specific anti-inflammatory agent used (76): Treatment should start as soon as possible after the beginning of the attack, preferably within several hours of symptom onset. More rapid and complete resolution of symptoms occurs the earlier the treatment is introduced. However, to reach that, treatment should be initiated at the recommended dose of the chosen anti-inflammatory agent. In addition, the therapy should be continued for the duration of the attack, usually until a complete cessation within two to three days is reached, but dosage can usually be reduced once a significant response is achieved. Oral glucocorticoids are an exception, slightly slower tapering may be needed to avoid a recurrent attack.

5.5.3 Urate lowering therapy

Urate-lowering therapies are of no benefit for acute gout and should generally not be initiated during an acute attack (54, 77). However, patents who already receive these agents should not discontinue the medication, as there is no benefit from temporary discontinuation, and subsequent reintroduction of the agent may predispose to another attack (54, 77). Therapeutic recommendations for acute gout attacks in patients receiving urate-lowering therapy are the same as those for patients without such a therapy (54, 77).

Uricosuric agents were first used at the end of the 19^{th} century and enhance the renal clearance of urate (79). Firstly, high doses of salicylates were used to induce uricosuria and resolution of tophi (79). Salicylates have a bimodal effect on urate excretion dependent on dosage: while low doses reduce urate excretion, high doses (4-6g/day) are uricosuric (80). Even though salicylates were effective, they were not used for long due to the toxicity and impracticality of high-dose therapy, and were replaced by probenecid, sulfinpyrazone, and benzbromarone (55, 81). In 2001 the antihypertensive agent losartan, an angiotensin receptor blocker, and the lipid-lowering fibrate fenofibrate were shown to have moderate uricosuric effects (82, 83). However, neither is tested nor licenced for the treatment of gout or hyperuricaemia.

Allopurinol, which was the first xanthine oxidase inhibitor, is an important advance in the treatment of hyperuricaemia and gout, and has become the most frequently used uric acid lowering drug in clinical practice (54). Xanthine oxidase inhibitors act by inhibiting the synthesis of uric acid from hypoxanthine and xanthine, are effective in reducing plasma and urinary urate levels, and have been shown to even dissolve tophaceous deposits (84). The indication of allopurinol is the reduction of urate formation where urate deposition has occurred or is predictable (84).

Clinical trials have shown febuxostat, a novel selective inhibitor of xanthine oxidase, to be very effective in lowering uric acid levels (78). Febuxostat is rec-

ommended as an option for chronic hyperuricaemia in gout when allopurinol is contraindicated or not tolerated (84).

Rasburicase catalyses the conversion of uric acid to allantoin, which is five to ten times more water-soluble than uric acid and is easier for the kidneys to excrete (85). However, rasburicase is much more expensive than conventional therapy (85). Its indication within the UK is the treatment and prophylaxis of acute hyperuricaemia in patients with haematological malignancy with a high tumour burden and who are at risk of rapid tumour lysis or shrinkage at initiation of chemotherapy (84).

5.5.4 Investigational therapy

Patients whose gouty flares are resistant to all above mentioned therapies may benefit from the use of a biologic agent canakinumab, which is a human monoclonal antibody, that inhibits the action of interleukin-1 beta, which is an important mediator of gouty inflammation and a potential therapeutic target in acute gout (77). This agent is under investigation for the treatment of acute gout and is up to now only used in patients who did not respond to all other available treatments and who suffer from frequent attacks (78).

Part II

OBJECTIVES

6. AIMS OF THE THESIS

The aim of this thesis was to contribute newsworthy information on associations with incident gout by using data from the well validated UK-based primary-care database CPRD:

- The ambition of the first project was a sound analysis of incidence rates stratified by age, gender, index year, region, and season. A secondary aim was the thorough description of the demographic characteristics, comorbidities, comedication, and treatment pattern of the nested case-control population.
- The purpose of the second project on diuretic drug use was to increase the awareness of these drugs in association with the development of gout and to clarify in more detail which diuretic drug classes are associated with the disease.
- The aim of the third project was to clarify the impact of anti-diabetic drugs, diabetes severity, and diabetes duration in type 2 diabetes mellitus patients on the risk of incident gout.
- The objective of the fourth project was to assess the risk of developing incident gout in association with use of hormone replacement therapy by type, timing, duration, and route of hormone replacement therapy administration.

Part III

RESULTS

7. GOUT PROJECTS

To investigate these aims three studies were carried out:

Study 1

Epidemiology of Gout in the United Kingdom:
A Population-Based Cohort Study with a Nested Case-Control Study

Study 2

Use of Diuretics and Risk of Incident Gout:
A Population-Based Case-Control Study

Study 3

Poorly Controlled Type 2 Diabetes Mellitus is Associated with a Decreased Risk of Incident Gout:
A Population-Based Case-Control Study

Study 4

Use of Hormone Replacement Therapy and Risk of Incident Gout:
A Population-Based Case-Control Study

Study 1

Epidemiology of Gout in the United Kingdom: a Population-Based Cohort Study with a Nested Case-Control Study

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Unpublished

ABSTRACT

Background and Objective

Detailed data on the course of incidence rates (IRs), demographic characteristics, and initial treatment of gout over the last decades are scarce. We aimed at assessing the IRs of and identify risk factors for incident gout.

Methods

Using data from the UK-based Clinical Practice Research Datalink (CPRD), we conducted a cohort study with an embedded nested case-control study between 1990 and 2010. One control from the population at risk was matched to each case (patients with a recorded incident gout diagnosis during follow-up) on age, sex, calendar time, general practice, and number of years of active history in the CPRD prior to the index date. We adjusted for potential confounders by applying multivariate conditional logistic regression analyses.

Results

A total of 91,790 patients had a recorded incident diagnosis of gout. The estimated IR per 10,000 person-years (PYs) yielded 18.0 (95% confidence interval [CI] 17.9−18.1), was markedly higher in man than in women, and increased over time. It was highest in Wales for both sexes (22.9, 95% CI 22.4−23.4), and reached a maximum in January and June. In the nested case-control study, 74.1% of patients were male. Current smoking was associated with a decreased

adjusted odds ratio (OR) of 0.76 (95% CI 0.71−0.92). Increasing alcohol consumption, comorbidities such as hypertension, kidney failure, congestive heart failure, and ischemic heart disease, and antihypertensive comedication (except and calcium channel blockers), were associated with an increased adjusted OR. Gout treatment remained unchanged over time except for colchicine whose use increased.

Conclusions

Incident gout was recorded in 18.0 patients per 10,000 PYs. Risk factors for incident gout included alcohol consumption, comorbidities (especially kidney failure and congestive heart failure), and antihypertensive comedication.

INTRODUCTION

Gout is a common inflammatory, painful arthritis with acute onset (1, 2). Gout results from a deposition of monosodium urate crystals in peripheral joints and soft tissues due to elevated uric acid levels above threshold for saturation (1). With the possibility of urate lowering treatment gout is the only chronic arthritis that can be *cured*(3). Increasing age and male sex (4, 5), obesity (6, 7), alcohol intake (7, 8), hyperuricaemia (1, 5), and some co-morbidities such as hypertension, cardiovascular diseases, or renal failure are associated with gout (4, 7, 9).

The prevalence of gout was reported to be 1.4% between 1999 and 2005 (4, 10, 11) and 2.5% in 2012 (12) in the United Kingdom (UK) population. A study derived from the United States (US)-based Claims database reported a rising prevalence between 1990 and 1999 (13), while a study derived from the UK-based Clinical Practice Research Datalink (CPRD) reported a relatively stable incidence within this time frame (4). A recent study reported an increasing prevalence and incidence after 1997 (12). Reported incidence rates (IRs) derived from the UK range from 11.2 to 26.8 per 10,000 person-years (PYs) and are the highest reported within Europe (10-12, 14, 15). Despite publication of European (16) and UK (17) guidelines in 2006 and 2007, the management of gout appears to be suboptimal. Especially, only a minority of patients receives urate lowering therapy (12).

Taken together, detailed data on IRs, demographic characteristics, and initial treatment of gout over the course of time are scarce. We therefore conducted a cohort study with a nested case-control study to assess the IRs between 1990 and 2010, as well as demographics and characteristics, comorbidities, co-medication and current treatment patterns of gout.

METHODS

Study design and data source

We conducted a cohort study with a nested case-control study using data from the UK-based CPRD, a large, primary care database that was established in 1987. The individuals enrolled in the database are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate (4, 18). The CPRD holds anonymised information regarding demographics, and patient characteristics, as well as lifestyle variables, such as body mass index (BMI), smoking status, and alcohol consumption, and information on symptoms, medical diagnoses, referrals to consultants, and hospitalizations. General practitioners generate drug prescriptions electronically. The database has been described in detail elsewhere (19, 20) and has been validated extensively (21-25).

The Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research approved the study.

Study population

Cohort population

For the cohort study we included all patients in the CPRD from the start of the database in 1987 until 2010. We excluded patients with less than three years of active history in the database prior to the start of follow-up. We further excluded patients with a history of cancer (except non-melanoma skin cancer), human immunodeficiency virus infection, or with any code for gout

prior to the start of follow-up. We followed all patients from the start of follow-up until they developed incident gout, died, left the practice, or follow-up ended in the medical record (either because the study period ended or the practice stopped delivering data), whichever occurred first.

Nested case-control population

The date of the first-time recorded gout diagnosis was subsequently referred to as the index date. Additionally, to minimize misclassification, we excluded patients with a diagnosis of hemochromatosis, osteoarthritis, septic arthritis, or rheumatoid arthritis within 180 days prior to until 90 days after the index date. From the cohort population, we identified at random one control patient without any evidence of gout for each case patient, matched them on age (same year of birth), sex, calendar time (same index date), general practice, and number of years of active history in the CPRD prior to the index date. Similar case definitions of gout have been used and validated in previous studies based on CPRD data (4, 26, 27).

Statistical analysis

Cohort analysis

We assessed crude IRs with 95% CIs of gout per 10,000 PYs for the overall population derived from the CPRD, stratified by sex, age ($<$25, 25$-$44, 45$-$64, 65$-$84, and $\geq$85 years), year of incident diagnosis (1990$-$2010), region within the UK (Northwest, Northeast, Yorkshire & The Humber, East Midlands, West Midlands, East of England, Southwest, South Central, London, Southeast Coast, Northern Ireland, Scotland, and Wales), and seasonality (by month). Rates were calculated as the number of incident gout cases divided by the total number of PYs at risk. PYs at risk were calculated by adding up person-time from the start of follow-up until the end of follow-up.

Nested case-control analysis

We conducted conditional logistic regression analyses to calculate relative risk estimates as odds ratios (ORs) with 95% CIs for gout in association with potential risk factors. A two-sided p-value of <0.05 was considered as statistically significant. The analyses were controlled for potential confounders such as sex, age, calendar time, general practice, and years of previous history on the database by matching. When we analysed the exposure odds, we adjusted for patient characteristics, comorbidities or concomitant drug use in the multivariate analysis a priori if these potential confounders were predictor variables for gout known from the literature, and build a core model with these variables. The predictor variables included smoking status (non, current, ex, unknown), body mass index (BMI 12.0−18.5, 18.5−24.9, 25−29.9, $\geq$30kg/m^2, unknown), alcohol consumption (never/ex, current [1−9, 10−19, $\geq$20 units per week], unknown). For demographics we included additionally the comorbidities hypertension, congestive heart failure, and renal failure, and for the drug exposures potassium sparing diuretics, thiazide diuretics, thiazide-like diuretics, loop diuretics, angiotensin-converting-enzyme inhibitors, beta-blockers, calcium channel blockers, and nitrates.

All analyses were done using the statistical software SAS, version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Cohort study

The initial study population for the cohort study encompassed 5,157,052 patients from the CPRD, whereof 2,367,908 (45.9%) were male and 2,789,144 (54.1%) were female.

The overall IR per 10,000 PYs was 18.0 (95% CI 17.9−18.1), 29.0 (95% CI 28.8−29.2) in men and 8.6 (95% CI 8.5−8.8) in women. The IR increased in both sexes over time, especially between 1999 and 2010. In males, the IR per 10,000 PYs in 1990 was 15.7 (95% CI 14.3−17.1) and in 2010 39.0 (95% CI 37.8−40.2). In females, the IR per 10,000 PYs in 1990 yielded 3.3 (95% CI 2.7−3.9), and in 2010 11.8 (95% CI 11.2−12.4). The IR increase for the period 1999−2010 overall was 61.2%, 56.6% in males and 66.2% in females. For more information see *Figure 1.*

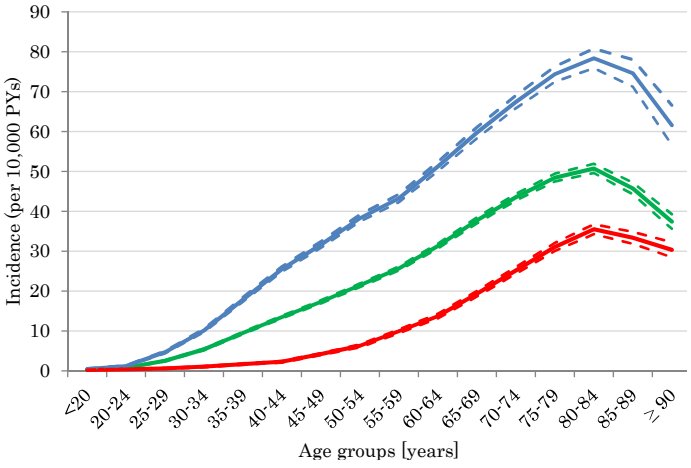
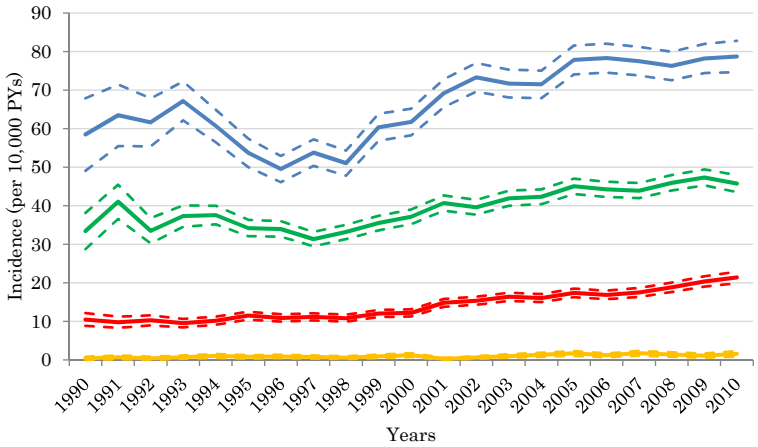


Figure 1 Sex differences in gout across age categories (blue: male population; red: female population; green: overall population; dotted lines: 95% confidence intervals; PYs: Person-Years)

Stratification by age strata yielded increasing IRs over time in all age strata except in patients <25 years. Age strata 64-84 years presented the greatest increase over time *(Figure 2)*.

(A) Men



(B) Women

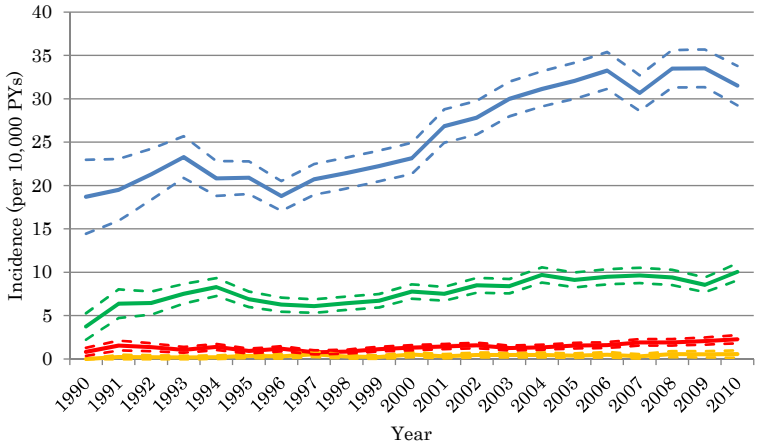
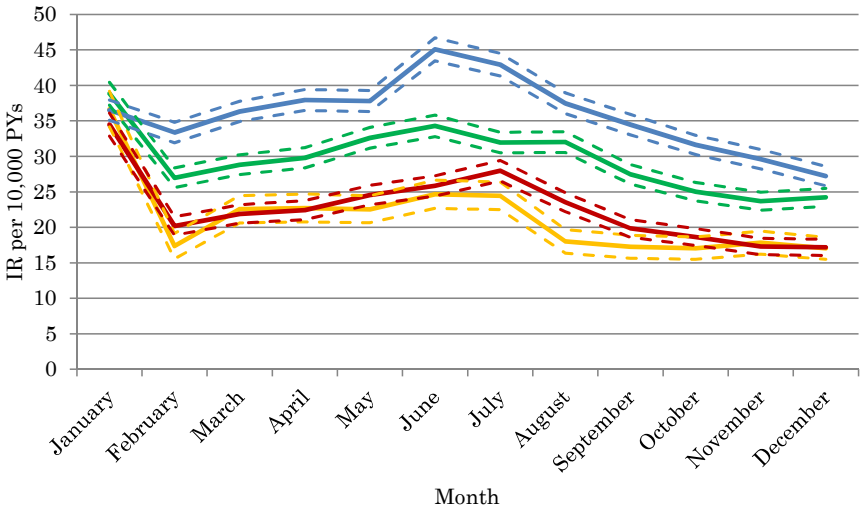


Figure 2 Age-specific annual incidence rates of gout in men (A) and women (B) between 1990 and 2010 (blue: 64−84 years; green: 45−64 years; red: 25−44 years; orange: <25 years; dotted lines: 95% confidence intervals; PYs: Person-Years)

Stratification by month of onset of incident gout presented highest IRs per 10,000 PYs in January (22.0, 95% CI 21.6−22.5) and June (21.7, 95% CI

21.2−22.1). This was true across all time strata and for both sexes. However, the most recent time strata (2005−2010) reached the highest IR in June, namely 45.1 per 10,000 PYs (95% CI 43.4−46.7) for men and 13.9 per 10,000 PYs (95% CI 13.0−14.7) for women *(Figure 3)*.

(A) Men



(B) Women

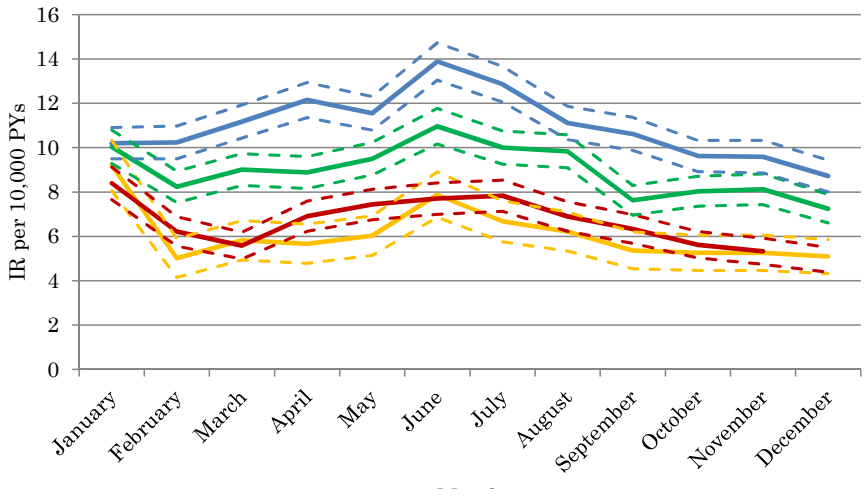


Figure 3 Seasonal incidence rates in 5 year strata in men (A) and women (B) between 1990−2010 (blue: 2005−2010; green: 2000−2004; red: 1995−1999; orange: 1990−1994; dotted lines: 95% confidence intervals; PYs: Person-Years)

Stratification by region and sex yielded highest IRs in Wales with 22.9 (95% CI 22.4−23.4) per 10,000 PYs overall, 37.2 (95% CI 36.3−38.2) per 10,000 PYs in men and 10.9 (95% CI 10.4−11.3) per 10,000 PYs in women *(Figure 4)*.

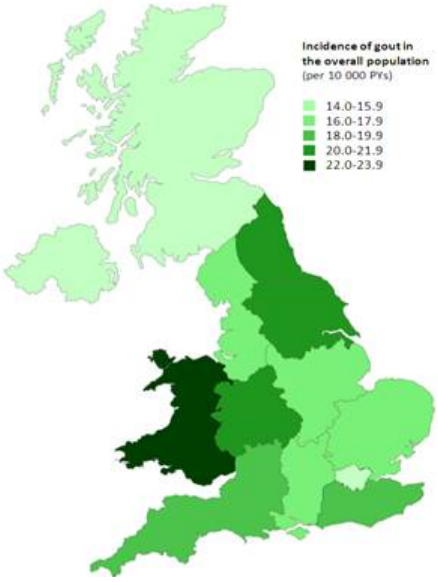


Figure 4 Regional incidence rates from 1990−2010 in the overall Gout population

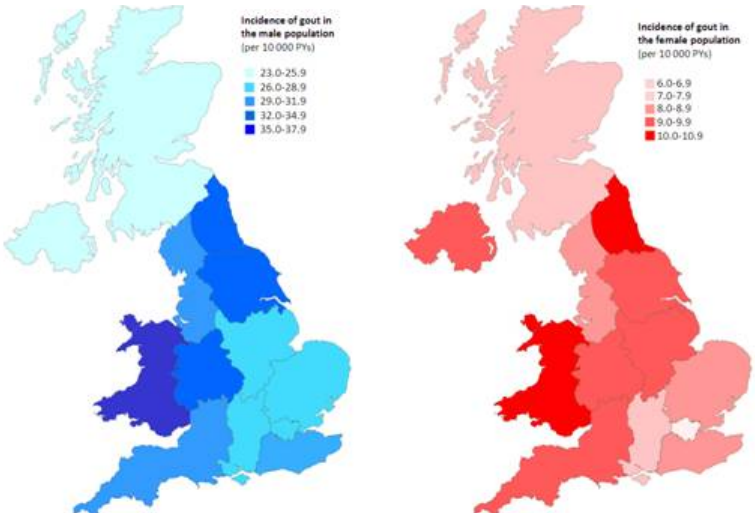


Figure 5 Sex-specific regional incidence rates between 1990 and 2010

Nested case-control study

Demographic and disease factors

From the cohort population 91,790 patients developed incident gout during follow-up, whereof 67,987 (74.1%) were male and 23,803 (25.9%) were female; this resulted in a male to female ratio of 2.9:1. Current smoking was associated with a decreased OR of 0.76 (95% CI 0.71−0.92). Increasing number of alcohol units per week in current alcohol consumers was associated with an increasing OR. Increasing number of general practitioner visits within the last year prior to the index date presented increasing OR.

Comorbidities such as hypertension, kidney failure, congestive heart failure and ischemic heart disease were associated with an increased adjusted OR of 2.03 (95%CI 1.98−2.08), 2.76 (95% CI 2.63−2.91), 3.02 (95% CI 2.82−3.24), and 1.33 (95% CI 1.29−1.38), respectively. Dyslipidaemia and stroke/transient ischemic attack (TIA) only marginally increased the risk estimate. Diabetes mellitus was associated with a decreased adjusted OR of 0.70 (95% CI 0.67−0.73). For further results see *Table 1.*

Table 1 Demographics and characteristics of patients with incident gout and matched controls

Variable	No. of cases (%) (n=91,790)	No. of controls (%) (n=91,790)	OR crude (95% CI)	OR adj.* (95% CI)
Sex°				
Male	67987 (74.1)	67987 (74.1)	NA	NA
Female	23803 (25.9)	23803 (25.9)	NA	NA
Age-group [years]°				
<25	479 (0.5)	481 (0.5)	NA	NA
25-44	14711 (16.0)	14712 (16.0)	NA	NA
45-64	34441 (37.5)	34446 (37.5)	NA	NA
65-84	36789 (40.1)	36832 (40.1)	NA	NA
≥85	5370 (5.9)	5319 (5.8)	NA	NA
BMI-group [kg/m^2]				
12.0-18.4	441 (0.5)	1007 (1.1)	0.70 (0.62 - 0.79)	0.81 (0.71 - 0.92)
18.5-24.9	15946 (17.4)	25240 (27.5)	NA	NA
25.0-29.9	31081 (33.9)	26517 (28.9)	1.91 (1.86 - 1.96)	1.73 (1.68 - 1.79)
30.0-60.0	23325 (25.4)	11682 (12.7)	3.35 (3.24 - 3.45)	2.72 (2.63 - 2.82)
Unknown	20997 (22.9)	27344 (29.8)	1.11 (1.08 - 1.15)	1.42 (1.37 - 1.48)
Smoking status				
Non-smoker	38584 (42.0)	37021 (40.3)	NA	NA
Current smoker	13067 (14.2)	16548 (18.0)	0.74 (0.72 - 0.76)	0.76 (0.74 - 0.79)
Ex-smoker	26659 (29.0)	20245 (22.1)	1.34 (1.31 - 1.38)	1.11 (1.08 - 1.14)
Unknown	13480 (14.7)	17976 (19.6)	0.64 (0.62 - 0.66)	0.94 (0.90 - 0.99)
Alcohol consumption (Units/week)§				
Never / Ex	10667 (11.6)	11822 (12.9)	NA	NA
Current unknown	15884 (17.3)	16035 (17.5)	1.11 (1.07 - 1.15)	1.18 (1.13 - 1.23)
Current 1-9	18589 (20.3)	20640 (22.5)	1.05 (1.02 - 1.09)	1.16 (1.11 - 1.20)
Current 10-19	11259 (12.3)	9228 (10.1)	1.49 (1.43 - 1.55)	1.69 (1.61 - 1.76)
Current >20	16175 (17.6)	8356 (9.1)	2.42 (2.33 - 2.52)	2.86 (2.73 - 2.99)
Unknown	19216 (20.9)	25709 (28.0)	0.79 (0.76 - 0.82)	1.09 (1.03 - 1.14)
GP visits last year				
0-2	17527 (19.1)	29725 (32.4)	NA	NA
3-4	6266 (6.8)	7420 (8.1)	1.54 (1.48 - 1.60)	1.45 (1.38 - 1.51)
5-9	13534 (14.7)	13761 (15.0)	1.95 (1.89 - 2.01)	1.75 (1.69 - 1.82)
≥10	54463 (59.3)	40884 (44.5)	3.21 (3.12 - 3.30)	2.38 (2.31 - 2.46)
Comorbidities				
Hypertension	39967 (43.5)	24090 (26.2)	2.58 (2.52 - 2.64)	2.03 (1.98 - 2.08)
Diabetes mellitus	7561 (8.2)	6530 (7.1)	1.18 (1.14 - 1.22)	0.70 (0.67 - 0.73)
Dyslipidaemia	13799 (15.0)	9073 (9.9)	1.72 (1.67 - 1.77)	1.20 (1.16 - 1.24)
Kidney failure	14311 (15.6)	7510 (8.2)	3.97 (3.79 - 4.16)	2.76 (2.63 - 2.91)
Congestive heart failure	8056 (8.8)	2517 (2.7)	3.90 (3.71 - 4.10)	3.07 (2.90 - 3.24)
Ischemic heart disease	16614 (18.1)	10408 (11.3)	1.86 (1.81 - 1.91)	1.33 (1.29 - 1.38)
Stroke/TIA	6464 (7.0)	4822 (5.3)	1.39 (1.34 - 1.45)	1.09 (1.04 - 1.14)

BMI, body mass index; CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack
°Matching variables; NA: not applicable; § 1U (Unit) = 10ml of pure ethanol (8g of ethanol)
*Adjusted for all variables in table: BMI, smoking status, alcohol consumption, hypertension, kidney failure, congestive heart failure, ischemic heart disease

Co-medication

Current use of most antihypertensive drugs except losartan and calcium channel blockers yielded increased gout risks compared to never-use. More details see *Table 2*.

Table 2 Current use of co-medication in patients with incident gout and matched controls

Co-medication	No. of cases (%) (n=91,790)	No. of controls (%) (n=91,790)	OR crude (95% CI)	OR adj.* (95% CI)
ACE-I	19127 (20.8)	9810 (10.7)	2.71 (2.63 - 2.79)	1.46 (1.41 - 1.51)
ARB (excl. Losartan)	4080 (4.4)	1992 (2.2)	2.30 (2.18 - 2.44)	1.18 (1.10 - 1.26)
Losartan	1424 (1.6)	886 (1.0)	1.66 (1.52 - 1.81)	0.86 (0.78 - 0.94)
Loop diuretics	13510 (14.7)	4109 (4.5)	4.70 (4.50 - 4.90)	3.28 (3.13 - 3.45)
Thiazide diuretics	14545 (15.9)	7783 (8.5)	2.43 (2.35 - 2.51)	1.94 (1.87 - 2.01)
Potassium-sparing diuretics	2373 (2.6)	577 (0.6)	4.40 (4.01 - 4.83)	2.08 (1.87 - 2.30)
Beta-blocker	19561 (21.3)	9973 (10.9)	2.57 (2.50 - 2.65)	1.82 (1.76 - 1.89)
Calcium channel blockers	13291 (14.5)	9384 (10.2)	1.73 (1.68 - 1.79)	0.98 (0.95 - 1.02)
Nitrates	7647 (8.3)	4281 (4.7)	2.03 (1.95 - 2.12)	1.14 (1.09 - 1.20)
Statins	17126 (18.7)	11437 (12.5)	1.90 (1.85 - 1.96)	1.04 (1.01 - 1.08)
ASA low dose	15986 (17.4)	11410 (12.4)	1.72 (1.67 - 1.77)	1.01 (0.97 - 1.05)
Pyrazinamide	22 (0.0)	15 (0.0)	1.47 (0.76 - 2.83)	1.39 (0.65 - 2.95)
Cyclosporine	264 (0.3)	29 (0.0)	9.10 (6.20 - 13.36)	6.23 (4.12 - 9.41)

ACE-I, Angiotensin-Converting-Enzyme-Inhibitors; ARB, Angiotensin-Receptor Blocker; ASA, Acetylsalicylic acid

*Adjusted for all variables in table: BMI, smoking status, alcohol consumption, potassium sparing diuretics, thiazide diuretics, thiazide-like diuretics, loop diuretic, ACE-Is, beta-blockers, calcium channel blockers, nitrates

Trends in current gout treatment

Non-steroidal anti-inflammatory drugs (NSAIDs) were the most commonly used drugs to treat acute gout. In the last decade the use of NSAIDs was stable, while in the last two decades, the use of colchicine was increasing. The use of allopurinol remained stable between 1999 and 2010 *(Figure 5)*.

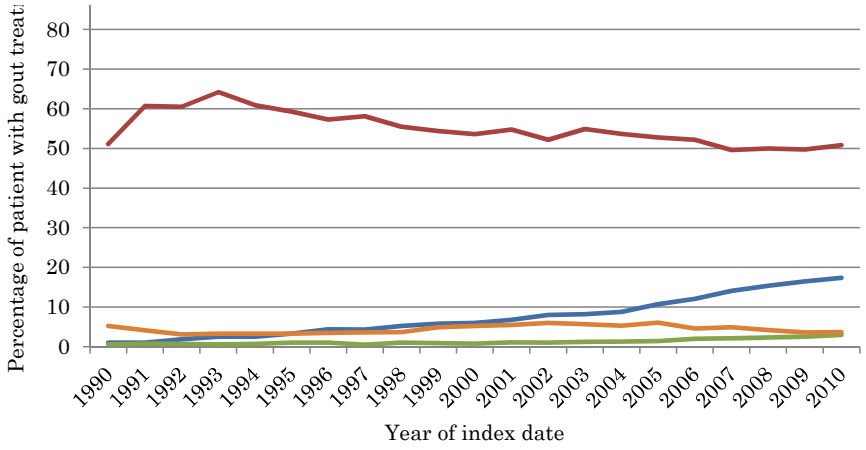


Figure 5 Treatment patterns of patients with incident gout between 1990−2010 (red: NSAIDs; blue: colchicine; green: corticosteroids; orange: allopurinol)

DISCUSSION

In this large population-based observational study from a UK primary care setting, the overall IR of general practitioner-diagnosed gout was 18.0 (95% CI 17.9−18.1) per 10,000 PYs. IR estimates were higher in men than in women, and gout tended to develop earlier in men. Since 1999, the IRs have slightly increased, with the highest IR in men in 2010 (39.0 [95% CI 37.8−40.2] per 10,000 PYs); this was consistent with previous published IRs from the UK (4, 10, 12). Gout presented the highest IRs in January (22.0 [95% CI 21.6−22.5] per 10,000 PYs) and June (21.7 [95% CI 21.2−22.1] per 10,000 PYs,). Furthermore, the highest IR within the UK for both sexes was found in Wales. From the cohort population 91,790 patients developed incident gout during follow-up, which resulted in a male to female ratio of 2.9:1, consistent with previous findings (4, 10, 12).

Alcohol consumption, comorbidities such as kidney failure, congestive heart failure, ischemic heart disease, and hypertension, as well as antihypertensive comedication (except losartan and calcium channel blockers), were associated with an increased risk for incident gout, consistent with previous findings (9, 28). Current smoking status and a history of diabetes mellitus were associated with a decreased risk of gout. Gout treatment patterns remained stable over time, except colchicine whose use slightly increased over time.

Cohort study

Gout prevalence within the UK has been reported to be 1.4% between 1999 and 2005 (4, 11), and has increased up to a prevalence of 2.5% in 2012 (12). Only few studies assessed the incidence of gout within the UK with an IR of 14.0 per 10,000 PYs in 1981 (15), 11.9 to 18.0 per 10,000 PYs in the period between 1990 and 1999 (4), 11.2 to 13.5 per 10,000 PYs between 1994 and 2007 (10), 26.8 per 10,000 PYs in the period between 2000 and 2007 (14), and 17.7 per 10,000 PYs in 2012 (12). The IR of this study with data derived between 1990 and 2010 was 18.0 per 10,000 PYs overall (29.0 per 10,000 PYs in men and 8.6 per 10,000 PYs in women) and is comparable to previously published data. In concordance with published findings we observed a rise in incidence especially between 2000 and 2010 (12).

Gout presented the highest IRs in January (22.0 [95% CI 21.6−22.5] per 10,000 PYs) and June (21.7 [95% CI 21.2−22.1] per 10,000 PYs). Consistent with our results, a previous study derived from England and Wales found the highest IR in the summer period (14). Furthermore, only one study derived from the CPRD reported regional differences for IRs (12). However, regional variations for gout within the UK have been noted previously (29, 30). Small aberrations of regional IRs may be explained by different lengths of follow-up in the study from Kuo and co-workers (12). A possible explanation for the reason in regional differences might be a difference in socioeconomic status, lifestyle, and nutrition (30, 31). In concordance, increasing prevalence of overweight and obesity (6), hypertension and cardiovascular diseases (6, 9), as well as diabetes (32) might be further possible explanations for regional differences.

Nested case-control study

The onset of gout in men was mostly between 45−64 years of age, and in women between 65-84 years of age, which is congruent with previous literature (4). We observed a male to female ratio of 2.9:1 which is similar to previous

published ratios (4, 10, 12). We detected a positive association for increasing BMI, for increasing alcohol units per week, and for increasing general practitioner visits within the last year prior to the index date and incident gout; these findings were consistent with a previously published study from the UK-based THIN database (10). We further observed a significantly decreased risk estimate for current smokers when compared with non-smokers.

This study yielded modestly increasing prevalence for colchicine use, while use of NSAIDs, corticosteroids, and allopurinol remained relatively unchanged, consistent with previous findings (10). According to previous studies, gout management is rather poor and treatment patterns differ between regions (4, 12). Even after the new treatment guidelines of the British Society for Rheumatology and British Health Professionals in Rheumatology (BSR/BHPR) in 2007 (17) and European League Against Rheumatism Recommendations (EULAR) in 2006 (16) treatment has not improved (12). There were some novel approaches and key advances during the past decade that will hopefully lead to improved management of hyperuricaemia and gout in the UK (3, 33).

Strengths and limitations

Our large population-based study has several strengths. We were in a position to study a large number of cases with incident gout in a well-established primary care database (21-25). We were able to address the role of and adjust our analyses for important potential confounders such as BMI, smoking status, alcohol consumption, renal failure, hypertension and concomitant drug therapies. Since information on diseases and drug exposure was prospectively entered in the CPRD in the absence of any study hypothesis, recall bias is not an issue. Lastly, exclusion of all patients with less than three years of recorded history in the database prior to the index date reduced the risk of including prevalent rather than incident gout cases.

Some limitations of our study have to be acknowledged. Misclassification

of some gout cases may occur, although a previous study has shown that gout diagnoses are recorded with high validity in the CPRD (27). To minimize misclassification, we excluded patients with recorded diagnoses of other rheumatic diagnoses around the index date, and we further excluded all patients with less than 3 years of recorded history in the database prior to the index date to reduce the risk of including prevalent rather than incident gout cases.

We were not able to adjust for all known potential risk factors for gout since, for example, dietary habits or physical activity (1, 6) are not routinely recorded in the CPRD. However, we adjusted for BMI, a factor that is related both to physical activity and dietary habits. We were unable to assess race/ethnicity because this information is also not consistently available in the CPRD. However, as 86% of individuals living in the UK are white (34), our results are most likely representative of that ethnic group. Finally, we could not address potential confounding by socioeconomic status, but we partially controlled for this parameter by matching cases and controls on general practitioner, since patients from the same neighbourhood tend to see the same general practitioner.

Conclusions

In summary, the incidence of gout in the UK has risen, especially between 1999 and 2010, and depends on season and region. The burden of gout remains substantial in the UK and further research should be done based on different patient populations such as patients with cardiovascular diseases or renal failure.

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Study 2

Use of Diuretics and Risk of Incident Gout: a Population-Based Case-Control Study

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Use of Diuretics and Risk of Incident Gout

A Population-Based Case–Control Study

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Objective. **Use of diuretics has been associated with an increased risk of gout. Data on different types of diuretics are scarce. We undertook this study to investigate the association between use of loop diuretics, thiazide or thiazide-like diuretics, and potassium-sparing agents and the risk of developing incident gout.**

Methods. **We conducted a retrospective population-based case–control analysis using the General Practice Research Database established in the UK. We identified case patients who were diagnosed as having incident gout between 1990 and 2010. One control patient was matched to each case patient for age, sex, general practice, calendar time, and years of active history in the database. We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs), and we adjusted for potential confounders.**

Results. **We identified 91,530 incident cases of gout and the same number of matched controls. Compared to past use of diuretics from each respective drug class, adjusted ORs for current use of loop diuretics, thiazide diuretics, thiazide-like diuretics, and potassium-sparing diuretics were 2.64 (95% CI 2.47–2.83), 1.70 (95% CI 1.62–1.79), 2.30 (95% CI 1.95–2.70), and 1.06 (95% CI 0.91–1.23), respectively. Combined use of loop diuretics and thiazide diuretics was associated with the highest relative risk estimates of gout (adjusted OR 4.65 [95% CI 3.51–6.16]). Current use of calcium channel blockers or losartan slightly attenuated the risk of gout in patients who took diuretics.**

Conclusion. **Use of loop diuretics, thiazide diuretics, and thiazide-like diuretics was associated with an increased risk of incident gout, although use of potassium-sparing agents was not.**

Gout is a painful, inflammatory, acute-onset arthritis, characterized by deposition of monosodium urate monohydrate crystals in affected joints (1,2). The disease is common in Western countries, with a reported prevalence of ~1.4% in the overall UK population (3,4). Gout predominantly affects men >40 years of age, and prevalence increases as individuals age (3). Other risk factors include obesity (5) and alcohol intake (6).

Most patients with gouty arthritis have hyperuricemia, which is considered an important risk factor (2,7). Hyperuricemia mainly results from decreased uric acid excretion or increased uric acid reabsorption in the kidneys. Diuretics, including loop diuretics, most thiazide diuretics, and potassium-sparing agents (such as spironolactone or eplerenone), have been linked to hyperuricemia via a presumed mechanism of decreased renal uric acid excretion or increased uric acid reabsorption (8–10). Volume contraction and direct effects on urate transporters in the proximal tubule have been proposed as potential explanations (10). Studies have demonstrated that hydrochlorothiazide increases urate absorption by inhibition of organic anion transporter 4 (11), and the reduction of urate secretion by multidrug resistance protein 4 (similar to furosemide) has also been seen (9). Since diuretics predispose individuals to

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Table 1. Demographic and clinical characteristics of the patients with gout and the age- and sex-matched control patients*

Variable	No. (%) of cases (n = 91,530)	No. (%) of controls (n = 91,530)	Crude OR for incident gout (95% CI)	*P*	Adjusted OR for incident gout (95% CI)	*P*
Sex						
Male	67,823 (74.1)	67,823 (74.1)	NA	NA	NA	NA
Female	23,707 (25.9)	23,707 (25.9)	NA	NA	NA	NA
Age group, years						
18–29	1,721 (1.9)	1,711 (1.9)	NA	NA	NA	NA
30–39	7,242 (7.9)	7,250 (7.9)	NA	NA	NA	NA
40–49	13,548 (14.8)	13,552 (14.8)	NA	NA	NA	NA
50–59	17,344 (19.0)	17,316 (18.9)	NA	NA	NA	NA
60–69	19,544 (21.4)	19,586 (21.4)	NA	NA	NA	NA
70–79	19,595 (21.4)	19,590 (21.4)	NA	NA	NA	NA
>79	12,536 (13.7)	12,525 (13.7)	NA	NA	NA	NA
BMI group, kg/m^2						
12.0–18.4	440 (0.5)	1,003 (1.1)	0.67 (0.60–0.76)	<0.001	0.76 (0.67–0.87)	<0.001
18.5–24.9	15,912 (17.4)	25,050 (27.4)	1 (referent)	NA	1 (referent)	NA
25.0–29.9	31,027 (33.9)	26,518 (29.0)	1.89 (1.84–1.94)	<0.001	1.72 (1.67–1.77)	<0.001
30.0–60.0	23,304 (25.5)	11,645 (12.7)	3.32 (3.22-3.43)	<0.001	2.73 (2.64–2.83)	<0.001
Unknown	20,847 (22.8)	27,314 (29.8)	1.09 (1.06-1.13)	<0.001	1.42 (1.37–1.48)	<0.001
Smoking status						
Nonsmoker	38,532 (42.1)	36,776 (40.2)	1 (referent)	NA	1 (referent)	NA
Current smoker	13,031 (14.2)	16,388 (17.9)	0.74 (0.72–0.77)	<0.001	0.76 (0.74–0.79)	<0.001
Former smoker	26,625 (29.1)	20,348 (22.2)	1.33 (1.30–1.36)	<0.001	1.10 (1.07–1.13)	<0.001
Unknown	13,342 (14.6)	18,018 (19.7)	0.62 (0.60–0.64)	<0.001	0.91 (0.87–0.95)	<0.001
Alcohol use, units/week†						
Never used	10,648 (11.6)	11,902 (13.0)	1 (referent)	NA	1 (referent)	NA
Current use						
Unknown	15,816 (17.3)	15,995 (17.5)	1.12 (1.08–1.16)	<0.001	1.17 (1.12–1.22)	<0.001
1–9	18,574 (20.3)	20,280 (22.2)	1.08 (1.04–1.12)	<0.001	1.16 (1.11–1.20)	<0.001
10–19	11,261 (12.3)	9,460 (10.3)	1.47 (1.41–1.53)	<0.001	1.63 (1.56–1.71)	<0.001
≥20	16,171 (17.7)	8,255 (9.0)	2.48 (2.38–2.58)	<0.001	2.83 (2.70–2.96)	<0.001
Unknown	19,060 (20.8)	25,638 (28.0)	0.79 (0.76–0.82)	<0.001	1.08 (1.02–1.13)	0.004
Comorbidities						
Hypertension	39,890 (43.6)	23,904 (26.1)	2.61 (2.55–2.67)	<0.001	2.05 (2.00–2.10)	<0.001
Diabetes mellitus	7,555 (8.3)	6,416 (7.0)	1.20 (1.16–1.25)	<0.001	0.72 (0.69–0.75)	<0.001
Dyslipidemia	13,798 (15.1)	9,064 (9.9)	1.72 (1.67–1.78)	<0.001	1.20 (1.15–1.24)	<0.001
Chronic kidney disease	14,328 (15.7)	7,490 (8.2)	4.03 (3.85–4.22)	<0.001	2.83 (2.69–2.98)	<0.001
CHF	8,038 (8.8)	2,503 (2.7)	3.93 (3.73–4.13)	<0.001	3.18 (3.01–3.36)	<0.001
Ischemic heart disease	16,584 (18.1)	10,487 (11.5)	1.84 (1.79–1.89)	<0.001	1.30 (1.26–1.34)	<0.001
Stroke/TIA	6,453 (7.1)	4,819 (5.3)	1.40 (1.34–1.45)	<0.001	1.10 (1.05–1.15)	<0.001

* Patients without evidence of gout served as controls. Controls were additionally matched for general practice, calendar time, and years of active history in the database. The odds ratios (ORs) were adjusted for the following variables: body mass index (BMI), smoking status, alcohol consumption, hypertension, chronic kidney disease, congestive heart failure (CHF), and ischemic heart disease. 95% CI = 95% confidence interval; NA = not applicable; TIA = transient ischemic attack.
† One unit is equivalent to 10 ml of pure ethanol (8 gm of ethanol).

hyperuricemia, use of these drugs has repeatedly been associated with an increased risk of gouty arthritis (5,10,12–21).

However, although most studies have demonstrated an increased risk of gouty arthritis among those who used diuretics, the magnitude of the observed risks varied considerably among studies. Most investigators studied diuretics as a class of drugs rather than as individual drugs (5,13,14,16–19,21–23), and in many studies, findings related to different types of diuretics were based on small numbers of exposed patients (n < 50) (12,15,20). In addition, no association of the disease with the duration of diuretic use has yet been reported. Finally, potential confounding factors, such as concomitant treatment with antihypertensive drugs, acetylsalicylic acid (ASA), cyclosporine, or pyrazinamide, as well as comorbid conditions, such as hypertension, chronic kidney disease, congestive heart failure (CHF), and diabetes mellitus (which all have been linked to an increased risk of gout [3,24]), have not routinely been controlled for in previous studies. We therefore conducted an observational study to investigate the association between use of different types of diuretics and the risk of developing incident gouty arthritis.

Table 2. Concomitant medications taken by the patients with gout and the matched control patients (current use)*

Concomitant medication	No. (%) of cases (n = 91,530)	No. (%) of controls (n = 91,530)	Crude OR for incident gout (95% CI)	*P*	Adjusted OR for incident gout (95% CI)	*P*
ACE inhibitor	19,121 (20.9)	9,759 (10.7)	1.04 (1.00–1.10)	0.073	1.14 (1.08–1.20)	<0.001
ARB (excluding losartan)	4,086 (4.5)	1,979 (2.2)	1.07 (0.95–1.21)	0.289	1.24 (1.07–1.42)	0.003
Losartan	1,429 (1.6)	896 (1.0)	0.74 (0.64–0.85)	<0.001	0.89 (0.76–1.04)	0.150
Beta-blockers	19,540 (21.4)	10,048 (11.0)	1.60 (1.54–1.67)	<0.001	1.66 (1.59–1.73)	<0.001
Calcium-channel blockers	13,290 (14.5)	9,425 (10.3)	0.76 (0.73–0.80)	<0.001	0.87 (0.83–0.92)	<0.001
Nitrates	7,641 (8.4)	4,381 (4.8)	1.29 (1.23–1.36)	<0.001	1.14 (1.08–1.21)	<0.001
Statins	17,142 (18.7)	11,502 (12.6)	1.09 (1.02–1.17)	0.010	0.95 (0.88–1.03)	0.228
Low-dose ASA	15,983 (17.5)	11,444 (12.5)	1.01 (0.97–1.06)	0.560	0.97 (0.92–1.03)	0.284
Pyrazinamide	22 (0.0)	20 (0.0)	0.88 (0.46–1.67)	0.693	0.94 (0.46–1.91)	0.855
Cyclosporine	263 (0.3)	39 (0.0)	1.56 (0.89–2.71)	0.120	1.56 (0.84–2.87)	0.157

* The odds ratios (ORs) were adjusted for the following variables: body mass index, smoking status, alcohol consumption, and use of potassium-sparing diuretics, thiazide diuretics, thiazide-like diuretics, loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium-channel blockers, and nitrates prior to the index date. 95% CI = 95% confidence interval; ARB = angiotensin II receptor blocker; ASA = acetylsalicylic acid.

PATIENTS AND METHODS

Data source. Data were derived from the General Practice Research Database, a large, UK-based primary care database that was established in 1987. It encompasses data on some 7 million patients registered with selected general practitioners (~7% of the UK population is represented in the database) (25–27). The individuals enrolled in the database are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate (3,28,29). General practitioners have been trained to record medical information for research purposes using standard software and coding systems. The General Practice Research Database holds anonymized information regarding demographics and patient characteristics, as well as lifestyle variables, such as body mass index (BMI), smoking status, and alcohol consumption, and information on symptoms, medical diagnoses, referrals to consultants, and hospitalizations. General practitioners generate drug prescriptions electronically using a coded drug dictionary; therefore, prescriptions include the name of the preparation, route of administration, dose of a single unit, and number of units prescribed. The database has been described in detail elsewhere (30,31) and has been validated extensively (26,32–35). Data from the General Practice Research Database have been used in numerous epidemiologic studies (27,30,31,36,37), including studies pertaining to gout (3,38,39). The Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research approved this study.

Study population. *Case patients.* Using READ codes (a standard clinical terminology system), we identified all patients who were ≥18 years of age and who had received a first-time diagnosis of gout between 1990 and 2010. For this study, the index date is the date at which the first diagnosis of gout was received.

Exclusion criteria. We excluded all patients with <3 years of recorded history in the database prior to the index date, as well as all patients with any recorded cancer diagnosis (except nonmelanoma skin cancer) or a human immunodeficiency virus infection prior to the index date. Additionally, we excluded all patients who were diagnosed as having hemochromatosis, osteoarthritis, septic arthritis, or rheumatoid arthritis within the 180 days that preceded the index date or within the 90 days that followed the index date. Similar case definitions of gout have been used and validated in previous studies based on General Practice Research Database data (3,38,39).

Control patients. From the base population, one control patient without any evidence of gout was matched at random to each gout case. Cases and controls were matched for calendar time (same index date), age (same year of birth), sex, general practice, and number of years of active history in the General Practice Research Database prior to the index date. We applied the same exclusion criteria to control patients as to case patients.

Definition and classification of diuretic use. We assessed the records of cases and controls to determine their use of different types of diuretics prior to the index date. We classified the diuretics into 4 groups according to World Health Organization (WHO) classification: loop diuretics, thiazide diuretics, thiazide-like diuretics, and potassium-sparing diuretics.

Exposed patients were classified as follows, based on the date the last prescription was issued: "current users" (last prescription issued 1–180 days prior to the index date), "past users" (last prescription issued >180 days prior to the index date), or "non-users" (no prescription issued prior to the index date). Most diuretics are available in packages of 90 tablets or more; therefore, we chose a cutoff date of 180 days prior to the index date to increase the likelihood of properly separating current users of diuretics from past users. Duration of exposure was classified as follows, based on the number of recorded prescriptions for the various types of diuretics prior to the index date: short-term duration of use (1–9 prescriptions), intermediate duration of use (10–19 prescriptions), or long-term duration of use (≥20 prescriptions).

Covariates and sensitivity analyses. For both cases and controls, we assessed whether arterial hypertension, chronic kidney disease, ischemic heart disease, CHF, transient ischemic attack (TIA)/stroke, diabetes mellitus, or dyslipidemia

Table 3. ORs for incident gout in association with current use of different types of diuretics*

Diuretics	No. (%) of cases (n = 91,530)	No. (%) of controls (n = 91,530)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Loop diuretics						
Never used	74,177 (81.0)	84,387 (92.2)	0.57 (0.54–0.60)	<0.001	0.75 (0.71–0.80)	<0.001
Current use (<180 days)						
Overall	13,487 (14.7)	4,136 (4.5)	2.63 (2.48–2.80)	<0.001	2.64 (2.47–2.83)	<0.001
1–9 prescriptions	2,652 (2.9)	1,104 (1.2)	1.81 (1.66–1.98)	<0.001	1.95 (1.77–2.15)	<0.001
10–19 prescriptions	2,330 (2.6)	780 (0.9)	2.36 (2.14–2.60)	<0.001	2.36 (2.12–2.62)	<0.001
≥20 prescriptions	8,505 (9.3)	2,252 (2.5)	3.18 (2.96–3.42)	<0.001	3.16 (2.93–3.42)	<0.001
Past use (>180 days)						
Overall	3,866 (4.2)	3,007 (3.3)	1 (referent)	NA	1 (referent)	NA
Thiazide diuretics						
Never used	68,835 (75.2)	78,335 (85.6)	0.49 (0.47–0.51)	<0.001	0.85 (0.81–0.88)	<0.001
Current use (<180 days)						
Overall	13,332 (14.6)	7,203 (7.9)	1.16 (1.11–1.22)	<0.001	1.70 (1.62–1.79)	<0.001
1–9 prescriptions	2,605 (2.9)	1,483 (1.6)	1.05 (0.97–1.13)	0.209	1.51 (1.39–1.64)	<0.001
10–19 prescriptions	2,463 (2.7)	1,297 (1.4)	1.15 (1.06–1.24)	<0.001	1.64 (1.51–1.79)	<0.001
≥20 prescriptions	8,264 (9.0)	4,423 (4.8)	1.21 (1.15–1.27)	<0.001	1.81 (1.71–1.92)	<0.001
Past use (>180 days)						
Overall	9,363 (10.2)	5,992 (6.6)	1 (referent)	NA	1 (referent)	NA
Thiazide-like diuretics						
Never used	89,258 (97.5)	90,376 (98.7)	0.59 (0.53–0.65)	<0.001	0.95 (0.85–1.07)	0.425
Current use (<180 days)						
Overall	1,260 (1.4)	537 (0.6)	1.45 (1.25–1.67)	<0.001	2.30 (1.95–2.70)	<0.001
1–9 prescriptions	314 (0.3)	130 (0.1)	1.47 (1.17–1.85)	<0.001	2.08 (2.61–2.70)	<0.001
10–19 prescriptions	270 (0.3)	101 (0.1)	1.64 (1.27–2.10)	<0.001	2.36 (1.79–3.12)	<0.001
≥20 prescriptions	676 (0.7)	306 (0.3)	1.37 (1.16–1.62)	<0.001	2.44 (2.01–2.97)	<0.001
Past use (>180 days)						
Overall	1,012 (1.1)	617 (0.7)	1 (referent)	NA	1 (referent)	NA
Potassium-sparing diuretics						
Never used	87,452 (95.5)	90,392 (98.8)	0.31 (0.28–0.34)	<0.001	0.62 (0.55–0.69)	<0.001
Current use (<180 days)						
Overall	2,372 (2.6)	572 (0.6)	1.37 (1.20–1.57)	<0.001	1.06 (0.91–1.23)	0.470
1–9 prescriptions	769 (0.8)	182 (0.2)	1.37 (1.14–1.66)	0.001	1.14 (0.92–1.40)	0.230
10–19 prescriptions	516 (0.6)	109 (0.1)	1.57 (1.25–1.98)	<0.001	1.21 (0.94–1.57)	0.141
≥20 prescriptions	1,087 (1.2)	281 (0.3)	1.29 (1.10–1.52)	0.002	0.96 (0.80–1.15)	0.623
Past use (>180 days)						
Overall	1,706 (1.9)	566 (0.6)	1 (referent)	NA	1 (referent)	NA

* The odds ratios (ORs) were adjusted for the following variables: body mass index, smoking status, alcohol consumption, and use of angiotensin-converting enzyme inhibitors, beta-blockers, calcium-channel blockers, and nitrates, as well as concomitant use of diuretic drugs of other classes prior to the index date. Loop diuretics included mainly furosemide and bumetanide, as well as torsemide. Thiazide diuretics included mainly bendroflumethiazide, as well as hydroflumethiazide, hydrochlorothiazide, chlorothiazide, polythiazide, cyclopenthiazide, and methyclothiazide. Thiazide-like diuretics included mainly indapamide and chlorthalidone, as well as metolazone, quinethazone, xipamide, mefruside, clorexolone, and clopamide. Potassium-sparing diuretics included mainly spironolactone and amiloride, as well as eplerenone and triamterene. 95% CI = 95% confidence interval; NA = not applicable.

had ever been recorded prior to the index date. Furthermore, we assessed the independent associations of antihypertensive drugs (beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], or calcium-channel blockers), organic nitrates, statins, pyrazinamide, cyclosporine, and low-dose ASA prior to the index date. Additionally, we classified cases and controls according to their smoking status (nonsmoker, current smoker, past smoker, or unknown), BMI (<25 kg/m^2, 25–29.9 kg/m^2, 30–59.9 kg/m^2, or unknown), alcohol consumption (never, current, past, or unknown), and alcohol use (1–9 units per week, 10–19 units per week, ≥20 units per week), and we assessed these covariates as potential confounders.

In a predefined sensitivity analysis, we restricted the analysis to cases and controls who had received only one type of diuretic or fixed combinations thereof. In addition, to further address potential bias by indication, we stratified our analyses by arterial hypertension, chronic kidney disease, and CHF. These comorbidities are all linked to an increased risk of gout and may be important confounders of the association of interest. Finally, we assessed the risk of gout in association with use of diuretics in the subset of cases (and their controls) who were treated with nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, or uricosuric/uricostatic drugs within 7, 30, and 90 days of the index date, respectively.

Statistical analysis. Conditional logistic regression analysis was performed using SAS statistical software (version 9.3; SAS Institute) to calculate relative risk estimates as odds ratios (ORs) with 95% confidence intervals (95% CIs). *P* values less than 0.05 (2-sided) were considered significant. In univariate

Table 4. ORs for incident gout in association with current use of combinations of diuretics of different drug classes*

Diuretics	No. (%) of cases (n = 91,530)	No. (%) of controls (n = 91,530)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
None	51,433 (56.2)	70,034 (76.5)	NA	NA	NA	NA
Loop diuretics						
Current use	4,303 (4.7)	1,644 (1.8)	3.29 (2.96–3.67)	<0.001	3.01 (2.69–3.37)	<0.001
Past use	1,070 (1.2)	1,216 (1.3)	1 (referent)	NA	1 (referent)	NA
Loop and thiazide diuretics						
Current use	469 (0.5)	103 (0.1)	5.03 (3.84–6.60)	<0.001	4.65 (3.51–6.16)	<0.001
Past use	352 (0.4)	382 (0.4)	1 (referent)	NA	1 (referent)	NA
Loop and thiazide-like diuretics						
Current use	34 (0.0)	9 (0.0)	4.59 (1.47–14.30)	0.009	3.66 (1.12–12.02)	0.032
Past use	12 (0.0)	14 (0.0)	1 (referent)	NA	1 (referent)	NA
Loop and potassium-sparing diuretics						
Current use	867 (1.0)	182 (0.2)	5.22 (3.49–7.80)	<0.001	4.53 (2.96–6.93)	<0.001
Past use	65 (0.1)	67 (0.1)	1 (referent)	NA	1 (referent)	NA
Thiazide diuretics						
Current use	9,732 (10.6)	5,605 (6.1)	1.91 (1.79–2.04)	<0.001	1.90 (1.77–2.04)	<0.001
Past use	2,851 (3.1)	3,029 (3.3)	1 (referent)	NA	1 (referent)	NA
Thiazide and potassium-sparing diuretics						
Current use	39 (0.0)	24 (0.0)	1.14 (0.46–2.78)	0.782	1.22 (0.48–3.06)	0.679
Past use	22 (0.0)	14 (0.0)	1 (referent)	NA	1 (referent)	NA
Thiazide-like diuretics						
Current use	567 (0.6)	282 (0.3)	2.09 (1.55–2.82)	<0.001	2.08 (1.53–2.85)	<0.001
Past use	139 (0.2)	131 (0.1)	1 (referent)	NA	1 (referent)	NA
Potassium-sparing diuretics						
Current use	61 (0.1)	48 (0.1)	1.39 (0.79–2.42)	0.252	1.13 (0.63–2.03)	0.674
Past use	57 (0.1)	61 (0.1)	1 (referent)	NA	1 (referent)	NA
Other combinations	19,457 (21.3)	8,685 (9.5)	NA	NA	NA	NA

* The odds ratios (ORs) were adjusted for the following variables: body mass index, smoking status, alcohol consumption, and use of angiotensin-converting enzyme inhibitors, beta-blockers, calcium-channel blockers, and nitrates prior to the index date. Loop diuretics included mainly furosemide and bumetanide, as well as torsemide. Thiazide diuretics included mainly bendroflumethiazide, as well as hydroflumethiazide, hydrochlorothiazide, chlorothiazide, polythiazide, cyclopenthiazide, and methyclothiazide. Thiazide-like diuretics included mainly indapamide and chlorthalidone, as well as metolazone, quinethazone, xipamide, mefruside, clorexolone, and clopamide. Potassium-sparing diuretics included mainly spironolactone and amiloride, as well as eplerenone and triamterene. 95% CI = 95% confidence interval; NA = not applicable.

analysis, we explored the association of arterial hypertension, chronic kidney disease, ischemic heart disease, CHF, TIA/stroke, diabetes mellitus, dyslipidemia, smoking status, BMI, alcohol consumption, as well as use of ACE inhibitors, beta-blockers, calcium-channel blockers, nitrates, pyrazinamide, cyclosporine, statins, and low-dose ASA, with the risk of gout. We tested the association of each of these potential confounders in multivariate analyses and included them in the final model if they altered the association of diuretic use with the risk of gout by >10%. To avoid overadjustment, we did not include arterial hypertension, chronic kidney disease, and CHF in the final model, since diuretics are routinely used to treat these medical conditions. However, we stratified our analyses by these important comorbidities.

RESULTS

The study population encompassed 91,530 patients with a first-time diagnosis of gout and 91,530 matched control patients. Of these, 25.9% were female, and 74.1% were male. The mean ± SD age at the index date was 69 ± 14.5 years in women and 59 ± 15.3 years in men. Time of active history in the database prior to the index date was 11.4 ± 5.3 years for cases and controls. Being overweight or obese was associated with an increased risk of gout, as was alcohol consumption (where the risk increased as alcohol use increased), while current smoking was associated with a decreased risk of gout.

Comorbidities such as arterial hypertension, dyslipidemia, chronic kidney disease, CHF, ischemic heart disease, and TIA/stroke were all associated with an increased risk of incident gout (Table 1). Analysis of treatment with most antihypertensive drugs, except losartan and calcium-channel blockers (which were both associated with decreased relative risks of gout), revealed increased gout risks. Cyclosporine therapy was also associated with an increased risk of gout, while neither low-dose ASA nor statin use was associated with an altered risk (Table 2).

Compared with past use of diuretics from the

Table 5. Risk of gout in association with the use of different types of diuretics, stratified by the presence or absence of chronic kidney disease*

	No. (%) of cases	No. (%) of controls	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Chronic kidney disease						
Loop diuretics						
Never used	6,707 (46.8)	5,064 (67.6)	0.84 (0.76–0.93)	<0.001	1.01 (0.91–1.13)	0.821
Current use (<180 days)						
Overall	6,313 (44.1)	1,506 (20.1)	3.01 (2.69–3.37)	<0.001	3.02 (2.67–3.40)	<0.001
1–9 prescriptions	870 (6.1)	277 (3.7)	2.08 (1.75–2.47)	<0.001	2.26 (1.88–2.72)	<0.001
10–19 prescriptions	955 (6.7)	236 (3.2)	2.83 (2.36–3.38)	<0.001	2.92 (2.41–3.53)	<0.001
≥20 prescriptions	4,488 (31.3)	993 (13.3)	3.35 (2.97–3.78)	<0.001	3.30 (2.90–3.76)	<0.001
Past use (>180 days)						
Overall	1,308 (9.1)	920 (12.3)	1 (referent)	NA	1 (referent)	NA
Thiazide diuretics						
Never used	7,105 (49.6)	4,003 (53.4)	0.51 (0.48–0.54)	<0.001	1.01 (0.93–1.09)	0.886
Current use (<180 days)						
Overall	3,616 (25.2)	1,746 (23.3)	1.16 (1.08–1.25)	<0.001	1.46 (1.33–1.61)	<0.001
1–9 prescriptions	418 (2.9)	196 (2.6)	0.89 (0.74–1.08)	0.236	1.50 (1.21–1.86)	<0.001
10–19 prescriptions	487 (3.4)	240 (3.2)	0.89 (0.75–1.06)	0.208	1.34 (1.10–1.62)	0.003
≥20 prescriptions	2,711 (18.9)	1,310 (17.5)	0.99 (0.90–1.08)	0.766	1.48 (1.34–1.65)	<0.001
Past use (>180 days)						
Overall	3,607 (25.2)	1,741 (23.2)	1 (referent)	NA	1 (referent)	NA
Thiazide-like diuretics						
Never used	13,493 (94.2)	7,126 (95.1)	0.83 (0.70–0.99)	0.042	1.15 (0.94–1.40)	0.168
Current use (<180 days)						
Overall	405 (2.8)	154 (2.1)	1.29 (0.99–1.67)	0.059	1.95 (1.45–2.61)	<0.001
1–9 prescriptions	94 (0.7)	38 (0.5)	1.25 (0.81–1.92)	0.317	1.52 (0.93–2.48)	0.092
10–19 prescriptions	72 (0.5)	31 (0.4)	1.00 (0.62–1.60)	0.983	1.38 (0.82–2.33)	0.223
≥20 prescriptions	239 (1.7)	85 (1.1)	1.42 (1.04–1.94)	0.029	2.40 (1.69–3.41)	<0.001
Past use (>180 days)						
Overall	430 (3.0)	210 (2.8)	1 (referent)	NA	1 (referent)	NA
Potassium-sparing diuretics						
Never used	12,240 (85.4)	7,087 (94.6)	0.36 (0.31–0.43)	<0.001	0.59 (0.49–0.71)	<0.001
Current use (<180 days)						
Overall	1,228 (8.6)	212 (2.8)	1.25 (1.00–1.56)	0.056	1.32 (1.04–1.68)	0.022
1–9 prescriptions	375 (2.6)	56 (0.7)	1.40 (1.00–1.95)	0.049	1.38 (0.97–1.97)	0.073
10–19 prescriptions	258 (1.8)	35 (0.5)	1.53 (1.02–2.29)	0.038	1.76 (1.15–2.69)	0.010
≥20 prescriptions	595 (4.2)	121 (1.6)	1.09 (0.84–1.41)	0.532	1.17 (0.88–1.55)	0.280
Past use (>180 days)						
Overall	860 (6.0)	191 (2.6)	1 (referent)	NA	1 (referent)	NA
No chronic kidney disease						
Loop diuretics						
Never used	67,470 (87.4)	79,323 (94.4)	0.55 (0.52–0.59)	<0.001	0.74 (0.69–0.79)	<0.001
Current use (<180 days)						
Overall	7,174 (9.3)	2,630 (3.1)	2.20 (2.03–2.38)	<0.001	2.15 (1.98–2.34)	<0.001
1–9 prescriptions	1,782 (2.3)	827 (1.0)	1.67 (1.50–1.85)	<0.001	1.77 (1.58–1.98)	<0.001
10–19 prescriptions	1,375 (1.8)	544 (0.6)	1.97 (1.75–2.22)	<0.001	1.84 (1.61–2.09)	<0.001
≥20 prescriptions	4,017 (5.2)	1,259 (1.5)	2.68 (2.44–2.93)	<0.001	2.57 (2.33–2.84)	<0.001
Past use (>180 days)						
Overall	2,558 (3.3)	2,087 (2.5)	1 (referent)	NA	1 (referent)	NA
Thiazide diuretics						
Never used	61,730 (80.0)	74,332 (88.4)	0.50 (0.48–0.53)	<0.001	0.82 (0.78–0.86)	<0.001
Current use (<180 days)						
Overall	9,716 (12.6)	5,457 (6.5)	1.28 (1.22–1.36)	<0.001	1.61 (1.52–1.71)	<0.001
1–9 prescriptions	2,187 (2.8)	1,287 (1.5)	1.12 (1.03–1.22)	0.006	1.42 (1.30–1.55)	<0.001
10–19 prescriptions	1,976 (2.6)	1,057 (1.3)	1.25 (1.15–1.37)	<0.001	1.57 (1.43–1.73)	<0.001
≥20 prescriptions	5,553 (7.2)	3,113 (3.7)	1.37 (1.29–1.46)	<0.001	1.72 (1.60–1.84)	<0.001
Past use (>180 days)						
Overall	5,756 (7.5)	4,251 (5.1)	1 (referent)	NA	1 (referent)	NA
Thiazide-like diuretics						
Never used	75,765 (98.1)	83,250 (99.1)	0.57 (0.50–0.65)	<0.001	0.93 (0.80–1.07)	0.318
Current use (<180 days)						
Overall	855 (1.1)	383 (0.5)	1.55 (1.29–1.86)	<0.001	2.09 (1.72–2.56)	<0.001
1–9 prescriptions	220 (0.3)	92 (0.1)	1.61 (1.22–2.14)	<0.001	2.01 (1.47–2.74)	<0.001
10–19 prescriptions	198 (0.3)	70 (0.1)	1.90 (1.40–2.59)	<0.001	2.25 (1.61–3.12)	<0.001
≥20 prescriptions	437 (0.6)	221 (0.3)	1.41 (1.14–1.74)	0.002	2.07 (1.64–2.62)	<0.001
Past use (>180 days)						
Overall	582 (0.8)	407 (0.5)	1 (referent)	NA	1 (referent)	NA

Table 5. *(Cont'd)*

	No. (%) of cases	No. (%) of controls	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Potassium-sparing diuretics						
Never used	75,212 (97.4)	83,305 (99.1)	0.37 (0.33–0.42)	<0.001	0.69 (0.60–0.79)	<0.001
Current use (<180 days)						
Overall	1,144 (1.5)	360 (0.4)	1.39 (1.17–1.66)	<0.001	1.26 (1.05–1.52)	0.015
1–9 prescriptions	394 (0.5)	126 (0.1)	1.38 (1.08–1.75)	0.010	1.29 (1.00–1.68)	0.053
10–19 prescriptions	258 (0.3)	74 (0.1)	1.52 (1.13–2.03)	0.005	1.25 (0.91–1.72)	0.162
≥20 prescriptions	492 (0.6)	160 (0.2)	1.35 (1.08–1.68)	0.008	1.24 (0.98–1.58)	0.074
Past use (>180 days)						
Overall	846 (1.1)	375 (0.4)	1 (referent)	NA	1 (referent)	NA

* For chronic kidney disease, 14,328 cases and 7,490 controls are represented. For no chronic kidney disease, 77,202 cases and 84,040 controls are represented. The odds ratios (ORs) were adjusted for the following variables: body mass index, smoking status, alcohol consumption, and use of angiotensin-converting enzyme inhibitors, beta-blockers, calcium-channel blockers, and nitrates, as well as the concomitant use of diuretic drugs of other classes prior to the index date. Loop diuretics included mainly furosemide and bumetanide, as well as torsemide. Thiazide diuretics included mainly bendroflumethiazide, as well as hydroflumethiazide, hydrochlorothiazide, chlorothiazide, polythiazide, cyclopenthiazide, and methylclothiazide. Thiazide-like diuretics included mainly indapamide and chlorthalidone, as well as metolazone, quinethazone, xipamide, mefruside, clorexolone, and clopamide. Potassium-sparing diuretics included mainly spironolactone and amiloride, as well as eplerenone and triamterene. 95% CI = 95% confidence interval; NA = not applicable.

respective diuretic drug classes, current use of loop diuretics (adjusted OR 2.64 [95% CI 2.47–2.83]), thiazide diuretics (adjusted OR 1.70 [95% CI 1.62–1.79]), and thiazide-like diuretics (adjusted OR 2.30 [95% CI 1.95–2.70]) was associated with increased risks of incident gout, although current use of potassium-sparing diuretics (adjusted OR 1.06 [95% 0.91–1.23]) was not. The risk increased in current users of loop diuretics as the duration of use increased (Table 3).

Concomitant treatment with losartan attenuated the ORs for gout in users of loop diuretics (adjusted OR 0.81 [95% CI 0.59–1.12]), thiazide diuretics (adjusted OR 0.76 [95% CI 0.56–1.02]), and thiazide-like diuretics (adjusted OR 0.85 [95% CI 0.39–1.86]), compared to past use of losartan and current use of the respective diuretic drugs. Similarly, concomitant treatment with calcium-channel blockers decreased relative risk estimates for gout in current users of loop diuretics (adjusted OR 0.64 [95% CI 0.57–0.72]) and thiazide diuretics (adjusted OR 0.82 [95% CI 0.74–0.91]) compared to past use of calcium-channel blockers and current use of the respective diuretic drugs, although the same was not true for thiazide-like diuretics (adjusted OR 1.31 [95% CI 0.95–1.80]).

In the sensitivity analysis of the mutually exclusive groups of different diuretic drug classes, current use of loop diuretics (adjusted OR 3.01 [95% CI 2.69–3.37]), combined use of loop diuretics and thiazide diuretics (adjusted OR 4.65 [95% CI 3.51–6.16]), and combined use of loop diuretics and potassium-sparing agents (adjusted OR 4.53 [95% CI 2.96–6.93]) yielded substantially increased relative risk estimates (Table 4). When the analysis was restricted to gout patients treated with NSAIDs, colchicine, uricosuric drugs, or uricostatic drugs, results did not materially differ from those of the main analysis (data not shown). Stratification by presence or absence of arterial hypertension did not alter results when compared to the results of the main analysis (data not shown). Stratification by presence or absence of chronic kidney disease also did not meaningfully alter the relative risk estimates (Table 5). Finally, when we stratified by presence or absence of CHF, relative risk estimates remained increased in users of loop diuretics and thiazide-like diuretics; however, among patients who used thiazide diuretics, the significant increase in gout risk overall was not observed in the subgroup with CHF (Table 6).

To investigate whether using different cutoff dates to define current diuretic drug use could impact our findings, we tested different cutoff dates (90 days and 180 days prior to the index date). No meaningful difference was observed, but since packages could last for >90 days, we used 180 days as the cutoff in all analyses to increase the likelihood of properly separating current from past use (data not shown).

DISCUSSION

Using the General Practice Research Database, we explored the risk of incident gout in association with the use of different diuretic drugs. Current use of loop diuretics was associated with a markedly increased risk of incident gout compared to past use. Use of thiazide and thiazide-like diuretics was also associated with a

Table 6. Risk of gout in association with the use of different types of diuretics, stratified by the presence or absence of congestive heart failure*

	No. (%) of cases	No. (%) of controls	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Congestive heart failure						
Loop diuretics						
Never used	1,237 (15.4)	714 (28.5)	0.96 (0.82–1.12)	0.581	1.20 (1.01–1.42)	0.036
Current use (<180 days)						
Overall	6,069 (75.5)	1,358 (54.3)	2.62 (2.28–3.01)	<0.001	2.53 (2.18–2.94)	<0.001
1–9 prescriptions	815 (10.1)	275 (11.0)	1.60 (1.33–1.94)	<0.001	1.77 (1.45–2.17)	<0.001
10–19 prescriptions	1,027 (12.8)	254 (10.1)	2.34 (1.94–2.84)	<0.001	2.26 (1.84–2.76)	<0.001
≥20 prescriptions	4,227 (52.6)	829 (33.1)	3.06 (2.64−3.55)	<0.001	2.90 (2.48–3.40)	<0.001
Past use (>180 days)						
Overall	732 (9.1)	431 (17.2)	1 (referent)	NA	1 (referent)	NA
Thiazide diuretics						
Never used	5,735 (71.3)	1,817 (72.6)	0.79 (0.70–0.89)	<0.001	1.01 (0.89–1.15)	0.898
Current use (<180 days)						
Overall	515 (6.4)	194 (7.8)	0.69 (0.57–0.85)	<0.001	0.86 (0.69–1.07)	0.169
1–9 prescriptions	161 (2.0)	60 (2.4)	0.68 (0.49–0.94)	0.019	0.94 (0.66–1.35)	0.750
10–19 prescriptions	98 (1.2)	33 (1.3)	0.71 (0.47–1.09)	0.121	0.72 (0.46–1.13)	0.149
≥20 prescriptions	256 (3.2)	101 (4.0)	0.70 (0.54–0.90)	0.007	0.86 (0.65–1.14)	0.308
Past use (>180 days)						
Overall	1,788 (22.2)	492 (19.7)	1 (referent)	NA	1 (referent)	NA
Thiazide-like diuretics						
Never used	7,823 (97.3)	2,451 (97.9)	0.84 (0.60–1.19)	0.322	1.20 (0.83–1.74)	0.333
Current use (<180 days)						
Overall	50 (0.6)	8 (0.3)	1.64 (0.71–3.77)	0.244	2.51 (1.04–6.06)	0.042
1–9 prescriptions	12 (0.1)	3 (0.1)	0.96 (0.25–3.62)	0.947	1.14 (0.28–4.69)	0.858
10–19 prescriptions	8 (0.1)	1 (0.0)	2.63 (0.31–22.72)	0.379	3.71 (0.42–32.82)	0.238
≥20 prescriptions	30 (0.4)	4 (0.2)	1.93 (0.64–5.86)	0.245	3.33 (1.02–10.87)	0.047
Past use (>180 days)						
Overall	165 (2.1)	44 (1.8)	1 (referent)	NA	1 (referent)	NA
Potassium-sparing diuretics						
Never used	5,725 (71.2)	2,102 (84.0)	0.53 (0.45–0.63)	<0.001	0.67 (0.56–0.81)	<0.001
Current use (<180 days)						
Overall	1,416 (17.6)	228 (9.1)	1.18 (0.94–1.47)	0.149	1.22 (0.96–1.53)	0.101
1–9 prescriptions	434 (5.4)	70 (2.8)	1.17 (0.86–1.58)	0.326	1.22 (0.88–1.69)	0.225
10–19 prescriptions	341 (4.2)	41 (1.6)	1.64 (1.13–2.37)	0.010	1.70 (1.15–2.51)	0.008
≥20 prescriptions	641 (8.0)	117 (4.7)	1.03 (0.79–1.33)	0.852	1.05 (0.79–1.38)	0.755
Past use (>180 days)						
Overall	897 (11.2)	173 (6.9)	1 (referent)	NA	1 (referent)	NA
No congestive heart failure						
Loop diuretics						
Never used	72,940 (87.4)	83,673 (94.0)	0.60 (0.56–0.63)	<0.001	0.81 (0.76–0.86)	<0.001
Current use (<180 days)						
Overall	7,418 (8.9)	2,778 (3.1)	2.30 (2.14–2.47)	<0.001	2.27 (2.10–2.45)	<0.001
1–9 prescriptions	1,837 (2.2)	829 (0.9)	1.80 (1.63–1.99)	<0.001	1.90 (1.70–2.12)	<0.001
10–19 prescriptions	1,303 (1.6)	526 (0.6)	2.07 (1.83–2.33)	<0.001	1.97 (1.73–2.24)	<0.001
≥20 prescriptions	4,278 (5.1)	1,423 (1.6)	2.71 (4.49–2.94)	<0.001	2.64 (2.41–2.89)	<0.001
Past use (>180 days)						
Overall	3,134 (3.8)	2,576 (2.9)	1 (referent)	NA	1 (referent)	NA
Thiazide diuretics						
Never used	63,100 (75.6)	76,518 (85.9)	0.49 (0.47–0.51)	<0.001	0.81 (0.78–0.85)	<0.001
Current use (<180 days)						
Overall	12,817 (15.4)	7,009 (7.9)	1.30 (1.24–1.36)	<0.001	1.63 (1.55–1.72)	<0.001
1–9 prescriptions	2,444 (2.9)	1,423 (1.6)	1.15 (1.07–1.24)	<0.001	1.45 (1.34–1.58)	<0.001
10–19 prescriptions	2,365 (2.8)	1,264 (1.4)	1.26 (1.17–1.37)	<0.001	1.58 (1.45–1.72)	<0.001
≥20 prescriptions	8,008 (9.6)	4,322 (4.9)	1.36 (1.29–1.44)	<0.001	1.71 (1.61–1.81)	<0.001
Past use (>180 days)						
Overall	7,575 (9.1)	5,500 (6.2)	1 (referent)	NA	1 (referent)	NA
Thiazide-like diuretics						
Never used	81,435 (97.5)	87,925 (98.8)	0.58 (0.52–0.65)	<0.001	0.95 (0.84–1.08)	0.428
Current use (<180 days)						
Overall	1,210 (1.4)	529 (0.6)	1.53 (1.32–1.78)	<0.001	2.06 (1.74–2.43)	<0.001
1–9 prescriptions	302 (0.4)	127 (0.1)	1.56 (1.23–1.98)	<0.001	1.88 (1.44–2.45)	<0.001
10–19 prescriptions	262 (0.3)	100 (0.1)	1.71 (1.32–2.21)	<0.001	2.01 (1.52–2.65)	<0.001
≥20 prescriptions	646 (0.8)	302 (0.3)	1.46 (1.22–1.74)	<0.001	2.16 (1.77–2.63)	<0.001
Past use (>180 days)						
Overall	847 (1.0)	573 (0.6)	1 (referent)	NA	1 (referent)	NA

Table 6. *(Cont'd)*

	No. (%) of cases	No. (%) of controls	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Potassium sparing diuretics						
Never used	81,727 (97.9)	88,290 (99.2)	0.42 (0.37–0.48)	<0.001	0.72 (0.63–0.83)	<0.001
Current use (<180 days)						
Overall	956 (1.1)	344 (0.4)	1.36 (1.14–1.62)	<0.001	1.27 (1.05–1.55)	0.014
1–9 prescriptions	335 (0.4)	112 (0.1)	1.40 (1.09–1.80)	0.008	1.26 (0.96–1.66)	0.095
10–19 prescriptions	175 (0.2)	68 (0.1)	1.23 (0.90–1.68)	0.185	1.11 (0.79–1.56)	0.552
≥20 prescriptions	446 (0.5)	164 (0.2)	1.38 (1.11–1.73)	0.005	1.36 (1.07–1.74)	0.013
Past use (>180 days)						
Overall	809 (1.0)	393 (0.4)	1 (referent)	NA	1 (referent)	NA

* For congestive heart failure, 8,038 cases and 2,503 controls are represented. For no congestive heart failure, 83,492 cases and 89,027 controls are represented. The odds ratios (ORs) were adjusted for the following variables: body mass index, smoking status, alcohol consumption, and use of angiotensin-converting enzyme inhibitors, beta-blockers, calcium-channel blockers, and nitrates, as well as the concomitant use of diuretic drugs of other classes prior to the index date. Loop diuretics included mainly furosemide and bumetanide, as well as torsemide. Thiazide diuretics included mainly bendroflumethiazide, as well as hydroflumethiazide, hydrochlorothiazide, chlorothiazide, polythiazide, cyclopenthiazide, and methylclothiazide. Thiazide-like diuretics included mainly indapamide and chlorthalidone, as well as metolazone, quinethazone, xipamide, mefruside, clorexolone, and clopamide. Potassium-sparing diuretics included mainly spironolactone and amiloride, as well as eplerenone and triamterene. 95% CI = 95% confidence interval; NA = not applicable.

significantly increased risk of developing incident gout, although use of potassium-sparing diuretics was not. These findings were further strengthened by the results obtained from the mutually exclusive model and from the analysis that was restricted to cases with recorded pharmacologic treatment of gout (results of which were similar to those found in the main model). Of interest, combined use of diuretics of different drug classes, namely, loop diuretics in combination with thiazide diuretics or potassium-sparing agents, further increased the relative risk estimates. Of note, the risk increase in association with different types of diuretics was most pronounced in individuals who used loop diuretics and was further increased by concomitant use of other diuretic drugs. This observation is consistent with the proposed mechanism of hypovolemia-induced increases in renal reabsorption of urate (8–10).

Our results did not materially differ when the analyses were stratified by the presence or absence of important indications for diuretic drug use, such as arterial hypertension or chronic kidney disease. However, in the analysis stratified by presence or absence of CHF, use of thiazide diuretics was no longer associated with an increased risk in patients with CHF. Taken together, these findings indicate that residual confounding by indication by arterial hypertension or chronic kidney disease does not seem to explain our findings. However, a recorded diagnosis of CHF must be considered as a confounder of the association between the risk of gout and the use of thiazides (but not other types of diuretics).

We observed a decreased relative risk estimate for gout in current users of losartan or calcium-channel blockers in combination with loop diuretics or thiazide diuretics. This observation may be of clinical importance for patients receiving diuretic therapy; treatment with losartan and/or calcium-channel blockers may be considered in patients with an increased risk of gout where appropriate.

To our knowledge, this large population-based study of >90,000 patients with incident gout is the first to assess the association of current versus past use of diuretics of different groups on the risk of gout. In a recent systematic review, Hueskes et al (10) reported on the results of 2 randomized controlled trials (12,13) and 12 population-based studies that explored the association between diuretics and gout. Randomized controlled trials that were based on small numbers of participants were limited to use of bendrofluazide (n = 30) (12) and the combination of hydrochlorothiazide/triamterene (n = 7) (13); a markedly increased risk of incident gout in patients treated with these drugs was seen. Of the 12 available population-based studies, only the study by Gurwitz et al (15) demonstrated the relative risks of developing gout among individuals who used diuretic drugs of a specific class (thiazide diuretics), while no other studies differentiated between the various types of diuretics. All but one study demonstrated an increased risk of gout in association with diuretic drug use, although relative risk estimates varied considerably (10). In the study by Janssens et al (22), which included 70 cases of incident gout, the reported incidence rate ratio of gout in association with use of diuretics was 0.6 (95% CI 0.2–2.0) after adjustment for cardiovascular comor-

bidities such as hypertension, CHF, and myocardial infarction. However, the number of participants in that study was small, the reported 95% CIs were wide, and results for specific diuretic drug classes were not reported.

Potential confounding is an important issue when exploring the risk of gout in association with use of diuretics, since these drugs are used to treat medical conditions (such as arterial hypertension, chronic kidney disease, and CHF) that have themselves been linked to an increased risk of gout (3,40). In addition, concomitant treatment with medications from other drug classes, such as antihypertensive drugs, has also been linked to an altered risk of developing gout, as seen in this study as well as in another (40). In our study, adjusting the analyses for potential confounders markedly attenuated relative risk estimates, but relative risk estimates remained significantly increased among current users of different types of diuretics. Furthermore, relative risk estimates were slightly increased among current users of loop diuretics as the number of prescriptions increased, and relative risk estimates remained increased in analyses stratified by presence or absence of arterial hypertension, CHF, or chronic kidney disease, with the exception of use of thiazide diuretics in cases and controls with recorded CHF. Taken together, these findings likely suggest that loop, thiazide, and thiazide-like diuretics play a role in the development of incident gout. However, the causality of such a relationship cannot be proven in an observational study.

In our study and in accordance with the findings of other studies, being overweight or obese (5,24), consuming alcohol (6,24), and having comorbidities, such as hypertension, chronic kidney disease, and CHF (3,40), were associated with an increased risk of incident gout. Use of ACE inhibitors and beta-blockers was associated with marginally increased risks of incident gout, while use of losartan and calcium-channel blockers was associated with slightly decreased risks. These findings were similar to the results reported by Choi et al in a recently published General Practice Research Database–based study (40).

Our large population-based study has several strengths. We studied a large number of cases with incident gout in a well-established validated primary care database (26,32–35). Furthermore, we studied different types of diuretics and the role of the duration of diuretic use, and we conducted various sensitivity analyses that yielded consistent findings. We further addressed the role of important potential confounders such as BMI, alcohol consumption, comorbidities, and/or concomitant drug therapy. Since information on diseases and drug exposure was prospectively entered in the General Practice Research Database in the absence of any study hypothesis, recall bias is not an issue. Lastly, exclusion of all patients with <3 years of recorded history in the database prior to the index date reduced the risk of including prevalent rather than incident gout cases.

Some limitations of our study have to be acknowledged. Misclassification of some gout cases may have occurred, although previous studies (based on a limited number of cases [i.e., 38]) have shown that gout diagnoses are recorded with high validity in the General Practice Research Database (38), and similar case definitions have been used in other studies (38,39). However, gout diagnoses are often made based on clinical presentation and are rarely confirmed in routine clinical practice by analysis of aspirated joint fluid for evidence of urate crystals. To minimize misclassification, we excluded subjects with differential diagnoses such as osteoarthritis, arthropathy due to hemochromatosis, septic arthritis, or rheumatoid arthritis that were recorded around the index date. Nevertheless, misclassification could, in theory, distort our findings toward the observed increased risk of gout among users of different diuretic drug classes through the introduction of a diagnostic bias (i.e., from a general practitioner who may be aware of an association between use of diuretics and gout). However, it is rather implausible that such a diagnostic bias accounts for the substantially increased relative risk estimates we observed. Furthermore, presence of such a bias would also be expected in individuals who used potassium-sparing agents.

Residual confounding by indication by chronic kidney disease and CHF, which are causally linked to development of hyperuricemia, cannot be excluded in the current study despite every effort to minimize such a bias. Of note, we decided not to include these comorbidities in the final model due to concerns regarding overadjustment (41). However, we adjusted for use of drugs indicated for treatment of these comorbidities, and we stratified our analyses by the most important comorbidities, namely, arterial hypertension, chronic kidney disease, and CHF. By including "past users" as the reference group, we intended to further minimize bias by indication.

We did not adjust for all potential risk factors for gout, since, for example, dietary habits or physical activities (2,5) are not routinely recorded in the General Practice Research Database. However, we adjusted for BMI, a factor that is related to physical activity and

dietary habits. We were unable to assess race/ethnicity because this information is also not consistently available in the General Practice Research Database. However, as 86% of individuals living in the UK are white (42), our results are most likely representative of that same demographic. Finally, we could not address potential confounding by socioeconomic status; however, we partially controlled for this potential confounder by matching cases and controls from the same general practice, since it is likely that patients from the same neighborhood see the same general practitioner. In summary, this large observational study provides evidence that current use of loop diuretics, thiazide diuretics, and thiazide-like diuretics is associated with a substantially increased risk of incident gout.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Meier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bruderer, Bodmer, Meier.
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Study 3

Poorly Controlled Type 2 Diabetes Mellitus is Associated with a Decreased Risk of Incident Gout: a Population-Based Case-Control Study

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EXTENDED REPORT

Poorly controlled type 2 diabetes mellitus is associated with a decreased risk of incident gout: a population-based case-control study

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ABSTRACT

Objective The aim of this study was to explore the risk of incident gout in patients with type 2 diabetes mellitus (T2DM) in association with diabetes duration, diabetes severity and antidiabetic drug treatment.

Methods We conducted a case-control study in patients with T2DM using the UK-based Clinical Practice Research Datalink (CPRD). We identified case patients aged ≥18 years with an incident diagnosis of gout between 1990 and 2012. We matched to each case patient one gout-free control patient. We used conditional logistic regression analysis to calculate adjusted ORs (adj. ORs) with 95% CIs and adjusted our analyses for important potential confounders.

Results The study encompassed 7536 T2DM cases with a first-time diagnosis of gout. Compared to a diabetes duration <1 year, prolonged diabetes duration (1–3, 3–6, 7–9 and ≥10 years) was associated with decreased adj. ORs of 0.91 (95% CI 0.79 to 1.04), 0.76 (95% CI 0.67 to 0.86), 0.70 (95% CI 0.61 to 0.86), and 0.58 (95% CI 0.51 to 0.66), respectively. Compared to a reference A1C level of <7%, the risk estimates of increasing A1C levels (7.0–7.9, 8.0–8.9 and ≥9%) steadily decreased with adj. ORs of 0.79 (95% CI 0.72 to 0.86), 0.63 (95% CI 0.55 to 0.72), and 0.46 (95% CI 0.40 to 0.53), respectively. Neither use of insulin, metformin, nor sulfonylureas was associated with an altered risk of incident gout.

Conclusions Increased A1C levels, but not use of antidiabetic drugs, was associated with a decreased risk of incident gout among patients with T2DM.

INTRODUCTION

Gout is a common painful inflammatory arthritis with acute onset, characterised by deposition of monosodium urate crystals in affected joints.[1 2] The reported prevalence in the UK is about 1.4%.[3] Increasing age and male gender,[3] obesity,[4] alcohol intake,[5] and hyperuricaemia[1 6] are the most important risk factors for gout. Congestive heart failure (CHF), chronic kidney disease (CKD), arterial hypertension and various drug treatments, such as different types of diuretics, are also associated with a markedly increased risk of gouty arthritis.[7] Diabetes mellitus is a comorbid condition to CHF, CKD and arterial hypertension, which has also been associated with an increased risk of gout in several studies.[3 8–11] However, confounding by these comorbidities and concomitant drug treatments was not routinely controlled in these studies[3 8–11] which were mostly based on a limited number of patients.[8–11] Of note, a recent observational study from the UK found a decreased gout risk in individuals with diagnosed type 2 diabetes mellitus (T2DM) as compared to diabetes-free subjects.[12] Relative risk estimates decreased with increasing diabetes duration and were lower in treated than in untreated patients with diabetes mellitus.[12] It could not be determined from the information provided whether the observed risks were further modified by certain antidiabetic treatments or by diabetes disease severity.[12] We therefore conducted an observational study in patients with T2DM to explore the association between diabetes duration, diabetes severity and use of different types of antidiabetic drugs and the risk of developing incident gout in T2DM patients.

PATIENTS AND METHODS

Data source

The data were derived from the UK-based Clinical Practice Research Datalink (CPRD) which was established around 1987 and encompasses data from 450 general practices, representative of the UK population.[13 14] The individuals enrolled in the database are representative of the UK population with regard to age, sex, geographic distribution and annual turnover rate.[3 15 16] General practitioners have been trained to record medical information for research purposes using standard software and coding systems. The CPRD holds information regarding patient demographics and characteristics, lifestyle variables, such as Body Mass Index (BMI), smoking status, and alcohol consumption, symptoms, medical diagnoses, referrals to consultants and hospitalisations. The general practitioner generates drug prescriptions directly with the computer using a coded drug dictionary. The database has been described in detail elsewhere[17 18] and has been validated extensively.[13 19–22] The CPRD has been the source of numerous epidemiological studies published in peer-reviewed journals, including pharmacoepidemiological studies on gout using similar case definitions.[3 7 23 24] Gout diagnoses are recorded with high validity in the CPRD.[24] The Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare products Regulatory Agency (MHRA) database research approved the study.

Study population

Case patients

Using READ codes, we identified all patients aged 18 years or older with a first-time diagnosis of gout

between 1 January 1990 and end June 2012 and with an antecedent history of T2DM based on READ codes; we refer to the date of the first gout diagnosis as the 'index date'.

Exclusion criteria

We excluded all cases with less than 3 years of recorded history in the database prior to the index date, and all patients with any recorded diagnosis of type 1 diabetes mellitus, cancer (except non-melanoma skin cancer), or a HIV infection. Additionally, to minimise the risk of misclassification of cases with incident gout, we excluded all patients with other conditions associated with joint inflammation, such as haemochromatosis, osteoarthritis, septic arthritis, or rheumatoid arthritis within 180 days preceding the index date, or within 90 days after the index date. Similar case definitions of gout have been used or validated in previous studies based on CPRD data.[3 7 23 24]

Control patients

From the base population of patients with a history of T2DM, we identified at random one control patient with no evidence of gout, per case patient. Control patients were matched to cases on age (same year of birth), sex, BMI (max ±2.0 kg/m^2), calendar time (same index date), general practice and number of years of active history in the CPRD prior to the index date. We applied the same exclusion criteria to control patients as to case patients.

Exposure

The exposures of interest in this study were diabetes severity, duration and treatment. Diabetes severity was classified according to A1C levels recorded within 365 days prior to the index date (no A1C-level recorded, <7%, 7.0–7.9%, 8.0–8.9%, ≥9.0%). We defined diabetes duration as the time interval between the date of the first recorded diagnosis of T2DM and the index date by counting the number of days (<1, 1–3, 3–7, 7–10, >10 years). We assessed the use of different types of antidiabetic drugs based on prescriptions in the computer records. Cases and controls were classified as current users if their last prescription was within 180 days prior to the index date; or as past users if their last prescription was more than 180 days prior to the index date. We also classified them into the following groups: insulin users, metformin users, and sulfonylureas users. Due to the low number of users of other antidiabetic drugs, we did not assess their use separately. The duration of antidiabetic drug exposure was classified based on the number of recorded prescriptions for these drugs prior to the index date into 1–19 prescriptions, 20–39 prescriptions, 40–59 prescriptions, or ≥60 prescriptions.

Covariates

We classified demographics and lifestyle factors, such as smoking status (non-smoker, current, past or unknown), alcohol consumption (never, current (1–9 units per week; 10–19 units per week; ≥20 units per week, unknown), past, unknown), and number of general practitioner visits ever (0–19, 20–39, ≥40) prior to the index date in cases and controls, and assessed these covariates as potential confounders. We further assessed for cases and controls whether they had arterial hypertension, CKD, CHF, ischaemic heart disease (IHD), transient ischaemic attack/stroke, dyslipidemia, or diabetes-related complications, such as diabetic nephropathy, diabetic neuropathy, or diabetic angiopathy at any time prior to the index date.

Furthermore, we assessed the independent effects of current (last prescription within 180 days prior to the index date) use of certain drugs of interest such as diuretics (loop, thiazide and thiazide-like, or potassium-sparing diuretics), β-blockers, ACE inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), organic nitrates, statins and low-dose acetylsalicylic acid (ASA) prior to the index date, and we assessed these covariates as potential confounders.

Sensitivity analyses

In a predefined sensitivity analysis, we additionally matched cases and controls on diabetes duration (±1 year) to ensure that cases and controls had an equal length of diabetes history and, therefore, equal exposure opportunity. To further address the impact of this potential exposure time-related bias on our results, we assessed diabetes duration across different exposure duration strata for all antidiabetic drugs under study. In another sensitivity analysis we assessed the risk of gout in association with A1C level stratified by diabetes duration to explore whether increasing A1C levels, irrespective of diabetes duration, were associated with an altered risk of gout. To assess whether diabetes duration or A1C levels are potential mediators of the association between antidiabetic drug use and the risk of gout, we additionally matched on diabetes duration and A1C (±1%). In another sensitivity analysis we only included patients with incident diabetes mellitus and incident antidiabetic drug use to address potential prevalent user bias. Finally, we restricted our analyses to cases and their matched controls who were treated with either non-steroidal anti-inflammatory drugs (NSAIDS), colchicine, or uricosuric or uricostatic drugs within 7, 30 and 90 days after the index date, respectively, to decrease the risk of possible outcome misclassification.

Statistical analysis

We conducted conditional logistic regression analyses using SAS statistical software V.9.3 (SAS Institute, Cary, North Carolina, USA) to calculate relative risk estimates as ORs with 95% CIs. We performed a χ^2 test for trend ($p<0.05$) for diabetes duration and A1C levels. We explored the association between potential risk factors and the risk for gout in univariate analyses. We tested the effects of each of these potential confounders in multivariate analyses and included them in the final model if they altered the effect of antidiabetic drug use on the risk of gout by more than 10%. We a priori decided to adjust the analysis of antidiabetic drug use for smoking status, alcohol consumption, and number of general practitioner visits.

RESULTS

There were 7536 cases of incident gout in the T2DM study population, matched to 7536 diabetic, but gout-free controls. Of these, 62.5% were male, and the mean age (±SD) was 69.9 ±11.0 years. Alcohol consumption was associated with an increased risk of gout, while current smoking was associated with a decreased risk. Comorbidities, such as arterial hypertension, CKD, CHF and IHD were all associated with an increased risk of incident gout. The characteristics of cases and controls are displayed in table 1.

Current use of most antihypertensive drugs except CCBs, which was associated with a decreased adj. OR of 0.87 (95% CI 0.80 to 0.95), yielded increased relative risk estimates for incident gout (table 2).

The adjusted ORs for gouty arthritis in association with duration of T2DM of <1 (reference), 1–3, 3–7, 7–10 or >10 years were 0.91 (95% CI 0.79 to 1.04), 0.76 (95% CI 0.67 to 0.86), 0.70 (95% CI 0.61 to 0.81), and 0.58 (95% CI 0.51 to 0.66), respectively. Compared to a reference A1C level of <7%, the

Table 1 Multivariable effects of various patient characteristics on the risk of gout in T2DM patients and matched controls

Variable	Number of cases (%) (n=7536)	Number of controls (%) (n=7536)	OR crude (95% CI)	OR adj.* (95% CI)
Sex†				
Male	4712 (62.5)	4712 (62.5)	NA	NA
Female	2824 (37.5)	2824 (37.5)	NA	NA
Age group (years)†				
30–39	61 (0.8)	51 (0.7)	NA	NA
40–49	311 (4.1)	313 (4.2)	NA	NA
50–59	947 (12.6)	944 (12.5)	NA	NA
60–69	2027 (26.9)	2057 (27.3)	NA	NA
70–79	2684 (35.6)	2712 (36.0)	NA	NA
≥80	1506 (20.0)	1459 (19.4)	NA	NA
BMI group (kg/m^2)†				
12.0–18.4	17 (0.2)	26 (0.4)	NA	NA
18.5–24.9	914 (12.1)	1043 (13.8)	NA	NA
25.0–29.9	2651 (35.2)	2731 (36.2)	NA	NA
30.0–60.0	3954 (52.5)	3736 (49.6)	NA	NA
Smoking status				
Non-smoker	2747 (36.5)	3009 (39.9)	1 (reference)	1 (reference)
Current smoker	758 (10.1)	987 (13.1)	0.84 (0.75 to 0.94)	0.82 (0.72 to 0.92)
Ex-smoker	3912 (51.9)	3448 (45.8)	1.29 (1.19 to 1.38)	1.17 (1.08 to 1.27)
Unknown	119 (1.6)	92 (1.2)	1.40 (1.06 to 1.86)	1.57 (1.13 to 2.18)
Alcohol consumption (units/week)‡				
Never/ex	1845 (24.5)	2021 (26.8)	1 (reference)	1 (reference)
Current unknown	1939 (25.7)	2061 (27.4)	1.04 (0.95 to 1.14)	1.06 (0.96 to 1.17)
Current 1–9	1821 (24.2)	1833 (24.3)	1.12 (1.02 to 1.23)	1.14 (1.02 to 1.26)
Current 10–19	736 (9.8)	612 (8.1)	1.40 (1.23 to 1.59)	1.56 (1.35 to 1.79)
Current ≥20	790 (10.5)	541 (7.2)	1.72 (1.50 to 1.97)	1.94 (1.68 to 2.25)
Unknown	405 (5.4)	468 (6.2)	0.95 (0.81 to 1.11)	1.01 (0.84 to 1.21)
General practitioner visits				
0–19	435 (5.8)	443 (5.9)	1 (reference)	1 (reference)
20–39	697 (9.3)	843 (11.2)	0.85 (0.72 to 1.01)	0.73 (0.61 to 0.88)
≥40	6404 (85.0)	6250 (82.9)	1.12 (0.96 to 1.31)	0.78 (0.66 to 0.93)
Comorbidities				
Diabetic angiopathy	23 (0.3)	17 (0.2)	1.35 (0.72 to 2.53)	1.31 (0.64 to 2.70)
Diabetic nephropathy	425 (5.6)	334 (4.4)	1.30 (1.12 to 1.52)	1.07 (0.90 to 1.26)
Diabetic neuropathy	249 (3.3)	259 (3.4)	0.96 (0.80 to 1.15)	0.85 (0.70 to 1.03)
Hypertension	5658 (75.1)	4971 (66.0)	1.63 (1.51 to 1.76)	1.58 (1.46 to 1.72)
Dyslipidemia	2569 (34.1)	2282 (30.3)	1.21 (1.12 to 1.30)	1.06 (0.98 to 1.15)
Chronic kidney disease	3176 (42.1)	2234 (29.6)	2.78 (2.52 to 3.07)	2.36 (2.12 to 2.62)
Congestive heart failure	1478 (19.6)	493 (6.5)	3.62 (3.23 to 4.06)	3.04 (2.69 to 3.43)
Ischaemic heart disease	2798 (37.1)	1945 (25.8)	1.73 (1.61 to 1.86)	1.38 (1.27 to 1.50)
Stroke/TIA	1015 (13.5)	799 (10.6)	1.33 (1.20 to 1.47)	1.13 (1.01 to 1.26)

*Adjusted for: smoking status, alcohol consumption, general practitioner visits, hypertension, dyslipidemia, chronic kidney disease, congestive heart failure, ischaemic heart disease, stroke/TIA.
†Matching variables age, sex, BMI, general practice, history in the database and index date.
‡1U (Unit)=10 mL of pure ethanol (8 g of ethanol).
BMI, Body Mass Index; NA: not applicable; TIA, transient ischaemic attack; T2DM, type 2 diabetes mellitus.

risk estimates of increasing A1C levels (7.0–7.9, 8.0–8.9 and ≥9%) steadily decreased with adj. ORs of 0.79 (95% CI 0.72 to 0.86), 0.63 (95% CI 0.55 to 0.72) and 0.46 (95% CI 0.40 to 0.53), respectively (table 3). Tests for trend were statistically significant for prolonged diabetes duration and increasing A1C levels. In the analysis where we stratified the A1C by diabetes duration, increasing A1C levels were associated with a decreasing relative risk estimate of gout irrespective of diabetes duration (table 4).

Compared to non-use, current use of insulin, metformin and sulfonylureas was associated with a decreased risk of developing gout in the main analysis; however, we did not observe a consistent duration effect (table 5). In this analysis, diabetes duration was closely similar (<3% difference) in cases and controls among corresponding exposure duration for all antidiabetic drugs studied (data not shown). In the sensitivity analysis where we additionally matched on diabetes duration, relative risk estimates were closely similar to the findings of the main analysis (table 6). Finally, when we additionally matched our analyses on A1C level, we did not observe decreased relative risk estimates for use of any antidiabetic drugs (table 6).

In the sensitivity analyses in which we included patients with incident diabetes mellitus and incident antidiabetic drug use only and in which we restricted the population to gout patients

Table 2 ORs (current use vs non-use) for co-medications in relation to the risk of gout

Co-medication	Number of cases (%) (n=7536)	Number of controls (%) (n=7536)	OR crude (95% CI)	OR adj.* (95% CI)
ACE-Is	3946 (52.4)	3303 (43.8)	1.81 (1.68 to 1.96)	1.35 (1.24 to 1.48)
ARBs (excl. losartan)	1027 (13.6)	757 (10.1)	1.50 (1.35 to 1.66)	1.26 (1.12 to 1.41)
Losartan	353 (4.7)	292 (3.9)	1.25 (1.07 to 1.47)	1.06 (0.68 to 1.63)
Loop diuretics	2742 (36.4)	1103 (14.6)	3.81 (3.48 to 4.17)	3.07 (2.77 to 3.41)
Thiazide diuretics	1815 (24.1)	1445 (19.2)	1.51 (1.38 to 1.64)	1.74 (1.58 to 1.92)
Potassium sparing diuretics	584 (7.8)	163 (2.2)	3.97 (3.31 to 4.76)	2.34 (1.92 to 2.84)
β-blockers	2776 (36.8)	1984 (26.3)	1.86 (1.72 to 2.01)	1.51 (1.38 to 1.65)
Calcium channel blockers	2295 (30.5)	2371 (31.5)	1.16 (1.07 to 1.25)	0.87 (0.80 to 0.95)
Nitrates	1364 (18.1)	893 (11.9)	1.79 (1.63 to 1.98)	1.26 (1.12 to 1.41)
Statins	4679 (62.1)	4449 (59.0)	1.30 (1.19 to 1.41)	1.02 (0.92 to 1.12)
ASA low-dose	3370 (44.7)	3218 (42.7)	1.21 (1.12 to 1.30)	0.95 (0.87 to 1.04)

*Adjusted for: smoking status, alcohol consumption, general practitioner visits, ACE-Is, ARBs excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, β-blockers, calcium channel blockers, nitrates, statins, low dose ASA.
ACE-Is, ACE inhibitors; ARBs, angiotensin receptor blockers; ASA, acetylsalicylic acid.

treated with NSAIDs, colchicine, uricosuric or uricostatic drugs, results did not materially differ from the main analysis (data not shown).

DISCUSSION

In this large observational study using the UK-based CPRD, we found a markedly decreased risk of incident gout among patients with increasing levels of A1C compared to patients with an A1C level <7%. The risk of gout was also decreased in association with increasing diabetes duration, a finding which is consistent with reported results of a recent population-based study in UK patients using the health improvement network database (THIN).[12] Of interest, when we assessed the risk of gout in association with different A1C levels stratified by diabetes duration, increasing A1C levels irrespective of diabetes duration were associated with a decreased risk of gout. We are not aware of another observational study exploring the association between A1C as the surrogate marker for disease severity of T2DM and the risk of incident gout. Of note, Choi and Ford,[25] using the US Third National Health and Nutrition Examination Survey (1988–1994), explored the association between A1C levels and serum uric acid levels, an important risk factor for gouty arthritis. Interestingly, they found that subjects with an A1C level of 6.0–6.9% had increased serum uric acid levels compared to patients with lower A1C levels. However, in patients with diagnosed diabetes mellitus and/or markedly increased A1C levels, they reported substantially decreased uric acid levels. The authors finally concluded that individuals with diabetes mellitus and markedly elevated A1C levels may be at a lower risk of hyperuricaemia and gout.[25] Possible mechanistic explanations for this observed association include an uricosuric effect of glycosuria [25–27] or an impaired inflammatory response in patients with severe and long-lasting diabetes mellitus.[1] By contrast with our findings, and arguing against the proposed mechanisms discussed above, several small observational studies suggested an increased risk of gout in patients with T2DM.[8–11] Two studies from Taiwan [9 10] explored the association between gout and manifestations of the metabolic syndrome[9] and trends in the manifestation of gout[10] using a hospital-derived database. They found an increased risk of

Table 3 ORs for A1C levels and diabetes duration in relation to the risk of gout

Variable	Number of cases (%) (n=7536)	Number of controls (%) (n=7536)	OR crude (95% CI)	OR adj.* (95% CI)
Diabetes duration (years)				
<1	909 (12.1)	721 (9.6)	1 (reference)	1 (reference)
1–3	1515 (20.1)	1334 (17.7)	0.90 (0.79 to 1.02)	0.91 (0.79 to 1.04)
3–7	2281 (30.3)	2289 (30.4)	0.78 (0.70 to 0.88)	0.76 (0.67 to 0.86)
7–10	1095 (14.5)	1166 (15.5)	0.73 (0.65 to 0.84)	0.70 (0.61 to 0.81)
>10	1736 (23.0)	2026 (26.9)	0.67 (0.59 to 0.75)	0.58 (0.51 to 0.66)
A1C level†				
Unknown	798 (10.6)	718 (9.5)	0.97 (0.85 to 1.12)	1.01 (0.87 to 1.18)
<7%	3730 (49.5)	3186 (42.3)	1 (reference)	1 (reference)
7.0–7.9%	1858 (24.7)	1989 (26.4)	0.79 (0.74 to 0.86)	0.79 (0.72 to 0.86)
8.0–8.9%	636 (8.4)	795 (10.6)	0.67 (0.60 to 0.76)	0.63 (0.55 to 0.72)
≥9%	514 (6.8)	848 (11.3)	0.50 (0.45 to 0.57)	0.46 (0.40 to 0.53)

χ^2 test for trend ($p<0.05$) was statistically significant for diabetes duration and A1C level.
*Adjusted for: smoking status, alcohol consumption, general practitioner visits, hypertension, dyslipidemia, chronic kidney disease, congestive heart failure, ischaemic heart disease, stroke/TIA.
†A1C-level if a value was recorded within 1 year prior to the index date.
TIA, transient ischaemic attack.

Table 4 Risk of gout in association with A1C stratified by diabetes duration

Variable	Number of cases n=7536 (%)	Number of controls n=7536 (%)	OR crude (95% CI)	OR adj.* (95% CI)
<1 year				
Unknown	228 (3.0)	154 (2.0)	1.11 (0.86 to 1.44)	1.02 (0.77 to 1.35)
<7%	428 (5.7)	324 (4.3)	1 (reference)	1 (reference)
7.0–7.9%	163 (2.2)	131 (1.7)	0.95 (0.73 to 1.25)	1.06 (0.79 to 1.43)
8.0–8.9%	40 (0.5)	45 (0.6)	0.67 (0.42 to 1.05)	0.71 (0.44 to 1.17)
≥9%	50 (0.7)	67 (0.9)	0.57 (0.38 to 0.84)	0.65 (0.42 to 1.00)
1–3 years				
Unknown	155 (2.1)	136 (1.8)	0.92 (0.70 to 1.20)	0.92 (0.69 to 1.24)
<7%	905 (12.0)	715 (9.5)	1 (reference)	1 (reference)
7.0–7.9%	338 (4.5)	310 (4.1)	0.85 (0.71 to 1.02)	0.86 (0.70 to 1.05)
8.0–8.9%	67 (0.9)	94 (1.3)	0.54 (0.39 to 0.76)	0.51 (0.35 to 0.73)
≥9%	50 (0.7)	79 (1.1)	0.48 (0.33 to 0.70)	0.55 (0.37 to 0.83)
3–7 years				
Unknown	196 (2.6)	186 (2.5)	0.93 (0.73 to 1.20)	1.01 (0.77 to 1.33)
<7%	1206 (16.0)	1062 (14.1)	1 (reference)	1 (reference)
7.0–7.9%	607 (8.1)	608 (8.1)	0.88 (0.77 to 1.02)	0.97 (0.83 to 1.13)
8.0–8.9%	149 (2.0)	219 (2.9)	0.59 (0.47 to 0.74)	0.66 (0.52 to 0.85)
≥9%	123 (1.6)	214 (2.8)	0.49 (0.39 to 0.63)	0.53 (0.40 to 0.69)
7–10 years				
Unknown	76 (1.0)	78 (1.0)	0.85 (0.60 to 1.21)	0.87 (0.59 to 1.29)
<7%	528 (7.0)	465 (6.2)	1 (reference)	1 (reference)
7.0–7.9%	277 (3.7)	331 (4.4)	0.73 (0.60 to 0.90)	0.78 (0.62 to 0.98)
8.0–8.9%	133 (1.8)	142 (1.9)	0.80 (0.61 to 1.05)	0.78 (0.57 to 1.05)
≥9%	81 (1.1)	150 (2.0)	0.44 (0.33 to 0.60)	0.44 (0.31 to 0.61)
>10 years				
Unknown	143 (1.9)	164 (2.2)	0.82 (0.62 to 1.07)	0.83 (0.62 to 1.12)
<7%	663 (8.8)	620 (8.2)	1 (reference)	1 (reference)
7.0–7.9%	473 (6.3)	609 (8.1)	0.72 (0.61 to 0.85)	0.72 (0.60 to 0.87)
8.0–8.9%	247 (3.3)	295 (3.9)	0.78 (0.64 to 0.96)	0.70 (0.55 to 0.88)
≥9%	210 (2.8)	338 (4.5)	0.58 (0.47 to 0.71)	0.51 (0.40 to 0.64)

*Adjusted for: smoking status, alcohol consumption, general practitioner visits, ACE-Is, ARBs excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, β-blockers, calcium channel blockers, nitrates, statins, low-dose ASA, and antidiabetic drugs.
ACE-Is, ACE inhibitors; ARBs, angiotensin receptor blockers; ASA, acetylsalicylic acid.

gout in patients with T2DM. However, the results were not adjusted for important risk factors of gout and comorbid conditions for T2DM.[9 10] Comorbidities, such as arterial hypertension, CKD and CHF, as well as co-medications, such as different types of diuretics, have been associated with a substantially increased risk of gout in this study as well as in previous studies,[7 28] and could, therefore, explain the positive association. In two questionnaire-based studies, one from Greece[11] and one from New Zealand,[8] the authors reported increased relative risks of gout in association with T2DM. Again, the results were not adjusted for important confounders. Finally, in a larger study using the General Practice Research Database (former name for the CPRD), diabetes mellitus was associated with a slightly increased risk for incident gout in univariate analysis.[3] Again, no adjusted results for important confounders were reported in that study.

In our study, increasing A1C levels were associated with a significantly decreased risk of incident gout. While a uricosuric effect of poorly controlled hyperglycaemia and/or impaired inflammatory response in prolonged and poorly controlled diabetes offer potential mechanistic explanations for these findings,[1 25–27] a potential effect of antidiabetic drug treatment on these risk estimates should also be considered. Rodriguez and coworkers[12] did not report detailed results, but observed that relative risk estimates for incident gout were lower in patients with treated T2DM compared to patients who did not receive treatment. Whether this observation reflects a beneficial effect of antidiabetic drug treatment or is explained by more severe and/or prolonged diabetes mellitus remains unclear. In our study, we did not find evidence that different types of antidiabetic drugs alter the risk of gouty arthritis. Although we observed marginally decreased relative risk estimates of gout in current antidiabetic drug users in the main analysis, there was no consistent trend with increasing number of prescriptions. Finally, in the sensitivity analysis in which we explored the association between different antidiabetic drugs and gout, which was additionally matched on diabetes duration and A1C level, current antidiabetic drug treatment was no more associated with an altered risk of gout, irrespective of the specific drug used. Taken together, our results strongly suggest that increasing A1C levels, but not prolonged diabetes duration, per se, nor different antidiabetic drug treatments, explain the observed decreased relative risk estimates of gout.

This large population-based study has several strengths. First, the diagnosis of gout has been validated in this well-established primary care database,[3 24] and similar case definitions for

Table 5 ORs for duration of use of different antidiabetic drugs among cases with incident gout and matched controls

Variable	Number of cases (%) (n=7536)	Number of controls (%) (n=7536)	OR crude (95% CI)	OR adj.* (95% CI)
Insulin				
Never used	6606 (87.7)	6600 (87.6)	1 (reference)	1 (reference)
Current use (<180 days)				
Overall	868 (11.5)	878 (11.7)	0.99 (0.89 to 1.09)	0.74 (0.65 to 0.85)
1–19 prescriptions	316 (4.2)	269 (3.6)	1.17 (0.99 to 1.38)	0.96 (0.79 to 1.17)
20–39 prescriptions	196 (2.6)	224 (3.0)	0.87 (0.72 to 1.06)	0.67 (0.53 to 0.85)
40–59 prescriptions	118 (1.6)	138 (1.8)	0.86 (0.67 to 1.10)	0.62 (0.46 to 0.82)
≥60 prescriptions	238 (3.2)	247 (3.3)	0.97 (0.81 to 1.16)	0.63 (0.50 to 0.79)
Past use				
Overall	62 (0.8)	58 (0.8)	1.07 (0.75 to 1.53)	0.91 (0.61 to 1.36)
Metformin				
Never used	3284 (43.6)	2812 (37.3)	1 (reference)	1 (reference)
Current use (<180 days)				
Overall	3218 (42.7)	3896 (51.7)	0.68 (0.64 to 0.74)	0.71 (0.65 to 0.77)
1–19 prescriptions	1197 (15.9)	1331 (17.7)	0.74 (0.68 to 0.82)	0.75 (0.67 to 0.83)
20–39 prescriptions	789 (10.5)	990 (13.1)	0.66 (0.59 to 0.73)	0.67 (0.59 to 0.76)
40–59 prescriptions	516 (6.9)	663 (8.8)	0.64 (0.57 to 0.73)	0.70 (0.60 to 0.81)
≥60 prescriptions	716 (9.5)	912 (12.1)	0.65 (0.58 to 0.73)	0.71 (0.62 to 0.82)
Past use				
Overall	1034 (13.7)	828 (11.0)	1.03 (0.92 to 1.15)	0.91 (0.80 to 1.04)
Sulfonylurea				
Never used	4239 (56.3)	3881 (51.5)	1 (reference)	1 (reference)
Current use (<180 days)				
Overall	2389 (31.7)	2708 (35.9)	0.80 (0.75 to 0.86)	0.82 (0.75 to 0.89)
1–19 prescriptions	823 (10.9)	863 (11.5)	0.87 (0.78 to 0.97)	0.88 (0.78 to 0.99)
20–39prescriptions	583 (7.7)	592 (7.9)	0.90 (0.79 to 1.01)	0.91 (0.79 to 1.04)
40–59prescriptions	374 (5.0)	477 (6.3)	0.72 (0.62 to 0.83)	0.75 (0.63 to 0.88)
≥60 prescriptions	609 (8.1)	776 (10.3)	0.71 (0.63 to 0.79)	0.71 (0.62 to 0.82)
Past use				
Overall	908 (12.1)	947 (12.6)	0.88 (0.79 to 0.97)	0.88 (0.77 to 1.01)

*Adjusted for: smoking status, alcohol consumption, general practitioner visits, ACE-Is, ARBs excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, β-blockers, calcium channel blockers, nitrates, statins, low-dose ASA, and antidiabetic drugs.
ACE-Is, ACE inhibitors; ARBs, angiotensin receptor blockers; ASA, acetylsalicylic acid.

incident gout have been used by other authors.[3 7 23 24] Second, we were in the position to study a large number of cases with T2DM and incident gout, to explore the role of duration and severity of T2DM, and to run various sensitivity analyses to address in-depth the potential role of different antidiabetic treatments on the risk of incident gout. Third, unlike in most former studies, we were able to address the role of important potential confounders such as age, sex and BMI by matching, and we adjusted our analyses for various important comorbidities and co-medications. Fourth, information in the CPRD is prospectively collected in the absence of any study hypothesis; therefore, recall bias is not an issue in this study. Fifth, exclusion of patients with less than 3 years of recorded history in the CPRD prior to the index date reduced the likelihood of including prevalent rather than incident gout cases. Finally, time-related biases, namely bias by different exposure opportunity (also named 'time-window bias') and immortal time bias were likely not an issue in this study in which we explored potential drug effects on the risk of incident gout. Furthermore, our findings were closely similar in the sensitivity analysis in which we matched cases and controls on diabetes duration.

Potential limitations of this study are possible misclassification of some gout cases, since diagnoses were mainly made by general practitioners, and not all by rheumatologists. However, a previous study has shown that gout diagnoses are recorded with high validity in the CPRD,[24] and other investigators used similar case definitions.[7 23 24] Furthermore, we excluded subjects with recorded differential diagnoses of gout, such as osteoarthritis, septic arthritis, arthropathy due to haemochromatosis, or rheumatoid arthritis to reduce the risk of misclassification. Furthermore, we were not able to adjust for all potential risk factors for gouty arthritis since dietary habits and physical activity [1 4] are not routinely recorded in the CPRD. However, by matching on BMI which is related to physical activity and dietary habits, we partly controlled for these risk factors. Additionally, we were not able to address potential confounding by socioeconomic status in-depth. However, we partially controlled for it by matching cases and controls on general practice attended, as it is likely that patients from the same neighbourhood see the same general practitioner. Finally, we were unable to assess race/ethnicity because this information is not consistently available in the CPRD. Our results are most likely representative of Caucasians, since 86% of individuals living in the UK are white.[29]

In summary, this large observational study provides evidence that increasing A1C levels are associated with a markedly

Table 6 Use of antidiabetic drugs and the risk of incident gout in cases and controls additionally matched on diabetes duration and on diabetes duration and A1C level

Variable	Cases and controls additionally matched on diabetes duration			Cases and controls additionally matched on diabetes duration and A1C level		
	Number of cases (%) (n=7106)	Number of controls (%) (n=7106)	OR adj.* (95% CI)	Number of cases (%) (n=5013)	Number of controls (%) (n=5013)	OR adj.* (95% CI)
Insulin						
Never used	6294 (88.6)	6365 (89.6)	1 (reference)	4596 (91.7)	4712 (94.0)	1 (reference)
Current use (<180 days)						
Overall	757 (10.7)	660 (9.3)	0.84 (0.72 to 0.98)	384 (7.7)	259 (5.2)	1.14 (0.91 to 1.42)
1–19 prescriptions	284 (4.0)	221 (3.1)	1.01 (0.82 to 1.24)	168 (3.4)	100 (2.0)	1.37 (1.02 to 1.85)
20–39 prescriptions	172 (2.4)	142 (2.0)	0.82 (0.63 to 1.08)	92 (1.8)	65 (1.3)	1.02 (0.69 to 1.50)
40–59 prescriptions	101 (1.4)	126 (1.8)	0.57 (0.42 to 0.78)	48 (1.0)	46 (0.9)	0.69 (0.42 to 1.12)
≥60 prescriptions	200 (2.8)	171 (2.4)	0.76 (0.58 to 1.00)	76 (1.5)	48 (1.0)	1.19 (0.75 to 1.89)
Past use						
Overall	55 (0.8)	81 (1.1)	0.50 (0.34 to 0.73)	33 (0.7)	42 (0.8)	0.66 (0.40 to 1.11)
Metformin						
Never used	3114 (43.8)	2827 (39.8)	1 (reference)	2204 (44.0)	2217 (44.2)	1 (reference)
Current use (<180 days)						
Overall	3046 (42.9)	3533 (49.7)	0.75 (0.69 to 0.82)	2243 (44.7)	2353 (46.9)	0.94 (0.85 to 1.05)
1–19 prescriptions	1147 (16.1)	1350 (19.0)	0.75 (0.67 to 0.84)	902 (18.0)	1096 (21.9)	0.81 (0.71 to 0.92)
20–39 prescriptions	758 (10.7)	909 (12.8)	0.72 (0.63 to 0.82)	596 (11.9)	677 (13.5)	0.90 (0.78 to 1.05)
40–59 prescriptions	482 (6.8)	557 (7.8)	0.80 (0.68 to 0.94)	369 (7.4)	301 (6.0)	1.38 (1.13 to 1.68)
≥60 prescriptions	659 (9.3)	717 (10.1)	0.78 (0.67 to 0.92)	376 (7.5)	279 (5.6)	1.35 (1.09 to 1.66)
Past use						
Overall	946 (13.3)	746 (10.5)	0.97 (0.85 to 1.12)	566 (11.3)	443 (8.8)	1.04 (0.88 to 1.23)
Sulfonylurea						
Never used	4029 (56.7)	3930 (55.3)	1 (reference)	3052 (60.9)	3216 (64.2)	1 (reference)
Current use (<180 days)						
Overall	2244 (31.6)	2400 (33.8)	0.90 (0.82 to 0.98)	1483 (29.6)	1431 (28.6)	1.11 (0.99 to 1.24)
1–19 prescriptions	789 (11.1)	841 (11.8)	0.91 (0.80 to 1.03)	558 (11.1)	568 (11.3)	1.06 (0.92 to 1.24)
20–39 prescriptions	555 (7.8)	601 (8.5)	0.89 (0.77 to 1.03)	389 (7.8)	387 (7.7)	1.06 (0.89 to 1.26)
40–59 prescriptions	346 (4.9)	382 (5.4)	0.86 (0.72 to 1.03)	231 (4.6)	201 (4.0)	1.12 (0.88 to 1.41)
≥60 prescriptions	554 (7.8)	576 (8.1)	0.85 (0.72 to 1.00)	305 (6.1)	275 (5.5)	1.09 (0.87 to 1.35)
Past use						
Overall	833 (11.7)	776 (10.9)	1.01 (0.88 to 1.17)	478 (9.5)	366 (7.3)	1.21 (1.00 to 1.46)

*Adjusted for: smoking status, alcohol consumption, general practitioner visits, ACE-Is, ARBs excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, β-blockers, calcium channel blockers, nitrates, statins, low-dose ASA, antidiabetic drugs for each other.
ACE-Is, ACE inhibitors; ARBs, angiotensin receptor blockers; ASA, acetylsalicylic acid.

decreased risk of incident gout in patients with T2DM. Neither use of insulin, metformin, nor sulfonylureas was associated with an altered risk of incident gout.

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Study 4

Use of Hormone Replacement Therapy and Risk of Incident Gout: a Population-Based Case-Control Study

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ABSTRACT

Background and Objective

Gout risk increases after menopause. The role of female sex hormones and of use of hormone replacement therapy (HRT) on the gout risk is not well known.

Objective

To assess the risk of developing incident gout in association with use of postmenopausal HRT, according to type, timing, duration, and route of HRT administration.

Design and setting

Case-control analysis within the UK Clinical Practice Research Datalink

Participants

We identified 13,489 female patients aged ≥45 years with incident gout between 1990 and 2010. We excluded all cases with less than 3 years of recorded history prior to the index date, with a diagnosis of human immunodeficiency virus (HIV) or cancer (except non-melanoma skin cancer) prior to the index date, and women with a diagnosis of hemochromatosis, septic arthritis, rheumatoid arthritis, or osteoarthritis. We identified at random one female control for each case, matched on age, general practice, calendar time, and years of active history in the database, and applied the same exclusion criteria to controls as to cases.

Main outcome measures

Odds ratios (ORs) with 95% confidence intervals (CIs)

Results

Adjusted ORs of gout for current use of oral formulations of opposed oestrogens (oestrogen plus progesterone) were 0.69 (95% CI 0.56 to 0.86) compared to never use. Current use was associated with a decreased risk of gout in patients without renal failure (adj. OR 0.71, 95% CI 0.57 to 0.87) and hypertension (adj. OR 0.62, 95% CI 0.44 to 0.87) compared to never use. Oestrogens alone did not alter the gout risk.

Conclusions

Current use of oral opposed, but not of unopposed oestrogens was associated with a decreased risk of incident gout in patients without renal failure, and it was more pronounced in patients with hypertension. The decreased gout risk associated with HRT use may be related to the progesterone rather than the oestrogen component.

INTRODUCTION

Gouty arthritis is a common painful inflammatory arthritis with acute onset, characterized by deposition of monosodium urate crystals in affected joints and surrounding tissue (1, 2). Older age, male gender, hyperuricemia, obesity, and alcohol are important risk factors for gout (3, 4). Furthermore, arterial hypertension, renal failure, congestive heart failure, and use of diuretics or antihypertensive drugs have also been associated with an increased risk of gout (5, 6).

The incidence of gout differs between males and females and is strongly related to age in females (7, 8). Gouty arthritis is rarely diagnosed in premenopausal women, but gout incidence and prevalence increase after menopause (7-9). Several authors demonstrated that urate levels, an important risk factor for gout, substantially increase with age in women, but not in men (10-12). This led to the notion that changes in serum levels of female sex hormones after menopause may be linked to increasing urate levels and to an increased gout risk (13-15), and that female sex hormones may protect against the development of gouty arthritis (7, 16-18). Indeed, investigations showed that both oestrogen and progesterone stimulate renal clearance of uric acid and thereby decrease serum urate levels (11, 12). Furthermore, postmenopausal hormone replacement therapy (HRT) was shown to also reduce serum uric acid levels (19, 20). Finally, postmenopausal HRT use was associated with a modestly reduced gout risk in one published study (9), but the investigators did not report details of dose, duration, or route of HRT administration or on possible differences between use of oestrogens alone versus use of opposed oestrogens, i.e. oestrogens plus progesterone.

HRT is licensed for relief of climacteric symptoms and for the prophylaxis of osteoporosis in peri- and postmenopausal women (21). Women with intact uteri usually take combination oestrogen and progesterone therapy, while women with prior hysterectomy may receive unopposed oestrogens (21). We conducted a large case-control analysis using a well validated primary care database to explore the risk of gout development in association with HRT use, with detailed analyses on the type of HRT, timing and duration of use and route of administration.

METHODS

Data source

We derived data from the United Kingdom (UK)-based Clinical Practice Research Datalink (CPRD), a large primary care database which was established in 1987 and encompasses data from some 450 general practices on some 7 million patients who are representative of the UK population (22, 23) with regard to age, sex, geographic distribution, and annual turnover rate (7, 24, 25). The CPRD holds information regarding patient demographics and characteristics, lifestyle variables such as body mass index (BMI), smoking status, and alcohol consumption, symptoms, medical diagnoses, referrals to consultants, and hospitalizations. The general practitioners generate drug prescriptions directly with the computer using a coded drug dictionary. The database has been described in detail (26, 27) and has been validated extensively (23, 28-31). The CPRD has been the source of numerous epidemiological studies published in peer-reviewed journals, including research on gout (6-8, 32, 33).

Study population

Case patients

Based on Read codes we identified in the CPRD female patients aged $\geq$45 years who had a first-time diagnosis of gout recorded between 1990 and 2010. The date of the first diagnosis of gout was referred to as the *index date*. We excluded all cases with less than three years of recorded history prior to the index date in order to reduce the likelihood of including prevalent gout cases.

We further excluded all patients with a diagnosis of human immunodeficiency virus (HIV) or cancer (except non-melanoma skin cancer) prior to the index date, as well as those with a diagnosis of hemochromatosis, septic arthritis, rheumatoid arthritis, or osteoarthritis at any time within their record (to reduce the risk of misclassification, i.e. inclusion of gout cases who in fact had another disease with similar symptoms). The diagnosis of gout in the CPRD has been validated in a previous study (32) in which the authors used similar case definitions (6-8, 33).

Control patients

We identified at random from the CPRD a control group of female patients without evidence of gout. We applied the same exclusion criteria to controls as to cases. We matched controls 1:1 to cases on age, general practice, number of years of previous recorded history in the database, and index date.

Definition and classification of HRT use

We identified HRT prescriptions prior to the index date and classified exposed patients into *current users* (last prescription ending <90 days prior to the index date), *past users* (last prescription ending ≥90 days prior to the index date), or *never users*. We determined a cut-off of 90 days for current use because this is the typical maximal length of a prescription in the UK. We further classified HRT users according to duration of use, taking the number of HRT prescriptions (1−9, 10−19, ≥20 prescriptions) prior to the index date as a proxy for treatment duration. In addition, we distinguished between opposed (oestrogen plus progesterone) and unopposed (oestrogen only) HRT prescriptions, and ran stratified analyses by route of administration (oral, transdermal patch, vaginal, or else, including gel, implant, nasal, and injection).

Covariates

We classified cases and controls according to their BMI (12.0−18.4, 18.5−24.9, 25.0−29.9, 30.0−34.9, 35.0−39.9, 40.0−44.9, ≥45.0 kg/m^2, or unknown), smoking status (non-smoker, current smoker, ex-smoker, or unknown), alcohol consumption (never, current [1−9 units per week; 10−19 units per week; ≥20 units per week], past, or unknown), and number of general practitioner visits within the year immediately preceding the index date (0−2, 3−4, 5−9, ≥10 visits/year).

We assessed whether cases and controls had a recording of hysterectomy, osteoporosis, hypertension, renal failure, ischemic heart disease, congestive heart failure, transient ischemic attack or stroke, diabetes mellitus, or dyslipidaemia at any time prior to the index date. Furthermore, we assessed the association between use of antihypertensive drugs (beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers, organic nitrates), statins, and low dose acetylsalicylic acid within 180 days prior to the index date and gout. A cut-off of 180 days was chosen in order to better distinguish between current and past users since these substances are prescribed for long-term use, and many of these drugs are also available in packages containing >90 tablets.

Statistical analysis

We conducted multivariate conditional logistic regression analyses to compare the exposure prevalence of HRT between cases and controls. We present relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs), and we considered a 2-sided p-value of <0.05 statistically significant. We conducted the statistical analysis using the software program SAS, Version 9.3 (SAS institute, Inc., Cary, North Carolina).

When we analysed the exposure odds, we adjusted for patient characteris-

tics, comorbidities or concomitant drug use in the multivariate analysis if these potential confounders were predictor variables for gout known a priori from the literature; these were BMI, smoking status, alcohol consumption, and general practitioner visits within the last year preceding the index date for all analyses. When we explored the association between incident gout and baseline characteristics including life style factors (alcohol consumption and smoking status) and different comorbidities, we additionally adjusted our analyses for hysterectomy status (yes/no), and for the comorbidities hypertension, congestive heart failure, ischemic heart disease, and renal failure. For all other analyses we simultaneously adjusted for use of diuretic and antihypertensive drugs, nitrates, statins, low dose acetylsalicylic acid, and opposed or unopposed oestrogen.

Sensitivity analyses

We conducted various sensitivity analyses. First, we assessed the risk of gout in association with use of HRT in the subset of cases (and their matched controls) who were treated with either non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and/or corticosteroids within 7 days, or uricosuric/uricostatic drugs within 90 days prior to or after the index date. This was done to reduce the risk of misclassification, i.e. to increase the likelihood of including valid gout cases. In a second sensitivity analysis, we excluded patients with a history of renal failure, congestive heart failure, or hypertension to eliminate residual confounding by these important risk factors for gout. In a third sensitivity analysis, we stratified the study population by the presence or absence of these comorbidities. In a fourth sensitivity analysis, we stratified the study population by hysterectomy status, because increased gout risks have previously been reported in younger females with natural or surgical menopause (9). In a fifth sensitivity analysis, we compared current HRT users to the reference group of past HRT users to limit the risk of potential confounding by indication. In a sixth sensitivity analysis we restricted the data to incident

users of HRT by excluding prevalent users to address potential prevalent user bias; incident users were women without any prescriptions for opposed or unopposed oestrogens within the first year of their registered history. Finally, we assessed the risk of gout (ever use compared to never use only) of HRT stratified by different routes of administration.

RESULTS

The study population encompassed 13,489 incident female gout cases ≥45 years of age and the same number of matched controls. Mean (± standard deviation) age at the index date was 70 ± 12.3 years. Increasing BMI was associated with a higher risk of gout, as was current alcohol consumption in a dose-dependent manner. Comorbidities known to be associated with an increased risk of gout, such as hypertension, renal failure, congestive heart failure, and ischemic heart disease were all associated with an increased risk of incident gout *(Table 1)*.

Table 1 Baseline characteristics of female incident gout cases and matched controls

Variable	No. of cases (%) (n=13,489)	No. of controls (%) (n=13,489)	OR crude (95% CI)	OR adj.* (95% CI)
Age-group [years]°				
45-49	786 (5.8)	786 (5.8)	NA	NA
50-54	984 (7.3)	988 (7.3)	NA	NA
55-59	1264 (9.4)	1256 (9.3)	NA	NA
60-64	1442 (10.7	1440 (10.7)	NA	NA
65-69	1304 (9.7)	1319 (9.8)	NA	NA
70-74	1527 (11.3	1525 (11.3)	NA	NA
75-79	1600 (11.9	1609 (11.9)	NA	NA
≥80	4582 (34.0	4566 (33.9)	NA	NA
BMI-group [kg/m^2]				
12.0-18.4	165 (1.2)	303 (2.3)	0.80 (0.66 - 0.98)	0.78 (0.62 - 0.98)
18.5-24.9	2871 (21.3	4386 (32.5)	1.00 (referent)	1.00 (referent)
25.0-29.9	3772 (28.0	3300 (24.5)	1.83 (1.71 - 1.96)	1.58 (1.46 - 1.71)
30.0-34.9	2422 (18.0	1276 (9.5)	3.23 (2.95 - 3.53)	2.50 (2.27 - 2.77)
35.0-39.9	1054 (7.8)	390 (2.9)	4.51 (3.95 - 5.15)	3.20 (2.76 - 3.71)
40.0-44.9	410 (3.0)	97 (0.7)	7.30 (5.75 - 9.26)	4.78 (3.69 - 6.20)
≥45.0	214 (1.6)	41 (0.3)	8.95 (6.34 - 12.64)	5.17 (3.58 - 7.49)
Unknown	2581 (19.1	3696 (27.4)	0.88 (0.82 - 0.96)	1.33 (1.19 - 1.49)
Smoking status				
Non-smoker	6521 (48.3	6698 (49.7)	1.00 (referent)	1.00 (referent)
Current smoker	1726 (12.8	1802 (13.4)	0.99 (0.91 - 1.07)	1.21 (1.11 - 1.33)
Ex-smoker	3682 (27.3	2547 (18.9)	1.57 (1.48 - 1.68)	1.30 (1.20 - 1.40)
Unknown	1560 (11.6	2442 (18.1)	0.54 (0.49 - 0.58)	1.15 (1.01 - 1.32)
Alcohol consumption [Units/week]§				
Never / Ex	3016 (22.4	2750 (20.4)	1.00 (referent)	1.00 (referent)
Current unknown	3146 (23.3	2936 (21.8)	0.98 (0.91 - 1.06)	1.05 (0.96 - 1.15)
Current 1-9	3238 (24.0	3160 (23.4)	0.95 (0.88 - 1.03)	1.13 (1.04 - 1.24)
Current 10-19	1045 (7.8)	818 (6.1)	1.21 (1.08 - 1.35)	1.59 (1.39 - 1.81)
Current >20	501 (3.7)	261 (1.9)	1.80 (1.54 - 2.12)	2.03 (1.68 - 2.46)
Unknown	2543 (18.9	3564 (26.4)	0.57 (0.53 - 0.62)	0.96 (0.85 - 1.09)
General practitioner visits last year				
0-2	1042 (7.7)	2976 (22.1)	1.00 (referent)	1.00 (referent)
3-4	407 (3.0)	864 (6.4)	1.39 (1.20 - 1.61)	1.21 (1.03 - 1.41)
5-9	1556 (11.5	2065 (15.3)	2.41 (2.17 - 2.68)	2.04 (1.81 - 2.29)
≥10	10484 (77.7	7584 (56.2)	5.15 (4.71 - 5.64)	3.19 (2.87 - 3.53)
Comorbidities				
Hysterectomy	2882 (21.4	2337 (17.3)	1.32 (1.24 - 1.40)	1.18 (1.09 - 1.27)
Osteoporosis	817 (6.1)	894 (6.6)	0.91 (0.82 - 1.00)	0.93 (0.83 - 1.05)
Hypertension	8186 (60.7	4833 (35.8)	3.18 (3.00 - 3.36)	2.09 (1.95 - 2.23)
Diabetes mellitus	1721 (12.8	900 (6.7)	2.08 (1.91 - 2.27)	1.05 (0.94 - 1.16)
Dyslipidaemia	2408 (17.9	1559 (11.6)	1.78 (1.65 - 1.91)	1.07 (0.98 - 1.17)
Renal failure	4689 (34.8	2583 (19.2)	4.44 (4.07 - 4.85)	2.39 (2.16 - 2.63)
Congestive heart failure	1646 (12.2	505 (3.7)	3.98 (3.56 - 4.45)	2.91 (2.57 - 3.31)
Ischemic heart disease	2544 (18.9	1308 (9.7)	2.27 (2.11 - 2.45)	1.42 (1.30 - 1.56)
Stroke/TIA	1292 (9.6)	905 (6.7)	1.51 (1.38 - 1.65)	1.14 (1.02 - 1.27)

BMI, body mass index; CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack
°Matching variables age, sex, general practice, history on the database and index date
§1U (Unit) = 10ml of pure ethanol (8g of ethanol)
*Adjusted for: BMI category, smoking status, alcohol consumption, number of general practitioner visits within last year, hysterectomy, hypertension, renal failure, congestive heart failure, ischemic heart disease

Current use of most antihypertensive drugs except calcium channel blockers, which were associated with decreased gout risks, were associated with increased risks of gout compared to never use of these drugs *(Table 2)*.

Table 2 ORs for gout in current use of various medications compared to never use of each medication in female gout cases and matched controls

Comedication	No. of cases (%) (n=13,489)	No. of controls (%) (n=13,489)	OR crude (95% CI)	OR adj.* (95% CI)
ACE-Inhibitors	3606 (26.7)	1656 (12.3)	3.46 (3.21 - 3.72)	1.53 (1.40 - 1.68)
ARBs (excl. Losartan)	1009 (7.5)	415 (3.1)	2.90 (2.56 - 3.28)	1.24 (1.06 - 1.45)
Losartan	354 (2.6)	148 (1.1)	2.51 (2.07 - 3.05)	1.11 (0.69 - 1.77)
Loop diuretics	3250 (24.1)	889 (6.6)	5.73 (5.23 - 6.29)	3.26 (2.92 - 3.63)
Thiazide diuretics	3440 (25.5)	1778 (13.2)	2.78 (2.59 - 2.98)	1.89 (1.73 - 2.06)
Potassium sparing diuretics	557 (4.1)	117 (0.9)	5.31 (4.31 - 6.54)	2.33 (1.84 - 2.94)
Beta-blockers	3846 (28.5)	1790 (13.3)	3.06 (2.86 - 3.28)	1.83 (1.68 - 1.99)
Calcium channel blockers	2500 (18.5)	1717 (12.7)	1.90 (1.77 - 2.05)	0.89 (0.82 - 0.98)
Nitrates	1283 (9.5)	551 (4.1)	2.67 (2.40 - 2.97)	1.29 (1.13 - 1.47)
Statins	3113 (23.1)	1768 (13.1)	2.45 (2.27 - 2.64)	1.15 (1.04 - 1.26)
ASA low-dose	2857 (21.2)	1755 (13.0)	2.07 (1.92 - 2.22)	0.98 (0.89 - 1.07)

*Adjusted for: body mass index category, smoking status, alcohol consumption, number of general practitioner visits within last year, hysterectomy, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, beta-blockers, calcium channel blockers, nitrates, statins, low dose acetylsalicylic acid, oestrogens opposed, oestrogens unopposed

Compared to never use, current use of opposed oestrogens (adj. OR 0.72, 95% CI 0.59 to 0.88), but not unopposed oestrogens (adj. OR 1.21, 95% CI 0.98 to 1.48), was associated with a decreased risk of incident gout. Relative risk estimates of gout did not materially change with increasing number of prescriptions in users of opposed or unopposed oestrogens *(Table 3)*.

Table 3 ORs for current use of hormone replacement therapy compared to never use in female gout cases and matched controls

Hormone replacement therapy	No. of cases (%) (n=13489)		No. of controls (%) (n=13489)		OR crude (95% CI)		OR adj.* (95% CI)	
Oestrogens opposed								
Never use	11772	(87.3)	11623	(86.2)	1.00	(reference)	1.00	(reference)
Current use								
Overall	267	(2.0)	332	(2.5)	0.78	(0.66 - 0.92)	0.72	(0.59 - 0.88)
1-9 prescriptions	85	(0.6)	113	(0.8)	0.72	(0.54 - 0.97)	0.68	(0.49 - 0.95)
10-19prescriptions	67	(0.5)	78	(0.6)	0.82	(0.59 - 1.15)	0.77	(0.52 - 1.14)
≥20 prescriptions	115	(0.9)	141	(1.1)	0.79	(0.62 - 1.02)	0.72	(0.53 - 0.97)
Past use								
Overall	1450	(10.8)	1534	(11.4)	0.92	(0.84 - 1.00)	0.88	(0.79 - 0.97)
1-9 prescriptions	857	(6.4)	836	(6.2)	0.99	(0.90 - 1.10)	0.95	(0.83 - 1.07)
10-19prescriptions	300	(2.2)	350	(2.6)	0.83	(0.71 - 0.98)	0.81	(0.67 - 0.98)
≥20 prescriptions	293	(2.2)	348	(2.6)	0.81	(0.69 - 0.96)	0.77	(0.63 - 0.94)
Oestrogens unopposed								
Never use	12021	(89.1)	12268	(91.0)	1.00	(reference)	1.00	(reference)
Current use								
Overall	343	(2.5)	234	(1.7)	1.54	(1.30 - 1.83)	1.21	(0.98 - 1.48)
1-9 prescriptions	84	(0.6)	59	(0.4)	1.49	(1.06 - 2.09)	1.28	(0.87 - 1.89)
10-19prescriptions	80	(0.6)	54	(0.4)	1.54	(1.08 - 2.18)	1.24	(0.83 - 1.87)
≥20 prescriptions	179	(1.3)	121	(0.9)	1.57	(1.23 - 1.99)	1.15	(0.87 - 1.53)
Past use								
Overall	1125	(8.3)	987	(7.3)	1.19	(1.08 - 1.30)	1.02	(0.91 - 1.14)
1-9 prescriptions	638	(4.7)	603	(4.5)	1.10	(0.98 - 1.23)	0.96	(0.84 - 1.11)
10-19prescriptions	217	(1.6)	180	(1.3)	1.27	(1.04 - 1.55)	1.16	(0.91 - 1.48)
≥20 prescriptions	270	(2.0)	204	(1.5)	1.38	(1.15 - 1.67)	1.09	(0.86 - 1.37)

*Adjusted for: body mass index category, smoking status, alcohol consumption, number of general practitioner visits within last year, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, beta-blockers, calcium channel blockers, nitrates, statins, low dose acetylsalicylic acid, oestrogens opposed and oestrogens unopposed for each other

Results from the sensitivity analysis restricted to pharmacologically treated gout patients or to patients without evidence for renal failure, congestive heart failure, or hypertension did not materially differ from the main analysis (data not shown).

When we stratified our analysis by renal failure, current use of opposed oestrogens was associated with a decreased risk of gout in patients without renal failure compared to never use (adj. OR 0.71, 95% CI 0.57 to 0.87), while in patients with renal failure no such association was found (adj. OR 0.99, 95% CI 0.53 to 1.86).

In the analysis stratified by hypertension, current use of opposed oestro-

gens was associated with a stronger protective effect risk (adj. OR 0.62, 95% CI 0.44 to 0.87) in patients with hypertension, while the association was closer to the null in cases and controls without hypertension (adj. OR 0.80, 95% CI 0.63 to 1.02) *(Table 4)*. We could not stratify by presence or absence of congestive heart failure as there were too few patients with the disease.

Table 4 ORs for use of hormone replacement therapy stratified by renal failure and by hypertension in female gout cases and matched controls

	with comorbidity prior to the index date						without comorbidity prior to the index date					
	No. of cases (%) (n=13489)	No. of controls (%) (n=13489)	OR crude (95% CI)		OR* adjusted (95% CI)		No. of cases (%) (n=13489)	No. of controls (%) (n=13489)	OR crude (95% CI)		OR* adjusted (95% CI)	
Renal failure	4689 (34.8)	2583 (19.2)					8800 (65.2)	10906 (80.9)				
Opposed oestrogens												
Non-use	4252 (31.5)	2328 (17.3)	1.00	(reference)	1.00	(reference)	7520 (55.8)	9295 (68.9)	1.00	(reference)	1.00	(reference)
Current use	40 (0.3)	21 (0.2)	0.91	(0.52 - 1.60)	0.99	(0.53 - 1.86)	227 (1.7)	311 (2.3)	0.80	(0.66 - 0.96)	0.71	(0.57 - 0.87)
Past use	397 (2.9)	234 (1.7)	0.82	(0.68 - 0.98)	0.82	(0.66 - 1.02)	1053 (7.8)	1300 (9.6)	0.97	(0.88 - 1.07)	0.90	(0.80 - 1.01)
Unopposed oestrogens												
Non-use	4250 (31.5)	2363 (17.5)	1.00	(reference)	1.00	(reference)	7771 (57.6)	9905 (73.4)	1.00	(reference)	1.00	(reference)
Current use	46 (0.3)	18 (0.1)	1.05	(0.59 - 1.87)	1.30	(0.67 - 2.52)	297 (2.2)	216 (1.6)	1.68	(1.40 - 2.03)	1.23	(0.99 - 1.52)
Past use	393 (2.9)	202 (1.5)	1.08	(0.89 - 1.31)	1.05	(0.84 - 1.30)	732 (5.4)	785 (5.8)	1.25	(1.12 - 1.40)	1.04	(0.91 - 1.19)
Hypertension	8186 (60.7)	4833 (35.8)					5303 (39.3)	8656 (64.2)				
Opposed oestrogens												
Non-use	7290 (54.0)	4267 (31.6)	1.00	(reference)	1.00	(reference)	4482 (33.2)	7356 (54.5)	1.00	(reference)	1.00	(reference)
Current use	104 (0.8)	79 (0.6)	0.65	(0.48 - 0.88)	0.62	(0.44 - 0.87)	163 (1.2)	253 (1.9)	0.92	(0.74 - 1.13)	0.80	(0.63 - 1.02)
Past use	792 (5.9)	487 (3.6)	0.90	(0.79 - 1.02)	0.77	(0.66 - 0.89)	658 (4.9)	1047 (7.8)	1.00	(0.89 - 1.12)	1.00	(0.88 - 1.14)
Unopposed oestrogens												
Non-use	7317 (54.2)	4391 (32.6)	1.00	(reference)	1.00	(reference)	4704 (34.9)	7877 (58.4)	1.00	(reference)	1.00	(reference)
Current use	182 (1.4)	73 (0.5)	1.38	(1.03 - 1.84)	1.17	(0.84 - 1.61)	161 (1.2)	161 (1.2)	1.55	(1.23 - 1.96)	1.25	(0.96 - 1.62)
Past use	687 (5.1)	369 (2.7)	1.15	(1.00 - 1.32)	0.95	(0.81 - 1.12)	438 (3.3)	618 (4.6)	1.23	(1.07 - 1.41)	1.14	(0.98 - 1.33)

*Adjusted for: body mass index category, smoking status, alcohol consumption, number of general practitioner visits within last year, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, beta-blockers, calcium channel blockers, nitrates, statins, low dose acetylsalicylic acid, oestrogens opposed and oestrogens unopposed for each other

In the analysis stratified by hysterectomy status (21.4% of cases and 17.3% of controls had prior hysterectomy), current use of opposed oestrogens was associated with a decreased risk (0.71, 95% CI 0.58 to 0.88) in patients without prior hysterectomy, while no such association was found in patients with recorded hysterectomy (data not shown).

To address potential bias by indication, we compared current use of opposed or unopposed oestrogens to past use of each, and observed findings closely similar to those of the main model (data not shown). Finally, in the analysis restricted to current incident users of HRT compared to non-users the results were closely similar to the main findings (data not shown).

Ever use of norethisterone acetate and oestrogen, medroxyprogesterone acetate and oestrogen, and tibolone were associated with a decreased risk for

incident gout compared to never use of these drugs *(Table 5)*.

Table 5 ORs for use of hormone replacement therapy stratified by progesterone component respectively by single substances in female gout cases and matched controls

Opposed oestrogens	No. of cases (%) (n=13489)	No. of controls (%) (n=13489)	OR crude (95% CI)	OR* adjusted (95% CI)
Non-use	11807 (87.5)	11652 (86.4)	1.00 (reference)	1.00 (reference)
Ever use by substance				
Dydrogesterone and oestrogen	65 (0.5)	70 (0.5)	0.90 (0.63 - 1.27)	0.97 (0.63 - 1.48)
Levonorgestrel and oestrogen	87 (0.6)	95 (0.7)	0.89 (0.66 - 1.19)	0.77 (0.55 - 1.10)
Norethisterone and oestrogen	607 (4.5)	671 (5.0)	0.88 (0.78 - 0.99)	0.81 (0.70 - 0.94)
Medroxyprogesterone acetat and oestrogen	199 (1.5)	251 (1.9)	0.77 (0.63 - 0.93)	0.69 (0.54 - 0.87)
Norgestrel and oestrogen	439 (3.3)	429 (3.2)	0.99 (0.86 - 1.14)	0.98 (0.83 - 1.17)
Raloxifen	35 (0.3)	39 (0.3)	0.88 (0.55 - 1.39)	1.23 (0.69 - 2.17)
Tibolone	250 (1.9)	282 (2.1)	0.86 (0.72 - 1.02)	0.77 (0.63 - 0.95)

*Adjusted for: body mass index category, smoking status, alcohol consumption, number of general practitioner visits within last year, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, beta-blockers, calcium channel blockers, nitrates, statins, low dose acetylsalicylic acid, oestrogens unopposed

Current use of oral opposed oestrogen preparations, but not of other routes of administration, was associated with a significantly decreased risk of incident gout (adj. OR 0.69, 95% CI 0.56 to 0.86). Further results are displayed in *Table 6*.

Table 6 ORs for current use of hormone replacement therapy compared to never use, stratified by route of administration in female incident gout cases and matched controls

Hormone replacement therapy	No. of cases (%) (n=13489)	No. of controls (%) (n=13489)	OR crude (95% CI)	OR* adjusted (95% CI)
Opposed oestrogens				
Never use	11772 (87.3)	11623 (86.2)	1.00 (reference)	1.00 (reference)
Current use by route of administration				
Patch	24 (0.2)	28 (0.2)	0.82 (0.47 - 1.43)	0.95 (0.50 - 1.82)
Oral	236 (1.8)	298 (2.2)	0.77 (0.64 - 0.91)	0.69 (0.56 - 0.86)
Past use by route of administration				
Patch	109 (0.8)	111 (0.8)	0.95 (0.73 - 1.24)	0.83 (0.60 - 1.16)
Oral	1292 (9.6)	1378 (10.2)	0.91 (0.83 - 0.99)	0.88 (0.79 - 0.98)
Else	56 (0.4)	51 (0.4)	1.07 (0.73 - 1.57)	1.03 (0.64 - 1.65)
Unopposed oestrogens				
Never use	12021 (89.1)	12268 (91.0)	1.00 (reference)	1.00 (reference)
Current use by route of administration				
Patch	73 (0.5)	62 (0.5)	1.27 (0.91 - 1.79)	1.02 (0.68 - 1.53)
Oral	216 (1.6)	124 (0.9)	1.85 (1.47 - 2.33)	1.37 (1.05 - 1.78)
Vaginal	37 (0.3)	34 (0.3)	1.10 (0.69 - 1.75)	0.87 (0.49 - 1.53)
Else	17 (0.1)	14 (0.1)	1.27 (0.62 - 2.57)	1.39 (0.63 - 3.10)
Past use by route of administration				
Patch	320 (2.4)	267 (2.0)	1.25 (1.06 - 1.48)	0.98 (0.79 - 1.20)
Oral	536 (4.0)	423 (3.1)	1.32 (1.15 - 1.50)	1.17 (0.99 - 1.37)
Vaginal	189 (1.4)	243 (1.8)	0.80 (0.66 - 0.97)	0.75 (0.59 - 0.95)
Else	80 (0.6)	54 (0.4)	1.56 (1.10 - 2.21)	1.32 (0.86 - 2.02)

*Adjusted for: body mass index category, smoking status, alcohol consumption, number of general practitioner visits within last year, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers excl. losartan, losartan, loop diuretics, thiazide diuretics, potassium sparing diuretics, beta-blockers, calcium channel blockers, nitrates, statins, low dose acetylsalicylic acid, oestrogens unopposed

DISCUSSION

In this large population-based case-control study, current use of opposed, but not unopposed oestrogens was associated with a decreased risk of incident gout (adj. OR 0.72, 95% CI 0.59 to 0.88). The risk reduction was not dependent on the duration of HRT use. The decreased risk of gout in current users of opposed oestrogens was only observed in patients without renal failure. Of interest, when we stratified by arterial hypertension, another comorbidity which has been associated with an increased risk of gout in this and other studies (5, 6), the observed relative risk reduction was more pronounced in cases and controls with recorded arterial hypertension. Again, no such risk reduction was seen in users of unopposed oestrogens. When we stratified by hysterectomy status, a protective effect of opposed oestrogens was observed in patients without prior hysterectomy, while no association was observed in unopposed oestrogen users. When we stratified opposed oestrogens by progesterone components, only norethisterone plus oestrogen, and medroxyprogesterone plus oestrogen were associated with a decreased risk of incident gout. Of note, tibolone, a synthetic steroid hormone acting as selective tissue estrogenic activity regulator acting as oestrogen receptor agonist (34), was also associated with a decreased risk of gout. When we stratified by route of administration, current use of oral opposed oestrogens was associated with a significantly decreased risk of incident gout, while transdermal patches were not associated with an altered risk.

Taken together, our results suggest that the progesterone component in opposed oestrogen formulations may explain the observed relative risk decrease of gout in association with use of opposed oestrogens, a risk reduction which was

only observed in absence of renal failure and which was more pronounced in the presence of diagnosed arterial hypertension, suggesting effect modification by these parameters.

Strengths and limitations

Our large population-based study has several strengths. We were in a position to study a large number of cases with incident gout in a well-established primary care database (23, 28-31). Furthermore, we were able to analyse opposed and unopposed oestrogens separately and to explore the gout risk in association with duration of HRT use and with route of administration. We were able to run various sensitivity analyses to address potential biases. We further adjusted our analyses for important potential confounders such as BMI, smoking status, alcohol consumption, renal failure, hypertension and concomitant drug therapies. Since information on diseases and drug exposure was prospectively entered in the CPRD in the absence of any study hypothesis, recall bias is not an issue.

Some limitations of our study have to be acknowledged. Misclassification of some gout cases may occur, although a previous study has shown that gout diagnoses are recorded with high validity in the CPRD (32). To minimize misclassification, we excluded patients with recorded diagnoses of other rheumatic diagnoses at any time within their history, and we further excluded all patients with less than 3 years of recorded history in the database prior to the index date to reduce the risk of including prevalent rather than incident gout cases.

We were not in a position to assess menopause, since menopause status is not consistently recorded by the general practitioner. However, HRT is prescribed mostly in postmenopausal women for symptomatic relief, usually as combined oestrogen plus progesterone therapy in women with an intact uterus (21). The analysis stratified by hysterectomy status was consistent with results from the main analysis; we therefore assume that our study population

is representative of postmenopausal women.

In addition, we were not able to adjust for all known potential risk factors for gout since, for example, dietary habits or physical activity (1, 3) are not routinely recorded in the CPRD. However, we adjusted for BMI, a factor that is related both to physical activity and dietary habits. Finally, we could not address potential confounding by socioeconomic status, but we partially controlled for this parameter by matching cases and controls on general practitioner, since patients from the same neighbourhood tend to see the same general practitioner.

Comparison with other studies

To our best knowledge the study by Hak et al. (9) is, to date, the only one which explored the association between HRT use and the risk of incident gout. The authors found a slightly decreased risk of gout in postmenopausal hormone users (relative risk 0.82, 95% CI 0.70 to 0.96) compared to non-users of HRT. However, the investigators neither reported findings on type of HRT (opposed versus unopposed), nor data on duration or route of HRT administration (9).

Serum uric acid levels increase in older postmenopausal women (10), and decreased serum uric acid levels have been observed in users of HRT compared to postmenopausal women not using HRT (10, 19, 20). In line with these observations, investigators showed that use of oestrogens and progesterone lead to increased renal clearance of urate and therefore decreased serum urate levels (11, 12, 20). However, the underlying causes of these age and sex differences remained unclear, and the number of participants analysed was small (11, 12, 20).

Of interest, use of opposed oestrogens was not associated with a decreased risk of gout in patients with renal failure in our study, i.e. in a patient subgroup with reduced renal uric acid excretion. However, since use of unopposed

oestrogens was not associated with an altered risk of gout in either the main or stratified analyses, these findings do not support the hypothesis that altered renal uric acid handling alone explains our findings. Furthermore, hypertension also had an influence on the observed risk reduction seen for opposed oestrogens.

Conclusions

In summary, this large observational study provides evidence that current oral use of opposed oestrogens is associated with a decreased risk of incident gout. The risk reduction was only observed in patients with normal renal function, and it was more pronounced in hypertensive patients. Current use of oral unopposed oestrogens was not associated with a decreased risk of gout in postmenopausal women. Thus, these findings provide evidence that the reduced gout risk seen with HRT use may be related to the progesterone rather the oestrogen component.

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Part IV

DISCUSSION, CONCLUSION, AND OUTLOOK

8. DISCUSSION

The knowledge about the pathophysiology of and risk factors for gout has improved within the last decades. Since gout is such an ancient disease many risk factors have been long-known and therefore accepted. However, some risk factors have not been investigated properly in medical research and good evidence has often been lacking. This thesis aimed at describing the natural history of gout and contribut evidence to certain predisposing factors such as the use of diuretics or antidiabetic drugs, diabetes severity or diabetes duration, and the use of hormone replacement therapy.

To conduct and understand studies and to evaluate feasibility and limitations of studies based on data from the CPRD, it is crucial to know the databases strengths and limitations. Database research is most of the times hypothesis generating. However, hypotheses can be tested to some extent, while no causal relationship can be proven (26).

The first part of the project described incidence rates, demographic characteristics of gout patients in the UK. A second part assessed the association of diuretic drug use as risk factors. A third part assessed the association of antidiabetic drugs, diabetes severity, and diabetes duration as risk factors or protective factors. Finally, a fourth part assessed the association of hormone replacement therapy as risk factors for incident gout. The study populations were described in terms of demographic characteristics and the prevalence of comorbidities and comedication prior to the index date.

In the first part of the project incident gout was recorded in 18.0 cases per 10,000 PYs, has risen, especially between 1999 and 2010, and seasonal and regional differences exist. Risk factors for incident gout included alcohol con-

sumption, comorbidities, especially kidney failure and congestive heart failure, and antihypertensive comedication. Gout treatment patterns remained stable over time, only colchicine use slightly increased over time. In the second project current use of loop diuretics, thiazide diuretics, and thiazide-like diuretics was associated with a substantially increased risk of incident gout. In the third project increasing glycosylated haemoglobin (A1C) levels were associated with a markedly decreased risk of incident gout in patients with type 2 diabetes mellitus. Neither use of insulin, metformin, nor sulfonylureas was associated with an altered risk of incident gout. In the fourth project current use of oral opposed, but not unopposed oestrogens, was associated with a decreased risk of incident gout in patients without renal failure, and it was more pronounced in patients with hypertension. The decreased gout risk associated with hormone replacement therapy use may be related to the progesterone rather than the oestrogen component.

The detailed evaluation and discussion of the main results of the individual studies are presented in the discussion section of the respective studies.

8.1 Strengths and limitations of the CPRD

Data for the studies conducted for this thesis were derived from the CPRD, one of the largest and most detailed computerised databases with longitudinal clinical records in primary care (12). The CPRD is known for its high quality, completeness of information, and its representativeness of the UK population. Therefore, studies with CPRD data are representative of the general population.

Misclassification of some gout cases may have occurred, since diagnoses were mainly made by general practitioners, and not all by rheumatologists. However, a previous study has shown that gout diagnoses are recorded with high validity in the CPRD (20). However, gout diagnoses are often made based on clinical presentation and are rarely confirmed in routine clinical practice

by analysis of aspirated joint fluid for evidence of urate crystals. To minimize misclassification, in this thesis, subjects with a differential diagnosis such as osteoarthritis, arthropathy due to hemochromatosis, septic arthritis, or rheumatoid arthritis were excluded from the study population.

In 2012, the CPRD was linked to several datasets, such as disease registries, mortality data, in-hospital and day-care drugs, mother-child linkage, and many more, to maximize the population coverage. This innovation provides additional opportunities for the investigation of gout, especially when patients are referred to rheumatologists. In addition, HES data in particular adds valuable information. Although if most information on diagnoses and prescriptions are complete, demographic characteristics are sometimes missing. For example, one such characteristic which is important in relation to gout is ethnicity. Different ethnicities require different correction factors to calculate glomerular filtration rate, which is associated with an increased risk of developing gout when reduced. For at least some patients information on ethnicity is now available in HES data. Of note, although information on prescriptions is complete, this does not necessarily mean that the medication prescribed is used. Furthermore, medication administered in the hospital is neither captured in the CPRD nor available from HES data.

In addition, information on dietary habits is unavailable at all. Especially in a research field like gout, which is highly affected by nutrition, these data are desired. Lack of dietary data may have introduced a certain amount of bias, however, in order to minimize this the multivariate analyses were adjusted for body mass index.

Furthermore, it would be very interesting within the rheumatologic research field to study genetic association. So far such information is not available, however, mothers and child linkage in the CPRD may allow for the study of the association with some heredity factors.

Despite these limitations, the results of this thesis remain meaningful, and

will hopefully lead to and encourage further research on gout. The burden of gout and its cost are immense, and even if it is has been a long known disease, further knowledge and especially improvement of prevention, treatment, and patient care is necessary.

8.2 Case-control versus cohort design

Cohort and case-control studies both intend to provide the same basic information, but the collection of data is from opposite directions; cohort studies recruit their population based on the presence or absence of an exposure while case-control studies recruit their population based on the presence or absence of an outcome (1). It is often convenient to study many different disease outcomes in relation to a given exposure in a cohort study, while with a case-control study it is often convenient to study many different exposures in relation to a single disease (29, 30). In addition, the cohort analysis is appropriate if one wants to assess incidence rates of a given outcome in a cohort of patients with a given exposure, while the case-control design is highly appropriate if one wants to assess the relative risk of developing an outcome in association with one or several exposures. Furthermore, case-control studies are prone to introduce recall bias. However, CPRD data prevent this issue since data are prospectively entered in the absence of any study hypothesis.

In some parts of this thesis, a case-control as well as a cohort analyses could have been chosen. However, a case-control design allowed for a significantly higher degree of adjustment for calendar time, since cases and controls had the same index date before which all exposures of interest were measured in the same way. Thus, the case-control design is a highly valid and efficient study design which is – contrary to the common mainstream opinion of several authors of articles and textbooks – at least as good as a cohort study design in many settings.

From a methodological point of view it is not relevant whether a cohort or

a case-control design is chosen; the crucial points are data validity, comprehensiveness (i.e. the quality of the database), and statistical power. There is no reason to discount a study simply because it is a case-control study. According to K. Rothman (26), the author of a standard textbook in epidemiology, a case-control design is not less valid than a cohort study. Validity issues can affect both cohort or case-control studies, and whether the data are captured prospectively or retrospectively. Case-control studies reach, if conducted well, the highest standards of validity.

8.3 Confounding by indication

Confounding by indication can be encountered in pharmacoepidemiological studies because the allocation of treatment is not randomized and the indication for treatment may be related to the risk of future health outcomes (41).

This might have been an issue in the study „Use of diuretics and risk of incident gout“, since arterial hypertension, chronic kidney diseases, or congestive heart failure are comorbidities associated with gouty arthritis. While chronic kidney disease and congestive heart failure may have causally led to hyperuricaemia due to decreased net urate secretion, no such mechanism is known for arterial hypertension. It may very well be that hypertension was associated with, but not responsible for the observed risk increase, and that maybe use of diuretics was the causal factor. One possibility to address this problem was to change the reference group to past users of the respective drug class as opposed to never user. This may have addressed potential confounding by indication to a certain degree. Another technique, would have been to entirely leave out the never use group, but this would not have materially affected the direct comparison of current to past use.

It is certainly possible that disease severity for these comorbidities was somewhat different between users and non-users of various diuretics; however, taking into account that the disease per se did not materially alter the risk

estimates, disease severity was unlikely responsible for the observed results. Finally, patients with past use of diuretics do not necessarily mean milder disease severity; these patients may have had adverse drug reactions and stopped or switched to another drug class.

8.4 Clinical gout diagnosis

A certain degree of misclassification cannot be ruled out in this thesis. A number of 38 case patients in the study of Meier et al. (20) who validated the gout diagnosis is rather low. However, the fact that sensitivity analyses in confirmed and probable cases revealed very similar findings and, combined with the observed overall acceptance rate of 90%, argues in favour of a high number of valid gout diagnoses recorded in the CPRD. Of note, other authors used a similar definition (7, 21, 22).

Gout diagnoses are often made on clinical grounds and are only rarely confirmed by evidence of urate crystals in aspirated joint fluid in routine clinical practice. To minimize misclassification, patients with important and/or frequent differential diagnoses to gout (such as osteoarthritis, rheumatoid arthritis, hemochromatosis, or septic arthritis) were excluded. It has to be acknowledged that other crystal arthropathies cannot always be distinguished from gouty arthritis by clinical presentation alone, and a certain degree of misclassification was likely present as in any other study of gout based on clinical data.

Of interest, misclassification could, in theory, have distorted our findings towards the observed increased risk of gout among users of various diuretic drug classes. This could arise if the general practitioner (or the rheumatologist, if the patient was referred) were aware of the previously reported associations between the use of diuretics and gout leading to the introduction of a diagnostic bias. However, it is rather implausible that such a diagnostic bias was responsible for the substantially increased relative risk estimates observed in

this particular study. Furthermore, such a bias may also be present in users of potassium-sparing agents which were not associated with an increased risk of gout.

8.5 Exact dosage

„Sola dosis facit venenum“ – „the dose alone makes the poison“, is a quote from Paracelsus. a Renaissance physician, botanist, alchemist, astrologer, and general occultist. Within the CPRD the prescriptions include amount of substance, number of tablets per package, date when the drug was prescribed, and number of prescriptions. In addition, general practitioners have the possibility to fill in the prescribed number of tablets per day in a text-field which can be analysed too. However, not all patient records contain this detailed information. Furthermore, for some medicaments, such as loop diuretics or insulin, which were part of two studies in this thesis, patients adapt the dosage on their own, e.g. loop diuretics in patients with congestive heart failure are adapted by body weight change and insulin due to measured blood glucose levels. This makes it difficult to evaluate the exact dosage. However, it is rather unlikely that this information was unequally distributed between cases and controls and therefore had an impact on results of this thesis.

Since information on number of prescriptions is available, it can be assumed that patients who had several prescriptions of a treatment such as insulin (that should be used permanently and regularly), in fact use the drug regularly even if no assumption on the compliance can be made. It is rather unlikely that someone who gets a drug will stop it and then restart it, especially for permanent treatments such insulin in patients with diabetes.

9. CONCLUSION

Based on several pharmacoepidemiological aspects addressed in this thesis, it can be concluded that:

- Incident gout was recorded in 18.0 cases per 10,000 PYs, has risen, especially between 1999 and 2010, and seasonal and regional differences exist. Risk factors for incident gout included alcohol consumption, comorbidities, especially kidney failure and congestive heart failure, and antihypertensive comedication. Gout treatment patterns remained stable over time, only colchicine use slightly increased over time.

- Current use of loop diuretics, thiazide diuretics, and thiazide-like diuretics was associated with a substantially increased risk of incident gout.

- Increasing glycosylated haemoglobin (A1C) levels were associated with a markedly decreased risk of incident gout in patients with type 2 diabetes mellitus. Neither use of insulin, metformin, nor sulfonylureas is associated with an altered risk of incident gout.

- Current use of oral opposed, but not unopposed oestrogens, was associated with a decreased risk of incident gout in patients without renal failure, and it was more pronounced in patients with hypertension. The decreased gout risk associated with hormone replacement therapy use may be related to the progesterone rather than the oestrogen component.

10. OUTLOOK

There are several interesting topics to be studied in association with gout within the CPRD in near future:

- One topic that is of major interest is to provide further information about the gender differences; currently data on demographic characteristics, comorbidities, and comedication in women with gout are lacking.
- Data availability and quality of serum urate levels on the CPRD should be validated.
- Since cyclosporine has been associated with an increased risk of gout it would be interesting to study a population with previous transplantation, especially with kidney transplantation, to assess the association of different immunosuppressive drugs.
- It would be interesting to assess the association between fenofibrate, which has been associated with a decreased risk of gout, with different concomitant drugs and incident gout.
- It would be interesting to conduct a cohort study within all gout patients from the CPRD to assess different outcomes of interest, such as tendon ruptures or hypothyroidism which have been associated with an increased risk in patients with gout.
- It would be of great interest within the rheumatologic research field to study genetic association. So far such information is not available. However, mothers and child linkage in the CPRD may allow for the study of the association with some heredity factors.

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Education

09/2011-present	Studies in Clinical Medicine, University of Basel, Switzerland
05/2010-05/2014	PhD position under the supervision of Prof. Dr. Christoph R. Meier at the Basel Pharmacoepidemiology Unit (BPU), Division of Clinical Pharmacy & Epidemiology, University of Basel, Basel, Switzerland and in collaboration with the Boston Collaborative Drug Surveillance Program (BCDSP), Boston University, Lexington, Massachusetts, United States
08/2010-08/2013	Federal Diploma Degree (FPH) in Clinical Pharmacy at the Hospital Pharmacy of the University Hospital Basel, Basel, Switzerland
	Diploma received on 21^{st} November 2013 by GSASA, the Swiss Association of Public Health Administration and Hospital Pharmacists
09/2009-12/2009	Venture Challenge Seminar at the University of Basel, Basel, Switzerland
	Diploma received in December 2009

09/2003-09/2008 Master of Science in Pharmacy and Federal Diploma Degree in Pharmacy, University of Basel, Basel, Switzerland

Diploma received in September 2008

Master thesis subject: Anti-inflammatory Effects of Hydroxy-Tyrosol and Ligustilide on Peripheral Blood Leucocytes
DSM Nutritional Product, Kaiseraugst, Switzerland

Academic Teaching Experience

05/2010-present Teaching assistant at the Division of Clinical Pharmacy & Epidemiology, University of Basel, Switzerland

Responsibilities:

- Guest lecturer, teaching of pharmacy students on the topic of pathophysiology and therapy of pulmonary hypertension
- Support of exam preparation and correction in Epidemiology, Public Health and Pharmacology
- Tutoring of students in exam preparation for the Federal Diploma Degree in Pharmacy
- Tutoring of candidates for the Federal Diploma Degree in Pharmacy in the pharmaceutical evaluation of clinical case patients
- Assistance in curricular pharmaceutical care workshops for the Federal Diploma Degree in Pharmacy
- Introduction to programming with SAS, the Statistical Analysis Software, for junior PhD students at the Basel Pharmacoepidemiology Unit

09/2011-09/2013 Federally approved examiner at the OSCE, the Objective Structured Clinical Examination for the Federal Diploma Degree in Pharmacy

Working Experience

08/2014-present Pharmacist (part-time 20%) at the Emergency Pharmacy Basel, Basel, Switzerland

05/2010-present Project manager of industry outsourced drug safety and utilization studies under the supervision of Prof. Christoph R. Meier on behalf of the Basel Pharmacoepidemiology Unit, Basel, Switzerland

05/2010-08/2013 Pharmacist (part-time 25%) at the Hospital Pharmacy of the University Hospital Basel, in the context of the specialization program in Clinical Pharmacy, Basel, Switzerland

05/2010-05/2011 Working experience at the Regional Pharmacovigilance Center Basel at the Department of Pharmacology & Toxicology, University Hospital Basel, Basel, Switzerland

01/2010-09/2012	Bahnhofapotheke (part-time 40% until 03/2010; 10% until 09/2012), Community Pharmacy, Basel, Switzerland
10/2008-03/2010	Hospital Pharmacy (part-time 60%), Community Hospital Liestal, Liestal, Switzerland
10/2008-12/2009	Flugplatzapotheke (part-time 40%), Community Pharmacy, Basel, Switzerland
08/2007-06/2008	Assistant pharmacist within the context of the education for the Masters Degree and Federal Diploma Degree in Pharmacy: – Hospital Pharmacy, Community Hospital Liestal, Liestal, Switzerland – Steinenapotheke, Community Pharmacy, Basel, Switzerland
10/2004-03/2007	Part-time assistant (parallel to university studies) at Pharmafocus AG, Münchenstein, Switzerland
08/2006-03/2007	Part-time assistant (parallel to university studies) at Viollier AG microbiologic laboratory, Allschwil, Switzerland

Publications

Manuscripts

Bruderer S, Bodmer M, Jick SS, Meier CR. Use of Diuretics and Risk of Incident Gout: a Population-Based Case-Control Study. Arthritis Rheumatol. 2014;66(1):185-96.

Bruderer S, Bodmer M, Jick SS, Bader G, Schlienger RG, Meier CR. Incidence of and Risk Factors for Severe Hypoglycemia in Treated Type 2 Diabetes Mellitus Patients in the United Kingdom: a Nested Case-Control Analysis. Diabetes Obes Metab. 2014. In press.

Bruderer S, Bodmer M, Jick SS, Meier CR. Poorly Controlled Type 2 Diabetes Mellitus is Associated with a Decreased Risk of Incident Gout: a Population-Based Case-Control Study. Ann Rheum Dis. 2014. In press.

Bruderer S, Bodmer M, Jick SS, Meier CR. Use of Hormone Replacement Therapy and the Risk of Incident Gout: a Population-Based Case-Control Study. Unpublished.

Abstracts

Bruderer S, Bodmer M, Jick SS, Meier CR. Diabetes and the Risk of Incident Gout. Pharmacoepidemiology and Drug Safety, August 2013.

Bruderer S, Bodmer M, Jick SS, Meier CR. Diuretics and the Risk of Developing Gout. Pharmacoepidemiology and Drug Safety, 2012; 21: S256.

Bruderer S, Bodmer M, Jick SS, Meier CR. Hormone Replacement Therapy and the Risk of Developing Gout. Pharmacoepidemiology and

Drug Safety, 2012; 21: S479.

International Presentations

2013	29^{th} International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) in Montreal, Canada
	Poster presentation: Diabetes and the Risk of Developing Gout
	42^{nd} European Symposium on Clinical Pharmacy (ESCP) in Prague, Czech Republic
	Poster presentation: Diabetes and the Risk of Developing Gout
	Oral presentation: Diabetes and the Risk of Developing Gout
	Poster presentation: Incidence of and Risk Factors for Severe Hypoglycaemia in Treated Type 2 Diabetes Mellitus Patients in the United Kingdom
2012	28^{th} International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) in Barcelona, Spain
	Poster presentation: Diuretics and the Risk of Developing Gout
	Poster presentation: Hormone Replacement Therapy and the Risk of Developing Gout
	41^{st} European Symposium on Clinical Pharmacy (ESCP) in Barcelona, Spain
	Poster presentation: Hormone Replacement Therapy and the Risk of Developing Gout
	Oral presentation: Hormone Replacement Therapy and the Risk of Developing Gout
2011	40^{th} European Symposium on Clinical Pharmacy (ESCP) in Dublin, Ireland
	Poster presentation: Antihypertensive Drugs, especially Diuretics and the Risk of Developing Gout
	Oral presentation: Antihypertensive Drugs, especially Diuretics and the Risk of Developing Gout

Languages

German	Mother tongue
English	Fluent, level C1, Cambridge Certificate in Advanced English (CAE)
French	Good, level B2
Spanish	Basic knowledge, level A2

Computer Skills

Software	Microsoft Office: Excel, Outlook, Power Point, Word
	SAS, the Statistical Analysis System
	LaTeX, a document preparation system

Basel, 10^{th} October 2014