Epidemiology of gout in the United Kingdom and Taiwan

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Abstract

Background: Gout is the most common inflammatory arthritis worldwide. The hallmarks of initial gout presentation are acute pain, swelling, erythema and tenderness in peripheral joints but eventually unremitting arthritis, joint deformity and tophus deposition may develop with long-standing hyperuricaemia. Patients with gout suffer not only arthritis but also cardiovascular, renal, metabolic and other comorbidities. Since gout is the consequence of chronic hyperuricaemia, urate-lowering treatments (ULT) helps prevent the formation of urate crystals and promote dissolution of existing crystals.

Methods: This thesis contained results from a series of observational studies relating to gout. The data sources included the Clinical Practice Research Data-link in the UK and the National Health Insurance Database in Taiwan, both of which are representative of the general population in these two countries. Six different analyses were carried out: (1) epidemiology of gout in the UK (chapter 3); (2) epidemiology of gout in Taiwan (chapter 4); (3) Nature history of gout following diagnosis in the UK (chapter 5); (4) familial aggregation and heritability of gout in Taiwan (chapter 6); (5) risk of comorbidities occurring before gout diagnosis (chapter 7) and (6) Effects of allopurinol on all-cause mortality (chapter 8).

Results: This study estimated that the prevalence of gout was 2.49% in the UK in 2012 and 6.24% in Taiwan. Incidence of gout was also higher in Taiwan (3.47 per 1,000 person years in 2010) than in the UK (1.77 per 1,000 person years in 2012). The prevalence and incidence were increasing in the UK in the past decade, however, both of which remained stable in the period 2005-2010 in Taiwan. Compared with the general population, individuals with a family history of gout had a two-fold increased risk of the disease. The relative contributions of heritability, shared and non-shared environmental factors to explain phenotypic variance of gout were 35.1%, 28.1% and 36.8% in men and 17.0%, 18.5% and 64.5% in women, respectively. Patients with gout were already at higher risk of multiple comorbidities at diagnosis, furthermore, gout was associated with higher all-cause mortality. In both countries, the management of gout remains poor. Most gout patients were eligible for ULT at diagnosis or shortly after. Allopurinol, the most commonly prescribed ULT in primary care in the UK, exerted a neutral effect on all-cause mortality, which reassures the safety of the drug in terms of all-cause mortality.

Conclusions: Gout is the most common inflammatory arthritis affecting one in 40 people in the UK and one in 16 people in Taiwan. It is influenced by both environmental and genetic factors. Both incidence and prevalence keep rising in the UK whilst they remain comparatively

stable in Taiwan. The management in the UK remains poor. Primary care physicians should be encouraged to screen for possible existing comorbidities at diagnosis. Most patients are eligible for ULT at diagnosis or shortly after diagnosis, and given the many benefits of ULT for gout patients, early discussion of ULT with patients seems reasonable practice. Allopurinol is not associated with heightened mortality which should reassure practitioners who avoid ULT for fear of serious adverse events.

Acknowledgements

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Published papers from this thesis

1. Familial aggregation of gout and relative genetic and environmental contributions: a nationwide population study in Taiwan. Kuo CF, Grainge MJ, See LC, Yu KH, Luo SF, Valdes AM, Zhang W, Doherty M. Ann Rheum Dis. 2013 Nov 21. doi: 10.1136/annrheumdis-2013-204067.
2. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Ann Rheum Dis. 2014 Jan 15. doi: 10.1136/annrheumdis-2013-204463.

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CHAPTER 1. Introduction

Gout is the most common inflammatory joint diseases with a wide range of clinical manifestations. It is a crystal deposition disease that results from formation of sodium urate crystals within and around peripheral joints.(Choi et al., 2005b) Chronic hyperuricaemia, resulting from inefficient renal excretion or excess production of uric acid, is the key predisposing factor. Clinically, gout is characterized by recurrent acute attacks of arthritis, chronic inflammatory and mechanical joint symptoms, subcutaneous urate crystal concretions (tophi), urate nephropathy and urolithiasis.(Wortmann, 2006) Although chronic hyperuricaemia is central to gout it does not inevitably cause the disease, but many studies have reported an increase in prevalence both of hyperuricaemia and gout.(Currie, 1979, Harris et al., 1995, Klemp et al., 1997)

Gout is not only a disease of joints. It also associates with many disorders which may affect longevity and well-being. Patients with gout suffer not only arthritis but also cardiovascular,(Abbott et al., 1988, Krishnan et al., 2006, De Vera et al., 2010, Kuo et al., 2013c, Chen et al., 2007b, Choi and Curhan, 2007) renal,(Yu et al., 2012) metabolic(Choi et al., 2007, Suppiah et al., 2008) and other comorbidities.(Boffetta et al., 2009, Kuo et al., 2012,

Kuzell et al., 1955, Durward, 1976, Maynard et al., 2014, McAdams-DeMarco et al., 2012) Collectively gout and associated comorbidities lead to reduced quality of life(Chandratre et al., 2013) and reduced overall survival.(Kuo et al., 2011, Kuo et al., 2010a, Stack et al., 2013, Kok et al., 2012, Teng et al., 2012, Krishnan et al., 2008, Choi and Curhan, 2007)

The aims of the present thesis were to study risk factors, prevalence, incidence, management, comorbidities and mortality of gout using two national administrative databases: the UK Clinical Practice Data-Link (CPRD) and the Taiwan National Health Insurance Research Database (NHIRD).

This chapter provides an introduction to gout regarding to its historical background, definitions, prevalence and incidence, aetiology, risk factors, comorbidities, treatment and prognosis. It mainly consists of a literature review of previous studies relevant to the scope of this thesis.

1.1 Historical aspect of gout

1.1.1 Prior to discovery of uric acid

Gout is a disease of antiquity, as demonstrated by fossil evidence of gout in a cast of the carnivorous dinosaur *Tyrannosaurus rex*(Rothschild et al., 1997) and skeletal remains of a pharaoh of the fourth dynasty of Egypt, Mycerinus (2620 BC to 2480 BC).(Smith and Dawson, 1924, Hartung, 1957) In addition, typical destructive features of gout have been observed in 3 male skeletons from England (AD 150)(McWhirr et al., 1982) and 5.6% of 250 skeletons from Guam dated to AD 950-1450.(Rothschild and Heathcote, 1995) Furthermore, gout has been recognised and described in ancient texts such as the Edwin Smith and George Ebers Papyri (1550 BC).(Haas, 1999) Interestingly, the George Ebers papyrus described the autumn crocus (*Colchicum autumnale*), the plant source of colchicine, as an early treatment for gout.(Graham and Roberts, 1953)

The manifestations of gout have been described accurately and in detail over the centuries. Aretaeus the Cappadocian in the first century described the onset of podagra, which is very similar to the famous later description by Sydenham.(Copeman, 1964). Hippocrates of Kos

and his followers laid the foundations for the theory about gout. He differentiated gout from rheumatism and coined the term "podagra" to describe severe pain and swelling in the foot, later to be restricted to the first metatarsophalangeal (MTP) joint, and regarded podagra as the outcome of excessive accumulation of bodily humours that dropped downwards to swell lower limb joints. Galen of Pergamon (AD 129 to AD 199) in the Roman period also supported the humoral theory for gout. However, he considered the local accumulation of humour as the cause of gout and describe tophi as local concentrations of humours.(Porter and Rousseau, 1998)

The word "gout" (derived from "gutta" which means 'drop") was coined to describe podagra by the Dominican monk Randolphus of Bocking, the domestic chaplain to the Bishop of Chichester (1197–1258) based on the four humour theory of the time. Thomas Sydenham (1624 AD to 1689 AD), a famous English physician and a gout sufferer, described well the gout symptoms and signs that he endured.(Clendening, 1960) In addition, he described most of the clinical features and associations of gout we currently acknowledge; for example, heritability, destruction to joints and the eventual appearance of tophi and renal stones.(Hartung, 1957)

1.1.2 Historical aspects of gout in ancient China

In the East, gout has also been described by the Chinese for a long time. The Ancient Chinese medical text "Suwen" (around 400 BC) categorized gout as "bi" syndrome which is caused by the mixture of wind, coldness and damp. In AD 150, the great physician Zhang Zhong Jing clearly described the symptoms of gout and suggested treating it by "strengthening circulation by improving kidney". Several terms were used to describe gout in Chinese medicine, such as "white-tiger wind pain" and "joint-running wind". More recently, gout is termed "tong feng" which literally means pain (tong) and wind (feng). This term was coined by Zhu Dan Xi (1281-1358) who wrote in "Further treatises on the properties of things - Treatise on gout":

"Gout is generally due to exposure of blood to heat, after which the person wades in cold water, is exposed to fanning to keep cool or is exposed to wind during sleep. The blood heat combines with the cold and congeals with filthy turbidity; hence there is pain which worsens at night (the time of yin). Treatment requires acrid and hot formulas to dissipate cold-damp, open the interstices and allow the blood to move in conformity with qi, thereby leading to recovery." (translated as in,(Deng, 2008) by Professor Deng Zhao-Zhi).

1.1.3 Monosodium urate crystal (MSU) deposition as the cause of gout

Gout is now recognised as a true crystal deposition disease that results from the formation of monosodium urate (MSU) crystals, the driving force of crystal deposition being persistently high levels of uric acid. The discovery of uric acid by Karl Wilhelm Scheele (1742-1786) dates back to 1776.(Scheele and Beddoes, 1786) Three years later W. H. Woolaston (1766-1828) demonstrated sodium urate to be the main content of a tophus from his own ear (Stukeley, 1735). Sir Alfred Garrod (1819-1907) was the first to postulate uric acid as "the specific morbid humour which inflames all joints in which it enters". In addition, he also devised the famous "thread test" as the first qualitative test for uric acid.(Mellen et al., 2006)

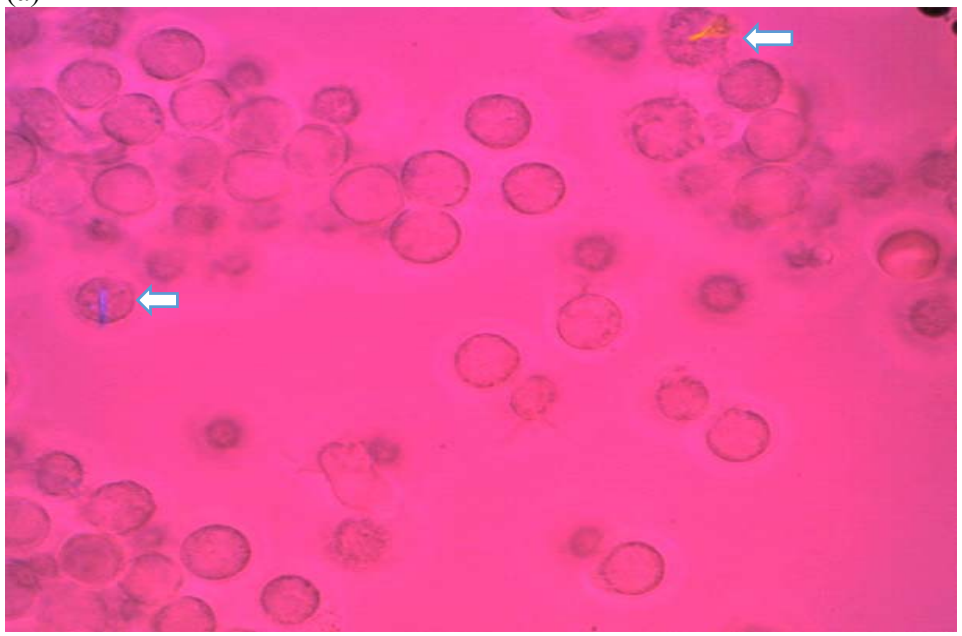
Later in 1897 Gustave Riehl (1855-1943) described MSU crystals in the phagocytic cells in two skin tophi and speculated that crystals might be the cause of the inflammation. Two years later, Wilhelm His Jr. at the University of Leipzig injected synthetic MSU crystals into his skin and then biopsied the site to confirm historical evidence of an inflammatory response. Freudweiler later demonstrated that MSU crystals cause both inflammation and necrosis by histological study of rabbits and chickens injected with MSU crystals.(Wortmann, 2006) Seegmiller in the early 1960s also performed a human experiment, injecting sterilized MSU

crystal into a knee of a volunteer. An intense inflammatory response was observed in the joint and the aspirated synovial fluid showed phagocytosed MSU crystals.(Buchanan et al., 1965) Faires and McCarty in Philadelphia independently produced similar results at the same time.(McCarty et al., 1965) Therefore, MSU crystals are identified unequivocally as the pathogenic agent in gouty arthritis.

1.2 The definition of gout

The concept of gout has evolved over a long period. Only after the discovery of uric acid by Karl Wilhelm Scheele, the observation by Sir Alfred Garrod of abnormal quantities of serum uric acid as a hallmark of gout, and the key demonstration by Gustave Riehl (and subsequently by Wilhelm His Jr., Seegmiller and McCarty) of monosodium urate (MSU) crystals as the aetiological agent in gout was gout established as a distinct crystal deposition disease. Nowadays, gout is recognised to have a range of phenotypic expression and characteristics which include: elevated serum urate concentration (hyperuricaemia); recurrent attacks of acute arthritis in which monosodium MSU crystals can be demonstrated in synovial fluid (figure 1.1a); compacted aggregates of MSU crystals (tophi; figure 1.1b) deposited chiefly in and around joints, which sometimes lead to joint damage and deformity; renal disease involving glomerular, tubular, and interstitial tissues and blood vessels; and uric acid urolithiasis (Firestein and Kelley, 2009).

(a)



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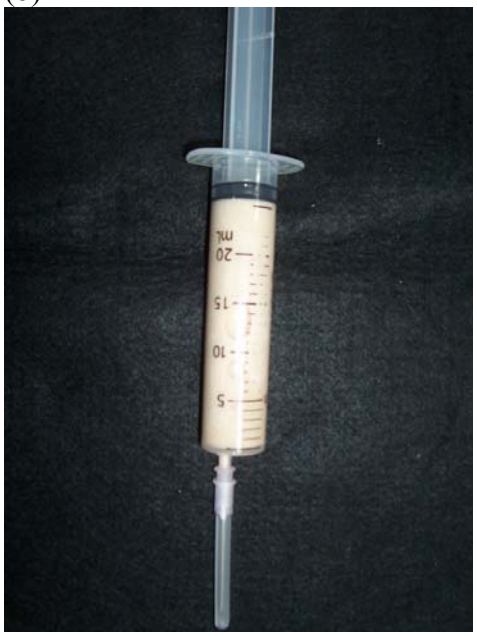


Figure 1-1 (a) Monosodium urate crystals (MSU; arrows) taken up by monocytic cells, viewed under polarising light microscopy (x400). The picture shows MSU crystals obtained from a liquefied tophus being co-cultured with monocytic cells. Note that MSU crystals present with different colours (blue or yellow) according to the relative angle of the long axis of the crystal to the optical axis (MSU crystals give a negative sign of birefringence). (b) Liquefied tophus from a knee aspirate of a gout patient appearing macroscopically as “joint milk”. (Personal collection, with patient consent)

1.2.1 **"Gold" standard**

The EULAR evidence based recommendations for gout state that "demonstration of MSU crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout".(Zhang et al., 2006b) Currently, the standard approach to crystal identification follows Hollander and McCarty's preparation of a single wet drop of synovial fluid.(McCarty and Hollander, 1961) First, the observers look for cells using 10x or 40x of magnification under ordinary light microscopy. Clumps of MSU crystals should be evident by themselves. Under compensated polarized light microscopy, the MSU crystals are long and needle-shaped with a length up to 30 µ and are either bright yellow or blue depending on their relative orientation with the planes of light. The finding of intracellular MSU crystals supports the diagnosis of acute gouty arthritis. Isolated clumps of crystals without accompanying inflammatory cells indicate resolution of acute arthritis or an inter-critical period of gout. Large amounts of MSU crystal aggregates indicate the presence of tophi, although this often can be ascertained grossly.

The value of synovial fluid examination for the diagnosis of gout has been examined in two systematic reviews (Segal and Albert, 1999, Swan et al., 2002). In general, crystal

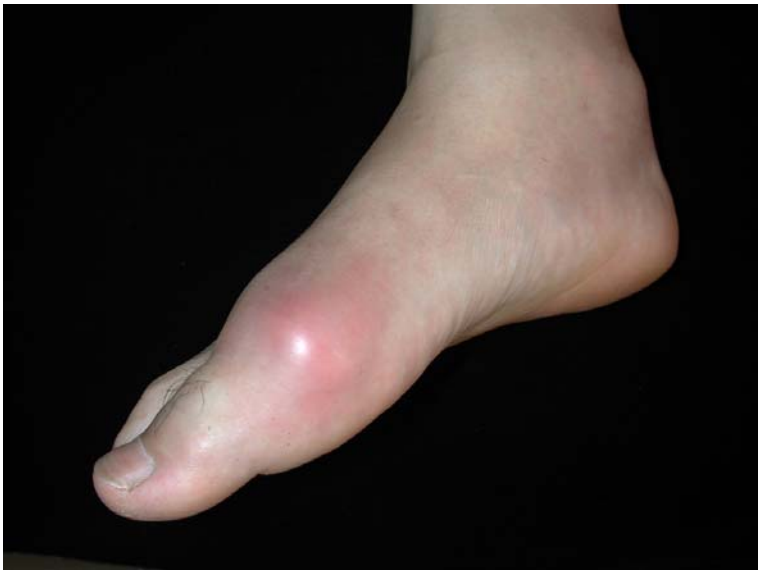
identification has been found to be highly specific, with a specificity of 97%.(Gordon et al., 1989) However, a comparatively lower sensitivity and inconsistency between different observers in MSU identification reduces the certainty of ruling out gout in patients without clear evidence of MSU crystals in synovial fluid. Despite inter-observer variability, the demonstration of MSU crystals in synovial fluid is undoubtedly accepted as the gold standard for diagnosis of gout.

1.2.2 Clinical diagnosis

As with the diagnosis of other diseases, the clinical diagnosis of gout depends on features in the medical history, physical examination, laboratory tests and other investigations such as imaging. An acute attack of gout usually involves a single joint, with the first MTP joint being the most common first affected joint (figure 1.2). Other typical characteristics include swelling, severe pain that reaches its maximum within 12-24 hours, marked tenderness, redness and self-resolution over a few days or weeks. Other patients may present with chronic joint symptoms related to joint damage, or with clinically evident tophi (figure 1.3). In those with classic tophi and hyperuricaemia the diagnosis is often explicit. Recent EULAR evidence based recommendations for gout found that based on the population risk of gout

of 1% the composite findings of painful joint, swelling, abrupt onset and remission within 2 weeks was associated with a likelihood of 3% for gout. When these findings focus on the first MTP and present with the presence of podagra the likelihood of gout rises to 49%. Certainly, the finding of a tophus is associated with a high confidence of gout diagnosis with a likelihood of 99%.(Zhang et al., 2006b)

(a)



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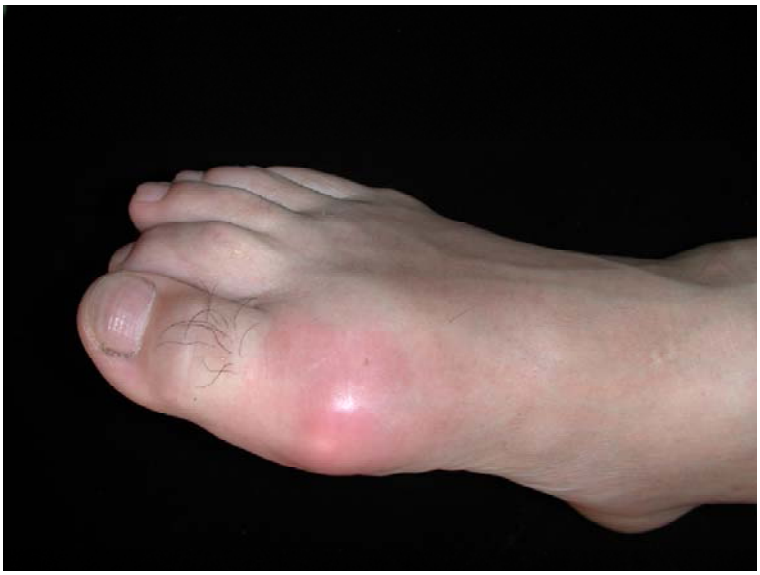
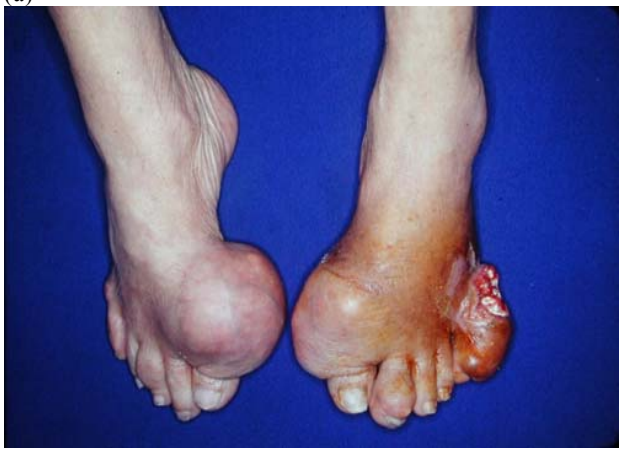


Figure 1-2 Acute gouty arthritis in the right first metatarsophalangeal joint (a) medial side (b) dorsal side (photos provided by Dr. Kuang-Hui Yu; with patient consent)

(a)



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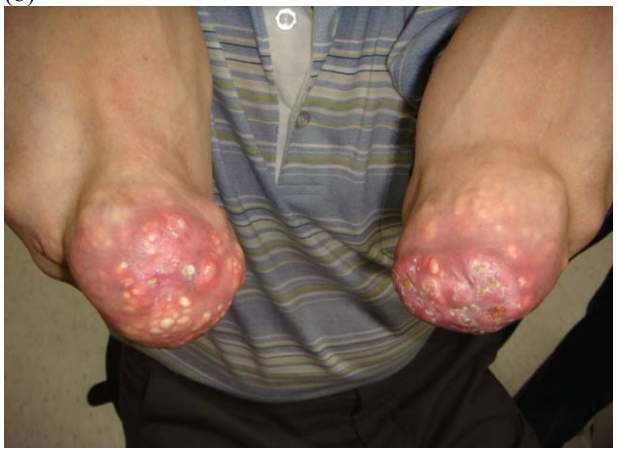

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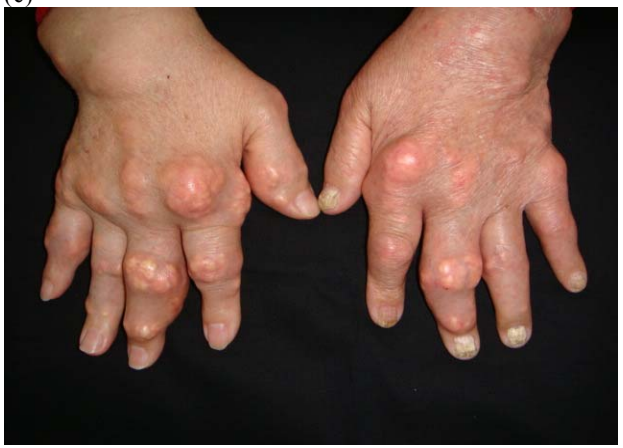


Figure 1-3 Tophus deposition in (a) feet (b) elbows (olecrenon) and (c) hands. (Photos provided by Dr. Kuang -Hui Yu; with patient consent)

1.2.3 Classification criteria

Three main classification criteria are available for study purposes: the Rome,(Kellgren JH, 1963) the New York (Bennett PH, 1968) and the ARA (American Rheumatism Association, now American College of Rheumatology [ACR]) preliminary criteria**.**(Wallace et al., 1977) ACR criteria also consider the survey setting, which is important in primary care when joint fluid examination is usually impractical. All these criteria have been validated with moderate performance when compared to MSU crystals in synovial fluid as the gold standard.(Malik et al., 2009) Recently Janssens et al. provided a gout diagnosing rule based on clinical symptoms and signs which is easy and modest in validity (Janssens et al., 2010) although ffurther validation is needed.

1.2.4 Case definition used in epidemiology

In many situations, especially in population studies utilising administration databases, these classification criteria cannot be applied due to insufficient clinical and laboratory information. In such situations, the identification of gout cases often depends on patient recall or physician diagnosis. For a self-reported physician diagnosis of gout, one recent study reports good reliability and sensitivity.(McAdams et al., 2011)

The utility and validity of gout diagnoses specifically within insurance claims data has also been assessed.(Harrold et al., 2007, Singh et al., 2007) Harrold et al. demonstrated that a diagnosis of gout recorded on 2 or more occasions had a positive predictive value of 61%.(Harrold et al., 2007) Another study found that an ICD-9 code for gout (274) had a sensitivity of 90%, a specificity of 100%, and positive and negative predictive values of 100% and 87%, respectively.(Singh et al., 2007) However, since the contents of administrative databases vary, separate validation of case definitions may be needed for each database.

1.3 Clinical manifestations of gout

The hallmark of gout is acute arthritis that occurs abruptly and resolves spontaneously. The affected joints may present with pain, swelling, redness and loss of function, which are all typical features of an inflammatory arthritis. The first attack of gouty arthritis is usually in small joints of the lower limb, in particular the first MTP joint ("podagra"). For a typical gout attack, maximal inflammation usually occurs within 4 to 12 hours after onset and the intensity reduces gradually to spontaneous resolution even without treatment. Constitutional symptoms such as fever may also manifest in severe attacks.

Generally, a mono-articular onset is characteristic in 70% to 90% of affected individuals and polyarticular attacks occur in 11% to 28% of patients.(Nishioka and Mikanagi, 1980, Lawry et al., 1988) In three UK series, the joints involved most commonly in descending order of frequency are the first MTP joint, ankle/foot, knee and then other joints.(Grahame and Scott, 1970, Currie, 1978, Roddy et al., 2007a) A small number of patients may present with extra-articular manifestations, such as bursitis or discharging subcutaneous tophi.

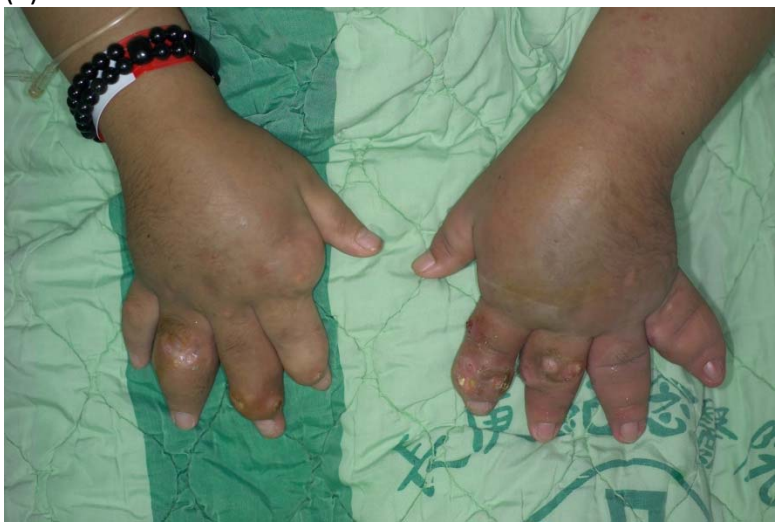
Tophi generally are white to yellow soft or firm lumps under the skin (figure 1-3). The most common sites of occurrence are the dorsum of the foot, Achilles tendon region, anterior knee, fingers and elbows. If the overlying skin breaks, which is quite common, pus-like fluid containing gritty white material (MSU crystal

aggregates) may discharge from the wound. Figure 1.4 shows a gout patient with massive tophus deposition under the skin of both hands and Figure 1.5 shows the typical radiographic features of tophi within bone and joints as well as under the skin, with marked eccentric soft tissue swelling, severe destructive arthropathy, “punched out” cystic lesions and overhanging “hooks” of bone.

Generally speaking, the acute arthritis of gout is rapidly escalating and then resolved spontaneously. Episodic attacks interspersed with long inter-critical asymptomatic periods are the norm. This is very characteristics of gout, no other chronic arthritis presents with such periodicity. Rheumatoid arthritis, for instance, presents with insidious arthritis at first, often with morning stiffness rather than outright arthritis and followed by unremitting chronic polyarticular arthritis if not treated. Septic arthritis can occur with explosive joint inflammation, often in large joint. But once treated completely, it is thought to be cured. Sometimes post-infectious arthritis can mimic gout. However, these kind of arthritis presents with a more modest progression; patients very rarely transit from asymptomatic to acute arthritis in several hours. Other crystal-induced arthritis, such as CPPD arthropathy, can also mimic gout. However, crystal-induced arthritis other than gout normally affects large joints, often slowly progresses and predominantly occurs in the elderly. Certainly, only synovial fluid examination can safely distinguish gout from other mimics with certainty.

With evident tophus, the diagnosis of gout is almost always correct. Rheumatoid nodules, often seen in patients with advanced rheumatoid arthritis, also present with subcutaneous nodules. However, rheumatoid nodules are often rubbery firm and 'cold' without marked inflammation. Tophus normally is hard but sometimes it can be soft if the urate crystals inside liquefies. Severe inflammation can be seen with tophus but is very uncommon with rheumatoid nodules. Gout and rheumatoid arthritis tend to be mutually exclusive; therefore the distinction between tophus and rheumatoid nodules can be obvious with background disease. In patients with advanced gouty arthritis, the radiographic manifestation is very characteristic. This is because tophus is radiographically translucent and calcification can occur alone the surface of tophus. Therefore a hook-like or overhanging appearance can be seen.

(a)



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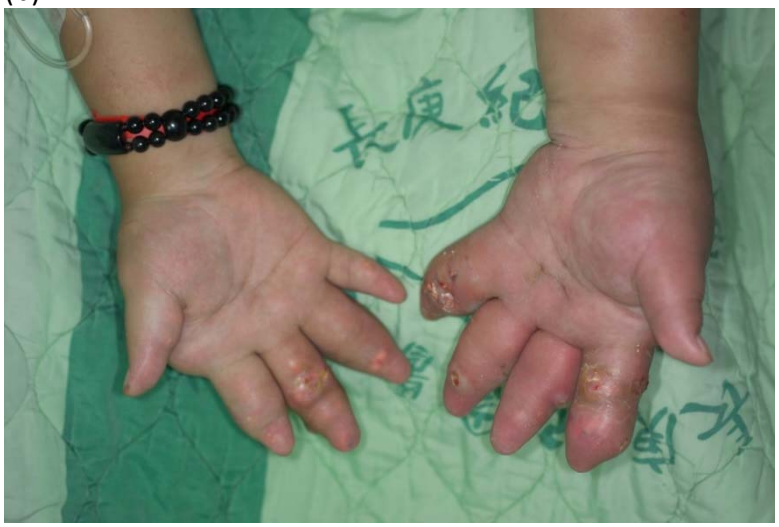


FIGURE 1-4 MASSIVE TOPHUS DEPOSITION ON BOTH HAND WITH SKIN ULCERATION (A) DORSAL AND (B) PALMER SIDES (PERSONAL COLLECTION; WITH PATIENT CONSENT).

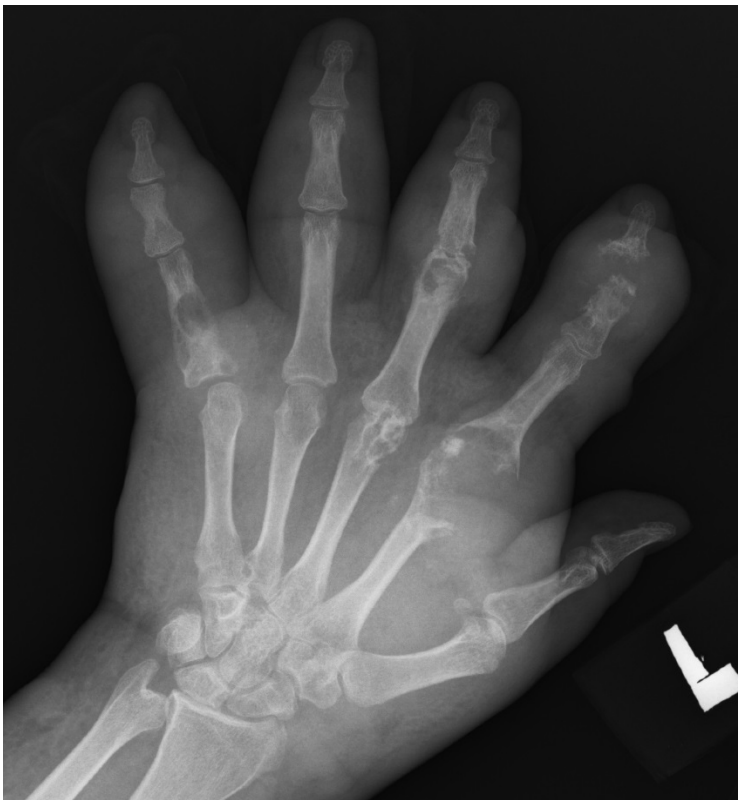


FIGURE 1-5 TYPICAL RADIOGRAPHIC FEATURES OF TOPHACEOUS DESTRUCTIVE ARTHROPATHY (PERSONAL COLLECTION; WITH PATIENT CONSENT).

The typical natural history of gout is generally considered to progress through the following phases: a prolonged period of asymptomatic hyperuricaemia during which MSU crystals are first forming and building in concentration; clinical presentation with acute attacks; asymptomatic inter-critical periods between attacks; chronic symptomatic gout; and eventually tophaceous gout. However, this order is not always followed, for example, some people present directly with tophi without preceding acute attacks.(Wernick et al., 1992) Recently, a new staging system has been proposed: stage A: hyperuricaemia without evidence of

MSU crystal deposition; stage B: MSU crystal deposition without signs or symptoms of gout; stage C: MSU deposition with prior or current symptoms of acute gout flares; stage D: advanced gout requiring specialist intervention.(Dalbeth and Stamp, 2014) This staging system incorporates our recent understanding that MSU crystals are also present in people without any symptoms and signs.(Puig et al., 2008, Howard et al., 2011, Pineda et al., 2011, De Miguel et al., 2012) However, further study is still needed to validate this system.

This new staging system marks a new era of gout understanding. Since the culprit of gout and golden standard of gout diagnosis – MSU crystal in synovial fluid can be identified in hyperuricaemic patients without outright symptoms, the so-called patients with 'asymptomatic' hyperuricaemia do not seem to be asymptomatic anymore. Therefore, if this findings is confirmed, the definition of gout could change drastically. If we define gout as patients having MSU crystals, one-third of current classified asymptomatic hyperuricaemic patients could be reclassified as gout. On the other hand, the demonstration of MSU crystals may not be the gold standard of gout diagnosis anymore if we define gout as a disease of acute arthritis. Not only staging of gout, the classification criteria may need to revise. This could fundamentally change the estimates of gout prevalence and incidence. In this study, we still adhere to traditional definition of gout, that is, acute arthritis secondary to MSU crystal deposition and patients with sole hyperuricaemia are not

included in the estimation of gout prevalence and incidence. However, we need to bear in mind that gout prevalence and incidence may be grossly underestimated, given that prevalence of hyperuricaemia in contemporary society is often several fold that of gout prevalence.

1.4 Epidemiology of gout

Measures of occurrence of diseases include: [1] prevalence – the number of cases of a given condition per population at a given time; and [2] incidence – the number of new cases of a given condition per population in a specified period of time. Estimates of the prevalence of gouty arthritis vary between studies, owing to the differences in the definition of the condition, geographic locations, race and method and time of investigation. Since the prevalence and incidence of gout vary greatly between countries, the following sections discuss prevalence and incidence of gout in the UK, Taiwan and in other countries

1.4.1 PREVALENCE

Data from the published papers describing the prevalence of gout in the UK and in Taiwan are summarised in Table 1.1. The prevalence of gout in the UK has been estimated in several studies with wide variability depending on study design, area, age range, diagnostic criteria and research settings. The prevalence in men ranges from 0.53% in the Scottish Highlands(Steven, 1992) to 1.68% in the Cotswolds.(Badley et al., 1978) For women, the prevalence ranged from 0.05% in Wales(Currie, 1979) to 0.29% in England.(Harris et al., 1995) A nationwide estimate by Mikuls indicated an overall prevalence of gout at 1.39%.(Mikuls et al., 2005b)

The prevalence of gout in Taiwan is much higher than that in the UK, especially in the aborigine population. A nationwide survey found the prevalence of self-reported gout to increase significantly from the periods 1993-1996 to 2005-2008, specifically from 4.74% to 8.21% in men and from 2.19% to 2.33% in women.(Chuang et al., 2011) The prevalence of gout is much higher in aboriginal areas. Chang et al. reported a prevalence of 15.2% in men in aboriginal areas compared to 3.4% in men in non-aboriginal areas. A similar pattern was observed in women.(Chang et al., 1997)

Racial and geographic differences appear to be significant. Early European studies, including the Netherlands,(De Blecourt, 1954) France,(Zalokar et al., 1974) Finland,(Isomaki and Takkunen, 1969) and Denmark(De Muckadell and Gyntelberg, 1976) indicated a generally low prevalence of gout. However, a more recent study found a prevalence of 1.4% in Germany, using the IMS disease analyser, which is equivalent to the UK prevalence in the same study.(Annemans et al., 2008) Early reports from the Framingham study in the US found a prevalence of 2.85% in men and 0.39 in women.(Hall et al., 1967) The NHANES study in the US found a prevalence of gout of 3.9% in 2007-2008, which is higher than estimate in the same study population in 1988-1994 (2.7%).(Zhu et al., 2011)

Japan and China both have a lower prevalence of gout than in neighbouring Taiwan. An early study in Nagono, Japan, showed a prevalence of only 0.27% in men and 0.03% in women.(Akizuki, 1982) In the Huangpu district of Shanghai, the prevalence of gout was 0.77% in men and 0.34% in women.(Chen et al., 1998) In contrast Pacific Islanders(Klemp et al., 1997, Gibson et al., 1984, Brauer and Prior, 1978, Zimmet et al., 1978), particularly Maoris, have the highest gout prevalence at 13.9% in men and 1.9% in women.(Klemp et al., 1997)

Although these studies on gout prevalence are of different design and with varied case definition, gout prevalence seems to be increasing on the whole. In general prevalence of gout was lower in the studies conducted in the 1980s compared to those conducted in 1990s. Studies conducted in the new millennium often are of highest prevalence. Since there were no major changes in gout definition and classification criteria (ACR criteria was released in 1977), we could not blame the increasing prevalence on the more inclusive classification criteria. Many studies suggest gout is poorly managed and patient adherence is worst of all chronic diseases. This pattern does not seem to change significantly. Therefore heightened awareness cannot explain such increasing prevalence. Therefore, this increase seems to be real in many different countries in the world. However, the causes of such increase still need further investigation to confirm.

In addition, gout prevalence varies significantly geographically and racially. In general, pacific islanders seem to have the highest prevalence of gout in the world. Aboriginals in Taiwan, cousins of Polynesians and Melanecians also have a very high prevalence of gout. In contrast, Caucasians have lower prevalence of gout. This racially diverse pattern suggests the importance of genetics in the determination of phenotype expression. However, other factors are also important. For instance, prevalence of gout in American White men is consistently higher than their European counterparts. Therefore, environmental factors are equally important in terms of prevalence of gout.

Several methodological issues need to be considered. First, the definitions of gout used in these studies are diverse. The golden standard of gout diagnosis is based on the identification of urate crystals. However, this is rarely done because it is painful. In addition, first few attacks are often in small joint such as joints in the big toes, technically it is difficult to aspirate synovial fluid for examination. Therefore there are classification criteria to assist diagnosis. While these criteria are useful clinically, they are seldom used in epidemiological surveys. Therefore for surveillance studies, the case definition is often self-reported. Recall may influence the accuracy of such reports. For database research, the case definitions are based on physician diagnosis, which may be more reliable but patients not under medical attention at the time of research cannot be identified. For instance Elliot et al reported a much lower prevalence than estimates at the same time. This

is because they only included patients seeking medical advice in the calendar year studied. Therefore, intercritical gout patients were excluded. In this regard, this measure should be termed consultation rate, rather than prevalence.

1.4.2 Limitations of current studies on gout epidemiology

Several limitations of current available studies on gout epidemiology deserve a more detailed discussion. Firstly, the case definitions of gout rarely rely on published classification criteria. Most surveillance-based studies were based on self-reported gout, which is prone to biased estimates due to inconsistent recall. Despite gout is relatively easy to diagnose, identification of gout cases depend on patients' willingness to seek medical advice, which is notoriously poor in gout patients. Secondly, the sampling strategies are varied and not consistent. Many studies have different age restrictions, therefore compromising comparability across studies. Further, some studies were based on hospital or clinic records of specific institutions, which could lead to a selection bias for more severe cases. Thirdly, since gout has long asymptomatic periods, definition of observation period could have biased the estimation of gout epidemiology. For instance, Elliot et al restrict the case definition to patients under medical attention in the year of interest, resulting in a gross underestimation of gout prevalence due to the exclusion of gout cases in intercrital periods.

Table 1-1 Prevalence of gout in the UK and Taiwan

Authors	Year	Area	Number	Age limit	Data source	Case definition	Prevalence (%; M/F)
				United Kingdom			
(Badley et al., 1978)	1971-1972	Cotswolds	3892	35+	Survey	Self-reported	1.68/0.28
(Currie, 1979)	1975	England Wales	259000 40500	15+	GP	Physician diagnosis	0.73/0.13 0.52/0.05
(Gardner et al., 1982)	1982	3 English towns	10539	45+	Survey	Self-reported	4.33/-
(Steven, 1992)	1987	Scottish Highlands	35251	nil	GP	Physician diagnosis	0.53/0.15
(Harris et al., 1995)	1992-1993	England	300376	nil	GP	Physician diagnosis	1.64/0.29
(Mikuls et al., 2005b)	1990-1999	Nationwide	1716276	nil	Database	Physician diagnosis	Overall: 1.39 M/F ratio: 3.6:1
(Annemans et al., 2008)	2000-2005	Nationwide	N/A	nil	Database	Physician diagnosis	Overall: 1.4
(Elliot et al., 2009)	2001-2007	Nationwide	N/A	45+	Surveillance	Physician diagnosis	0.76/0.18
				Taiwan			
(Chou et al., 1994)	1994	Hen-San (rural) Sien-Dien (suburban) Cu-Tien (urban)	8998	20+	Survey	Self-reported	0.16 0.67 0.67
(Chang et al., 1997)	1995	Aboriginal, Non-aboriginal	396 648	40+	Survey	Self-reported	15.2/4.8 3.4/2.8
(Chou and Lai, 1998)	1994	Ho-Ping county	342	18+	Survey	Self-reported	26.2/1.0
(Lin et al., 2000)	1991-1992	Kinmen county	3185	30+	Survey	Self-reported	11.5/3.0
(Chang et al., 2001)	1993-1996	Nationwide	5707	20+	Survey	Self-reported	3.3/1.1
(Lai et al., 2009)	2000-2002	Taichung	3397	20+	Hospital	Physician diagnosis	5.0/0.6
(Kuo et al., 2010b)	2000-2006	Taoyuan	67769	All age	Nationwide	Physician diagnosis	5.17/1.64
(Chuang et al., 2011)	1993-1996 2005-2008	Nationwide		20+	Survey	Self-reported	4.74/2.19 8.21/2.33

1.4.3 **Incidence**

Far fewer studies have addressed the incidence of gout. The largest population-based study was conducted in Rochester, Minnesota, which estimated an annual incidence of 0.45 per 1000 and 0.62 per 1000 person-years during the periods 1977-1978 and 1995-1996.(Arromdee et al., 2002) The Framingham study estimated an average annual incidence of 1.6 and 0.2 per 1000 person-years for men and women, respectively.(Abbott et al., 1988) Using data from the UK Second and Third National Studies of Morbidity in General Practice in the UK, overall gout incidence was estimated to be 1.4 per 1000 person-years in 1981.(Stewart and Silman, 1990) More recently Mikuls used the General Practice Research Database (GPRD) and estimated the UK all-age incidence of gout to be 1.31 cases per 1000 person-years in 1999.(Mikuls et al., 2005b)

Many considerations are needed to correctly interpret estimates of gout incidence. First, gout is generally regarded as a benign disease and affected patients often do not seek medical advice. This could potentially underestimate incidence of gout irrespective of case definitions, since these patients do not report to general practitioners resulting in a lack of formal physician diagnosis. Second, gout is an episodic disease with potentially long asymptomatic

period. Therefore, different observation periods in different physician-based studies may hinder comparability of these estimates. For survey based studies, estimates of gout incidence is subject to the length of recall of the respondents. Patients with remote attacks may thus being classified as incident cases, resulting in overestimation of gout incidence. Based on these considerations, the Rochester study may be the only study in which their incidence estimation can be compared. This study found an increasing incidence of gout. Mikuls study, despite based on physician diagnosis, did not consider observation periods. Therefore their earlier estimation is probably overestimated due to insufficient observation time to distinguish prevalent from incident cases and prevalent cases.

1.5 Risk factors for gout

The primary driving force for predisposition to MSU formation is hyperuricaemia. Several conditions may induce hyperuricaemia and therefore increase the risk of gout. However, hyperuricaemia alone is not a sufficient factor for development of gout. Several other factors influence the propensity to MSU deposition in joint tissues. These risk factors are discussed in the following section.

1.5.1 Hyperuricaemia

That hyperuricaemia is a genuine risk factor for gout which has been demonstrated epidemiologically in both the Framingham study(Hall et al., 1967) and Normative Aging study.(Campion et al., 1987) A clear dose response relationship exists between serum uric acid (SUA) levels and cumulative incidence of gout. In addition, in the Normative Aging study hyperuricaemia alone renders other predictors of gout, including age, body mass index, hypertension, and cholesterol level, and alcohol intake, non-influential in a Cox regression model.(Campion et al., 1987)

1.5.2 **Genetics**

A genetic component to development of gout is supported by clinical and epidemiological evidence as well as recent advances in genetic studies. The varying prevalence of gout, from 2.6% to 47.2% in different populations, suggests racial and genetic differences.(Currie, 1979, Klemp et al., 1997) SUA levels in the UK(Popert and Hewitt, 1962) and in North American Caucasians(O'Sullivan, 1972) are similar whereas US mixed racial studies demonstrate a greater prevalence of hyperuricaemia in African Americans than Caucasians.(Agamah et al., 1991) The Pacific Islanders, including Maoris, Cook Islanders and Micronesians, were long known to have a high prevalence of gout and hyperuricaemia (Rose, 1975, Prior et al., 1987, Reed et al., 1972). In Taiwan, a significantly higher prevalence of gout and hyperuricaemia was demonstrated among aborigines than in Han or Hakke Taiwanese.(Chang et al., 1997) All these studies clearly demonstrate a racial difference in gout and hyperuricaemia.

Early genetic studies of gout focused on rare monogenic disorders that cause marked hyperuricaemia and premature gout, for example, deficiency of hypoxanthine-guanine phosphoribosyl transferase (Lesch-Nyan syndrome), over-activity of phosphoribosyl-1-pyrophosphate synthetase, and hereditary renal disease (familial hyperuricaemia

nephropathy, medullary cystic kidney disease).(Choi et al., 2010) More recently different specific genetic associations, particularly polymorphisms of genes involved in renal clearance of urate by urate transporter 1 (URAT-1), have been identified that may be more relevant to the heritability of common gout.(Vitart et al., 2008, Kolz et al., 2009) Limited data, mainly from case series of patients with gout lend support for familial aggregation of gout.(Mituszova et al., 1992, Blumberg, 1965, Emmerson, 1960, Hauge and Harvald, 1955)

1.5.3 Age and gender

Epidemiological studies have confirmed the long recognised predisposition of male sex and older age as genuine risk factors for hyperuricaemia and gout.(Arromdee et al., 2002, Mikuls and Saag, 2006) A recent large study based on the health improvement network (THIN) UK primary care database found a roughly 2-fold increased incidence of gout in men compared to women. There was also a positive linear relationship between incidence of gout and age in both genders.(Cea Soriano et al., 2011)

1.5.4 Other socioeconomic factors

Several European studies report rural residents to have lower risk of gout,(Isomaki and Takkunen, 1969, Popert and Hewitt, 1962) a finding also supported by a study in Taiwan which found a lower gout prevalence in rural (0.16%) than suburban and urban areas (0.67).(Chou et al., 1994) Areas with higher socioeconomic status seem to have a lower prevalence of gout.(Gardner et al., 1982) The UK morbidity statistics from general practice (1970-71) reported that people with non-manual skilled occupations had the highest whereas professional occupations had the lowest standardised consulting ratio for gout (133 vs. 79), compared with the overall frequency of consultations.(Great Britain. Office of Population et al., 1982)

1.5.5 Diet and alcohol consumption

It has long been recognised that diet and alcohol consumption play an important role in the development of gout.(Zollner and Griebsch, 1974, Gordon and Kannel, 1983) However, only recently has robust evidence emerged to support this notion. Numerous studies have demonstrated that a purine-rich diet increases the risk of gout. The most robust evidence

linking purine-rich diet with gout came from the Health Professional Follow-up Study (HPFS), which enrolled 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians aged 40 to 75 years of age in 1986. The HPFS assessed dietary intake using questions on 13 foods and beverages, (Rimm et al., 1992) to enquire about the diet of enrolees.(Choi et al., 2004b, Choi et al., 2004a)

The HPFS reported a relative risk of incident gout of 1.41 for the highest quintile of meat intake and 1.51 for those with the highest quintile of seafood intake. Intriguingly, purine-rich vegetables did not result in an excess risk of gout.(Choi et al., 2004b) A dose response relationship was found between alcohol consumption and risk of gout. Choi et al. report a relative risk of 1.71 for every 10g increase in daily alcohol consumption. Among various alcoholic beverages, beer confers the greatest risk, with a relative risk of 1.49 for each additional daily unit of beer.(Choi et al., 2004a)

1.5.6 **Lead exposure**

Historically, two epidemics of gout, one in the Roman period and the other in the European Renaissance, are linked to lead intoxication.(Ball, 1971) Recent evidence from Taiwan showed

that gout patients had a higher total body lead burden than healthy controls.(Lin et al., 2002) Blood lead levels also correlate with SUA levels.(Shadick et al., 2000) The exact mechanism of lead-induced hyperuricaemia is not clear but low-level environmental lead exposure may accelerate progressive renal insufficiency and hence cause hyperuricaemia.(Lin et al., 2003a) An earlier study suggested that lead may predispose to MSU crystal deposition under physiological conditions by enhancement of nucleation.(Tak et al., 1981) All these mechanisms predispose people with higher lead levels to develop gout.

1.6 Comorbidities and health outcomes of gout

Accumulating evidence suggests that comorbidity is epidemic in gout.(Zhu et al., 2012, Annemans et al., 2008, Richette et al., 2013) For instance, a recent large study found that only 12% of prevalent cases were considered to be isolated gout without significant associated comorbidities.(Richette et al., 2013). These comorbidities may cause severe problems but are often clinically occult, especially in their early stages. These conditions include: (1) conditions associated with metabolic syndrome - diabetes mellitus, hypertension and dyslipidaemia; (2) renal conditions such as chronic kidney disease and urolithiasis; (3) cardiovascular disease such as myocardial infarction, stroke and heart failure; (4) cancer; and (5) osteoarthritis.

However, the relationships between gout and comorbidities seem to be bidirectional. Some categories, particularly cardiovascular and renal diseases, can serve as risk factors and adverse outcomes of gout, suggesting intertwined causality pathway. Risk factors of gout have been discussed in the previous section. The following sections focus on comorbidities as outcomes.

1.6.1 Metabolic syndrome

Insulin resistance, glucose intolerance, obesity, hypertension and dyslipidaemia constitute a cluster of disorders that characterize the so-called metabolic syndrome. Metabolic syndrome is a major risk factor for adverse cardiovascular outcomes.(Wilson et al., 2005, Bonora, 2006, de Zeeuw and Bakker, 2008)

Hyperuricaemia is the hallmark of gout. It is also a common component of metabolic syndrome. Choi et al. reported a progressive increase in the prevalence of metabolic syndrome with increasing uric acid levels.(Choi and Ford, 2007) A recent study from Korea found the prevalence of metabolic syndrome among gout patients to be almost 5 times higher than in controls.(Yoo et al., 2011) Choi et al. reported a 62.8% prevalence of metabolic syndrome among gout patients, compared to 25.4% in controls in the third National Health and Nutrition Examination Survey.(Choi et al., 2007) In addition, presentation with gout preceded the occurrence of metabolic syndrome features.(Hernandez-Cuevas et al., 2009)

1.6.2 Diabetes mellitus (DM)

Recent evidence has linked hyperuricaemia with an increased risk of DM. In the Framingham heart study, hyperuricaemia was associated with a multivariable relative risk of 1.20 and 1.15 for incident type 2 DM in the original and offspring cohort, respectively.(Bhole et al., 2010a) Another study showed the multivariate hazard ratios for incident DM to be 1.08, 1.12 and 1.68 for the second, third and fourth quartile of SUA compared with the first quartile of SUA levels.(Dehghan et al., 2008b) Gout is also associated with a higher risk for DM. The Multiple Risk Factor Intervention Trial (MRFIT) reported a relative risk of 1.34 for type 2 DM in gout compared to non-gout participants.(Choi et al., 2008)

1.6.3 Hypertension

Many studies have investigated the relationship between hyperuricaemia and hypertension. A recent meta-analysis, incorporating results from 18 prospective studies with a total of 55,607 participants, reported that hyperuricaemia was associated with an adjusted relative risk of 1.41 for incident hypertension.(Grayson et al., 2011) However, recent trials with

febuxostat, a xanthine oxidase inhibitor, did not find beneficial blood pressure lowering effects despite significant urate lowering effects.(Becker et al., 2010, Schumacher et al., 2008)

The association between gout and hypertension has long been observed.(Wallace, 1975, Rapado, 1974, Breckenridge, 1966) In the Normative Aging Study, gout was 3 times more common among hypertensive than non-hypertensive participants.(Campion et al., 1987) Riedel et al. found the prevalence of hypertension in 9,482 patients to be 60.9%.(Riedel et al., 2004) In a large US cohort with 5,942 gout patients, the prevalence of hypertension was 36.2% in newly diagnosed gout patients and 45.7% in previous diagnosed gout patients.(Sarawate et al., 2006)

1.6.4 **Kidney diseases**

Chronic kidney disease (CKD) is a condition with progressive loss of renal function over a period of months or years. Continued deterioration of renal function in patients with CKD eventually leads to the development of end-stage renal disease (ESRD). Studies in humans have provided limited evidence of the link between hyperuricaemia and deterioration of renal function.(Avram and Krishnan, 2008, Chonchol et al., 2007, Obermayr et al., 2008, See et al.,

2011, Iseki et al., 2004) As shown in Figure 1.6, annual renal function accelerated in patients with higher SUA levels. In one study, the risk for CKD increased 1.69-fold for every 2 mg/dl increase in SUA levels.(Obermayr et al., 2008) In addition, hyperuricaemia is strongly associated with CKD, independent of the presence or absence of the metabolic syndrome.(See et al., 2011) Moreover, subjects with hyperuricaemia are more likely to develop ESRD than those without.(Iseki et al., 2004)

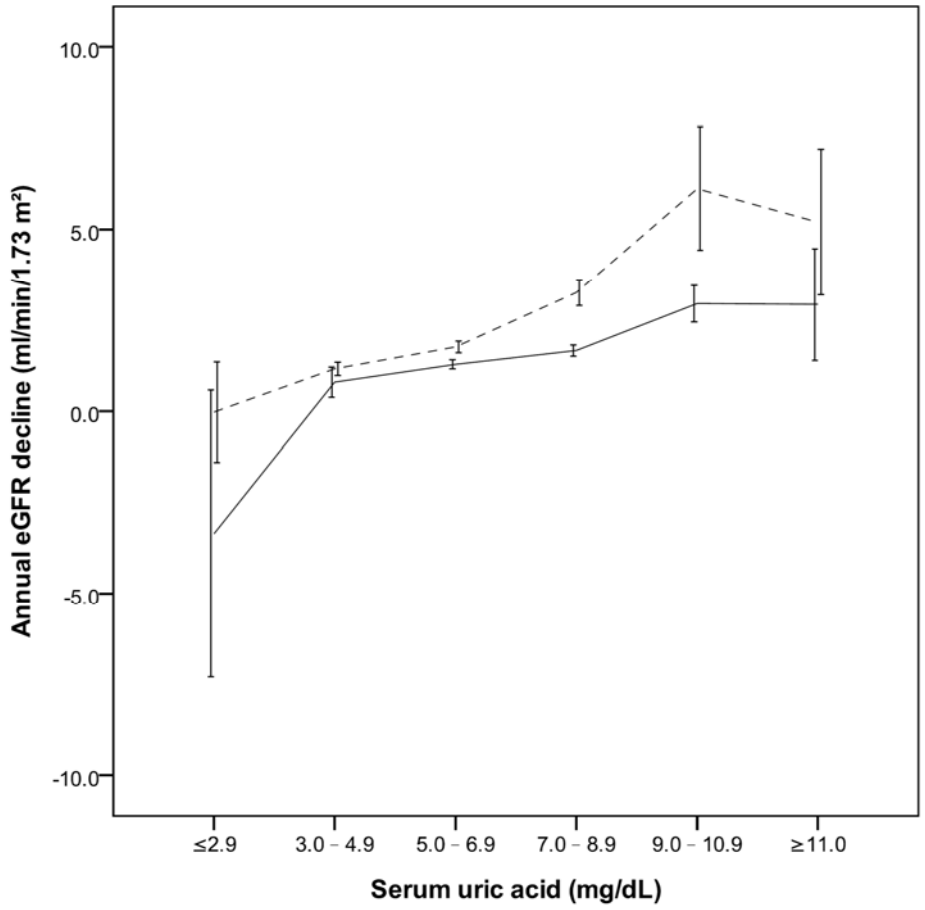


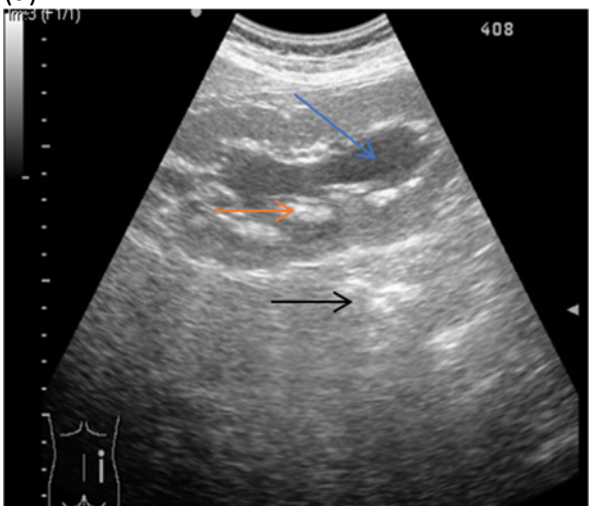
Figure 1-6 Relationship between serum uric acid levels and annual eGFR decline (men: solid line; women: dashed line; figure adapted from Hyperuricaemia and accelerated reduction in renal function. Scand J Rheumatol. 2011 Mar;40(2):116-21. With author's approval).

Traditionally, DM and hypertension have been considered the most important risk factors for CKD.(Brancati et al., 1997, Keane et al., 2003, Valderrabano et al., 1998) Since gout frequently coexists with both DM(Choi et al., 2008) and hypertension,(Mellen et al., 2006) it is often overlooked as a separate risk factor for CKD and subsequent ESRD.(Yu and Berger, 1982) The prevalence of CKD in gout patients was 71%, as reported from the NHANES 2007-2008.(Zhu et al., 2012) A nationwide study in Taiwan found that gout was associated with a hazard ratio of 1.57 for ESRD.(Yu et al., 2012) In conclusion, both hyperuricaemia and gout are associated with a high risk of CKD and ESRD.

1.6.5 **Urolithiasis**

Uric acid crystals may deposit in the renal tubules and cause kidney stones. The risk of common calcium containing stones is also increased in people with hyperuricaemia. The Health Professional follow-up study found that the diagnosis of gout was associated with a relative risk of 2.12 for incident kidney stone.(Kramer et al., 2003) However, it should be noted that the prevalence of urolithiasis may be underestimated because many patients have no symptoms.(Shimizu and Hori, 2009) Figure 1.7 shows typical findings of 'gouty' kidney on ultrasonography and retrograde pyelogram.

(a)



(b)

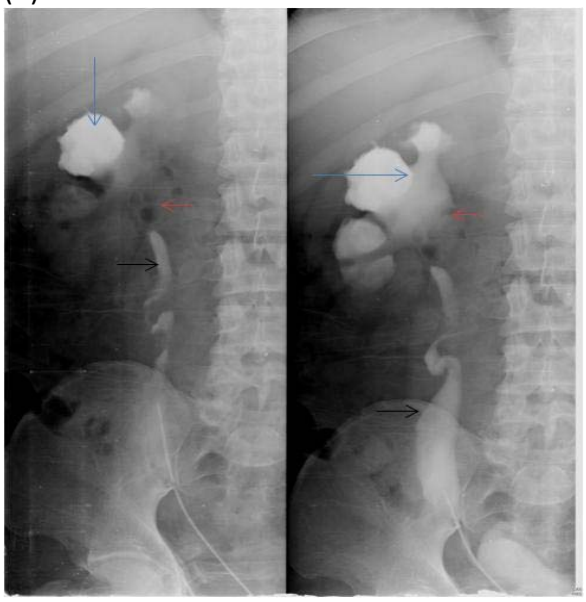


Figure 1-7 (a) Ultrasonographic finding of a 'gouty' kidney', which shows medullary nephrocalcinosis (black arrow), kidney stone (red arrow) and hydronephrosis (blue arrow). (b) Retrograde pyelogram of the same patients, which shows filling defects of contrast (red arrow), hydronephrosis (blue arrow) and hydroureter (black arrow) (personal collection; with patient consent).

1.6.6 Cardiovascular diseases

The Framingham study found a 60% excess risk for coronary heart disease among gout patients.(Abbott et al., 1988) A high risk of acute myocardial infarction (AMI) in gout patients has been observed in other studies, including the MRFIT(Krishnan et al., 2006) and a study utilising the British Columbia Linked Health Database.(De Vera et al., 2010) The MRFIT study focused on high-risk patients requiring a Framingham risk score in the upper 15% band of the score, so the findings of that study were representative of high-risk patients. Similarly, De Vera et al. selected patients older than 65 years, who were presumed to be at higher risk. Other evidence also supported higher risk of cardiovascular diseases in gout patients.(Kuo et al., 2013c, Chen et al., 2007b, Choi and Curhan, 2007)

Whether SUA levels are neuro-protective or neurotoxic has long been debated. A recent cohort study found no significant association between SUA levels and ischemic stroke outcomes.(Seet et al., 2010) However, a meta-analysis found that hyperuricaemia associated with a significantly higher risk both of stroke incidence (relative risk [RR], 1.41) and mortality (RR 1.36).(Kim et al., 2009) Another more recent meta-analysis focusing on prospective studies also documented that hyperuricaemia was associated with a modest increase in the

risk of stroke.(Li et al., 2014) In patients with acute stroke, acute gout attacks associated with a more prolonged stay in the acute ward.(Lin et al., 2009)

A greater risk for incident heart failure was recently demonstrated in hyperuricaemic patients.(Ekundayo et al., 2010, Krishnan, 2009) In addition, higher SUA associated with a poorer prognosis in patients with systolic heart failure.(Wu et al., 2010) Whether hyperuricaemia is a risk factor or a bystander biomarker is still under debate. While earlier studies suggested lower mortality in heart failure patients receiving long-term allopurinol treatment, a more recent study found no changes in brain natriuretic peptide, left ventricular ejection fraction, and dimensions on echocardiographic assessment after therapy with benzbromarone (a urate-lowering agent).(Ogino et al., 2010)

1.6.7 **Cancer**

Only a few studies have examined the risk of cancer in gout patients. One case control study found no association between gout and haematopoietic malignancies.(Doody et al., 1992) Because hyperuricaemia is a hallmark of gout, several studies have examined the association between cancer and SUA levels. However, the results are contradictory. Criqui et al. reported

that cancer risk was not associated with SUA.(Criqui et al., 1991) However, Petersson et al. found significant associations between SUA and cancer deaths(Petersson et al., 1984) and Strasak et al found a 1.41-fold increased risk of cancer death in patients with the highest SUA levels.(Strasak et al., 2007) More recently, in a Swedish study, Boffetta et al. linked hospital admission records for the period from 1965 to 1995 to cancer registry data and found that gout was associated with a standardised incidence ratio for cancer of 1.25.(Boffetta et al., 2009)

A recent study found the annual incidence of cancer in gout patients to be more than double that of the national population of Taiwan.(Kuo et al., 2012) After adjustment for age and sex, cancer risk was still higher in gout patients (age- and sex-adjusted HR, 1.15). Of the various types of cancer, the risk for prostate cancer was 1.7 times that of controls. Conversely, there was a trend toward a negative association between gout and breast cancer.

1.6.8 **Osteoarthritis (OA)**

Limited evidence supports an association between gout and OA. Several case reports suggested the coexistence of gout and OA.(Simkin et al., 1983, Foldes et al., 1996) A recent

study found that the sites of acute attacks of gout were highly likely to be affected by OA, with an adjusted odds ratio of 7.94.(Roddy et al., 2007a) However, as later reported by the same group, nodal OA is not more common in gout sufferers than controls.(Roddy et al., 2008) Further study is needed to confirm the association between gout and OA.

1.6.9 Neurodegenerative disorders

Several epidemiological studies suggest that uric acid may be protective against Parkinson's disease, (De Vera et al., 2008, Alonso et al., 2007) presumably due to its potent antioxidant property.(Alonso and Sovell, 2010) Alonso et al. reported that a prior history of gout was associated with an odds ratio (OR) of 0.69 for Parkinson's disease, this negative association being apparent in men (OR 0.60) but not in women (OR 1.26).(Alonso et al., 2007) Using the British Columbia Linked Health Database and PharmaCare data, De Vera et al. identified 11,258 gout patients and 56,199 controls. After an 8-year median follow-up, gout was associated with a 30% reduced risk of Parkinson's disease.(De Vera et al., 2008) In contrast to Alonso's study, both sexes were equally protected by a history of gout.

1.7 Death

The overall risk of death among individuals with gout, especially women, has seldom been investigated. Two recent studies, the MRFIT (Krishnan et al., 2008) and HPFS (Choi and Curhan, 2007) studies, both confined to men, reported excess cardiovascular mortality in people with gout. Although a recent study found women with gout to have a relative risk of 1.39 for acute myocardial infarction,(De Vera et al., 2010) the survival impact of gout in women is still uncertain.

Kuo et al. reported that individuals with a history of gout have a higher risk of death from all causes and from cardiovascular diseases, independent of age, sex, smoking, metabolic syndrome and proteinuria.(Kuo et al., 2010a) A more recent study investigated the mortality risk of gout patients in a cohort from the outpatient department of a single centre, in comparison with the general population of Taiwan.(Kuo et al., 2011) This study included 6,631 gout patients, of whom 1412 were women. The all-cause standardized mortality ratio (95% confidence interval) was 1.29 (1.21–1.37) for men and 1.70 (1.53–1.89) for women, the excess mortality risk being particularly evident for renal, endocrine, metabolic and cardiovascular diseases.

1.8 Treatment of gout

Several drugs are effective for acute attacks, including oral colchicine, oral non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (intra-articular, intramuscular or oral) and intramuscular adrenal corticotrophin hormone (ACTH).(Terkeltaub, 2010) Ice packs also help reduce pain and inflammation.(Schlesinger et al., 2002)

For long-term management the treatment priority is to reduce SUA to below the critical saturation point at which crystals may form, thus preventing further MSU crystal formation and dissolving away existing crystals.(Terkeltaub, 2010) Once all crystals are removed the person will have no further attacks and the risk of further joint damage due to crystals is removed. There are two categories of effective urate lowering therapy (ULT), specifically xanthine oxidase inhibitors and uricosuric drugs. The two xanthine oxidase inhibitors allopurinol and febuxostat are the main ULTs to be used in the UK, the three uricosuric agents, probenecid, benzbromarone and sulphinpyrazone suffering from only limited availability which restricts their use.

Acute attacks frequently occur after initiation of ULT possibly due to partial dissolution of MSU crystals which encourages their "shedding" from cartilage into the joint cavity. Prophylactic therapy with regular low dose colchicine or NSAID for the first few months following initiation of ULT may reduce the risk of acute attacks. This approach is effective in prevention of acute arthritis in 85% of patients.(Yu and Gutman, 1961) However, the treatment of patients with gout is often suboptimal as evident by the fact that only a minority of patients (<25%) become free of gout attacks.(Mikuls et al., 2005a, Neogi et al., 2006, Roddy et al., 2007c)

In addition to drug treatment, other factors are also important in management. These include avoidance of excess intake of alcohol (especially beer) and fructose containing beverages. Measures to keep ideal body weight, such as dietary caloric restriction and adequate exercise, should be encouraged. Liberal water consumption may enhance renal urate clearance and prevent calculi. Effective treatment of comorbid hypertension, insulin resistance and dyslipidaemia also increases renal urate excretion and reduces SUA.

In 2006, EULAR published recommendations for treatment of gout, (Zhang et al., 2006a) which proposed 12 recommendations. In brief, the recommendations suggested that gout

should be treated by both non-pharmacologic and pharmacologic means, and patient education and lifestyle advice are core concepts of individualised management. In addition to gout itself, comorbidities associated with gout should also be managed. For acute treatment, colchicine, NSAID and joint aspiration with corticosteroid injection are effective measures. Allopurinol is the appropriate first-line urate-lowering treatment while uricosuric agents can serve as an alternative. The treatment goal is to maintain the SUA levels below 360 umol/L. Colchicine and NSAID can be used as a prophylaxis and if possible, stop diuretic treatment and use losartan, which has a modest uricosuric action, to treat hypertension instead.

1.9 Epidemiological research based on administrative databases

Administrative databases contain secondary data derived from the running of a health care system. They record the "activities" incurred when enrolees seek medical care, such as registration, diagnoses, treatments, medication dispensing, paying claims, reimbursement and surveillance. Therefore, administrative databases offer a unique opportunity for medical research.

There are several important advantages of research based on an administrative database. The most obvious one is the large number of people available for study. Indeed, some administrative databases, such as the National Health Insurance Research Database in Taiwan along with linked health and social care databases which link the entire population of some Scandinavian countries, contain data on the entire population of a country. In addition, the data are obtained in a "natural" environment, rather than in specialised settings so avoid selection bias. Since the data accumulate over time, longitudinal tracking of people is possible. Linking of the database to other resources, such as mortality registration, enrich the dataset. Finally, access to the data for research is relatively inexpensive.(Iezzoni, 2003)

However, there are also several limitations. Firstly, the contents of an administrative database are limited to the population and medical services covered. Secondly, the accuracy, completeness and clinical interpretation of diagnostic codes are often questionable. Since the diagnosis is often coded according to an existing scheme, such as the International Classification of Diseases (ICD) system or the Read system, rare or novel diseases may not be correctly classified. Many administrative databases are created to facilitate claims and reimbursement based on certain diagnoses. Therefore the diagnoses may be influenced by the financial incentive. As the data are enormous in most administrative databases, specialised expertise is required to interrogate the database and derive meaningful results.(Iezzoni, 2003)

1.10 Summary

Gout is the most common form of inflammatory arthritis and with the aging of the population the prevalence and incidence of gout are expected to rise. Increasing evidence demonstrates that gout is not limited to joint manifestations, but also associates with many medical conditions that may affect general health and longevity. This study aimed to investigate the epidemiology of gout, specifically: prevalence and incidence; risk factors, including familial risk; and associations and consequences of comorbidities using two health care databases representative of the general population in the UK and Taiwan: the UK General Practice Research Database (GPRD, now Clinical Practice Research Data-link CPRD) and the National Health Insurance Database (NHID) in Taiwan.

1.11 Structure of this thesis

This thesis discusses the epidemiology of gout in the UK and Taiwan. The contents of each chapter are briefly summarised in the following paragraphs.

Chapter 2 describes methods common to all chapters, including more details of both databases, case definitions of gout and other diseases studied in this thesis, identification of

medications, risk measures, incidence and prevalence and methods of standardisation. Specific methods are described in relevant chapters.

Chapter 3 reports the use of the CPRD to investigate prevalence, incidence and management of gout in primary care in the UK. This study presents detailed estimates in 2012 and also trends of estimates from 1997 to 2012.

Chapter 4 reports the use of the NHIRD to study the epidemiology of gout and its management in Taiwan from 2005 to 2010. This study reports prevalence, incidence and management of gout in Taiwan.

Chapter 5 investigates the nature history of gout after the diagnosis of the disease and estimates the cumulative probability of fulfilling eligibility for ULT.

Chapter 6 investigates the nature of familial aggregation of gout and the partitioning of phenotypic variation. This study is the first to estimate heritability of gout, and environmental contribution to gout susceptibility on a nationwide basis.

Chapter 7 estimates the burden of comorbidities in incident gout patients at diagnosis and also estimates the relative risk of all-cause mortality in gout patients compared to non-gout controls.

Chapter 8 investigates the effects of allopurinol on all-cause mortality using the CPRD.

Chapter 9 is the general discussion summarising this thesis with implications of findings and future research questions.

CHAPTER 2. Methods

2.1 Ethical approval

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH, approval number: 97-1564C) and the National Health Research Institute (NHRI; approval number: 10092), the data holder of the National Health Insurance (NHI) Research Database (NHIRD). The approvals grant legitimacy and access to research based on the NHIRD. Currently, access to data from the NHIRD is permitted to estimate prevalence and incidence of gout in Taiwan, to identify risk factors and comorbidities associated with gout, to explore the relationships between gout and comorbidities, and to construct a user friendly risk assessment scoring system to assist general practitioners and specialists in early identification of those at risk of poor prognosis in an easy and straightforward fashion.

Approval was also obtained from the Independent Scientific Advisory Committee (ISAC) for conducting research using the UK CPRD (protocol number: 11-021). The approval grants the legitimacy to conduct research using the CPRD to compare the differences between the UK and Taiwan in terms of incidence, outcomes and associated risk factors, to develop and validate risk prediction models of gout and its adverse outcomes, including cardiovascular

diseases (CV) and chronic kidney disease (CKD) and to examine whether gout is negatively related to neurodegenerative conditions such as Parkinson's disease, dementia and multiple sclerosis. Ethical approval for the use of the CPRD was obtained through the Tent Multi-centre Research Ethics Committee (Reference number 05/MRE04/87).

2.2 Funding

The study of this thesis is jointly funded by two projects: Prediction of cardiovascular outcomes among gout patients: a population study based on the National Insurance Research Database and General Practice Research Database, which is sponsored by Chang Gung Memorial Hospital (CGMH) and Construction of predictive model for prognosis of gout patients: using the National Health Insurance database and the UK CPRD which is sponsored by the National Science Council (NSC) of Taiwan. The original protocols of the ethical approvals and submissions to Independent Scientific Advisory Committee (ISAC), National Health Research Institute (NHRI), CGMH and NSC are available upon request.

2.3 Data sources

2.3.1 Clinical Practice Research Data-link

The CPRD is one of the largest electronic health care databases and probably the most cited. Initially called the Value Added Medical Products (VAMP) research databank, it was started in 1987 for research based on data generated by general practitioners using an electronic medical record. Almost the entire UK population is covered by the National Health Service (NHS) and general practitioners are the primary gatekeepers to the whole medical service. Data within the CPRD therefore is representative of the UK population.

The CPRD covers the population of the UK, with the primary care component of the data previously recognised as the General Practice Research Database (GPRD). However, currently only patients from selected practices have data linked to external sources. The name was changed to CPRD to reflect linkage of data from other health care domains not contained in the original GPRD. Therefore, the CPRD provides access to multi-linked longitudinal data that may enhance health care research (website: www.cprd.com).

Contents of CPRD

CPRD contains data including diagnoses, symptoms, life style factors, prescribing, referrals, tests, immunisations, information on medical staffs, health promotion activities, management and quality outcome framework indicators. Vision software is an electronic system for general practitioners to manage patients, which records information primarily as "events". After collection of data, internal checks are performed to ensure internal consistency of patient data, complete longitudinal records, complete practice level data and compliance with CPRD recording guidelines. The CPRD provides a web-based portal to the database and dedicated research tools to facilitate extraction of data for research.

In September 2011 the CPRD contained data on 13,071,713 patients and for 88.1% of these the data were considered acceptable for research following internal quality control. There were 5,119,066 people registered in the CPRD in 2010 who fulfilled standard quality criteria (8.21% of the UK population). Over 1.1 billion records of consultations from 632 practices are available. With such a large amount of patient data and good representation of the UK population, the CPRD provides an excellent opportunity for research in areas such as clinical research planning, drug utilization, studies of treatment patterns, clinical epidemiology,

disease patterns, disease management, outcomes research, drug safety, health outcomes, pharmaco-economics and health service planning.

External Linkages

In addition to its core database, the CPRD also provides external linkage to other databases, including Hospital Episode Statistic (HES), Cancer Registry, Myocardial Ischaemia National Audit Project (MINAP), mother-baby link, national joint registry, socioeconomic status and Office for National Statistics (ONS) mortality data, which greatly extends the scope for potential research. Importantly, these linkages are not available for all enrolees of the CPRD. For instance, ONS mortality data and HES are only available for English practices.

Structure of CPRD

The structure of the CPRD is roughly divided into registration data, which records demographics of enrolees, medical staffs and practices, and clinical data, which records extensive clinical information on consultation, diagnoses, laboratory test/examination data, referral details, immunisation and therapy. Descriptions of the CPRD structure are shown in the following table.

Table 2-1 Contents of data files in CPRD

Data files	Contents
	Registration files
Patient	Patient identifier, birth year and month, marital status, family number, Child health registration details, socioeconomic status, registration details, death date
Practice	Practice identifier, region, data collection details
Staff	Staff identifier, staff gender, staff role
	Clinical data files
Consultation	Patient identifier, event date, consultation type, consultation identifier
Clinical	Patient identifier, event date, consultation identifier, medical code. additional identifier
Additional	Patient identifier, additional detail identifier, additional data including life styles, disease registers, maternity, asthma data, elderly, Child health surveillance, cardiovascular and diabetes data, diagnostic imaging
Referral	Patient identifier, consultation identifier, medical code, referral type, urgency
Immunisation	Patient identifier, event date, medical code, immunisation details
Tests	Patient identifier, event date, medical code, test data
Therapy	Patient identifier, event date, consultation identifier, details of prescription

Diagnostic codes and validations

Initially, diagnoses were based on the Oxford Medical Information system (OXMIS) but after 1995 this was replaced by the Read coding system. The validity and completeness of the CPRD have been evaluated before, with satisfactory results.(Herrett et al., 2010, Lewis et al., 2002, Khan et al., 2010a, Jick et al., 2003) A recent systematic review reported that the median percentage of cases confirmed by validation was 89% (33-100%).(Herrett et al., 2010)

HES recorded data regarding hospital admissions. The coding system for diagnosis, however, is ICD-10, rather than Read coding system. Procedures and operations are coded by OPCS Classification of Interventions and Procedures version 4. Importantly, 87% of diagnoses from secondary care specialists were captured.(Herrett et al., 2010)

Strength and limitations

The CPRD is broadly representative of the general population of UK and makes population-based studies feasible. Internal audits that exclude patients with non-continuous follow up or poor recording that questions the validity of the patient's record, maintains data quality. With approval, investigators can obtain access to original medical records and contact GPs for additional questionnaire surveys of enrolled individuals. The CPRD is a powerful tool to investigate epidemiology. Other strengths include the availability of laboratory and examination results data, multiple external linkage, and high recording rate of secondary care events in GP records.

The CPRD has several limitations. Socio-economic data, such as occupation and employment, are generally limited. However, recent external linkage to a Townsend score, an index of deprivation, helps to compensate for this. The CPRD records events within General Practice but information on hospital events may not be so complete. The addition of HES helps, though this is limited to data from England and Wales. In addition, test results may also be incomplete prior to 2002. With the HES linked practices there are accurate dates of hospital admission and discharge. The size and complexity of the CPRD requires technical expertise. The cost of the database is also a burden for researchers.(Strom and Kimmel, 2006)

2.3.2 National Health Insurance (NHI) Research Database (NHIRD)

Since 1995, Taiwan has a single-payer nationwide health insurance scheme that aims to cover the entire population. At the end of 2010, there were 23,074,487 citizens enrolled in the NHI, which is equivalent to over 99.7% of the population in Taiwan (based on the report from BNHI, Bureau of National Health Insurance, website: http://www.nhi.gov.tw/). The NHIRD contains registration information and data on original claims for reimbursement, including comprehensive information on demographics, dates of clinical visits, diagnostic codes, medical expenditure, and details of prescriptions, examinations, and procedures.

Contents of NHIRD

BNHI collect data from the NHI every year, which are then anonymised to form the original files of the NHIRD. The data are organised into registration files and original claims data. The

registration files contain demographic data of beneficiaries, a registry of catastrophic illness and details of medical facilities, medical personnel and drug prescriptions. Original claims data include claims summaries for inpatient and ambulatory care, expenditures, orders and dispensing details. The contents of each file is summarised in Table 2-2. (Data descriptions and codes are available from the NHIRD website: http://nhird.nhri.org.tw/en/index.htm).

Table 2-2 Contents of data files in NHIRD

Data files	Description	Key variables
	Registration files	
BED	Registry for contracted beds	Hosp_id: Facility identification Bed_type: grading and types of beds Udd_level: grading of intensive care unit
DETA	Registry for contracted specialty services	Hosp_id: Facility identification Func_type: sub-specialties provided
HOSB	Registry for contracted medical facilities	Hosp_id: Facility identification Hosp_type_id: contract type Hosp_grad_id: grading type
HOSX	Supplementary registry for contracted medical facilities	Hosp_id: Facility identification X01: have outpatient service X02: have inpatient service X03: have haemodialysis service
DOC	Registry for board-certified specialists	Prsn_id: Specialist identification Prov_type_id: sub-specialty
PER	Registry for medical personnel	Prsn_id: Specialist identification Work_status: current working condition Work_place: working place Prsn_type: types of medical personnel
HV	Registry for catastrophic illness patients	Id: Holder identification Dise_desc: diagnoses of catastrophic illness Id_birthday: birthday Id_sex: gender
HOX	Registry for medical services	Hosp_id: Facility identification Hosp_servisce_code: services provided
DRUG	Registry for drug prescriptions	Drug_id: drug identification Drug_name: generic name Drcon_name: substance name Dose_name: dose type, packaging
ID	Registry for beneficiaries	Id: Beneficiary identification Ins_id: insurant identification Id_birthday: date of birth Id_sex: gender

		Ins_relation: relationship to insurant Reg_zip_code: place of residence (post code) Unit_ins_type: unit of insurance (work place) Ins_amt: insurance amount
	Original claims data	
DT	Monthly claim summary for inpatient claims	Facility identification, summaries of hospitalised cases and amount of payment by types of reimbursement
CT	Monthly claim summary for ambulatory care claims	Facility identification, summaries of outpatient cases and amount of payment by types of reimbursement
DD	Inpatient expenditures by admissions	Id: patient identification Hosp_id: facility identification Func_type: subspecialty In_date/out_date: date of admission and discharge Prsn_id: responsible physician identification Tran_code: outcome code Icd9cm_code Icd9cm_code_1/2/3/4: diagnosis code Icd_op_code Icd_op_code_1/2/3/4: operation code *_amt: various types of fees incurred
DO	Details of inpatient orders	Seq_no: inpatient visit identification Order_type: order type Order_code: procedure code
CD	Ambulatory care expenditures by visits	Id: identification Cure_item_no1/2/3/4: treatment code Func_type: subspecialty Acode_icd_1/2/3: diagnosis *_amt: various types of fees incurred
OO	Details of ambulatory care orders	Seq_no: outpatient visit identification Order_type: order type Drug_no: drug code Drug_use: dosing information
GD	Expenditures for prescriptions dispensed at contracted pharmacies	Id: Patient identification Hosp_id: facility identification Prsn_id: ordering physician identification Phar_id: dispensing pharmacist identification Drug_amt: amount of reimbursement
GO	Details of prescriptions dispensed at contracted pharmacies	Seq_no: Sequence number of prescription Drug_no: drug code Drug_use: dosing frequency Total_qty: quantity

Linkages of NHIRD

For clinical research the most important data files are ambulatory expenditures by visits (CD) and Inpatient expenditures by admissions (DD), which record data on ambulatory and inpatient care. Both data files contain medical diagnostic and surgical codes of ambulatory

visits or hospitalisation. However, specific prescriptions in outpatient clinics and treatment in hospital are recorded in OO and DO files, respectively. Therefore, linking CD to OO and DD to DO files is necessary for treatment-orientated studies.

These files are linked by a set of variables. As DO and OO files are recorded in a row per event format, no personal identification is available for linking. Therefore, a set of 6 variables (table 2-3) are necessary to link CD to OO, DD to DO or GD to GO files. Other than these 3 sets of lineages, linkage between other datasets only require personal or hospital identification. To obtain complete demographic data, linking to an ID file is required, using personal identification as sole linking variable.

Table 2-3 Contents of data files in NHIRD

Linking variables	Description
	Linking CD to OO, DD to DO or GD to GO
Fee_ym	Fee occurring year and month of the outpatient, inpatient or pharmacy events
Hosp_id	Hospital identification
Appl_type	Application type
Appl_date	Application date
Case_type	Classification of the outpatient, inpatient or pharmacy events for administrative purpose
Seq_no	Sequence number for successive records belonging to the same events
	Other linkage
Hosp_id	Hospital identification
ID	Personal identification

Other special datasets

Other data files are briefly discussed. GD and GO files contain details of prescriptions dispensed at pharmacies. DT and CT files contain monthly summaries of ambulatory and inpatient claims for each medical facility. Various registration files (HOSB, HOSX, HOX, and DETA) contain information regarding subspecialties, medical services, grading and contract status of medical facilities. Registries of medical personnel and subspecialists contain information of the licence practice status of medical professionals.

Under NHI, insured citizens who suffer from major diseases will receive a catastrophic illness certificate, which waives outpatient and inpatient co-payments. The issuance of a certificate requires a formal review by the Bureau of National Health Insurance. In situ carcinoma was not included as these diseases do not qualify for a catastrophic illness certificate. The

catastrophic illnesses defined by NHI include cancers, congenital diseases and congenital anomalies such as haemophilia, chronic kidney disease requiring renal replacement treatment, systemic autoimmune disease, chronic psychiatric diseases, metabolic, those receiving organ transplantation, paralytic syndromes, major trauma, respiratory failure requiring mechanical ventilation, severe malnutrition due to enterectomy, decompression sickness, immunodeficiencies, several occupational diseases such as coal workers' pneumoconiosis, cerebrovascular diseases, leprosy, decompensated liver cirrhosis, complication due to prematurity, arsenic intoxication, motor neuron disease and Creutzfeldt-Jakob diseases.

Different sets of data: sampling files and packages of special interests

Because of the extremely large volume of data collected, the authorities that administer the NHIRD have released randomly sampled datasets, referred to as the longitudinal health insurance database (LHID), to reduce the complexity for research. The sampling was initially performed in year 2000 and then every 5 years sampling was done to build a new cohort. Currently, there are three LHIDs, based on the sampling year 2000, 2005 and 2010.

LHIDs contain all the original claims data from 1,000,000 beneficiaries who were randomly sampled from the respective year Registry of Beneficiaries of the NHIRD, where registration data of everyone who was a beneficiary of the NHI during the period of January 1st to December 31st of the year. All the registration and claims data for these 1,000,000 individuals for the period from 1996 to 2010 were collected and entered into the LHID. There were no

significant differences in the age or sex distributions of patients included in the LHID and the original NHIRD based on an internal assessment.

In addition to three LHIDs, there are also packages of data retrieved from the original database based on specific topics, for instance, cancer, Chinese herbal medicine, trauma, catastrophic illness and diabetes mellitus. These packages of data mostly retrieved data from CD files based on specific diagnostic codes. For specialised research needs, investigators can also provide specific criteria for bespoke datasets.

Strength and limitations

The NHIRD has several strengths. As the NHI covers the entire population of Taiwan, the NHIRD is a genuine nationwide database and the information recorded in the database reflects real world practices in Taiwan. With data of more than 27 million people since 1996, even a cohort of a rare disease can be established readily. Also, disease characteristics are based on physician diagnosis rather than patient self-report, thus improving diagnostic validity.

There are also limitations to the NHIRD. The anonymisation of personal and hospital identification makes external linkage to other databases difficult, if not impossible. The database is based on reimbursement from the NHI, therefore it does not contain results of specific laboratory tests or examinations. In addition, only limited socioeconomic data are available within the database. Finally, the logistics of research utilising the NHIRD requires

experience and vast computational power due to the huge amount of data and the complex structure.

2.4 Comparison between CPRD and NHIRD

The CPRD and NHIRD contain data from millions of patients, both being among the biggest and most cited health research databases in the world. They are representative of the national populations of the UK and Taiwan. However, there are key differences that are important when interpreting results from these databases.

Firstly, the sampling units are different. The CPRD contains data from patients in practices which agree to participate in. In the February 2014 version of the CPRD, there are 680 participating practices. Table 2-4 shows the numbers of participating practices in 13 areas in the UK. It is obvious that the distribution of practices is not even across the country. In 2012, registered patients residing in England, Scotland, Wales and Northern Ireland comprised 78.71%, 9.59%, 8.81% and 2.89% respectively. As shown in Table 2-5, England is slightly underrepresented and Wales is overrepresented comparing with mid-year census in 2012 according to Office of National Statistics. In addition, practices can join or leave the CPRD, therefore the number of practices in CPRD is not stable over time. Briefly, the data in CPRD reflect the geographical distribution of general practices. The sampling unit therefore is "practice". On the contrary, the NHIRD contains data from nearly all residents in Taiwan (over 99% coverage rate). In the main database, the data reflect essentially the entire population.

Several sampling files are available, each contains one million people sampled in 2000, 2005 and 2010. Therefore, these sampling unit in this instance is “individual beneficiary”.

Table 2-4 Number of participating practices and CPRD-registered patients in 13 areas in the UK in 2012.

Areas	**Number (%) of practices**	**Number (%) of patients**
North East	8 (1.47)	106,345 (1.65)
North West	67 (12.29)	681,526 (10.60)
Yorkshire & The Humber	6 (1.10)	64,159 (1.00)
East Midlands	5 (0.92)	61,562 (0.96)
West Midlands	44 (8.07)	549,184 (8.54)
East of England	33 (6.06)	450,858 (7.01)
South West	48 (8.81)	663,119 (10.31)
South Central	52 (9.54)	844,785 (13.14)
London	80 (14.68)	883,760 (13.74)
South East Coast	60 (11.01)	718,161 (11.17)
Northern Ireland	21 (3.85)	191,699 (2.98)
Scotland	71 (13.03)	633,869 (9.86)
Wales	50 (9.17)	581,301 (9.04)
Total	545 (100)	6,430,328 (100)

Table 2-5 Number of participating practices and CPRD-registered patients in 13 areas in the UK in 2013.

Countries	Number (%) of patients in CPRD in 2012	Number (%) of mid-year population in 2012
England	5165256 (78.71)	53107200 (83.97)
Scotland	629110 (9.59)	5299900 (8.34)
Wales	578232 (8.81)	3063800 (4.83)
Northern Ireland	189809 (2.89)	1814300 (2.86)
Total	6562407 (100)	63285200 (100)

Secondly, the primary purposes of these databases are different, reflecting in the contents of the databases. The CPRD contains data recorded by the general practitioners, which is more clinically oriented and contains laboratory and examination results data. No data on fee incurring during a consultation is available. The data in the NHIRD are more administrative oriented. The information on various kinds of incurred fees generated by medical staff (physicians, nurses, pharmacists, physical therapists and radiologists etc.) as a result of consultations, procedures, operations, laboratory tests, examinations and medications is very detailed. Data on diagnosis, operation and medications are also very detailed because they are an essential part of fee reimbursement. However, no data on results of laboratory tests and examinations are available.

Thirdly, the scope of these databases is different. The CPRD is essentially a primary care database with external linkages. The coverage of the main database and linkages differ, with the linkages being more limited in coverage. For example, ONS mortality data, HES and socioeconomic data are limited to English practices consenting to linkages. The NHIRD contains data from the entire health service in Taiwan. This is because the National Health Insurance is a single payer system with a mandatory enrolment. Private health services are very limited in Taiwan. Therefore, the NHIRD contains data in both primary and secondary care. However, external linkage to other databases is difficult because the National Health Research Institute, the data holder of the NHIRD, does not provide access to other databases and the personal identification has been encrypted to ensure confidentiality.

2.5 Case definition of gout

The primary case definition of gout used in this thesis is occurrence of at least one physician recorded diagnosis of gout (NHIRD: International Classification of Diseases, Ninth Revision [ICD-9] code: 274.x; CPRD: refer to Table 2-6). In CPRD, Read cords were used to identify gout patients. Since some Read codes apparently indicate prevalent gout (such as history of gout), only 18 codes for incident gout identification were used in addition to 39 codes for prevalent gout identification (see table 2-3). The case definition has been validated in a previous study.(Meier and Jick, 1997) Meier et al reviewed medical records and laboratory results of 10 confirmed gout patients (with recorded diagnosis, elevated serum urate and drug treatment) and 28 probable gout patients (with recorded diagnoses and drug treatment) gout

patients and ascertained 10 out of 10 confirmed cases and 24 out of probable cases to be true gout patients (overall positive predictive value 90%).

The primary case definitions used in this study are based on physician diagnosis, which may lead to misclassification bias. Despite gout is relatively easy to diagnose due to its very characteristic clinical presentation, the confirmation of gout diagnosis still rely on the demonstration of MSU crystals in the synovial fluid of patients. Alternatively, there are two sets of classification criteria that have been validated before.(Wallace et al., 1977)(Kellgren JH, 1963) However, both CPRD and NHIRD do not contain necessary information to apply such classification criteria. Therefore, two alternative definitions were used: (1) physician diagnosis plus the receipt of non-steroid anti-inflammatory drugs, corticosteroid or gout-specific treatment (colchicine, benzbromarone, allopurinol, probenecid, sulphinpyrazone) or (2) gout-specific drugs at either an outpatient or emergency department. These two alternative case definitions are more conservative than primary diagnosis. Therefore a lower prevalence and incidence of gout based on alternative case definitions is expected.

Table 2-6 Read codes to identify prevalent and incident cases of gout

Read codes	Description	Prevalent definition	Incident definition
1443	H/O: gout	+	
6691	Initial gout assessment	+	
6692	Follow-up gout assessment	+	
6693	Joints gout affected	+	+
6695	Date gout treatment started	+	
6696	Date of last gout attack	+	
6697	Gout associated problems	+	
6698	Gout drug side effects	+	
6699	Gout treatment changed	+	
669..00	Gout monitoring	+	
669A.00	Date gout treatment stopped	+	
669Z.00	Gout monitoring NOS	+	
C34..00	Gout	+	+
C340.00	Gouty arthropathy	+	+
C341.00	Gouty nephropathy	+	+
C341z00	Gouty nephropathy NOS	+	+
C342.00	Idiopathic gout	+	+
C345.00	Gout due to impairment of renal function	+	+
C34y.00	Other specified gouty manifestation	+	+
C34y000	Gouty tophi of ear	+	+
C34y100	Gouty tophi of heart	+	+
C34y200	Gouty tophi of other sites	+	+
C34y300	Gouty iritis	+	+
C34y400	Gouty neuritis	+	+
C34y500	Gouty tophi of hand	+	+
C34yz00	Other specified gouty manifestation NOS	+	+

C34z.00	Gout NOS	+	+
G557300	Gouty tophi of heart	+	+
N023.00	Gouty arthritis	+	+
N023100	Gouty arthritis of the shoulder region	+	+
N023200	Gouty arthritis of the upper arm	+	+
N023300	Gouty arthritis of the forearm	+	+
N023400	Gouty arthritis of the hand	+	+
N023600	Gouty arthritis of the lower leg	+	+
N023700	Gouty arthritis of the ankle and foot	+	+
N023800	Gouty arthritis of toe	+	+
N023x00	Gouty arthritis of multiple sites	+	+
N023y00	Gouty arthritis of other specified site	+	+
N023z00	Gouty arthritis NOS	+	+

2.6 Case definition of comorbidities

The definition of comorbidities will be stated on an individual study basis. Here I provide case definitions for cardiovascular related comorbidities.

For the NHIRD, the complete outpatient records database was screened for patients who required 2 or more treatments for DM (ICD-9 code: 250), hypertension (ICD-code: 401-405), coronary heart disease (CHD; ICD-9 code: 411-414), or stroke (ICD-9 code: 430-438). Since end-stage renal disease (ESRD) requiring renal replacement therapy necessitates that the patient is issued a catastrophic illness certificate in Taiwan, ESRD patients were defined by linking the main database to catastrophic illness registry. The specific code list is shown in the table 2-4.

Table 2-7 Specific code list for cardiovascular comorbidities in NHIRD

ICD-9 code	Category	Description
		Ischemic stroke
433	Cerebrovascular disease (430-438)	Occlusion and stenosis of pre-cerebral arteries
434		Occlusion of cerebral arteries
435		Transient cerebral ischemia
436		Acute, but ill-defined , cerebrovascular disease
437		Other and ill-defined cerebrovascular disease
438		Late effects of cerebrovascular disease
		Coronary heart disease
410	Ischemic heart disease (410-414)	Acute myocardial infarction
411		Other acute and sub-acute forms of ischemic heart disease
412		Old myocardial infarction
413		Angina pectoris
414		Other forms of chronic ischemic heart disease
		Hypertension
401	Hypertensive disease (401-405)	Essential hypertension
402		Hypertensive heart disease
403		Hypertensive chronic kidney disease
404		Hypertensive heart and chronic kidney disease
405		Secondary hypertension
		Diabetes mellitus
250	Diseases of other endocrine glands (249-259)	Diabetes mellitus
		Hyperlipidaemia
2720	Disorders of lipoid metabolism (272)	Pure hypercholesterolemia
2721		Pure hyperglyceridaemia
2722		Mixed hyperlipidaemia
2723		Hyperchylomicronaemia
2724		Other and unspecified hyperlipideamia
		Chronic kidney disease/ESRD
585	Nephritis, nephrotic syndrome and nephrosis (580-589)	Chronic kidney disease (CKD) End-stage renal disease (if with catastrophic illness certificate)

For the CPRD, the code list for important comorbidities is obtained using the medical browser provided by the CPRD interface. A further refinement is necessary and a consultation of code list from previously published CPRD-based paper is undertaken if possible. Some important comorbidity code list based on the results from the medical browser is listed in table 2-8. Full code lists used in the subsequent chapters are available on request.

Table 2-8 Specific code list for cardiovascular comorbidities in CPRD

Medcode	Read code	Read term
		Ischemic stroke
28753	9Om0.00	Stroke/transient ischaemic attack monitoring first letter
34245	9Om1.00	Stroke/transient ischaemic attack monitoring second letter
13707	8HBJ.00	Stroke / transient ischaemic attack referral
34375	9Om2.00	Stroke/transient ischaemic attack monitoring third letter
31218	9Om..00	Stroke/transient ischaemic attack monitoring administration
51465	9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitation
89913	9Om4.00	Stroke/transient ischaemic attack monitoring telephone invitation
		Coronary heart disease (including AMI)
240	G3...00	Ischaemic heart disease
241	G30..00	Acute myocardial infarction
1792	G3...13	IHD - Ischaemic heart disease
14658	G30z.00	Acute myocardial infarction NOS
1677	G30..15	MI - acute myocardial infarction
10562	G307100	Acute non-ST segment elevation myocardial infarction
1676	G3z..00	Ischaemic heart disease NOS
1678	G308.00	Inferior myocardial infarction NOS
4017	G32..00	Old myocardial infarction
12229	G30X000	Acute ST segment elevation myocardial infarction
14897	G301z00	Anterior myocardial infarction NOS
5387	G301.00	Other specified anterior myocardial infarction

28138	G34..00	Other chronic ischaemic heart disease
22383	G3y..00	Other specified ischaemic heart disease
23892	G304.00	Posterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
15754	G34z.00	Other chronic ischaemic heart disease NOS
		Hypertension
799	G20..00	Essential hypertension
		Diabetes
711	9OL..00	Diabetes mellitus
		Hyperlipidemia
637	C324.00	Hyperlipidaemia NOS
5791	C322.00	Mixed hyperlipidaemia
95952	C328.00	Dyslipidaemia
26019	C320200	Hyperlipidaemia, group A
		Chronic kidney disease
12566	1Z12.00	Chronic kidney disease stage 3
12586	1Z11.00	Chronic kidney disease stage 2
12479	1Z13.00	Chronic kidney disease stage 4
29013	1Z10.00	Chronic kidney disease stage 1
95123	1Z1C.00	Chronic kidney disease stage 3 without proteinuria
94965	1Z15.00	Chronic kidney disease stage 3A
12585	1Z14.00	Chronic kidney disease stage 5
95175	1Z1E.00	Chronic kidney disease stage 3A without proteinuria
95179	1Z16.00	Chronic kidney disease stage 3B
95177	1Z1G.00	Chronic kidney disease stage 3B without proteinuria
94793	1Z1B.00	Chronic kidney disease stage 3 with proteinuria
95121	1Z1A.00	Chronic kidney disease stage 2 without proteinuria
95406	1Z1J.00	Chronic kidney disease stage 4 without proteinuria
95408	1Z1D.00	Chronic kidney disease stage 3A with proteinuria
95122	1Z1H.00	Chronic kidney disease stage 4 with proteinuria
95178	1Z1F.00	Chronic kidney disease stage 3B with proteinuria
95146	1Z19.00	Chronic kidney disease stage 2 with proteinuria
95508	1Z1K.00	Chronic kidney disease stage 5 with proteinuria

95572	1Z18.00	Chronic kidney disease stage 1 without proteinuria
94789	1Z17.00	Chronic kidney disease stage 1 with proteinuria
95405	1Z1L.00	Chronic kidney disease stage 5 without proteinuria

2.7 Medication identification in the CPRD and NHIRD

The most important medications used by gout patients are ULT (allopurinol, febuxostat, benzbromarone, sulphinpyrazone, and probenecid) and colchicine. The specific codes of these drugs are listed in the appendix.

2.8 Identification of kinships and ascertainment of family

The definition of a family in this study was a cluster of individuals who were first-degree relatives (father, mother, son, daughter, brother, and sister) or who have at least one common relative linked to their first-degree relatives. The NHIRD provides relationship identification between the insured and their dependents. The direct relationships recorded in the NHIRD include spouse, parent, offspring, paternal and maternal grand-parents, grand-children, great grand-parent and great grand-children. For simplicity, spouse, parent, grand-parent, offspring and grand-children were used to identify the links between individuals.

It is important to note that the relationship between the insured and the dependents may change over time. For instance, children may register independently after they have jobs and they may also serve as the insured once they are married and have children. The registry updates annually. To maximise the possibility of relationship identification, all the relationship recorded in the NHIRD between1996 and 2010 were utilised. During the period, there were 28,402,865 individuals registered with the NHI. The registry recorded 16,761,602 pairs of direct relationships.

The first step in the identification of kinship is to ascertain parent-offspring relationships. Direct parenthood was recorded in the registry. Indirect identification of parent-offspring relationship is also possible. A parent-offspring relationship exists between grand-parents and parents if paternal/maternal grand-parents and father/mother of an individual registered with him/herself together. Offspring were also recorded in the registry. If one's spouse and offspring registered with him/her, a parent-offspring relationship also exist between one's spouse and offspring. If an individual married more than once, the registration time of one's spouse and offspring should be in the same period in order to establish parent-offspring relationship. Grand-parents of an individual were identified as parents of the individual's parents. Grand-children of an individual were identified as children of the individual's children. After consideration of all the aforementioned scenarios, there were 18,695,180 pairs of parent-offspring relationships.

The next step is to ascertain siblings of an individual. The identification of siblings was based on sharing one or more common parents. In this study half-siblings were not examined although identification of half-siblings is possible. Only spouses from first marriages were used to construct a family. Cousins of an individual were identified as children of the individual's sibling. If a couple did not have offspring, they were not assigned to the same family because they were not related based on a common blood relative.

To assign related individuals into one family, everyone was treated as the proband to build the core family. The definition of a core family included parents, offspring, siblings, grand-

parents, grand-children and cousins. All the individual identifications were linked together to form a record. For siblings and descendants, up to 5 members were included as 99.9% of the Taiwanese family had less than or equal to 5 children.

Next, a temporary family number was given to each record (one to around 28 million). All personal identifications with the same temporary family number were extracted and formed a 2 variable dataset (personal identification and temporary family number). One individual may have multiple temporary family numbers because one may serve many different roles in relation to other people. For a given individual with multiple temporary family numbers, the smallest temporary family number was chosen. This process was iterated until all the individuals had only one temporary family number. A final family identification was assigned to each record based on the last temporary family number.

Among 28,402,865 individuals contained in the registry of beneficiaries, 8,186,069 registered with themselves over a span of 15 years. The remaining 20,216,796 were classified into 4,229,301 families. The mean family size was 4.8 persons and the largest families contained 144 members. There were 2 to 5 generations in these families.

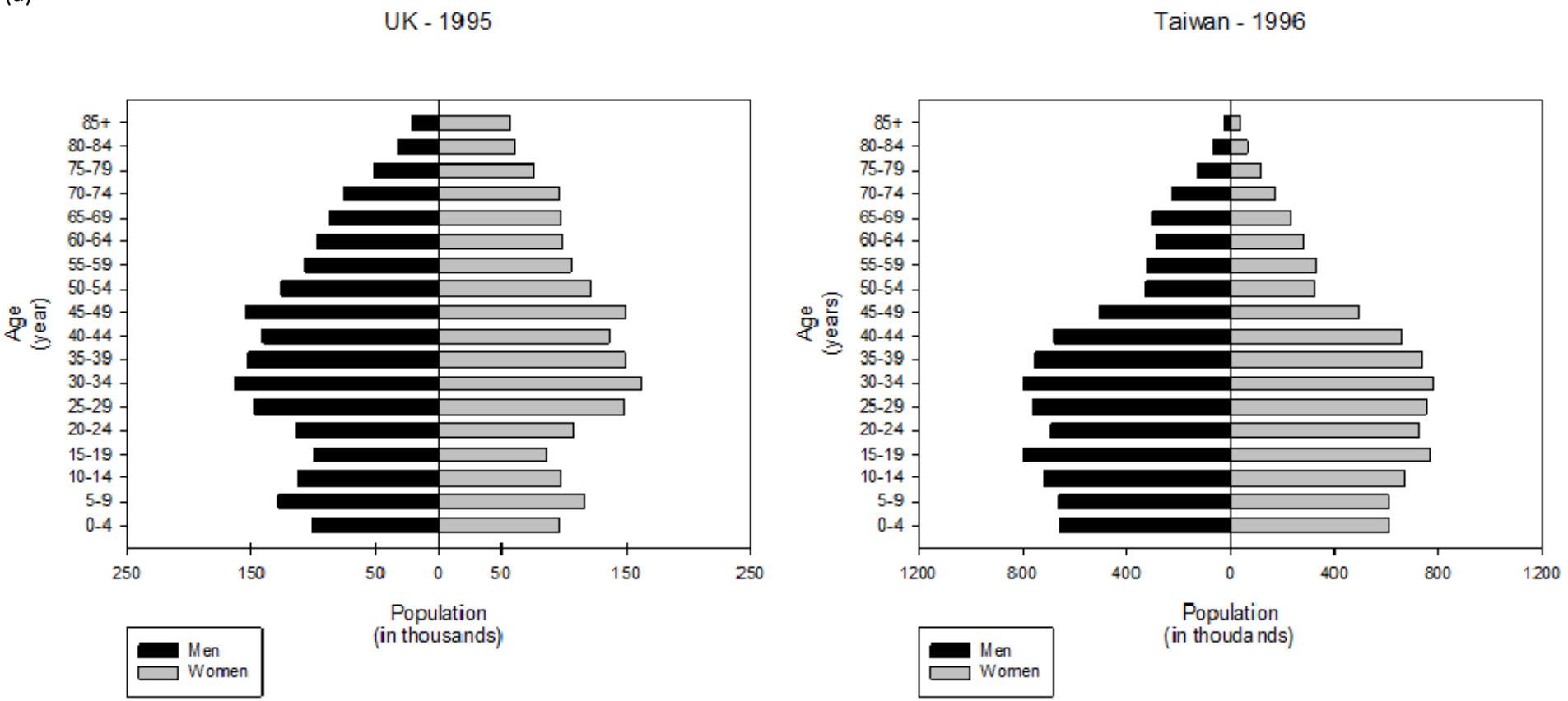
2.9 Population structures in the UK and Taiwan

This thesis investigated gout epidemiology in the UK and Taiwan. To make epidemiology estimates more relevant, a brief understanding of the population structure is needed. The population pyramid represents the breakdown of the population by gender and age at a given

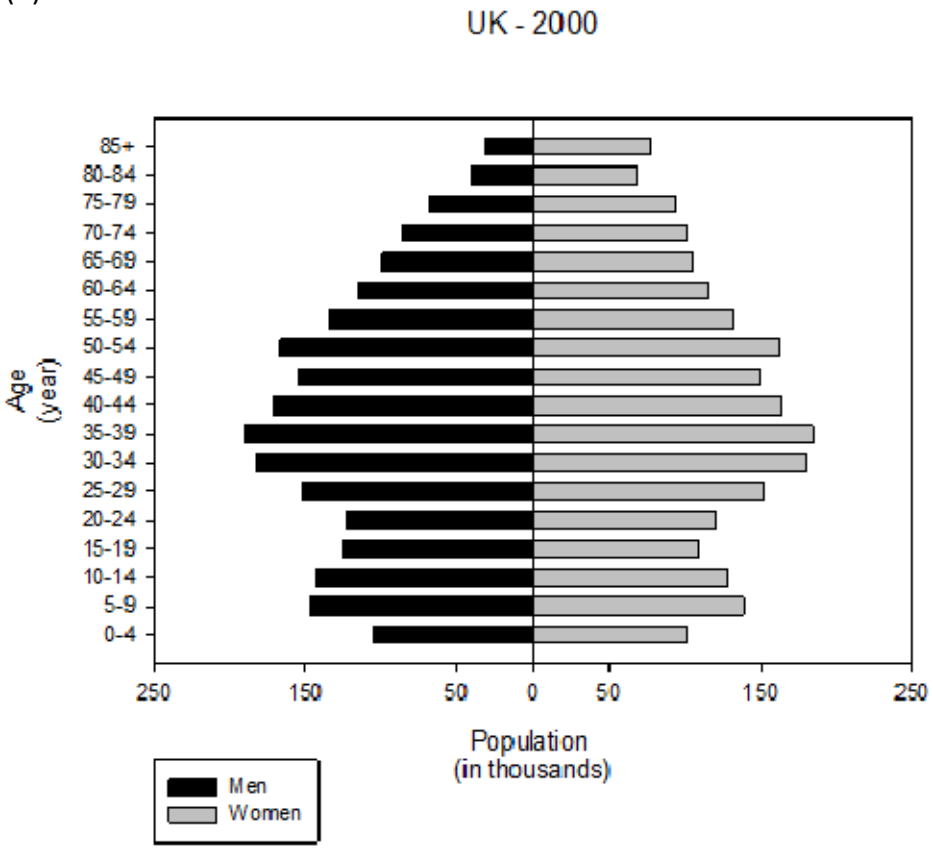
point in time. In Figure 2-1, population pyramids, using the source populations of the CPRD and NHIRD, are shown in 4 time points. It is obvious that the population structure is more stable in the UK, while the population structure in Taiwan is rapidly aging.

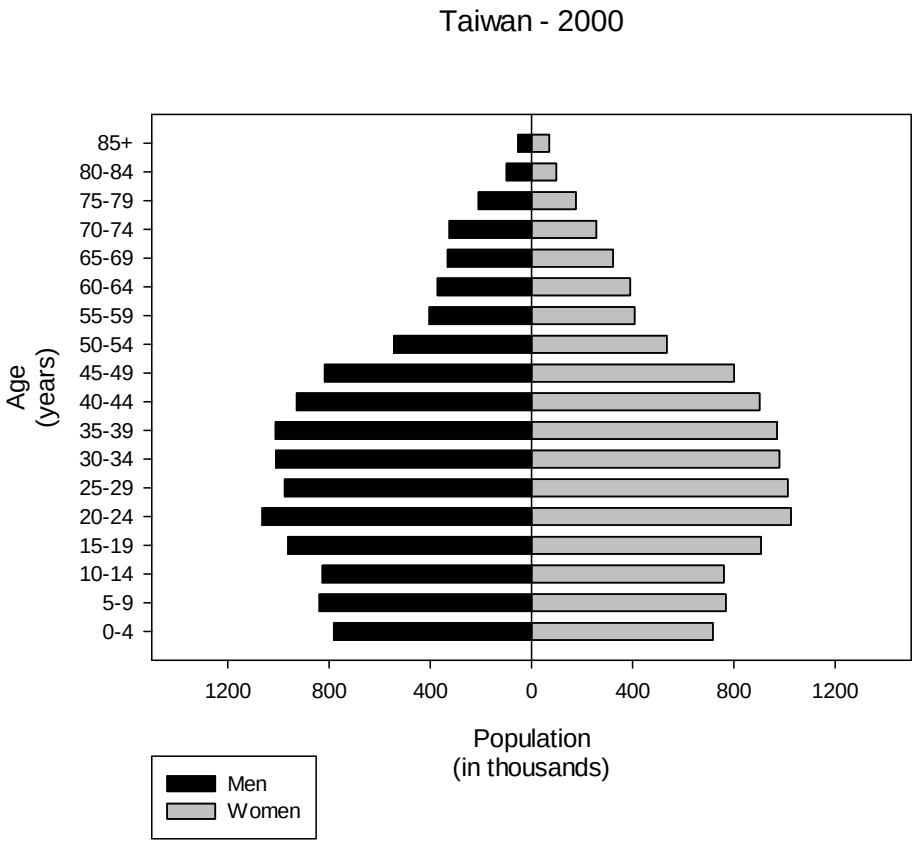
Figure 2-1 Comparison of population structure in absolute number between UK and Taiwan during 1995 to 2010 (a) 1995 in UK and 1996 in Taiwan; (b) 2000; (c) 2005; (d) 2010 in UK and 2009 in Taiwan.

(a)

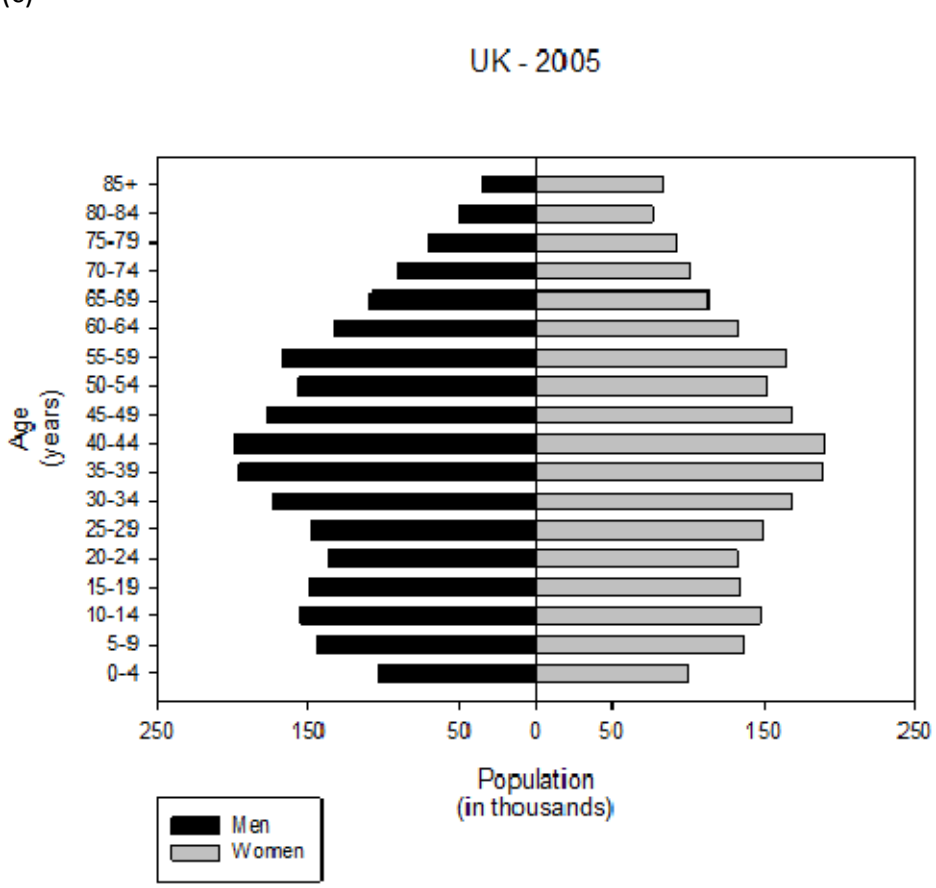


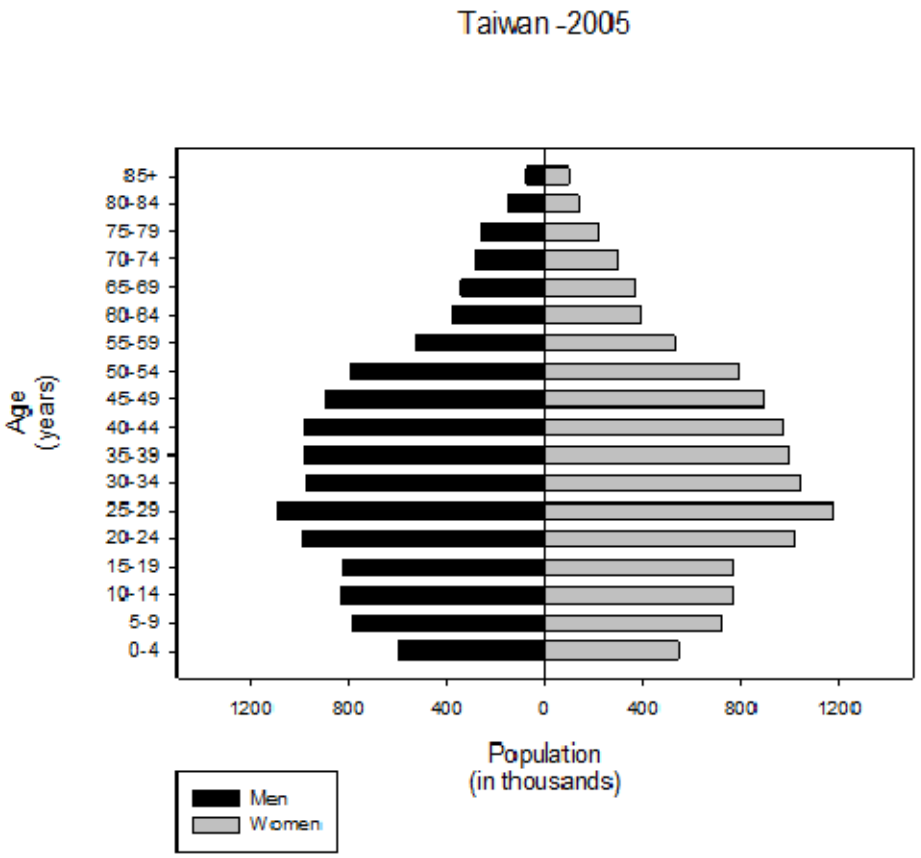
(b)


UK - 2000
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
Age (year)
250
150
50
0
50
150
250
Population (in thousands)
Men
Women

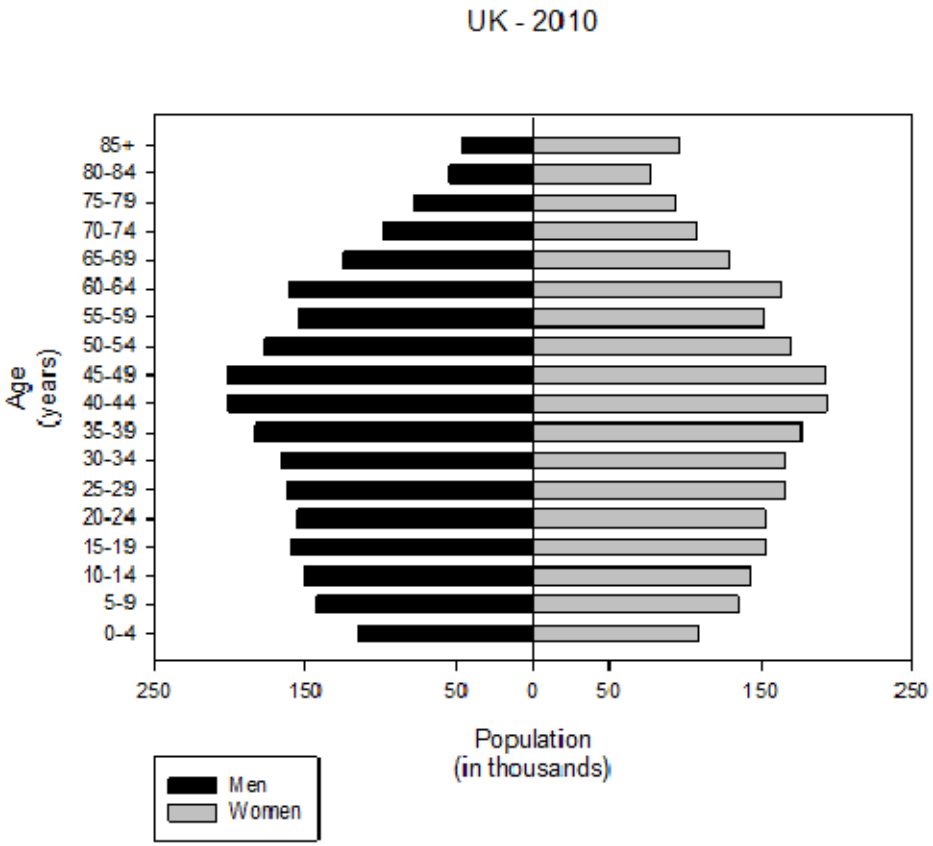

Taiwan - 2000
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
Age (years)
1200
800
400
0
400
800
1200
Population (in thousands)
Men
Women

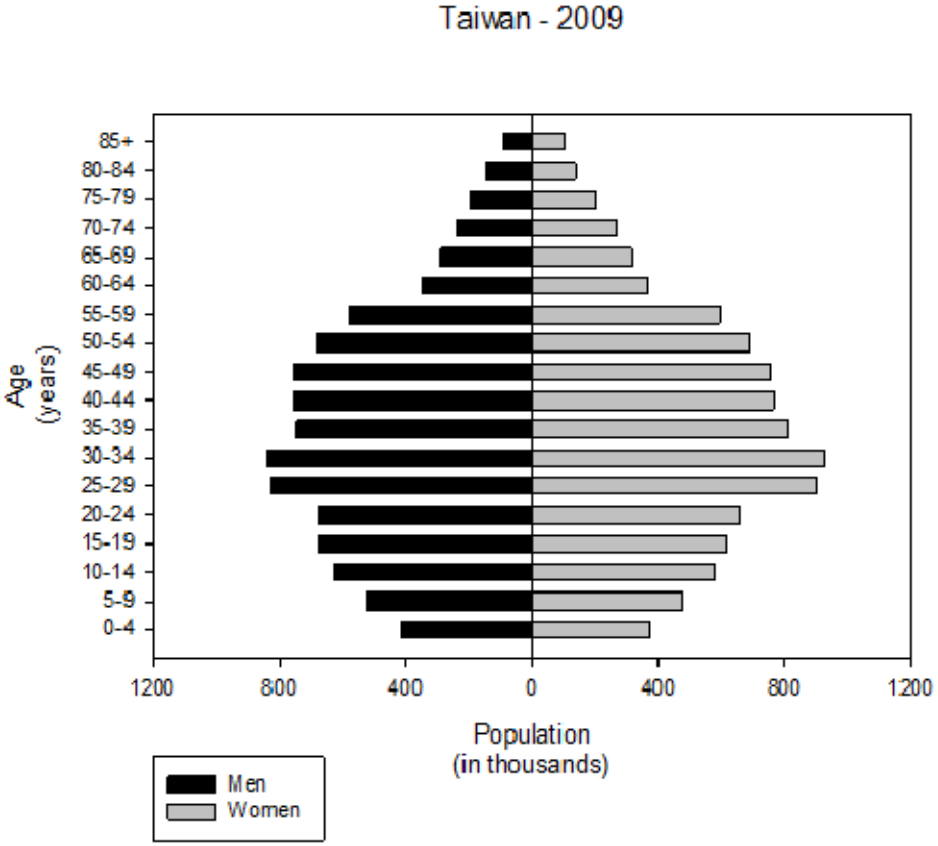
(c)


UK - 2005
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
Age (years)
250
150
50
0
50
150
250
Population (in thousands)
Men
Women


Taiwan -2005
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
Age (years)
1200
800
400
0
400
800
1200
Population (in thousands)
Men
Women

(d)


UK - 2010
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
Age (years)
250
150
50
0
50
150
250
Population (in thousands)
Men
Women


Taiwan - 2009
85+
80-84
75-79
70-74
65-69
60-64
55-59
50-54
45-49
40-44
35-39
30-34
25-29
20-24
15-19
10-14
5-9
0-4
Age (years)
1200
800
400
0
400
800
1200
Population (in thousands)
Men
Women

CHAPTER 3. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study

3.1 Introduction

Gout is the most common inflammatory arthritis with a diverse spectrum of clinical manifestations. In addition to recurrent acute arthritis, subcutaneous tophi and chronic painful arthritis, (Zhang et al., 2006b) it also has an impact on morbidity (Abbott et al., 1988, Krishnan et al., 2006, Sheane and Cunnane, 2007) and premature mortality.(Choi and Curhan, 2007, Krishnan et al., 2008, Kuo et al., 2010a) Gout results from the deposition of monosodium urate (MSU) crystal in peripheral joints and soft issues due to persistent elevation of uric acid levels above the saturation point for crystal deposition. Effective urate-lowering treatment (ULT) that maintains uric acid below this critical level will prevent further MSU crystal formation and dissolve away existing crystals,(Terkeltaub, 2010) making gout the only chronic arthritis that can be 'cured'. However, studies show that only a minority of gout patients receive effective treatment, the majority continuing to experience recurrent acute attacks, further joint damage and other complications.(Chin et al., 1999, Mikuls et al., 2005a, Neogi et al., 2006, Roddy et al., 2007c)

In the United Kingdom, several studies have estimated the prevalence of gout since the 1970's.(Badley et al., 1978, Currie, 1979, Gardner et al., 1982, Steven, 1992, Harris et al., 1995, Mikuls et al., 2005b, Annemans et al., 2008, Elliot et al., 2009) Two of these both report a

prevalence of 1.4% onward from 1999(Mikuls et al., 2005b) to 2005(Annemans et al., 2008) suggesting a plateau of prevalence, whereas three studies using different population-based databases have reported a rise in the incidence of gout in the past decade.(Mikuls et al., 2005b, Elliot et al., 2009, Cea Soriano et al., 2011) In addition, only approximately a quarter of gout patients in the UK receive ULT within one year from diagnosis, (Cea Soriano et al., 2011) which should contribute substantially to the elevated prevalence.

Currently, UK data from the current millennium exploring gout incidence and prevalence, assessed at multiple time points in the same population, are sparse. Therefore, this study was undertaken to examine the prevalence and incidence of gout and patterns of gout management using the CPRD from 1997-2012.

3.2 Methods

The study was approved by the Trent Multi-centre Research Ethics Committee (reference number: 05/MRE04/87) and the Independent Scientific Advisory Committee (11-021R).

3.2.1 Source of data

Please refer to section 2.3.1.

3.2.2 Study population

This study comprised all participants who contributed data to the CPRD between 1st January 1997 and 31th December 2012. The denominator for prevalence estimation (eligible population) for each calendar year included all individuals registered on 1st July of each calendar year with the general practices which were up-to-standard for CPRD research. For incidence of gout, at-risk cohorts were constructed for each calendar year which comprised all individuals registered with up-to-standard practices during the year specified who had no history of gout diagnosis before the latest of current registration date plus 365 days or 1st Jan of the calendar year specified. Person-years of follow-up were then calculated from the latest of 1st Jan or the date of registration plus 365 days to the earliest date of transfer-out, incident gout diagnosis, death or 31st December of the specified year.

3.2.3 Case definition of gout

Prevalent cases of gout were defined as participants who had gout on 1st July of each calendar year, whereas incident cases of gout were those who had no gout prior to the latest of current registration date plus 365 days or 1st January of each calendar year but developed gout during the year. To be eligible as an incident case, participants had to have at least one-year registration prior to the first date of gout diagnosis.(Cea Soriano et al., 2011) Gout was defined according to Read coding. Details were discussed in Chapter 2. In addition to physician diagnosis, we also used two different definitions to identify gout patients: 1. Gout diagnosis plus use of non-steroid anti-inflammatory drug, corticosteroid, colchicine or ULT or 2. Gout diagnosis plus use of colchicine or ULT.

3.2.4 Estimation of prevalence and incidence

Prevalence was calculated using the number of people diagnosed with gout at any time before the mid-point of a calendar year as the numerator and the number of all individuals contributing CPRD data at the same time point as the denominator. Incidence was calculated using the number of incident gout cases during a calendar year as the numerator and the total person-years occurring during the same year as the denominator.

Prevalence and incidence were calculated for 13 regions in the UK: North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, South West, South Central, London, South East Coast, Northern Ireland, Scotland, and Wales. To remove the

effect of different age and gender structures in these regions, prevalence and incidence were standardised with the overall population structure using 2012 as the reference. Choropleth maps were used to represent geographic variations of gout in the UK.(Inc., 2009)

3.2.5 Pattern of treatment

The proportion of prevalent gout patients who were being consulted specifically for gout and being treated by ULT (allopurinol, febuxostat, benzbromarone, probenecid or sulfinpyrazone) was estimated in each calendar year during the period 1997-2012. The proportion of incident patients who were treated by ULT within 6 months and 12 months of diagnosis was also calculated.

3.2.6 Adherence to ULT

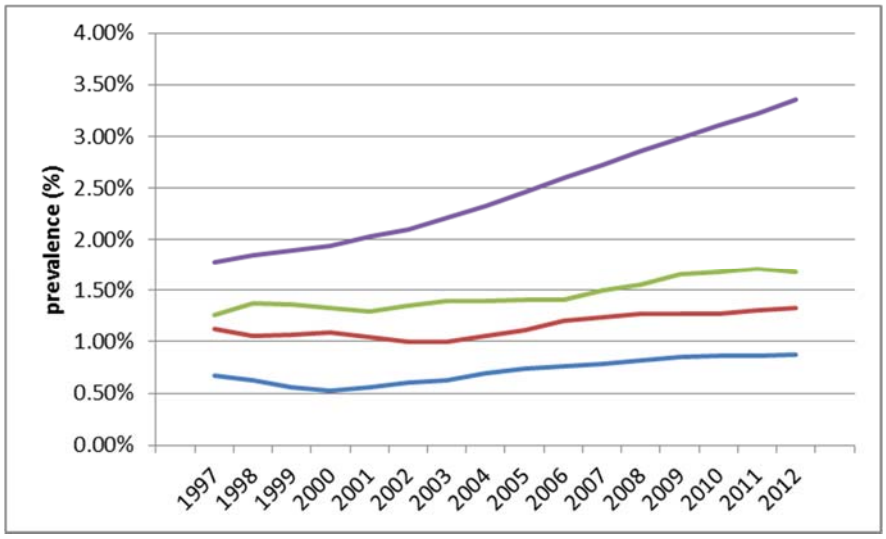
Adherence to ULT among prevalent gout patients was measured using proportion of days covered (PDC) to represent the degree of prescription-filling in a given interval specified. PDC was calculated as the proportion of days on which a patient had available prescriptions for ULT in each interval, which was defined as the period from the latest of registration date or 1st Jan to the earliest of transfer-out, death date or 31 Dec of the calendar year specified. For overlapping prescriptions, the later prescription was assumed to start from the end of the prior prescription; this was to avoid double counting of days covered. The gout patients were then divided into 4 groups according to status of being treated and adherence at each calendar year: not treated, non-adherent (those with a PDC less than 20%), partially adherent

(those with a PDC of 20% to 79%) and adherent (those with a PDC of at least 80%). The management of incident gout patients was assessed by the percentage of incident gout patients treated with ULT at 6 months and one year after diagnosis.

3.2.7 Trends of prevalence, incidence and management of gout

To determine the trends of prevalence, incidence and management of gout the following were calculated: the age-, sex- and length of data contribution-standardised prevalence, incidence of gout and pattern of ULT in each calendar year from 1997 to 2012 with the population structure in year 2012 as reference. The length of data contribution of each patient was defined as the period from the current date of registration to 1st July of each calendar year for prevalence, or to 1st Jan of the calendar year specified for incidence. The reasons to include length of data contribution to standardise prevalence, incidence and PDC were that incidence and especially prevalence were found to be higher for participants who contributed more follow-up prior to the year of interest (Figure 4-1). As this length of data contribution was longer for more recent years (Figure 4- 2) this naturally needed to be accounted for when comparing incidence and prevalence across years

(a)



(b)

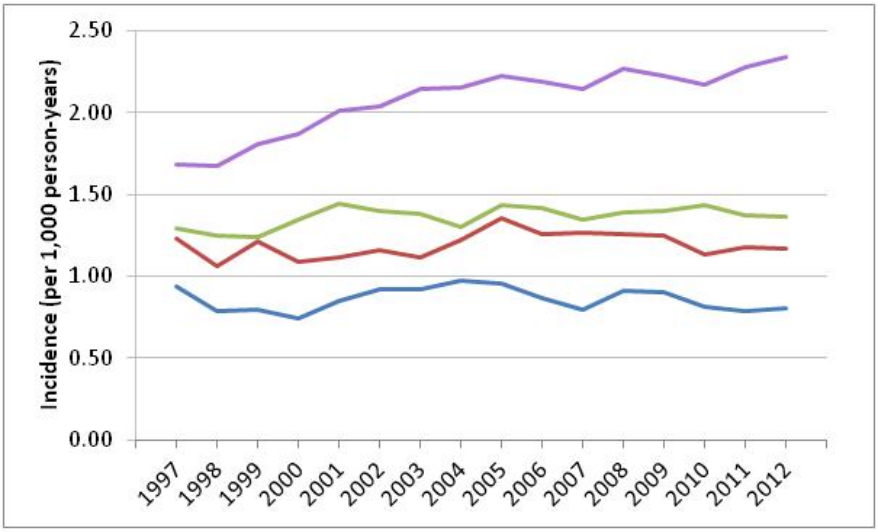
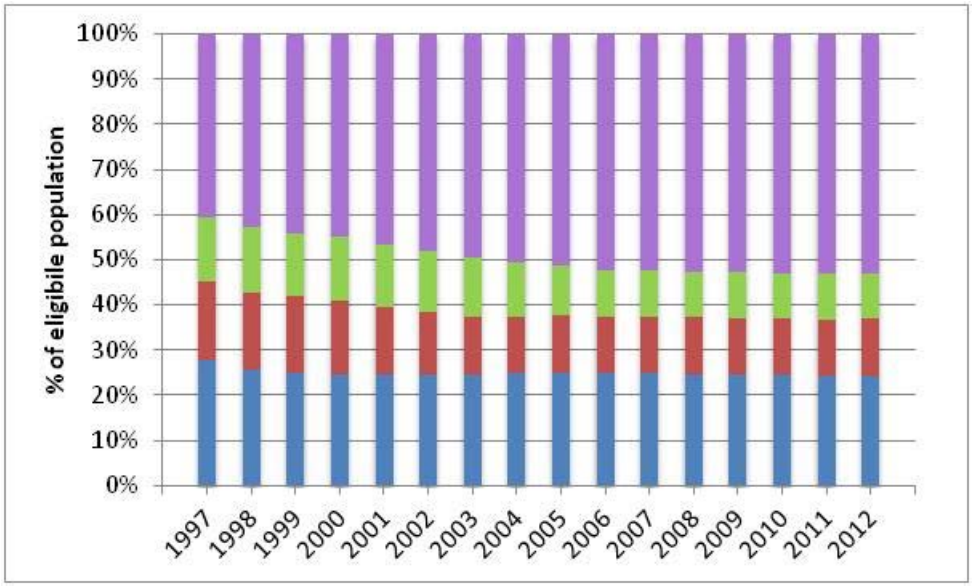


Figure 3-1 The relationships between length of data contribution and (a) crude prevalence and (b) crude incidence of gout during 1997 to 2012. (Blue: 0–3; red: 4-6; green: 7-9; purple: ≥10 years of data contribution).

(a)



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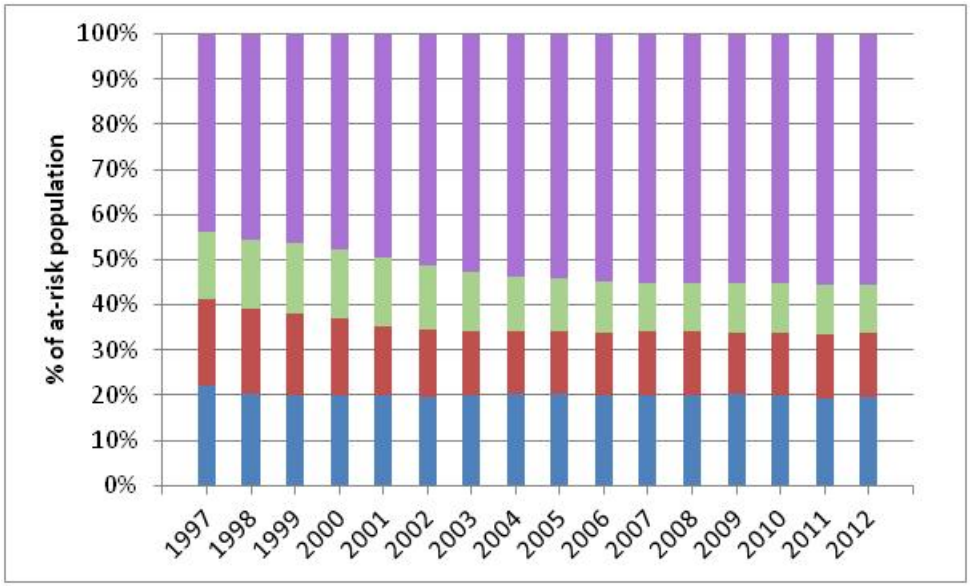


Figure 3-2 Proportions of (a) eligible population for prevalence and (b) at-risk population for incidence by length of data-contribution (blue: 1-3; red: 4-6; green: 7-9; purple: ≥10 years of data contribution)

3.2.8 Statistical analysis

The 95% confidence intervals (CIs) for prevalence and incidence were derived on the basis of the assumption of a Poisson distribution for the observed prevalent cases. The Joinpoint Regression Program (version 4.0.4) was used to estimate trends of prevalence and incidence of gout. The program uses Bayesian Information Criterion to generate different numbers of 'join points' in time when the trend of prevalence and incidence of gout change significantly and to determine the best-fit data series.(Kim et al., 2000) Initially models contained zero joinpoints (i.e. a straight line fitted to the data) with joinpoints added whenever a change in trend over time is statistically significant, with the user specifying the maximum number of allowable joinpoints. Using a Bayesian information criterion approach, a maximum of three joinpoints was selected. Annual percentage changes (APC) for each segment and average annual percentage changes (AAPC) for the entire study period of prevalence and incidence were calculated. The significance level was set at 0.05. All statistical analyses were performed by using SAS statistical software, version 9.3.

3.3 Results

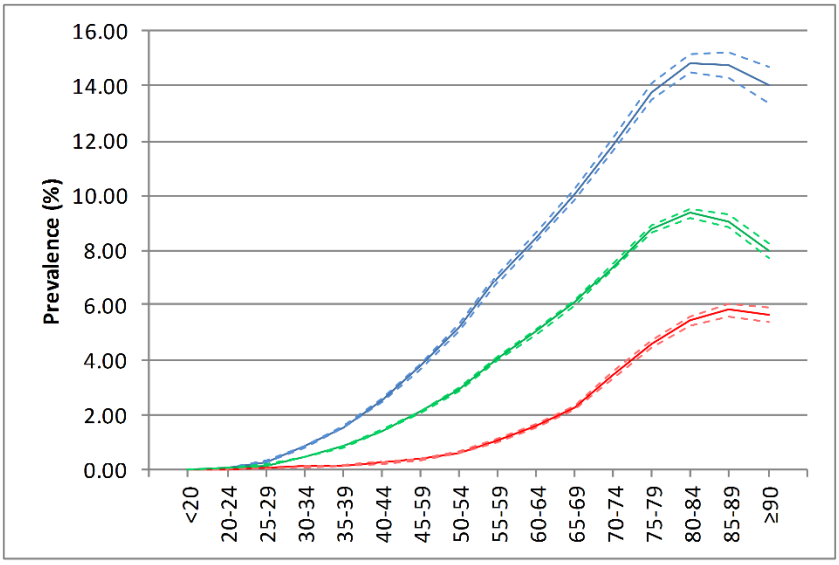
3.3.1 Prevalence and incidence in 2012

Of 4,634,974 eligible individuals in 2012, 115,608 prevalent cases of gout were identified, giving a prevalence of 2.49% (95% CI, 2.48%–2.51%). Men had a significantly higher prevalence of gout (3.97%; 95% CI, 3.96%–4.00%) than women (1.05%; 95% CI, 1.04%–1.06%). This gender difference was observed in all ages with a male to female ratio of 1.5 in individuals younger than 20 years, peaking at 11.2 in those aged 35-39 years bands and then decreasing to 2.5 for those older than 90 years. Gout was rare in people younger than 20 years (5.11 cases per 100,000 individuals) and it increased with age thereafter. In both men and women, the prevalence reached a plateau after the age of 80 years (figure 4-3a). In the adult population aged 20 years of more, the prevalence of gout (95% CI) was 3.22% (3.20%–3.23%) in the overall population, 5.17% (5.14%–5.20%) in men and 1.34% (1.33%–1.36%) in women.

There were a total of 4,159,043 person-years of follow-up in this year during which 7,343 incident cases of gout were identified (overall incidence 1.77 [95% CI, 1.73–1.81] per 1000 person-years). Men had a higher incidence of gout (2.58 [95% CI, 2.51–2.65] per 1000 person-year) than women (0.99 [95% CI, 0.95–1.04]) per 1000 person year). As shown in figure 4-3b, the incidence of gout was greatest in people aged 80-84 years in both men and women. The male to female ratio widened from the lowest in individuals younger than 20 years (1.2) to the a peak of 15.4 in those aged 30-34 years and thereafter the difference narrowed down. In the adult population, the incidence of gout (95% CI) was 2.26 (2.21–2.31) per 1,000 person-

years in the adult population overall, being 3.50 (3.26–3.44) per 1,000 person-years in men and 1.25 (1.20–1.31) per 1,000 person-years in women.

(a)



(b)

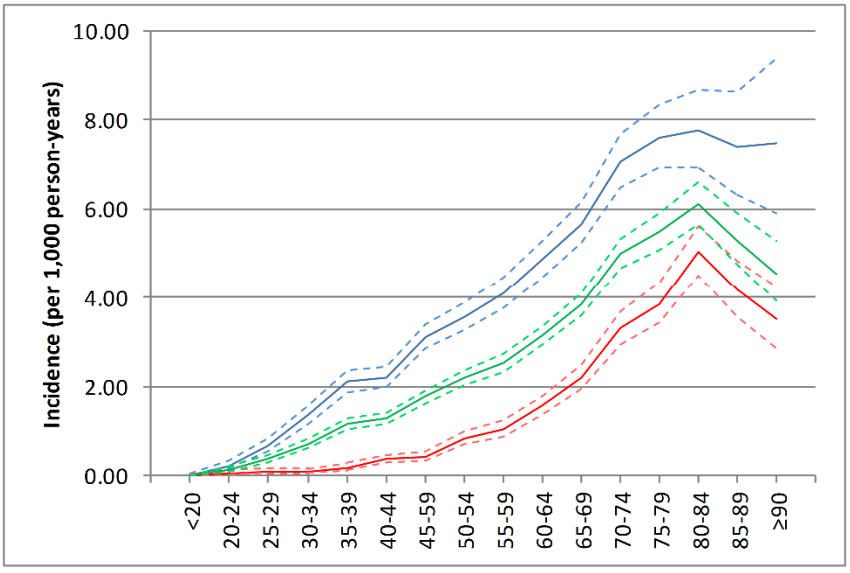


Figure 3-3 Age-specific prevalence (a) and incidence (b) of gout in 2012 (Blue: men; red: women; green: total; dotted lines show 95% confidence bounds).

3.3.2 Prevalence and incidence of gout between 1997 and 2012

Table 1 shows the temporal trends in prevalence and incidence of gout from 1997 to 2012. In general, both crude and standardised estimates increased over time during this period. The standardised estimates were slightly higher than the crude ones, accounting for the fact that the average length of data contribution was higher in 2012 than 1997.

The standardised prevalence of gout increased 63.9% over the study period. On average, the standardised prevalence increased 4.2% (95% CI, 3.9%–4.5%) per year, suggesting the prevalence of gout in UK was increasing over the study period. Furthermore, there were two joinpoints at 2000 and 2008 with respective APCs of 1.3 (0.5–2.1), 4.6 (4.3–4.9) and 3.3 (2.8–3.8) for segment 1997–2000, 2000–2008 and 2008–2012 respectively. As Figure 4-4a shows, the temporal trend of prevalence in men and women was not parallel ($p < 0.001$). On average, prevalence in women increased 4.6% (95% CI, 4.3%–5.0%) and was slightly higher than in men (4.1% [95% CI, 3.7%–4.4%]). However, the male-to-female ratio was only slightly narrowed from 4.8 fold in 1997 to 4.3 fold in 2012.

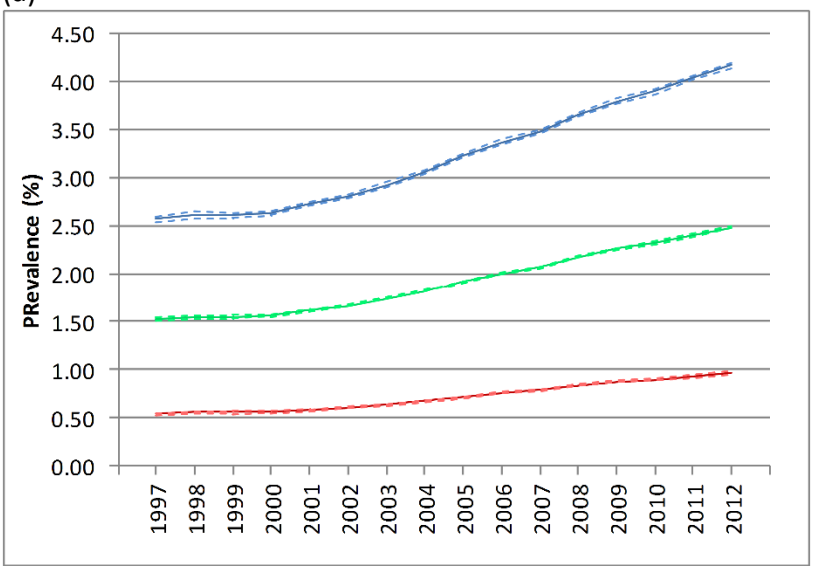
The standardised incidence also increased significantly (29.6%) during the study period. On average, the incidence of gout increased 1.5% (95% CI, 1.1%–1.9%) per year and there was only one joinpoint (2003). The annual change of incidence increased 3.8% (95% CI, 2.7%–4.9%) per year during the period between 1997 and 2003 but the incidence reached a plateau afterwards, with an annual change of 0.2 (95% CI, -0.4 to 0.9; $p = 0.45$). Figure 4-4b shows a very similar trend of gout incidence in men and women ($p = 0.171$), albeit a slightly higher

average annual change in women (2.0%, 95% CI, 1.3%–2.7%) than in men (1.5%, 95% CI, 0.9–2.0%). The male to female ratio in incidence slightly reduced from 3.4 in 1997 to 3.0 in 2012.

Table 3-1 Crude and standardised prevalence and incidence of gout from 1997 to 2012

Year	Prevalence (%)			Incidence (per 1000 person-years)		
	N	Crude	Standardised	Person-years	Crude	Standardised
1997	2209057	1.42 (1.40–1.43)	1.52 (1.50–1.54)	2069698	1.35 (1.30–1.40)	1.36 (1.31–1.41)
1998	2592984	1.46 (1.45–1.48)	1.55 (1.54–1.57)	2430671	1.29 (1.25–1.34)	1.32 (1.27–1.37)
1999	3138413	1.47 (1.45–1.48)	1.55 (1.54–1.57)	2937813	1.39 (1.35–1.43)	1.41 (1.37–1.46)
2000	3554201	1.48 (1.47–1.49)	1.57 (1.55–1.58)	3318520	1.42 (1.38–1.46)	1.44 (1.40–1.49)
2001	3929216	1.53 (1.52–1.55)	1.62 (1.61–1.63)	3668822	1.54 (1.50–1.58)	1.56 (1.52–1.60)
2002	4209993	1.59 (1.58–1.61)	1.67 (1.66–1.68)	3912097	1.58 (1.54–1.62)	1.60 (1.56–1.64)
2003	4375751	1.67 (1.66–1.69)	1.74 (1.73–1.75)	4060357	1.65 (1.61–1.69)	1.66 (1.62–1.70)
2004	4516966	1.76 (1.74–1.77)	1.82 (1.81–1.83)	4202025	1.67 (1.63–1.71)	1.68 (1.64–1.72)
2005	4605171	1.86 (1.85–1.87)	1.93 (1.91–1.94)	4299261	1.74 (1.70–1.78)	1.75 (1.71–1.79)
2006	4684243	1.96 (1.95–1.98)	2.02 (2.00–2.03)	4334086	1.70 (1.67–1.74)	1.71 (1.67–1.75)
2007	4736672	2.03 (2.02–2.05)	2.08 (2.07–2.09)	4374944	1.67 (1.63–1.71)	1.67 (1.63–1.71)
2008	4729771	2.16 (2.14–2.17)	2.19 (2.18–2.20)	4384072	1.75 (1.71–1.79)	1.75 (1.71–1.79)
2009	4727886	2.25 (2.24–2.26)	2.27 (2.26–2.29)	4384787	1.73 (1.69–1.77)	1.73 (1.69–1.77)
2010	4741179	2.31 (2.30–2.33)	2.33 (2.32–2.35)	4351414	1.68 (1.65–1.72)	1.69 (1.65–1.73)
2011	4624055	2.40 (2.39–2.42)	2.42 (2.40–2.43)	4235444	1.75 (1.71–1.79)	1.75 (1.71–1.79)
2012	4507059	2.49 (2.48–2.51)	2.49 (2.48–2.51)	4159043	1.77 (1.73–1.81)	1.77 (1.73–1.81)

(a)



(b)

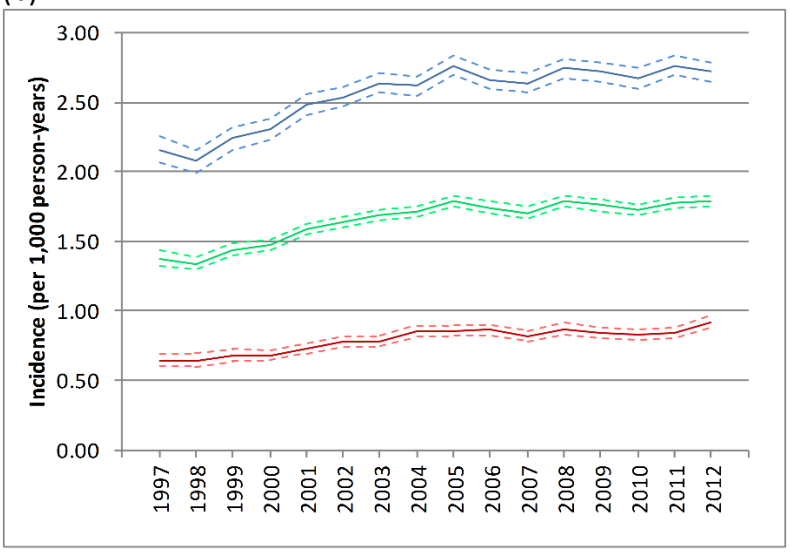
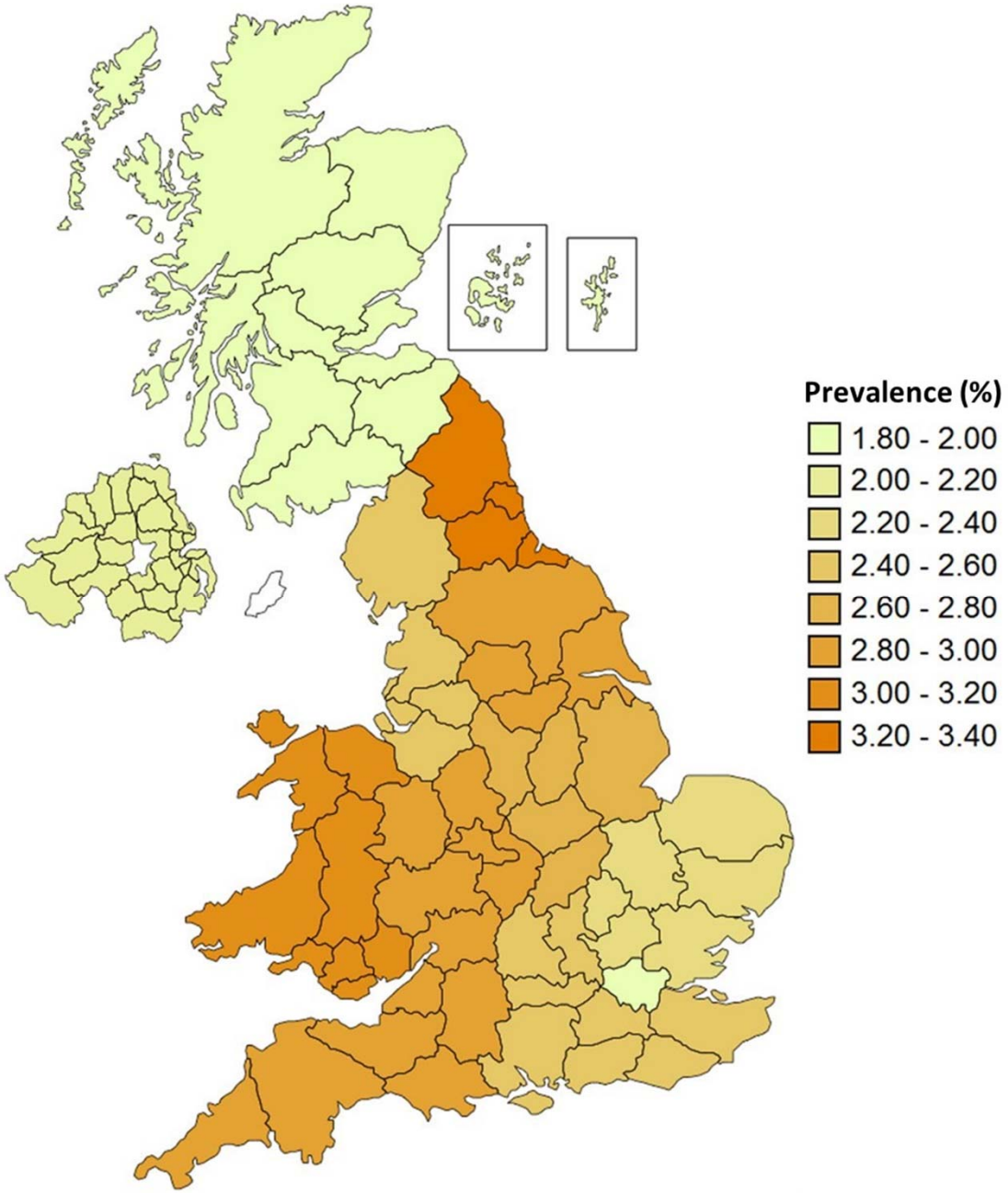


Figure 3-4 Gender differences in the trends of standardised prevalence (a) and incidence (b) of gout between 1997 and 2012 (blue: men; red: women; green overall; dotted line: 95% confidence bounds).

3.3.3 Geographic variation in 2012

Both the prevalence and incidence of gout were not uniform throughout the UK. As shown in Figure 4-5, the standardised prevalence (95% CI) of gout was highest in the North East (3.11% [3.00%–3.23%]) and Wales (2.98% [2.93–3.02]). Regions with the lowest prevalence of gout were Scotland (2.02% [1.98%–2.06%]) and Northern Ireland (2.15% [2.07–2.22]). The East of England and Northern Ireland were the regions with the lowest standardised incidence (95% CI) of gout (1.50 [1.37–1.65], 1.57 [1.45–1.69] per 1000 patient-years respectively), while Wales and the North East had the highest incidence (2.28 [95% CI, 2.13–2.43] and 2.17 [95% CI, 1.85–2.54] per 1,000 patient-years respectively).

(a)


Prevalence (%)
1.80 - 2.00
2.00 - 2.20
2.20 - 2.40
2.40 - 2.60
2.60 - 2.80
2.80 - 3.00
3.00 - 3.20
3.20 - 3.40

(b)

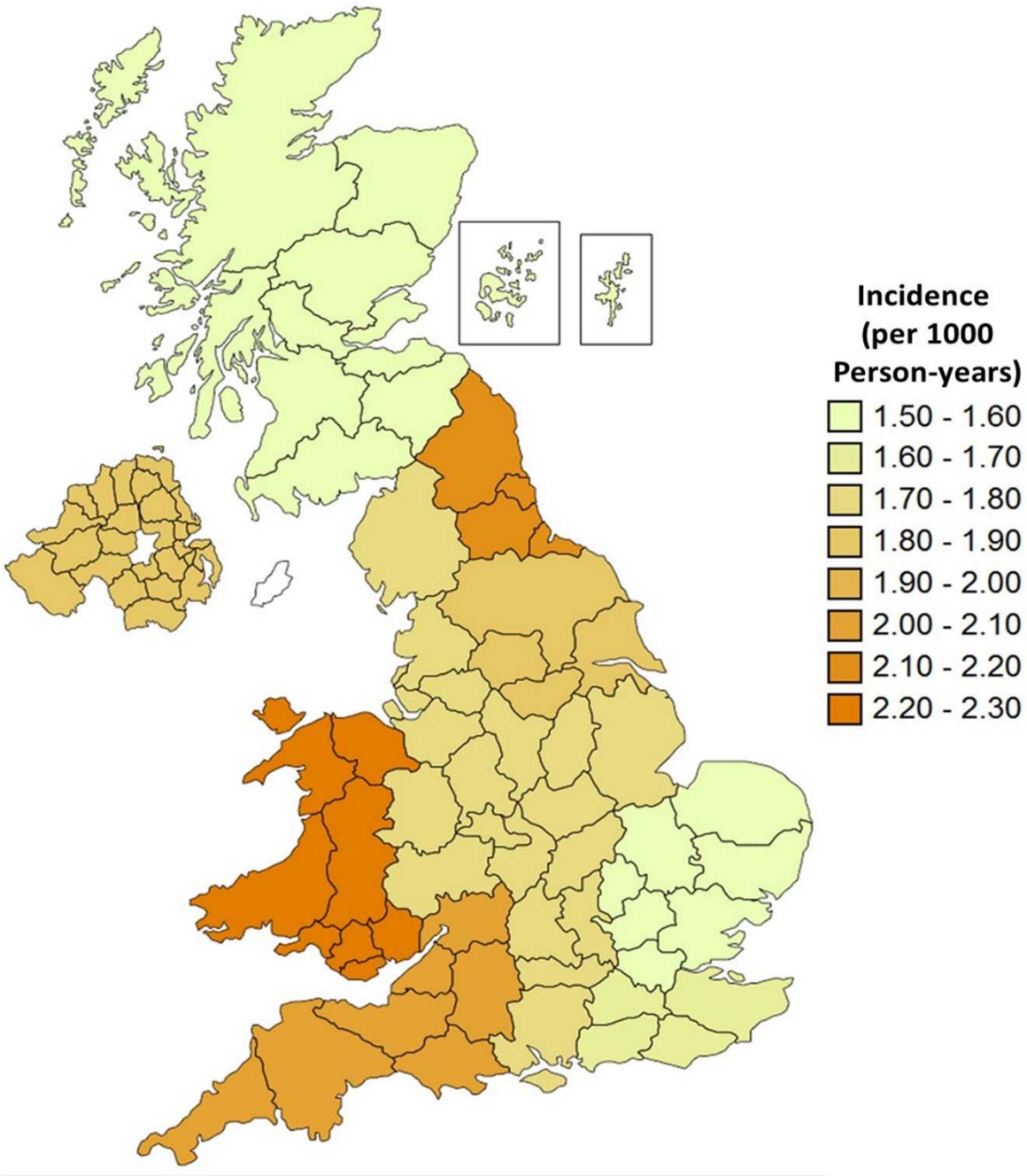


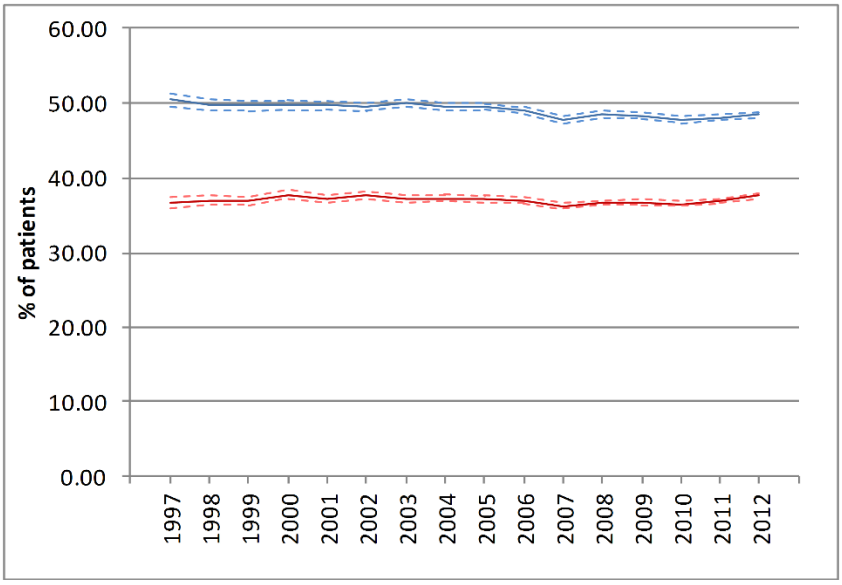
Figure 3-5 Geographic variations in the prevalence (a) and incidence (b) of gout in the United Kingdom in 2012.

3.3.4 Management of gout between 1997 and 2012

Among prevalent gout patients in 2012, approximately half were being consulted specifically for gout or being treated by ULT (48.48%; 95% CI, 48.08%–48.89%) and only one-third were being treated with ULT (37.63%, 95% CI, 37.28%–38.99%). As shown in Figure 4-6a, the percentage of patients being consulted for gout or treated by ULT remained poor and almost constant during the study period, with a APC (95% CI) of -0.3% (-0.4% to -0.2%). Similarly, the percentage of patients being treated by ULT has not changed, with an APC of -0.1% (-0.2% to 0.1%).

In 2012, only 18.6% (95% CI, 17.6%–19.6%) of incident gout patients received ULT within 6 months and approximately one in four were treated within 12 months of diagnosis (27.3%; 95% CI, 26.1%–28.5%). As Figure 4-6b shows, the percentage of patients receiving ULT within 6 and 12 months changed only marginally during the study period with APCs (95% CI) of -1.0% (-2.1 to 0.2; p = 0.100) and -0.8 (-1.6 to 0.1; p = 0.07), suggesting that the management of incident gout patients has remained essentially the same over the past 16 years.

(a)



(b)

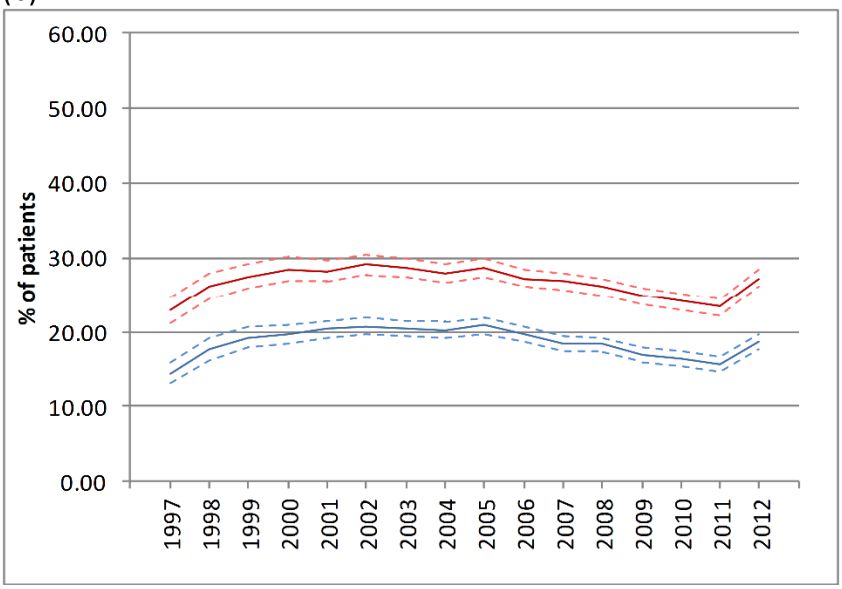


Figure 3-6 Management of gout (a) standardised percentage of prevalent patients under medical attention (blue line), and treated by urate-lowering agents (red line) and (b) standardised percentage of incident patients receiving urate-lowering treatment at 6 months (red line) and 12 months (blue line).

3.3.5 Adherence to urate-lowering treatment

Among ULT-treated patients in 2012 (n = 49395), 39.66% (95% CI, 39.11%–40.22%) were adherent to treatment. Partially adherent and non-adherent patients comprised 42.84% (95% CI, 42.27%–43.42%) and 17.50 (95% CI, 17.13%–17.87%), respectively. In contrast to the percentage of patients receiving ULT, patient adherence to ULT improved in the past 16 years (figure 4-7). Overall, the percentage of adherent patients improved from 28.28% (95% CI, 27.33%–29.26%) in 1997 to 39.66% (95% CI, 39.11%–40.22%) in 2012. The average APC was 2.0 (95% CI, 1.5–2.5). Joinpoints were attributed to 2002 and 2008, with APCs (95% CIs) of 4.5 (2.6–6.4) for 1997–2002, 2.2 (1.0–3.4) for 2002–2008 and 0.0 (-1.3 to 1.4) for 2008–2012. In contrast, the percentage of partially adherent and non-adherent patients reduced 13.0% and 22.0% respectively.

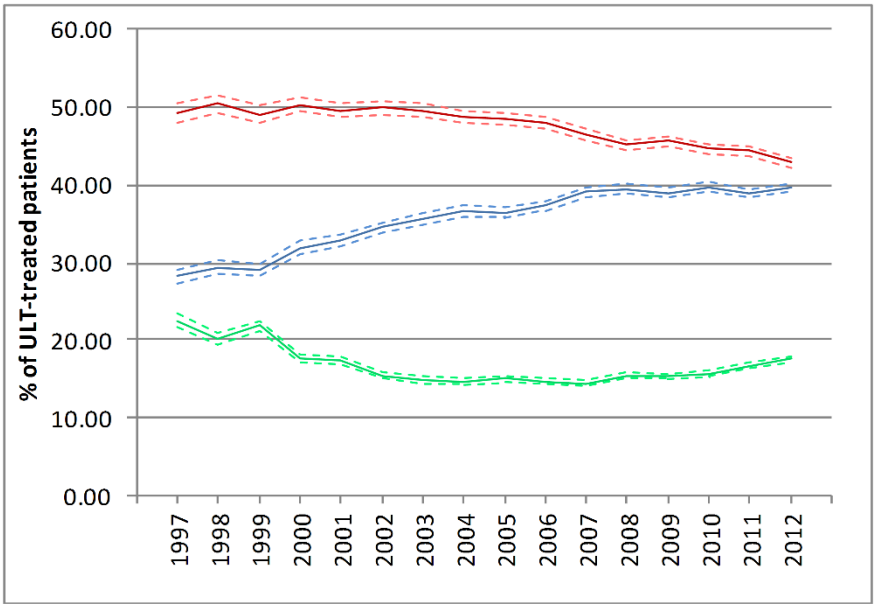


Figure 3-7 Secular trends of adherence of ULT-treated patients (blue: adherent; red: partially adherent; green: non-adherent patients)

3.3.6 *Estimates of prevalence and incidence based on alternative case definitions*

Next, estimates of prevalence and incidence based on alternative case definitions were examined. The first alternative case definition was a gout diagnosis plus the use of NSAID, corticosteroid or gout-specific drugs (colchicine and ULT) after the diagnosis of gout and the second was a gout diagnosis plus gout-specific drugs. In 2012, the prevalence of gout based on primary definition, alternative definition one and alternative definition 2 were 2.49% (2.48%–2.51%), 2.27% (2.26%–2.29%) and 1.39% (1.38%–1.40%), respectively (table 4-2). Prevalence based on alternative definition one and two were approximately 91% and 56% that of estimate based on primary case definition, respectively. This pattern is consistent in estimates across period 1997-2012. Male to female ratio was slightly higher in estimates based on alternative definitions; 4.4 for definition 1 and 3.9 for definition 2. Figure 4-8 shows age-specific prevalence of gout in 2012 based on different case definitions. It is apparent that the trends are similar. Estimates based on primary case definition shows nearly identical pattern with alternative case definition one, while estimates based on alternative case definition two shows a proportionally lower estimates across ages.

In 2012, the incidence of gout based on primary definition, alternative definition one and alternative definition 2 were 1.77 (1.73–1.81), 1.70 (1.66–1.74) and 0.85 (0.83–0.88) per 1,000 person-years, respectively. Incidence based on alternative definition one and two were approximately 97% and 54% that of estimate based on primary case definition, respectively. This pattern is consistent in estimates across period 1997-2012. Male to female ratio was

slightly lower in estimates based on alternative definitions; 2.4 for definition 1 and 2.2 for definition 2. Fig 4-8b compare age-specific incidence based on different definitions. The pattern is very similar between estimates based on primary case definition and alternative case definition one. The estimates based on alternative case definition 2 was significantly lower.

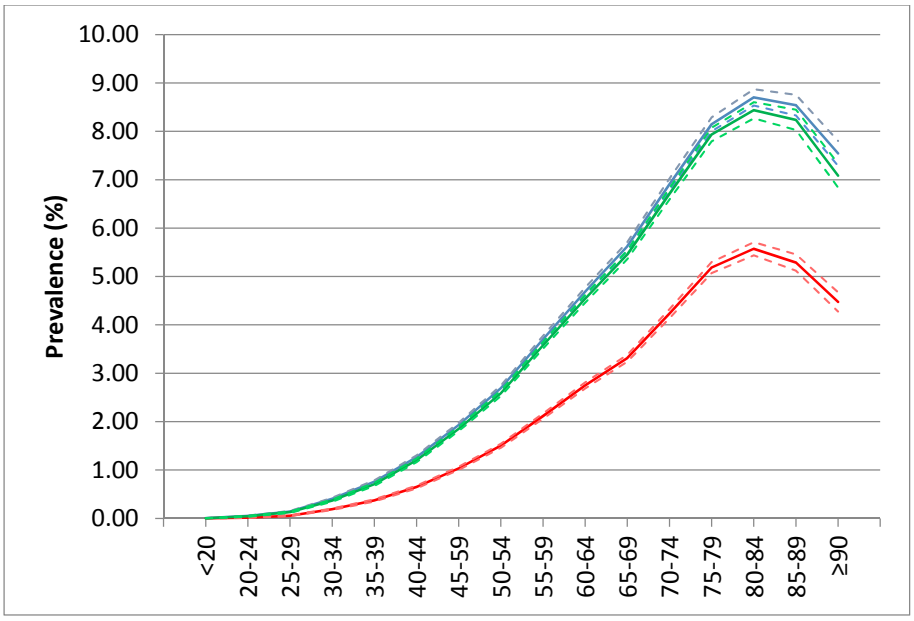
Table 4-2 compares the crude prevalence and incidence of gout based on different case definitions in calendar years from 1997 to 2012. In general, the estimates based on alternative case definition one is very close to estimated based on primary case definition. However, as only a minority of gout patients received ULT, therefore estimates based on alternative case definition two were significantly lower in all years. However, the general pattern is similar. Both prevalence and incidence of gout increased over time from 1997 to 2012, irrespective of which case definition used.

Table 3-2 Crude prevalence and incidence of gout from 1997 to 2012 based on primary definition: a gout diagnosis along, on alternative definition 1: a gout diagnosis plus receipt of NSAID, corticosteroid and gout-specific drugs (colchicine and ULT) and on alternative definition 2: a gout diagnosis and receipt of gout-specific drugs.

Year	Prevalence (%)					Incidence (per 1000 person-years)		
	N	Primary definition	Alternative definition 1	Alternative definition 2	Person-years	Primary definition	Alternative definition 1	Alternative definition 2
1997	2209057	1.42 (1.40–1.43)	1.22 (1.20–1.23)	0.78 (0.77–0.80)	2069698	1.35 (1.30–1.40)	1.31 (1.26–1.36)	0.70 (0.66–0.73)
1998	2592984	1.46 (1.45–1.48)	1.20 (1.18–1.21)	0.77 (0.75 –0.78)	2430671	1.29 (1.25–1.34)	1.25 (1.21–1.30)	0.69 (0.66–0.73)
1999	3138413	1.47 (1.45–1.48)	1.19 (1.18–1.20)	0.77 (0.76–0.78)	2937813	1.39 (1.35–1.43)	1.34 (1.30–1.39)	0.76 (0.73–0.79)
2000	3554201	1.48 (1.47–1.49)	1.30 (1.29–1.31)	0.84 (0.83–0.85)	3318520	1.42 (1.38–1.46)	1.38 (1.34–1.42)	0.79 (0.76–0.82)
2001	3929216	1.53 (1.52–1.55)	1.33 (1.32–1.34)	0.86 (0.85–0.87)	3668822	1.54 (1.50–1.58)	1.50 (1.46–1.54)	0.85 (0.82–0.88)
2002	4209993	1.59 (1.58–1.61)	1.42 (1.41–1.43)	0.92 (0.91–0.93)	3912097	1.58 (1.54–1.62)	1.55(1.51–1.58)	0.88 (0.85–0.91)
2003	4375751	1.67 (1.66–1.69)	1.50 (1.49–1.51)	0.97 (0.96–0.98)	4060357	1.65 (1.61–1.69)	1.61 (1.57–1.65)	0.90 (0.87–0.93)
2004	4516966	1.76 (1.74–1.77)	1.60 (1.59–1.62)	1.04 (1.03–1.05)	4202025	1.67 (1.63–1.71)	1.63 (1.59–1.66)	0.93 (0.90–0.96)
2005	4605171	1.86 (1.85–1.87)	1.71 (1.70–1.73)	1.10 (1.09–1.11)	4299261	1.74 (1.70–1.78)	1.70 (1.66–1.74)	0.96 (0.93–0.99)
2006	4684243	1.96 (1.95–1.98)	1.79(1.77–1.80)	1.14 (1.13–1.15)	4334086	1.70 (1.67–1.74)	1.66 (1.62–1.70)	0.92 (0.90–0.95)
2007	4736672	2.03 (2.02–2.05)	1.87 (1.86–1.88)	1.19 (1.18–1.20)	4374944	1.67 (1.63–1.71)	1.62 (1.58–1.66)	0.91 (0.88–0.94)

2008	4729771	2.16 (2.14–2.17)	1.97 (1.96–1.98)	1.25 (1.24–1.27)	4384072	1.75 (1.71–1.79)	1.70 (1.67–1.74)	0.95 (0.92–0.98)
2009	4727886	2.25 (2.24–2.26)	2.06 (2.04–2.07)	1.30 (1.29–1.31)	4384787	1.73 (1.69–1.77)	1.67 (1.64–1.71)	0.90 (0.87–0.93)
2010	4741179	2.31 (2.30–2.33)	2.10 (2.09–2.11)	1.31 (1.30–1.32)	4351414	1.68 (1.65–1.72)	1.63 (1.59–1.67)	0.83 (0.80–0.86)
2011	4624055	2.40 (2.39–2.42)	2.19 (2.18–2.20)	1.35 (1.34–1.36)	4235444	1.75 (1.71–1.79)	1.69 (1.65–1.73)	0.85 (0.82–0.88)
2012	4507059	2.49 (2.48–2.51)	2.27 (2.26–2.29)	1.39 (1.38–1.40)	4159043	1.77 (1.73–1.81)	1.70 (1.66–1.74)	0.85 (0.83–0.88)

(a)



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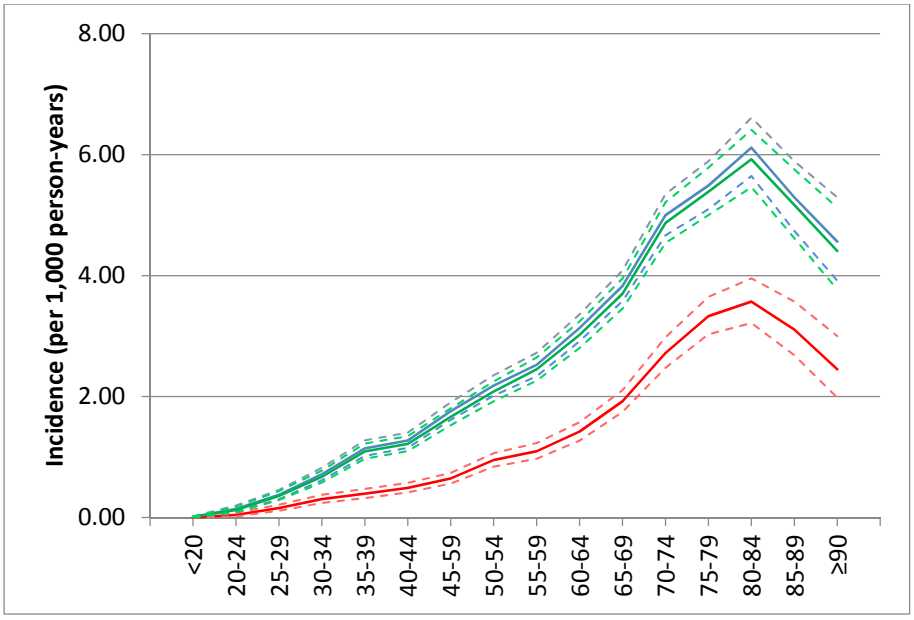


Figure 3-8 Age-specific prevalence of gout based on primary case definition (blue), alternative case definition one (green) and alternative case definition two (red).

3.4 Discussion

This study demonstrates that the burden of gout in the UK is higher than previously thought, with approximately one in 40 adults being affected. Furthermore the prevalence of gout has continued to increase from 1997 to 2012 despite a stabilised incidence after 2005. Gout is not distributed uniformly within the UK, the highest prevalence and incidence of gout being in the North East and Wales. Unfortunately, despite this rising prevalence and the publication of European (Zhang et al., 2006a, Zhang et al., 2006b) and UK (Jordan et al., 2007) guidelines in 2006 and 2007 respectively, the management of gout appears to be more than suboptimal with only one in three prevalent patients receiving ULT and only one in four newly diagnosed patients received ULT within one year of diagnosis. Although patient adherence to ULT has improved in the past decade this still remains poor.

Early studies showed an increase in gout prevalence in the UK up until 1999, when a nationwide study by Mikuls et al. using the GPRD reported an overall prevalence of 1.39%.(Mikuls et al., 2005b) Using the IMD analyser in the period 2000–2005, Annemans et al. reported an identical prevalence of 1.4% suggesting that gout prevalence may have reached a plateau.(Annemans et al., 2008) In contrast, the prevalence estimates were slightly higher during the period 1999–2005 and continued to increase throughout the study period. It is possible that this disparity primarily results from different degrees of identification of clinically silent patients, whose identification depends on a period of data contribution that is long enough to include a prior gout event. However, it is difficult to determine how many

years of observation are sufficient to exclude this bias since data on length of asymptomatic inter-critical gout period are sparse. Only one case series in 1961 reported that the length of inter-critical periods was less than 1 year in 62%, 1-5 years in 27%, 6-10 years in 4% and over 10 years in 7% of 614 patients.(Yu and Gutman, 1961) Therefore, rather than requiring a minimal length of data contribution, direct standardisation considering age, sex and length of data contribution was utilised to circumvent the incomplete identification of inter-critical gout patients. Studies that have not examined prior data contribution will have underestimated the prevalence of gout in the UK. When this bias is avoided it is apparent that the standardised prevalence of gout has risen since 1997. In addition, the prevalence of gout in the UK is higher than recent estimates in other European countries, specifically 1.4% in Germany (Annemans et al., 2008) and 0.91% in Italy.(Trifiro et al., 2013)

Very few studies have addressed the incidence of gout. Using data from the UK Second and Third National Studies of Morbidity in General Practice in the UK, overall gout incidence was estimated to be 1.4 per 1000 person-years in 1981.(Stewart and Silman, 1990) A previous CPRD study reported an increased incidence per 1,000 person-years from 1.19 in 1990 to 1.80 in 1999(Mikuls et al., 2005b) whilst the Royal College of General Practitioners Weekly Returns Service (WRS) reported rates increasing from 1.12 to 1.35 per 1,000 population between 1994 and 2007. Another study using the THIN database reported an incidence of 2.68 per 1,000 person-years in the adult population in the period 2000–2007.(Elliot et al., 2009) The estimates of incidence in the present study in general fall within these previous reported ranges. However, the incidence of gout was found to have increased by more than one

quarter during the study period. Although it reached a plateau after 2004, it has shown no signs of subsequent reduction, a finding echoed by the observations of an increasing prevalence. Therefore gout will remain a commonly encountered disorder and the prevalence may even continue to rise in the near future.

In addition to temporal changes there was clear evidence for regional variations in gout. The patterns for prevalence and incidence were similar, with the North East and Wales having the highest estimates for both. Regional variation within the UK has been noted previously in just two studies. In a survey in 1975 Currie et al. reported a higher prevalence of gout in England than in Wales(Currie, 1979) and in 2982 Gardner et al. reported a lower prevalence (3.9%) in adults over age 45 in Ipswich in Suffolk than in the two more northern towns of Wakefield (4.5%) and Preston (4.9%).(Gardner et al., 1982) No previous reports of geographical variation in incidence of gout in the UK could be identified. The reasons for current geographic variation in gout most likely relate to differences in socioeconomic status, life-style and nutrition and although gout historically was considered a disease of affluence, the converse may now be true. The UK morbidity statistics from general practice (1970-71) reported that people with non-manual skilled occupations had the highest whereas professional occupations had the lowest standardised consulting ratio for gout (133 vs. 79)(Great Britain. Office of Population et al., 1982) and Gardner's study found a lower prevalence of gout in the town with the most favourable socioeconomic status.(Gardner et al., 1982) In addition, a recent New Zealand study also found that the least deprived people had the lowest risk of gout.(Jackson et al.,

2012) However, further studies are needed to explore the reasons for current variation by socioeconomic group and region.

Regardless of the increasing prevalence and incidence of gout in the UK, the management of the disease remains poor. Throughout 1997–2012 only around one third of people with prevalent gout were prescribed ULT. The management for incident gout patients also remained unchanged with only a quarter to a third of patients being treated with ULT within one year of diagnosis. This shows no significant change in overall usage of ULT from Mikuls' estimates of 25.3%-29.5% from 1990 to 1999(Mikuls et al., 2005b). Apart from under-prescribing of ULT, Mikuls et al identified inappropriate prescribing of ULT in one quarter to one half of those people in whom quality indicators could be assessed(Mikuls et al., 2005a) and a more recent study also demonstrated suboptimal care in many aspects of gout management.(Roddy et al., 2010) Collectively these results reflect widespread lack of knowledge of gout and poor alignment with current recommendations of best practice within the UK.(Spencer et al., 2012, Rees et al., 2013, Doherty et al., 2012) Although guidelines do not explicitly advise discussion of ULT with every gout patient around the time of diagnosis, the majority of patients will have recommended specific indications (e.g. Further attacks,(Yu and Gutman, 1961) renal impairment,(Choi et al., 2012) required chronic diuretic use,(Choi et al., 2012) nephrolithiasis,(Kramer et al., 2003) peripheral joint damage or tophi(McGill and Dieppe, 1991)) at diagnosis or within 6-12 months. Furthermore, increasingly the trend is towards early treatment with ULT to prevent people developing further crystal deposition and complications such as subcutaneous tophi and joint damage.(Doherty et al., 2012) Best

practice requires full patient information concerning gout and its treatment (Zhang et al., 2006a, Zhang et al., 2006b, Jordan et al., 2007, Doherty et al., 2012) and in one recent UK study, when patients received this 100% wished to receive ULT.(Rees et al., 2013, Doherty et al., 2012) Being that gout is the only chronic arthritis for which there is “curative” treatment, the use of ULT would seem a useful indicator of standard of care.(Doherty et al., 2012)

This study also found that only approximately 40% of treated patients in 2012 adhered to ULT. This accords with a recent review of six studies which reported that only 18% to 44% of patients with gout adhere to ULT.(Reach, 2011) Such poor adherence to ULT has long been recognised, one review finding adherence in gout patients to be the worst of seven chronic diseases requiring chronic medication.(Briesacher et al., 2008) Nevertheless, there was an encouraging signal of a 40% improvement in percentage of adherent patients from 1997 to 2012. Although previous studies largely blame patients for poor adherence,(Reach, 2011, Solomon et al., 2008) a recent study indicated that appropriate patient education can effectively maintain high adherence to ULT and achieve therapeutic target in nine out of ten gout patients.(Rees et al., 2013) Therefore, as with low rates of ULT prescription, it is likely that the fault lies more with the health practitioners than with the patients.(Doherty et al., 2012) There are many recognised barriers to care of gout, both in patients and practitioners, but practitioner education seems the first prerequisite to address these problems.

Estimates of gout prevalence and incidence may vary according to case definitions used to identify patients. The primary case definition of this study was based on a physician diagnosis.

There are several limitations to the study. Firstly, this study based the case definition on diagnosis by the general practitioners, rather than according to American College of Rheumatology(Wallace et al., 1977) or Rome(Kellgren JH, 1963) classification criteria or to the 'gold standard' of urate crystal identification and this may lead to misclassification bias. However, the validity of gout diagnosis in the CPRD has been investigated and found to be high.(Meier and Jick, 1997) I also used two stricter case definitions to see whether the estimates change a lot. First kind of alternative case definition is the same as that had been validated by Meier et al.,(Meier and Jick, 1997) which requires a gout diagnosis plus NSAID, corticosteroid and gout-specific drugs (ULT and colchicine). Estimates based on this tighter definition were lower than estimates based on physician diagnosis alone. However, the estimates were very close, hardly having any statistical significance. Alternative case definition two, which requires a gout diagnosis and gout-specific drugs. The estimates were approximately half that of estimates based on physician diagnosis alone, which estimates were likely to be underestimated, since only a fraction of gout patients received colchicine or ULT.

Secondly, this study based the adherence estimation on PDC, which is generally believed to be more conservative than the more commonly used measure of medication possession ratio. It was assumed that patients took all prescribed pills since calculation of PDC relies on records of prescription refills, but this assumption may not hold true and may have led to an overestimation of adherence.

In conclusion, both the prevalence and incidence of gout have risen in the past 16 years and are the highest reported within Europe. However, despite being the commonest inflammatory arthritis the suboptimal management of gout continues unchanged, with only a minority of patients receiving ULT and new patients not being treated in a timely fashion. Although somewhat improved patient adherence to ULT remains poor. It is apparent that educational initiatives to improve practitioner knowledge, interest and standard of care of the only “curable” form of inflammatory arthritis are urgently required.

CHAPTER 4. Epidemiology of gout in Taiwan: a nationwide population study

4.1 Introduction

The prevalence and incidence of gout have a distinct geographical and racial distribution.{Roddy, 2007 #70} Taiwan is one of the countries with the highest prevalence of gout.{Chou, 1994 #91;Chang, 1997 #364;Chou, 1998 #338;Lin, 2000 #28;Chang, 2001 #27;Lai, 2009 #93;Kuo, 2010 #29;Chuang, 2011 #76} A recent nationwide survey (Nutrition and Health Survey in Taiwan) reported a gout prevalence of 8.2% in men and 2.3% in women in the period 2005-2008 (Chuang et al., 2011), which is close to the estimates in 2004 based on the National Health Insurance Research Database (NHIRD).(Kuo et al., 2013b) In particular, Taiwanese aborigines have a very high prevalence of gout (Chang et al., 1997, Chou and Lai, 1998), which is shared with their genetically related Polynesian cousins, the Maori and indigenous Oceanic-Pacific Islanders.(Klemp et al., 1997) Incidence of gout has not been estimated in Taiwan previously and the current standard of care in Taiwan as reflected by the use of urate-lowering therapy has not been examined.

Therefore this study was undertaken to examine the prevalence and incidence of gout and the patterns of gout management between 2005 and 2010 using the National Health Insurance Research Database (NHIRD), which contains comprehensive information on diagnosis, prescription and hospitalisations of essentially the entire population in Taiwan.

4.2 Methods

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number 101-2178C).

4.2.1 Source of data and study population

This study used data from the NHIRD, which contained registration files and original claims data from approximately 28.75 million (living and deceased) beneficiaries registered with the NHI between March 1995 and the end of 2010. This study comprised all beneficiaries registered continuously between 1st January 2005 and 31th December 2010.

4.2.2 Case definition of gout

Data were obtained from the National Health Research Institute, the data holder of NHIRD, on all patients with gout by searching the entire database from 1995 to 2010 for those with a least one outpatient record containing a gout diagnosis (based on the International Classification of Diseases [ICD] version 9 codes of 274).

4.2.3 Estimation of prevalence and incidence

Prevalent cases of gout were defined as individuals who had at least one record of a primary diagnosis of gout in primary care within the 10-year period before 1st July of each calendar year. The denominator for prevalence estimation (eligible population) for each calendar year

included all individuals registered on 1st July of each calendar year. Prevalence was calculated using the number of prevalent cases of gout divided by the eligible population in the specified calendar year.

Incident cases of gout were those who had no evidence of gout or use of ULT within the 10-year period prior to 1st January of each calendar year but who developed gout during that year. An observational period of 10 years was chosen for two reasons: 1. the NHIRD does not have data going back further than 10 years; 2. The majority of prevalent gout patients can be identified with a 10 year observation according to a previous cohort study.(Yu and Gutman, 1961) To be eligible to be considered incident gout patients, beneficiaries had to have at least one-year registration prior to 1st January of each calendar year. For the incidence of gout, at-risk cohorts were constructed for each calendar year which comprised all individuals registered during the given calendar year who had no history of gout diagnosis before 1st Jan of the year. Incidence was calculated using the number of incident gout cases during a calendar year as the numerator and the total person-years at-risk population accumulated during that year as the denominator.

Prevalence and incidence were calculated for 21 cities/counties in Taiwan (subsequently termed regions): Taipei city, Taipei county, Keelung city, Taoyuan county, Hsinchu city and county, Yilan county, Miaoli county, Taichung city, Taichung county, Changhua county, Yunlin county, Nantou county, Chiayi city and county, Tainan city, Tainan county, Kaohsiung city, Kaohsiung county, Pingtung county, Hualien county Taitung county and offshore islets

(Penghu, Kinmen and Lienchiang counties). To remove the effect of different age and gender structures in these regions, the prevalence and incidence were standardised with respect to the overall population structure of 2010. Choropleth maps were used to represent geographic variations in gout incidence and prevalence between different regions of Taiwan. (Inc., 2009)

4.2.4 Pattern of medication use

This study ascertained the proportion of prevalent gout patients who received ULT (allopurinol, benzbromarone, probenecid or sulfinpyrazone) in each calendar year from 2005 to 2010.

4.2.5 Trends of prevalence, incidence and management of gout

To determine the trends in prevalence, incidence and management of gout the following were calculated: age- and sex-standardised prevalence, incidence of gout and pattern of ULT prescribing in each calendar year from 2005 to 2010 with the population structure in year 2010 as the reference.

4.2.6 Statistical analysis

The 95% confidence intervals (CIs) for prevalence and incidence were derived on the basis of the assumption of a Poisson distribution for the observed number of prevalent and incident cases. The Joinpoint Regression Program (version 4.0.4) was used to estimate trends in prevalence and incidence of gout. The program used Bayesian Information Criterion to

generate different numbers of ‘join points’ in time when the linear trend of prevalence and incidence of gout change significantly and to determine the best-fit data series (Kim et al., 2000). A maximum of two joint points was used to determine statistical significance for trend. Annual percentage changes (APC) for each segment were calculated. The significance level was set at 0.05. All statistical analyses were performed by using SAS statistical software, version 9.3.

4.3 Results

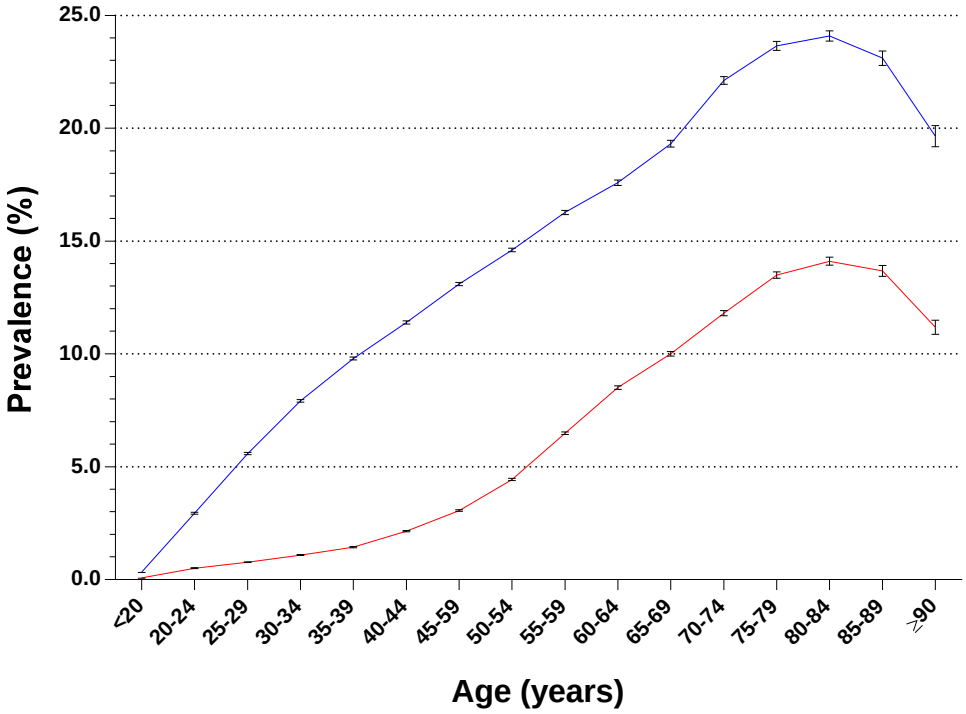
4.3.1 Prevalence and incidence of gout in 2010

Of 23,371,362 beneficiaries (men: 49.56%) included within the NHI in 2010, 1,458,569 prevalent cases of gout (men: 74.17%) were identified, giving a prevalence of 6.24% (95% CI, 6.23%–6.25%). Men had a significantly higher prevalence of gout (9.34%; 95% CI, 9.32%–9.36%) than women (3.20%; 95% CI, 3.19%–3.21%). Overall, the prevalence of gout was 2.9-fold higher than in women. This gender difference was observed in all ages with a male to female ratio of 4.5 in individuals younger than 20 years, peaking at 7.3 in those aged 30-34 years and then decreasing thereafter. Gout was rare in people younger than 20 years and it increased with age reaching a peak in the 80-84 year age band (figure 5-1a).

There were a total 21,241,996 person-years of follow-up in this year during which 73,706 incident cases of gout were identified (overall incidence 3.47 [95% CI, 3.44–3.50] per 1,000 person-years). Men had a higher incidence of gout (5.13 [95% CI, 5.09–5.18] per 1000 person-year) than women (1.32 [95% CI, 1.92–1.98]) per 1000 person year). As shown in figure 5-1b, incidence of gout in men was low in those younger than 20 years but increased rapidly until ages 35-39 years. After a relative plateau in gout incidence during middle age, gout incidence again showed a sharp increase, reaching a peak between ages 70 and 74 years. In women, the incidence of gout remained low before the age of 40 but thereafter started to increase rapidly, reaching a peak incidence at the age band of 80-84 years. The greatest male to female

ratio (6.7) was in those aged 20-24 years and thereafter the relative difference between males and females diminished with age.

(a)



(b)

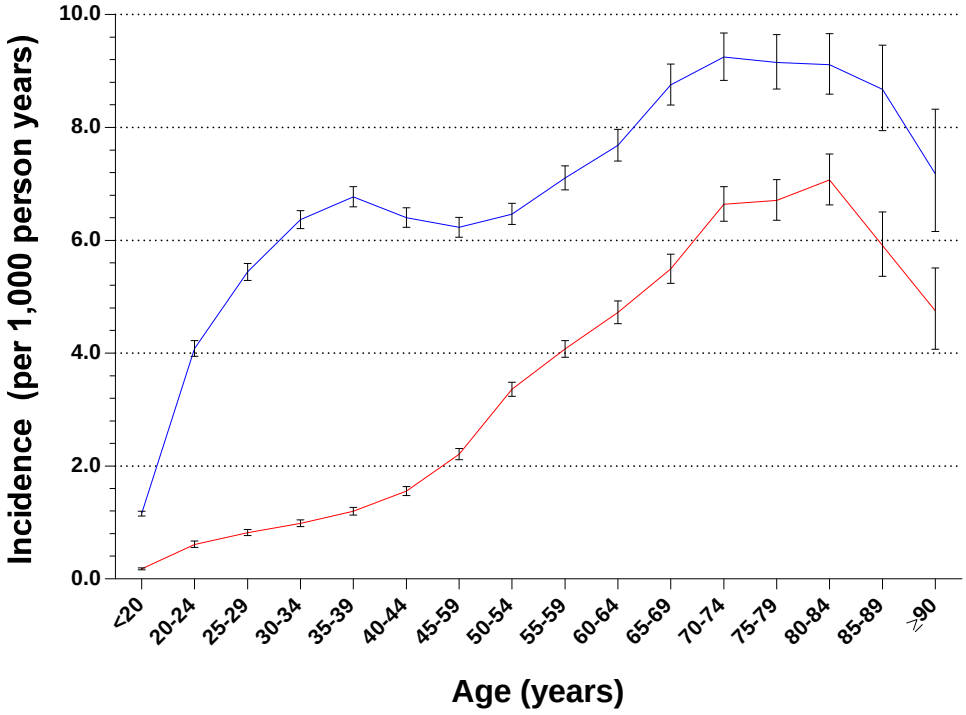


Figure 4-1 Age-specific prevalence (a) and incidence (b) of gout in 2010 (Blue: men; red: women)

4.3.2 **Prevalence and incidence of gout between 2005 and 2010**

Table 5-1 shows the temporal trends in prevalence and incidence of gout from 2005 to 2010. In general, the standardised estimates were slightly higher than the crude ones, accounting for the fact that the population was aging over time. Crude prevalence of gout increased 5.6% but standardised prevalence fluctuated throughout the study period. The standardised prevalence of gout in contrast decreased just 3.1% over the study period. The annual percentage change was -0.7 (95% CI, -1.7 to 0.3) but this was not statistically significant ($p = 0.14$), suggesting that the prevalence of gout was essentially the same throughout the study period after adjusting for age. As Figure 5-2a shows, the temporal trend of prevalence in men and women was not parallel ($p <0.001$). The annual percentage change was 1.0 (95% CI, 0.1–1.9) in men and -4.0 (95% CI, -5.4 to -2.7) in women. The male-to-female ratio increased slightly from 2.3 in 2005 to 2.9 in 2010.

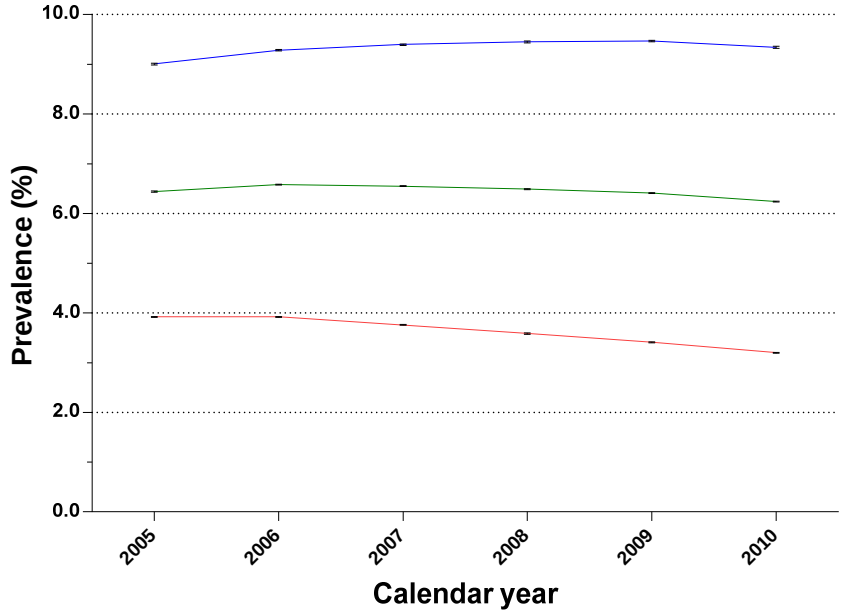
Both the crude and standardised incidence of gout reduced over time during this period; in particular the standardised incidence reduced by 33.3% over this period. The standardised incidence decreased significantly during the study period (figure 5-2b). On average, the annual percentage change of gout incidence was -7.9 (95% CI, -10.7 to -5.0) and there was one joinpoint (2007). The annual percentage change of incidence was -13.4 (95% CI, -16.1 to -10.6) during the period between 2005 and 2007 and -3.5 (95% CI, -5.3 to -1.6) during the

period 2007 to 2010. Figure 2b shows a similar trend in gout incidence for men and women (p = 0.04), with an annual percentage change of -7.4 (95% CI, -10.7 to -3.9) in men and -8.8 (95% CI, -11.9 to -5.7) in women. The male to female ratio in incidence slightly increased from 2.4 in 2005 to 2.7 in 2010.

Table 4-1 Crude and standardised prevalence and incidence of gout from 2005 to 2010

Year	Prevalence (%)			Incidence (per 1000 person-years)		
	N	Crude	Standardised	Person-years	Crude	Standardised
Overall						
2005	23,000,521	5.91 (5.90–5.92)	6.44 (6.43–6.45)	20,675,205	3.89 (3.86–3.92)	4.09 (4.06–4.11)
2006	23,127,946	6.14 (6.13–6.15)	6.58 (6.57–6.59)	20,502,927	3.29 (3.27–3.32)	3.43 (3.41–3.46)
2007	23,221,905	6.22 (6.21–6.23)	6.55 (6.54–6.56)	20,569,401	2.97 (2.95–2.99)	3.06 (3.04–3.09)
2008	23,315,001	6.27 (6.26–6.28)	6.49 (6.48–6.50)	20,616,155	2.95 (2.93–2.98)	3.01 (2.99–3.04)
2009	23,344,259	6.30 (6.29–6.31)	6.41 (6.40–6.42)	20,633,487	2.83 (2.80–2.85)	2.86 (2.85 –2.88)
2010	23,371,362	6.24 (6.23–6.25)	6.24 (6.23–6.25)	20,633,895	2.73 (2.71–2.75)	2.73 (2.71–2.75)
Men						
2005	11,550,180	8.35 (8.33–8.36)	9.01 (8.99–9.02)	10,021,292	5.67 (5.62–5.71)	5.94 (5.89–5.98)
2006	11,579,907	8.74 (8.72–8.76)	9.28 (9.27–9.30)	9,974,293	4.78 (4.73–4.82)	4.93 (4.89–4.98)
2007	11,598,597	8.98 (8.96–8.99)	9.40 (9.38–9.41)	9,952,078	4.37 (4.33–4.42)	4.48 (4.44–4.53)
2008	11,615,445	9.16 (9.14–9.18)	9.45 (9.43–9.47)	9,926,917	4.34 (4.30–4.38)	4.41 (4.37–4.45)
2009	11,597,439	9.32 (9.30–9.34)	9.47 (9.45–9.48)	9,889,211	4.18 (4.14–4.22)	4.21 (4.17–4.25)
2010	11,583,208	9.34 (9.32–9.36)	9.34 (9.32–9.36)	9,845,586	4.06 (4.02–4.10)	4.06 (4.02–4.10)
Women						
2005	11,450,341	3.46 (3.45–3.47)	3.92 (3.91–3.93)	10,468,285	2.22 (2.19–2.25)	2.46 (2.43–2.49)
2006	11,548,039	3.54 (3.53–3.55)	3.92 (3.91–3.93)	10,528,634	1.89 (1.86–1.91)	2.06 (2.03–2.09)
2007	11,623,308	3.48 (3.47–3.49)	3.76 (3.75–3.77)	10,617,323	1.65 (1.63–1.68)	1.76 (1.74–1.79)
2008	11,699,556	3.40 (3.39–3.41)	3.59 (3.57–3.60)	10,689,238	1.67 (1.64–1.69)	1.74 (1.72–1.77)
2009	11,746,820	3.31 (3.30–3.32)	3.41 (3.40–3.42)	10,744,276	1.58 (1.56–1.61)	1.62 (1.59–1.64)
2010	11,788,157	3.20 (3.19–3.21)	3.20(3.19–3.21)	10,788,309	1.52 (1.49–1.54)	1.52 (1.49–1.54)

(a)



(b)

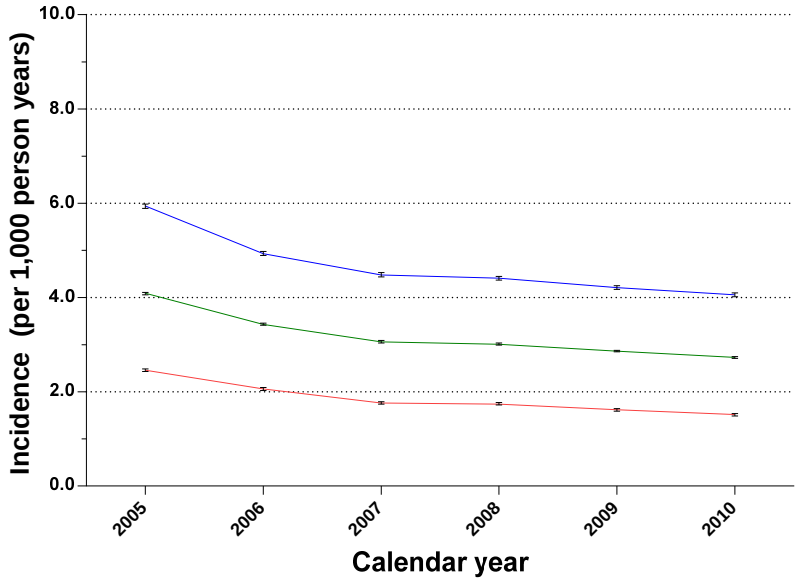
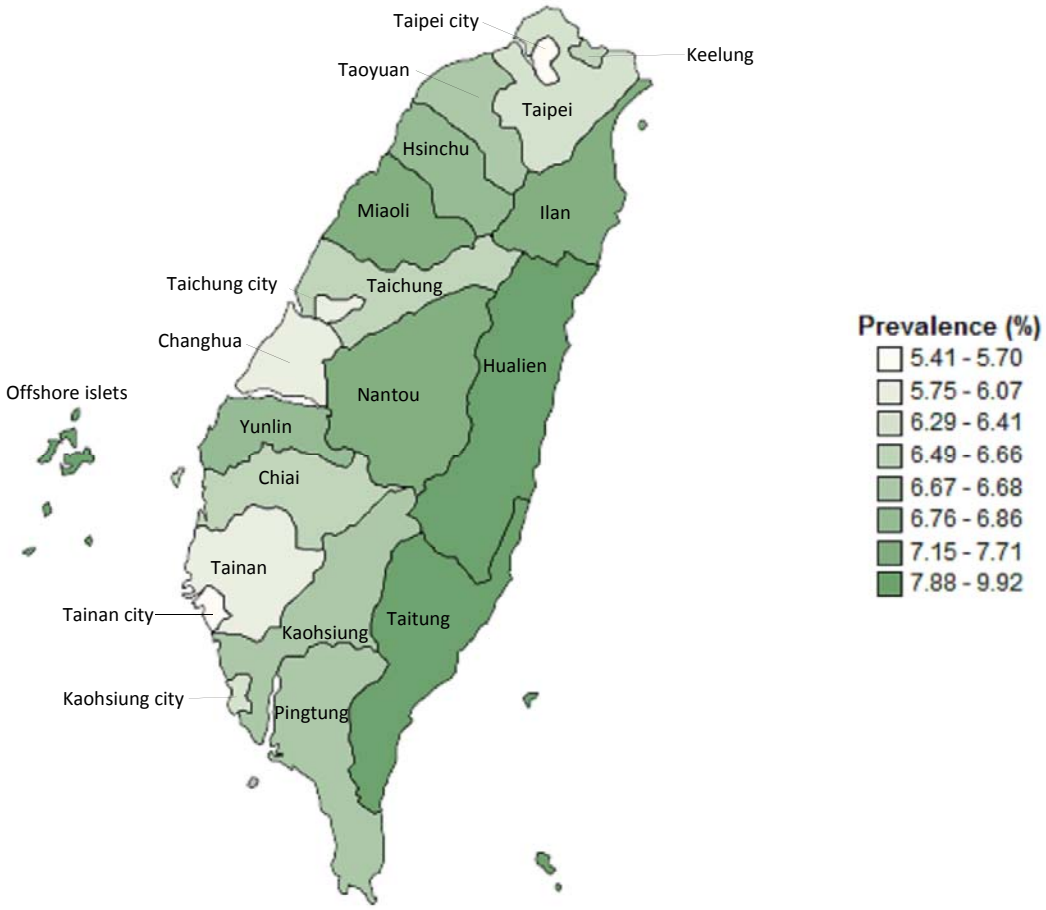


Figure 4-2 Gender differences in the trends of standardised prevalence (a) and incidence (b) of gout between 2005 and 2010 (blue: men; red: women; green overall).

4.3.3 Geographic variation in 2010

Both prevalence and incidence of gout were not uniform throughout Taiwan. As shown in Figure 5-3, the standardised prevalence (95% CI) of gout was highest in the eastern coast counties and offshore islets. The regions with the lowest prevalence of gout were mostly in the urban areas (Taipei city, Taichung city, Tainan city and Kaohsiung city). The regional pattern of gout incidence resembled that of gout prevalence, with a higher incidence in the eastern coast counties and offshore islets and a lower incidence in the urban areas.

(a)


Taipei city
Keelung
Taoyuan
Taipei
Hsinchu
Miaoli
Ilan
Taichung city
Taichung
Changhua
Hualien
Offshore islets
Nantou
Yunlin
Chiai
Tainan
Tainan city
Taitung
Kaohsiung
Kaohsiung city
Pingtung
Prevalence (%)
5.41 - 5.70
5.75 - 6.07
6.29 - 6.41
6.49 - 6.66
6.67 - 6.68
6.76 - 6.86
7.15 - 7.71
7.88 - 9.92

(b)

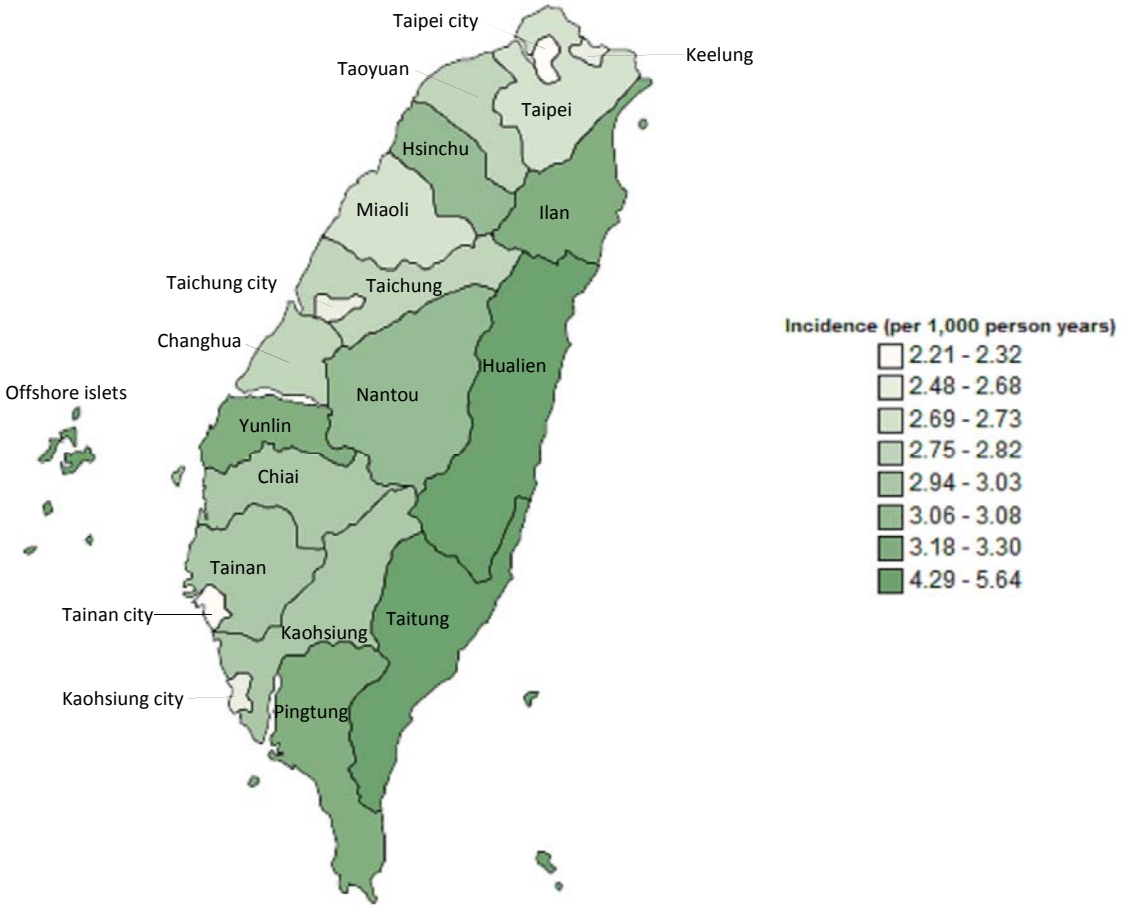


Figure 4-3 Geographic variations in the prevalence (a) and incidence (b) of gout Taiwan in 2010

4.3.4 Management of gout between 2005 and 2010

Of the 1,458,569 prevalent gout patients in 2010, approximately one-third had consulted for gout or been treated with ULT (n = 515,004; 35.31% [95% CI, 35.23%–35.39%]). However, only one in five prevalent gout patients in 2010 were treated with ULT (n= 334,518; 22.93% [95% CI, 22.87%–23.00%]). Among ULT-treated patients 60.08% (95% CI, 59.91%–60.25%) received uricosuric agents alone, 28.54% (95% CI, 28.39%–28.69%) received a xanthine oxidase inhibitor, and 11.38% (95% CI, 11.27%–11.49%) received both. As shown in Figure 5-4a, the proportion of prevalent patients who consulted for gout or were treated by ULT remained low during the study period, with an annual percentage change (95% CI) of -0.9 (-6.2 to 4.7). Similarly, the proportion of patients being treated by ULT did not change, with an APC of 0.0 (-3.8 to 4.0).

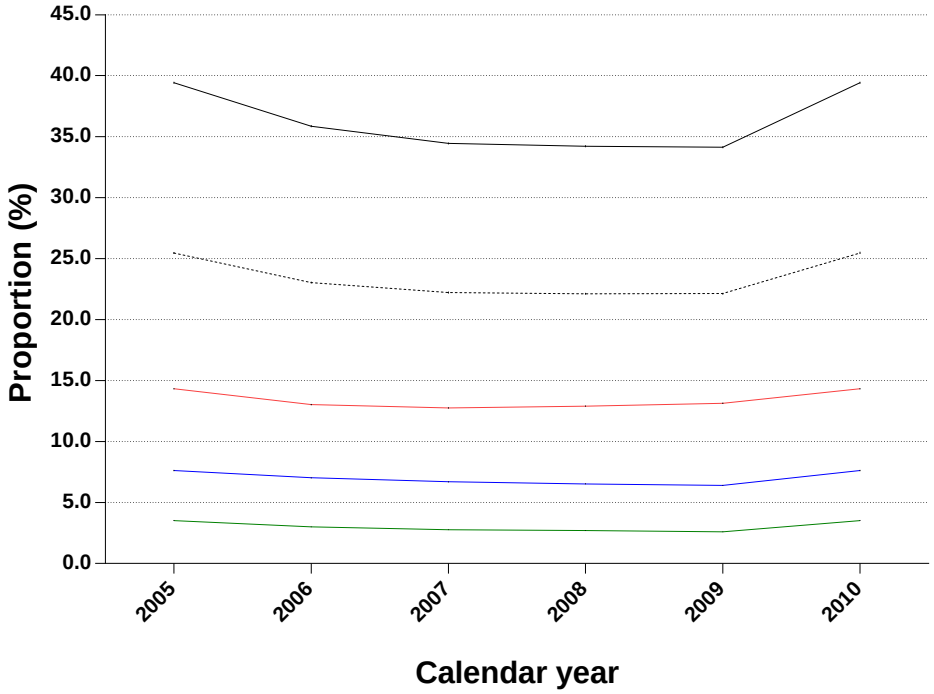


Figure 4-4 Treatment of gout in Taiwan in 2010. Proportion of prevalent gout patients having consulted for gout or receiving urate lowering treatment (black line), receiving urate lowering treatment (black dotted line), uricosuric agents (red line) xanthine oxidase inhibitor (blue line) or both (green line).

4.3.5 Comparison of gout epidemiology between the UK and Taiwan

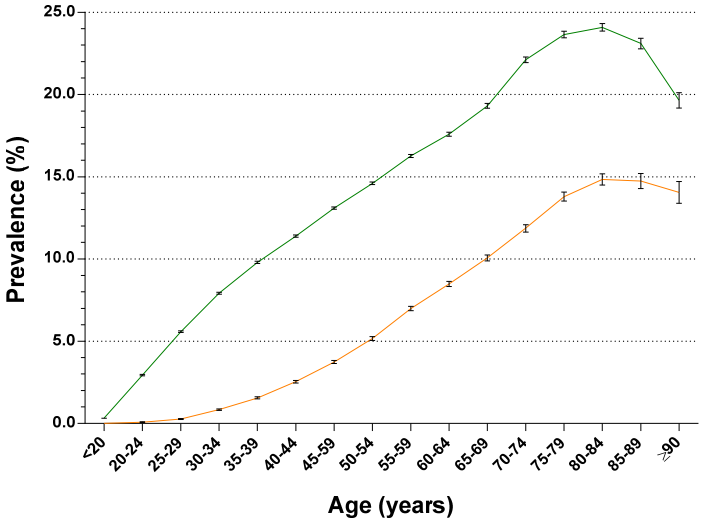
In general there is a consistently higher prevalence and incidence of gout in Taiwan than in the UK. Figure 5-5 shows a comparison of gout prevalence in men and women and Figure 5-6 shows a comparison of gout incidence between genders. It is obvious that prevalence of gout is consistent higher in Taiwan than in the UK in both men and women across all age bands. A similar trend was found in the incidence of gout, only in people older than 90 years were the estimates were similar in both countries (figure 5-6). As figure 5-7a shows, the prevalence of gout remains relatively stable in both countries in the period between 2005 and 2010, despite a slight increase in prevalence of gout from 1.93% to 2.33%. Figure 5-7b shows that incidence of gout decreased during the period 2005-2010 in Taiwan but was stable in the UK. In general, this proportion remains stable in both countries during the period 2005-2010. A higher proportion of prevalent patients were prescribed ULT in the UK than in Taiwan.

Figure 5-8 compares the proportion of prevalent patients being prescribed ULT in the UK and Taiwan. The treatment pattern is difficult to compare directly as the availability of ULT was more limited in the UK, where only allopurinol is routinely available for GP prescription. While allopurinol is almost exclusively prescribed in the UK, uricosuric

agents are more commonly prescribed than allopurinol. There is another xanthine oxidase inhibitor, febuxostat, which has been approved in both countries. The utilisation of febuxostat is not discussed here because it is approved in 2011, which year is beyond the study period. In general, both countries suffer low ULT prescription rate and the pattern did not change in recent years. In addition, this proportion remains stable in both countries during the period 2005-2010. A higher proportion of prevalent patients were prescribed ULT in the UK than in Taiwan. These results suggest that the treatment patterns of gout in the UK and Taiwan are essentially no change during study period.

As shown in Chapter 2, in general the UK population is older than the Taiwan population in the study period. However, it seems that the UK population structure remains similar in terms of age and gender distribution but the Taiwan population is rapidly aging, despite the difference between 2005 and 2010 seems to be small. Therefore the current study probably cannot depict population change in Taiwan in years prior to 2005. In terms of socioeconomic status, the UK is a traditionally developed country for decades but Taiwan can be classified as developing or emerging developed country depending on national matrices used.

(a)



(b)

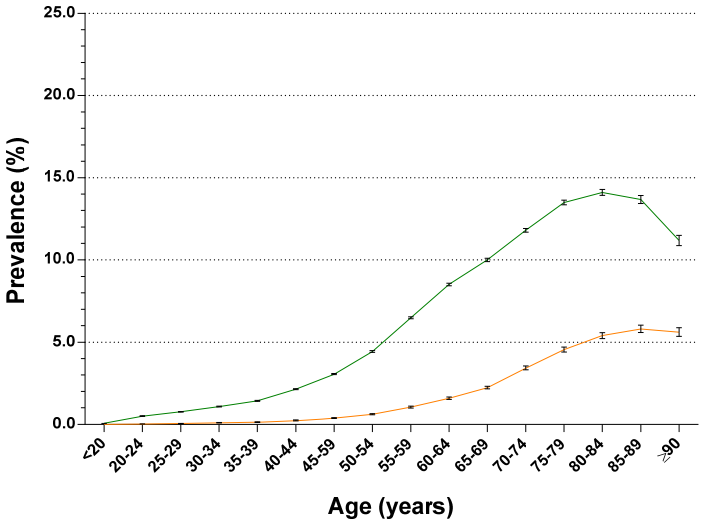
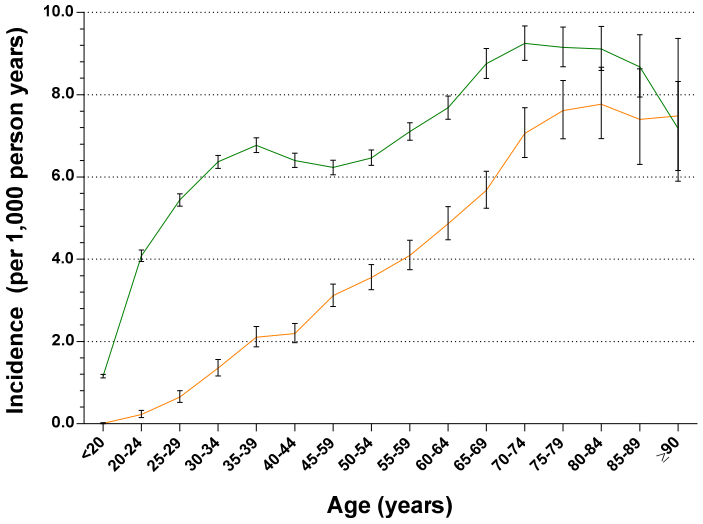


Figure 4-5 A comparison of prevalence of gout in men (a) and women (b) in the UK (orange line) and Taiwan (green line).

(a)



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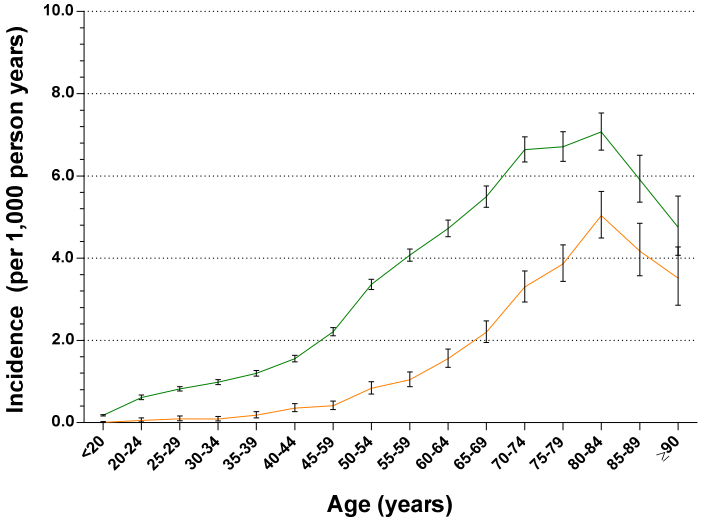
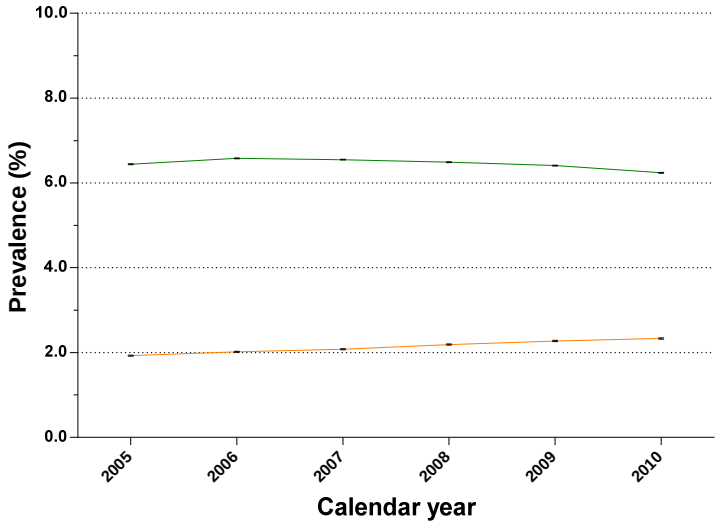


Figure 4-6 A comparison of incidence of gout in men (a) and women (b) in the UK (orange line) and Taiwan (green line).

(a)



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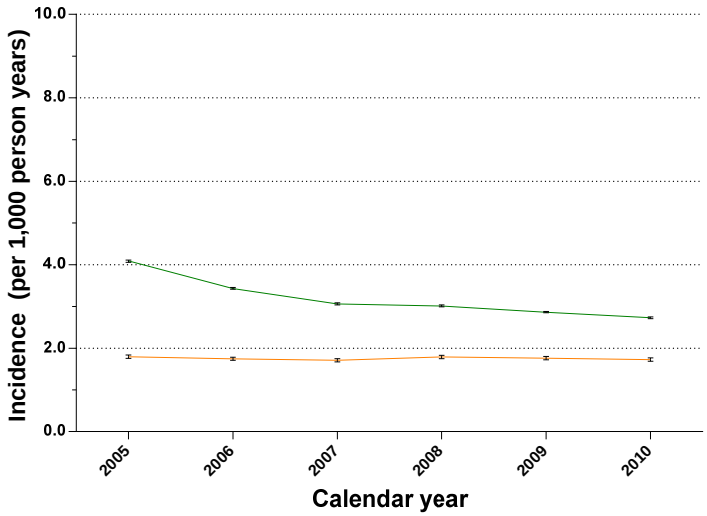


Figure 4-7 A comparison of secular trend in prevalence (a) and incidence (b) of gout in in the UK (orange line) and Taiwan (green line) during the period between 2005 and 2010.

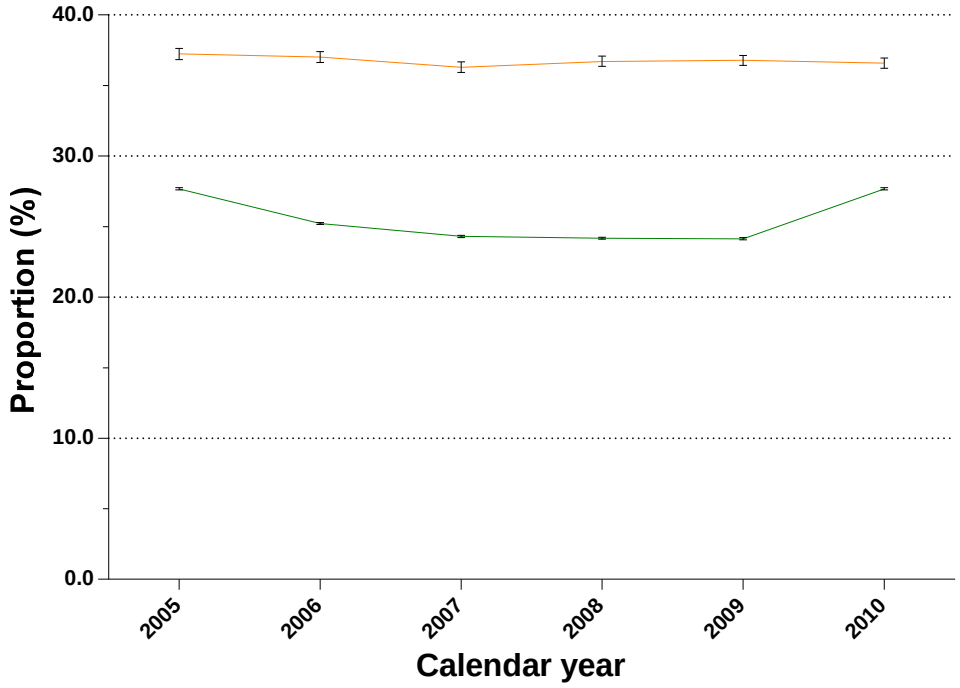


Figure 4-8 A comparison of secular trend in prevalence (a) and incidence (b) of gout in in the UK (orange line) and Taiwan (green line) during the period between 2005 and 2010.

4.4 Discussion

In this nationwide population study covering the entire population of Taiwan a substantial prevalence and incidence of gout was observed. In a population of 23 million people, approximately one in 16 residents of Taiwan is affected by gout. Despite a trend toward decreasing incidence, the prevalence of gout was fairly stable over the period between 2005 and 2010. Despite the small size of Taiwan (only 36,193 km^2) both the prevalence and incidence of gout showed marked geographical variation. This regional variation in gout generally coincides with the distribution of aboriginal people in Taiwan who primarily reside in eastern counties and rural areas. Although gout is one of the most common chronic diseases in Taiwan it seems that the management of gout remains poor, with only one-third of prevalent patients being under medical attention and only one-fifth being given ULT in 2010. Unfortunately, this suboptimal care has not changed over the study period, despite the publication of national and international guidelines on gout management during this period.

The trends of gout prevalence in Taiwan have not been robustly examined until now. In general, surveys conducted in the 1990s (Chou et al., 1994, Chang et al., 1997, Chou and Lai, 1998, Lin et al., 2000, Chang et al., 2001) reported a lower prevalence of gout than those conducted in the 2000s.(Lai et al., 2009, Kuo et al., 2010b, Chuang et al., 2011) The National Nutrition and Health survey in Taiwan (NAHSIT) undertaken in the period 1993-1996 found the prevalence of gout to be 4.74% in men and 2.19% in women,(Chang et al., 2001) whereas

the later survey conducted in 2005-2008 found a prevalence of gout of 8.21% in men and 2.33% in women.(Chuang et al., 2011) However, these estimates were based on self-reported gout and were not standardised for age structure, despite using a stratified probability sampling considering age, gender, geographical regions and ethnicities in respective study periods. This study found that the crude prevalence of gout increased over time but age- and gender-standardised prevalence remained stable between 2005 and 2010. However, men and women seemed to exhibit different trends in gout prevalence, the prevalence in men reaching a plateau after 2007 but the prevalence in women continuing to reduce during the study period. Several caveats should be considered before drawing conclusion about trends in gout prevalence in Taiwan. First, most previous studies were based on self-reported gout (Chou et al., 1994, Chang et al., 1997, Chou and Lai, 1998, Lin et al., 2000, Chang et al., 2001, Lai et al., 2009, Kuo et al., 2010b, Chuang et al., 2011) which has inherent bias. For example in the Atherosclerosis Risk in Communities (ARIC) cohorts (McAdams et al., 2011) only 73% of gout patients diagnosed by this means in 2000 also reported gout in the follow-up questionnaire in 2003 and only 65% in the 2003 and 2007 questionnaires. Another Dutch study found that only 64% of gout patients self-reported gout after just 6 months of follow-up (Picavet and Hazes, 2003). Furthermore an earlier study found that only 44% of self-reported gout cases had this confirmed by medical chart review and physician interview (O'Sullivan, 1972). These studies confirm significant recall bias for self-reported gout. A previous study conducted in 2004, also using the NHIRD as the primary data source, found a much lower prevalence of gout (4.62%) than the estimate in 2005 in this study (5.91%). It is

likely that this disparity primarily results from different lengths of observation (5 years in the previous study and 10 years in the current study) and therefore different degrees of identification of clinically silent patients. It is difficult to determine to what extent a shorter observation might lead to underestimation of prevalence. Only one case series in 1961 reported that the length of inter-critical periods was less than 1 year in 62%, 1-5 years in 27%, 6-10 years in 4% and over 10 years in 7% of 614 patients.(Yu and Gutman, 1961) Therefore, the previous estimate of gout prevalence in 2004 could have been an underestimate because the length of observation period was too short. Collectively, these various sources of data suggest that the prevalence of gout in Taiwan has reached a plateau in recent years.

The incidence of gout has not been estimated previously in Taiwan and data on incidence in other countries also are relatively scarce. The largest population-based study was conducted in Rochester, Minnesota, which estimated an annual incidence of 0.45 per 1,000 and 0.62 per 1,000 person-years during the periods 1977-78 and 1995-96 periods respectively (Arromdee et al., 2002). The Framingham study estimated an average annual incidence of 1.6 and 0.2 per 1,000 person-years for men and women, respectively during the period between 1948 and 1980 (Abbott et al., 1988) which was similar to that reported for men in the John Hopkins Precursors Study which found an incidence of 1.73 per 1,000 person years in 1,216 male medical students over a median of 29 years.(Hochberg et al., 1995) Using data from the UK Second and Third National Studies of Morbidity in General Practice, overall gout incidence was estimated to be 1.4 per 1000 person-years in 1981 (Stewart and Silman, 1990). More

recently Mikuls used the General Practice Research Database (GPRD) and estimated the UK all-age incidence of gout to be 1.31 cases per 1000 person-years in 1999,(Mikuls et al., 2005b) while the more recent estimate of UK gout incidence in 2012, using the same database, was 1.77 per 1000 person-years.(Kuo et al., 2014) However, all these estimates relate to Caucasians and gout incidence has rarely been estimated in people of other ethnicities. Hochberg et al. reported that the incidence of gout in the period between 1958 and 1965 in African Americans was 3.11 per 1,000 person years, which was 1.7 fold higher than that of Caucasians.(Hochberg et al., 1995) Similarly the ARIC study reported that the gout incidence in the period 1987—2012 was 1.55 and 0.94 per 1,000 person years for African American men and white American men, respectively.(Maynard et al., 2014) This study appears to be the first to report gout incidence in Asians. Gout incidence in Taiwan was much higher than previous reports in other countries, suggesting significant racial and geographic variation in gout incidence.

The age-specific incidence of gout is rarely reported. Data from both the UK Second and Third National Studies of Morbidity in General Practice and the Framingham study, each undertaken in the 1980s, found that gout incidence peaked around the 50s age band.(Abbott et al., 1988, Stewart and Silman, 1990) More recently, Mikuls et al using the General Practice Research Database found that gout incidence peaked later between the age of 65-84 years(Mikuls et al., 2005b) and the estimates conducted in 2012 also found a similar later age of peak incidence.(Kuo et al., 2014) In Taiwan gout incidence peaked later between the age

of 70 and 85 years. However, there was a significant difference in age-specific incidence between men and women. In men, there was a bimodal distribution of age-specific incidence of gout, where a marked increase in gout incidence occurred in the two age bands of 20-39 and 50-69 years of age. In contrast, in women age-specific incidence demonstrated a near-linear increase in the incidence of gout with age up to the peak incidence between ages 80 and 84 years. This appears unique compared with previous studies on age-specific incidence,(Abbott et al., 1988, Stewart and Silman, 1990, Mikuls et al., 2005b) which report a linear increase in the incidence of gout with age up to the peak and then a levelling off or slight decrease in both men and women. However, the findings of this study echo one previous study by Yu et al. indicating the onset of gout being earlier in Taiwan(Yu and Luo, 2003) than in Caucasians(Hall et al., 1967) and Japanese.(Nishioka and Mikanagi, 1980) The very high prevalence and incidence in Taiwan compared to that in China(Li et al., 2012) and Japan(Hosoya et al., 2011) and the unique age-specific distribution of incidence may partly reflect the composition of Taiwanese residents - a mixture of Han Chinese and indigenous people, who are known to be very prone to gout(Chang et al., 1997, Ko et al., 2002) and who are genetically related to gout-stricken Polynesians and Oceanic Pacific Islanders.(Friedlaender et al., 2008) This population stratification was also demonstrated by the regional variation in gout prevalence and incidence since the areas with highest prevalence and incidence were places with the highest density of indigenous people. However, genetic factors account for just one-third of phenotypic variation of gout in men and only one-fifth in women(Kuo et al., 2013b) so environmental factors could also contribute

to the variable geographical distribution of gout in Taiwan. Further studies are required to address this issue.

Regardless of the high prevalence of gout in Taiwan, the management of the disease remains poor. Only around one-third of people with prevalent gout were consulted about their gout or for prescription of ULT in primary care and only one quarter were actually prescribed ULT. There was no significant change in the pattern of ULT prescription pattern during the study period despite the publication of Taiwanese guidelines for the management of gout and hyperuricaemia in 2007.(Association, 2007) The poor management for gout seems to be a common problem globally.(Doherty et al., 2012, Mikuls et al., 2005b, Mikuls et al., 2005a, Roddy et al., 2010, Kuo et al., 2014, Neogi et al., 2006, Barber et al., 2009, Sarawate et al., 2006, Reaves and Arroll, 2014, Dalbeth et al., 2012) Taking the UK as an example, the overall usage of ULT in primary care has not changed in the past two decades, with only a quarter to one third of people with gout being given ULT.(Mikuls et al., 2005b, Kuo et al., 2014) Other deviations from recommended standard of care are also reported in the UK.(Mikuls et al., 2005a, Roddy et al., 2007c, Roddy et al., 2010) These lines of evidence underscore the lack of knowledge and interest in gout among primary care physicians, which in turn reflects a number of varied barriers to optimal care of gout patients. (Doherty et al., 2012, Spencer et al., 2012, Reach, 2011, Solomon et al., 2008) However, a recent proof-of-principle study conducted in UK found that all gout patients were willing to take long-term ULT once they were given full information on gout and its treatment.(Rees et al., 2013) In addition, these

well-informed patients exhibited excellent adherence and nine out of ten patients achieved the therapeutic target at one year. Therefore, the essential part to optimising care of gout patients is physician education to improve knowledge and promote interest in gout.

There are several limitations to this study. Firstly, this study based the case definition on physician-recorded diagnosis, rather than according to American College of Rheumatology(Wallace et al., 1977), Rome(Kellgren JH, 1963) classification criteria or urate crystal identification. Secondly, this study reported 10-year period prevalence, rather than life-time prevalence, which theoretically would be higher. This is because of the inability to identify clinically silent patients who had no outpatient record of gout over the 10-year period. It is difficult to determine how many gout patients were not included since data on the length of asymptomatic inter-critical gout periods are sparse. Based on estimates of the length of these inter-critical gout periods from the case series reported by Yu et al.,(Yu and Gutman, 1961) an underestimation of 7% is probable. In addition to underestimation of prevalence, incidence would also be overestimated as some incident gout patients could have gout attacks beyond 10-years of observation.

In conclusion, the prevalence of gout has been stable and the incidence has reduced in the past 6 years in Taiwan. However, both the prevalence and incidence were very high and are probably some of the highest reported in the world. Despite this, the management of gout remains poor with only one quarter of patients receiving ULT which can potentially cure gout.

An initiative to raise the profile of gout and to improve knowledge and interest of primary care physicians is urgently needed to optimise the care of gout.

CHAPTER 5. Nature history of gout and eligibility for urate-lowering treatment following diagnosis in the UK

5.1 Introduction

Current guidelines and recommendations endorsed by the European League against Rheumatism (EULAR),(Zhang et al., 2006a) American College of Rheumatology (ACR)(Khanna et al., 2012a) and British Society of Rheumatology (BSR)(Jordan et al., 2007) concur in recommending diet control and life style changes for all gout patients. ULT with xanthine oxidase inhibitors or uricosuric agents are generally recommended by these guidelines only for patients with more severe disease (such as the presence of tophi or radiographic changes) or with other concomitant conditions (such as the presence of urolithiasis, poor kidney function and use of diuretics) that merit earlier ULT. There is agreement that management should always be individualised to the patient and involve full information about gout, its consequences and its treatment options. However, when in the course of gout ULT should be initiated is not explicitly discussed and currently there is no suggestion that ULT should be considered and discussed with the patient when they first receive information on gout at or close to the time of first diagnosis.

In addition, current evidence regarding nature history of gout is outdated. The only evidence describing the risk of further acute attacks after first diagnosis dated back to 1960s. Higher risk of chronic kidney disease in gout patients has been reported but the timing of its

occurrence relative to the diagnosis of gout has not been investigated. Therefore this study was undertaken to investigate both the cumulative probability of further acute attacks and the timing of eligibility for ULT according to current guidelines following first diagnosis of gout using the UK Clinical Practice Research Data-link (CPRD).

5.2 Methods

5.2.1 Source of data

Please refer to section 2.3.1.

5.2.2 Study population

In this study, I only used CPRD data from patients registered in practices in England. Among these patients, I identified all incident gout patients residing in England during the period between 1997 and 2010. Gout was defined according to Read codes (please refer to table 2-3). To be eligible as an incident case, participants had to have at least one-year registration prior to the first date of gout diagnosis.(Cea Soriano et al., 2011) This case definition has been validated in a previous study.(Meier and Jick, 1997) Some patients were given ULT prior to date of first diagnosis of gout. This practice may reflect ULT for asymptomatic hyperuricaemia or failure to record a formal diagnosis of gout by the general practitioners. To prevent ambiguity, these patients were excluded from analysis.

5.2.3 Study outcomes

The main outcomes used were the recurrence of acute attacks, which was defined as one or more consultations for gout with prescription of non-steroid anti-inflammatory drugs (NSAID), colchicine or corticosteroid at least three months apart after the first diagnosis of gout. The occurrence of tophi, CKD and urolithiasis were main complications after the

diagnosis of gout. We further estimate the proportion of patients indicated for ULT based on the British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Gout,(Jordan et al., 2007) which include (1) recurrence of acute arthritis; (2) the presence of tophi according to Read codes (please refer to appendix); (3) the presence of urolithiasis (please refer to appendix); (4) chronic kidney disease (CKD) as defined by Read codes (appendix) or by renal function impairment with an estimated glomerular filtration rate estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) formulae (National Kidney, 2002) less than 60 ml/min per minutes on two separate occasions; and (5) prescriptions of diuretics. If tophi, urolithiasis and CKD occurred earlier than gout diagnosis date plus 3 months, these conditions were defined as occurring at diagnosis of gout. Only patients receiving diuretics within 3 months of diagnosis were defined as a diuretics user at diagnosis of gout.

5.2.4 Statistical analysis

All patients were followed from the date of first gout diagnosis until the outcome under consideration, death, transfer out of practice, last data collection date of the practice or the end of follow-up at 31st August 2013, whichever occurred first. Kaplan–Meier plots were used to estimate the cumulative probability of ULT prescription or fulfilling ULT indications over time from the first diagnosis of gout. Separate analyses were performed for each specific indication for ULT.

Prescription rates of ULT, calculated as the number of ULT-treated patients divided by the total number of incident gout patients during the study period, were estimated in each of 486 (642 in the entire database) practices included in the CPRD. The proportion of prescription variance explained (R-squared) by patient-level factors (age at diagnosis, gender, ethnicity, quintiles of 2004 Index of Multiple deprivation [IMD], year of gout diagnosis, Charlson comorbidity index [validated version for the use with Read coded data (Khan et al., 2010b)] and specific indications for ULT) and practice-level factors (total number of patients, total number of gout patients, practice median for patient year of birth, sex ratio, practice region, practice location IMD quintiles, and percentages of patients having each of the 17 Charlson morbidity groups) were estimated using a two-level linear model (Recchia, 2010) To assess factors that affect the prescription of ULT, Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) using years since the date of first gout diagnosis as the time to event outcome. Similarities of patients within practices were considered by using a marginal model with robust sandwich estimate.(Lin, 1994) Covariates were the aforementioned patient- and practice-level factors. Age and fulfilling specific indications for ULT were time-dependent covariates, which were modelled using a counting process method.(Therneau and Grambsch, 2000) A 2-sided p value 0.05 was considered statistically significant. All analyses were performed using SAS 9.3 (SAS institute, Cary, NC).

5.3 Results

5.3.1 Demographic characteristics

A total of 52,164 incident gout patients residing in England were identified from the CPRD in the period between 1997 and 2010. Of these 38,272 were men (73.37%) and 13,892 (26.63%) were women. Women tended to be older at the time of gout diagnosis than men (mean age at diagnosis 69.2 ± 14.2 years and 60.1 ± 14.9 years respectively; $p<0.01$). Overall 20,144 patients (44.18%) had a score of one or more on the Charlson co-morbidity index with more women (55.15%) than men (40.19%) having a score of one or more. The characteristics of incident gout patients are presented in Table 6-1.

Table 5-1. Patient characteristics at the time of first gout diagnosis

	Overall (n =52,164)	**Men (n = 38,272)**	**Women (n = 13,892)**
Age at diagnosis (years)	62.5 ± 15.2	60.1 ± 14.9	69.2 ± 14.2
Age distribution (n, %)			
<35 years	1,855 (3.56)	1,585 (4.14)	270 (1.94)
35–49 years	9,482 (18.18)	8,404 (21.96)	1,078 (7.76)
50-64 years	15,906 (30.49)	12,629 (33.00)	3,277 (23.59)
≥65 years	24,921 (47.77)	15,654 (40.90)	9,267 (66.71)
Years of follow-up (median, interquartile range)	6 (4–9)	6 (4–9)	5 (3–8)
Ethnicity (n, %)			
Caucasians	25,629 (49.13)	17,909 (46.79)	7,720 (55.57)
Black	406 (0.78)	300 (0.78)	106 (0.76)
Asian	190 (0.36)	135 (0.35)	55 (0.40)
Other	5,925 (11.36)	4,314 (11.27)	1,611 (11.60)
Unknown	20,014 (38.37)	15,614 (40.80)	4,400 (31.67)
Socioeconomic			
Quintile 1 (least deprived)	10,390 (19.92)	7,885 (20.60)	2,505 (18.03)
Quintile 2	9,357 (17.94)	6,960 (18.19)	2,397 (17.25)
Quintile 3	8,109 (15.55)	5,939 (15.52)	2,170 (15.62)
Quintile 4	6,647 (12.74)	4,673 (12.21)	1,974 (14.21)
Quintile 5 (most deprived)	4,427 (8.49)	3,100 (8.10)	1,327 (9.55)
Unknown	13,234 (25.37)	9,702 (25.38)	3,519 (25.33)
Charlson comorbidity index (n, %)			
0	29,120 (55.82)	22,890 (59.81)	6,230 (44.85)
1–2	1,676 (3.21)	1,008 (2.63)	668 (4.81)
3–4	16,573 (31.77)	11,327 (29.60)	5,246 (37.76)
5–6	3,806 (7.30)	2,426 (6.34)	1,380 (9.93)
≥6	989 (1.90)	621 (1.62)	368 (2.65)
Year of diagnosis			
1997–1998	4,006 (7.68)	2,951 (7.71)	1,055 (7.59)
1999–2000	5,717 (10.96)	4,199 (10.97)	1,518 (10.93)
2001–2002	7,443 (14.27)	5,478 (14.31)	1,965 (14.14)
2003–2004	8,382 (16.07)	6,119 (15.99)	2,263 (16.29)
2005–2006	8,941 (17.14)	6,520 (17.04)	2,421 (17.43)
2007–2008	8,890 (17.04)	6,522 (17.04)	2,368 (17.05)
2009–2010	8,785 (16.84)	6,483 (16.94)	2,302 (16.57)

5.3.2 Timing of recurrence of acute attacks and the occurrence of complications

Kaplan-Meier analysis was used to estimate cumulative probabilities of gout recurrence and occurrence of complications (Table 6-3). The cumulative probabilities of consulting for further attacks were 29.16% in the first year and 46.46% in the second year from diagnosis. Eventually, 83.74% of all incident gout patients were consulting for acute attacks. The percentages of patients having tophi and urolithiasis were small but steadily increased over time. After one year follow-up from first diagnosis of gout, 25.85% of patients had CKD.

Table 5-2 Cumulative probability of ULT prescription or fulfilling specific indications for ULT by gender

	All patients						Male patients						Female patients				
	At diagnosis	1 year	2 year	3 years	5 year	10 year	At diagnosis	1 year	2 year	3 years	5 year	10 year	At diagnosis	1 year	2 year	3 years	y
Further attacks	0	29.16	46.46	57.05	70.02	83.74	0	28.00	45.74	56.87	70.52	84.63	0	32.34	48.45	57.52	68
Tophi	0.46	0.51	0.57	0.63	0.74	1.09	0.27	0.31	0.35	3.39	0.48	0.75	0.98	1.09	1.17	1.28	1
Urolithiasis	1.72	1.80	1.91	1.99	2.15	2.64	1.93	2.02	2.14	2.23	2.41	2.93	1.15	1.20	1.28	1.32	1
CKD	22.98	25.85	29.09	31.98	37.53	47.11	17.30	19.68	22.36	24.79	29.75	39.15	38.62	42.84	47.66	51.81	58

5.3.3 Percentages of patients fulfilling ULT at diagnosis and the end of the study

As shown in Table 6-2, approximately two-thirds of women (67.10%) and one-third of men (36.19%) with gout fulfilled indications for ULT at the time of first diagnosis. The most common indications for ULT at first diagnosis were use of diuretics (36.83%) and CKD (23.12%), whereas the presence of tophi (0.47%) and urolithiasis (1.73%) were uncommon at first presentation. The vast majority of patients (87.49%) were eligible for ULT at the end of follow-up (median of 5 years duration) and women became eligible sooner than men. The most common indications for ULT were multiple acute attacks (70.15%), use of diuretics (49.11%) and CKD (40.47%).

Despite a majority of patients fulfilling indications by the end of the study, only 32.78% of all patients received ULT eventually. Compared to men, a higher percentage of women with gout were eligible for ULT but a lower percentage had received ULT by the end of the study.

Table 5-3. The percentage of patients being eligible for or treated with ULT at diagnosis and at the end of the study

Treatment or eligibility criteria	Overall (n =52,164)	Men (n = 38,272)	Women (n = 13,892)
Eligibility and treatment at diagnosis			
ULT eligible patients (n, %)	23,172 (44.42)	13,851 (36.19)	9,321 (67.10)
Eligible due to tophi (n, %)	246 (0.47)	106 (0.28)	140 (1.01)
Eligible due to urolithiasis (n, %)	902 (1.73)	742 (1.94)	160 (1.15)
Eligible due to chronic kidney disease (n, %)	12,062 (23.12)	6,663 (17.41)	5,399 (38.86)
Eligible due to diuretic use (n, %)	19,212 (36.83)	11,119 (29.05)	8,093 (58.26)
Eligibility and treatment at the end of study			
ULT eligible patients (n, %)	45,637 (87.49)	32,775 (85.64)	12,862 (92.59)
Eligible due to further attacks (n, %)	36,593 (70.15)	27,158 (70.96)	9,435 (67.92)
Eligible due to tophi (n, %)	444 (0.85)	223 (0.58)	221 (1.59)
Eligible due to urolithiasis (n, %)	1,204 (2.31)	991 (2.59)	213 (1.53)
Eligible due to chronic kidney disease (n, %)	21,111 (40.47)	12,540 (32.77)	8,571 (61.70)
Eligible due to diuretic use (n, %)	25,617 (49.11)	15,872 (41.47)	9,745 (70.15)
ULT treated patients (n, %)	1,101 (32.78)	12,940 (33.81)	4,161 (29.95)

5.3.4 Cumulative probability of fulfilling ULT indications

Figure 6-1a shows the cumulative probabilities of fulfilling ULT indications over time since the date of first gout diagnosis in men and women. Overall, the median time to first ULT indication was 5.00 (95% CI, 4.70 to 5.30) months and the cumulative probabilities of fulfilling ULT indications were 44.26%, 61.02%, 72.11%, 78.87%, 86.81% and 94.27% at 0, 1, 2, 3, 5, and 10 years from diagnosis, respectively. Women were more likely to fulfil indications for ULT in the initial years following gout diagnosis but men subsequently caught up quite quickly. Overall the probability of fulfilling ULT indications was higher in women than men over time (log-rank test $p < 0.001$). Cumulative probability of receiving ULT prescription

There were large discrepancies in the cumulative probability of fulfilling indications and receiving prescriptions for ULT in both genders (figure 6-1b). The cumulative probability of receiving ULT at the end of follow-up (201 months) was 49.50% and the cumulative probabilities for ULT prescription were much lower at 0%, 16.90%, 21.14%, 24.52%, 30.39% and 40.52% at 0, 1, 2, 3, 5 and 10 years from diagnosis, respectively.

5.3.5 Age and cumulative probability of fulfilling ULT indications

Figure 6-2 shows the cumulative probability of ULT eligibility and ULT prescription across different age groups. Despite younger patients tending to have lower likelihood of fulfilling ULT indications at diagnosis or in the first few years following diagnosis, the percentage of young patients who fulfilled criteria caught up quickly and the difference in the percentage with indications were small.

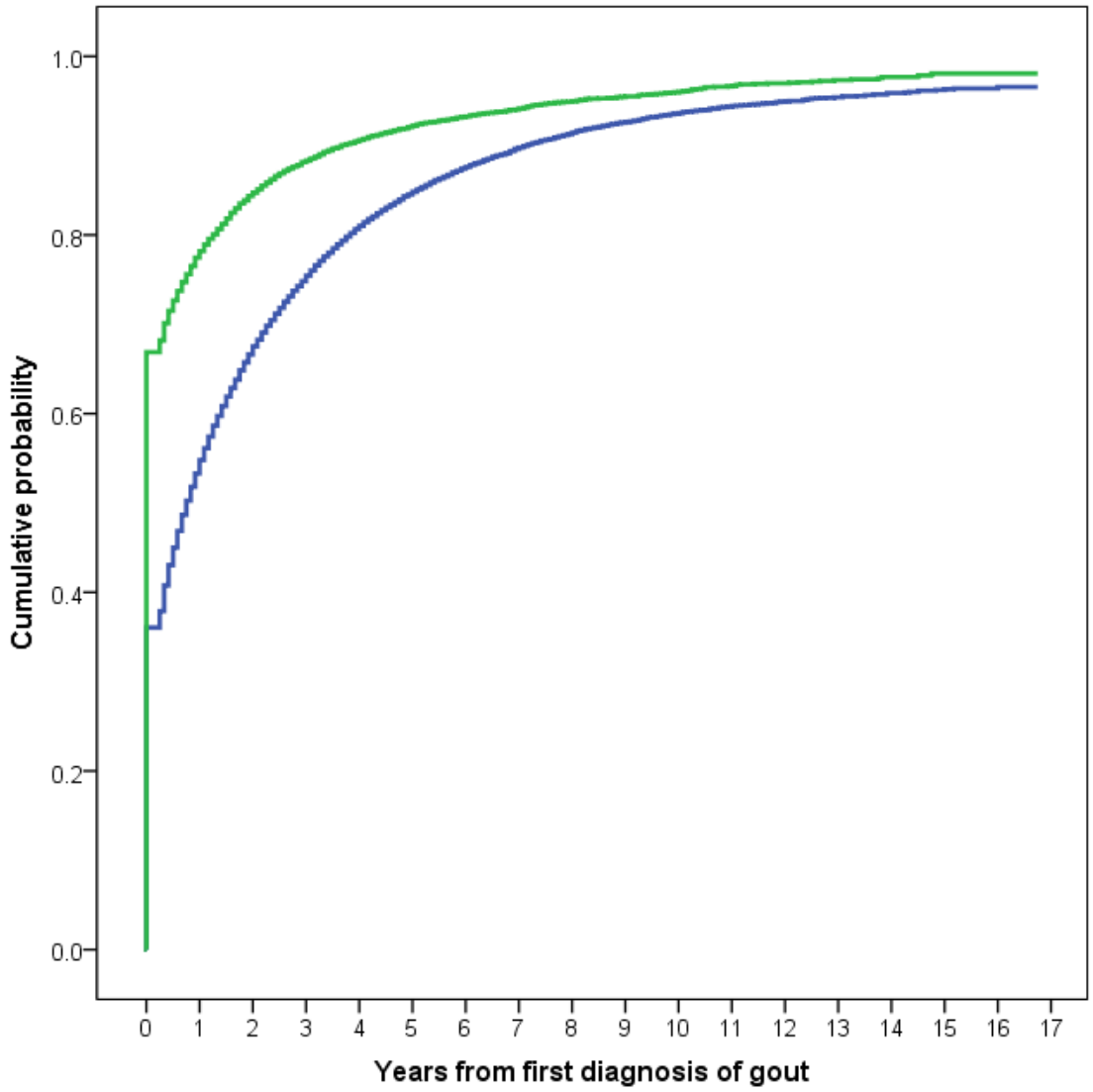


Figure 5-1 The cumulative probability of ULT eligibility in male (blue line) and female gout patients (green line).

(a)

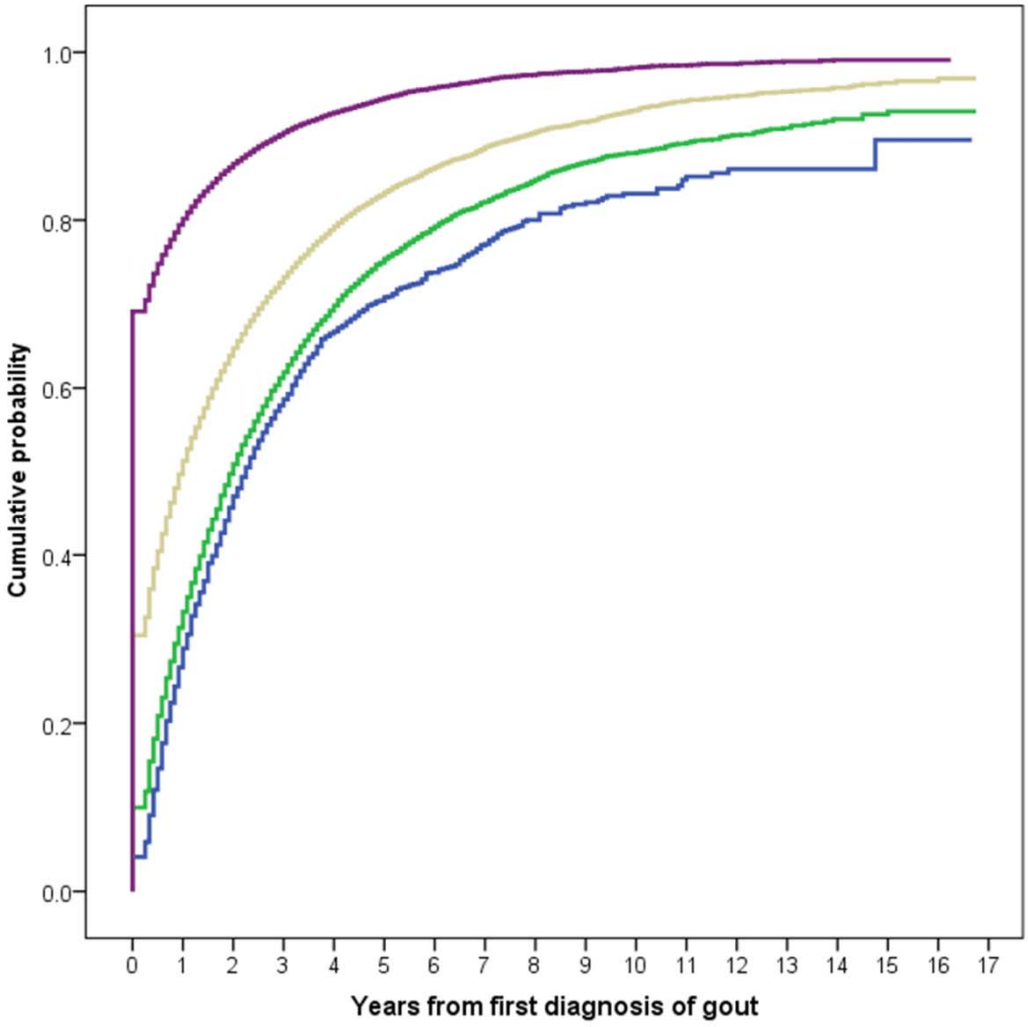


Figure 5-2 The cumulative probability of ULT eligibility in gout patients aged <35 years (blue), 35–49 years (green), 50-64 years (yellow) and ≥65 years (purple).

5.4 Discussion

Overall, this study in a large cohort representative of general practice in the UK found that the majority of gout patients suffer further attacks in 5 years from the first diagnosis of gout. The risk of CKD is very high, over one third of patient had CKD within 5 years of from diagnosis. Approximately one-third of men and two-thirds of women with incident gout fulfilled ULT indications at the time of first diagnosis. The majority (87%) of patients with gout fulfilled the indications within 5 year from diagnosis and the median time to ULT indication was only 5 months. Female patients tend to fulfil eligibility criteria earlier in the course of gout than male patients. Young patients tend to have lower probability for fulfilling ULT indications but after 5 years of disease course, the difference between age groups diminished. This study provides the first population-based study of the timing of when people with incident gout fulfil accepted indications for ULT.

Despite the nature history of gout seems well-known, direct evidence on the timing of acute attack recurrence and occurrence of complications is rare. Previous only on paper in 1961 reported the risk of acute attack recurrence after initial diagnosis of gout.(Yu and Gutman, 1961) Their results suggested that only 7% of patient did not have any acute attacks after 10 years of observation, which is consistent with our data. Previous studies also found high risk of CKD (Choi et al., 2012, Yu et al., 2012, Richette et al., 2013) and urolithiasis (Kramer et al., 2003) in gout patients. However, this study reported the timing of such occurrence relative to the diagnosis of gout for the first time. The risk of comorbidity at the time of diagnosis was

already high and the risk continues to be elevated afterwards. At only 5 years of diagnosis, one quarter of patients already had CKD, which is alarmingly high.

Although existing guidelines provide specific indications for ULT in patients with gout, currently there is no explicit evidence-based advice concerning when in the course of gout patients should be considered for ULT, particularly around the time of diagnosis. Current trends increasingly favour early treatment with ULT to prevent people developing further crystal deposition and long-term complications, such as subcutaneous tophi and joint damage rather than wait until these have occurred.(Doherty et al., 2012) Since frequent attacks, CKD, urolithiasis, diuretic use and tophi(McGill and Dieppe, 1991) are specific indications for ULT,(Zhang et al., 2006a, Jordan et al., 2007, Khanna et al., 2012a, Sivera et al., 2014) it is conceivable that the majority of gout patients should be treated early. Balanced against early rather than late ULT are the concerns over rare but serious side effects from allopurinol,(Gutierrez-Macias et al., 2005) the inconvenience of daily medication and the documented common poor adherence to chronic ULT.(Briesacher et al., 2008) However, the data of this study argue in favour of early treatment with ULT since many people with gout fulfil currently recommended indications for ULT at the time of diagnosis or within just one or a few years of diagnosis. Management should always be individualised and involve full information to the patient concerning the nature, causes and consequences of gout and the treatment strategies that are available.

Currently, the three major professional bodies, European League against Rheumatism,(Zhang et al., 2006a) British Society for Rheumatology and British Health Professionals in Rheumatology(Jordan et al., 2007) and American College of Rheumatology(Khanna et al., 2012a) generally advise dietary and lifestyle modification as the initial step to manage gout. ULT is indicated for patients showing evidence of uncontrolled arthritis, joint damage, excessive urate load (such as tophi or urolithiasis) or having conditions that may promote long-standing hyperuricaemia (renal disease or use of diuretics). However, gout patients in modern society tend to be older and often have multiple co-morbidities. For instance, a recent cluster analysis of comorbidity in gout found that only 12% of gout patients can be classified as 'isolated gout with few comorbidities'.(Richette et al., 2013) Similarly, this study found 23.12% and 36.83% of patients having CKD and hypertension requiring diuretic use, resulting in almost half of incident gout patients being eligible for ULT at the time of diagnosis. Even if patients are not eligible at diagnosis, they often fulfil the ULT indications due to frequent attacks, higher risk for renal impairment and need for diuretics shortly following diagnosis. This is especially true for older patients and in this cohort three quarters of gout patients were diagnosed after the age of 50. However, although less than 10% of younger patients fulfilled indications for ULT at diagnosis, approximately half of these became eligible within 2 years from diagnosis, which can still be considered to be early in the course of their life-long gout. Overall, therefore, early discussion and possible initiation of ULT seems warranted regardless of the age of onset.

There are several limitations to the study. Firstly, gout patients were not identified according to American College of Rheumatology(Wallace et al., 1977) or Rome(Kellgren JH, 1963) classification criteria or to the 'gold standard' of urate crystal identification, but by recorded physician diagnosis for case definition so misclassification bias may occur. However, since the validity of gout diagnosis in the CPRD has been investigated and found to be high,(Meier and Jick, 1997) this bias should have a minimal effect on the results. Secondly, the identification of fulfilled patient indications was based on the recording in the CPRD, which may be liable to different degrees of certainty. The validity of prescription data in CRPD has been reported, suggesting a high accuracy to identify diuretic user based on prescription data.(Jick et al., 2003) The case definition of CKD has been validated in a similar database where medical events were recorded using Read codes.(Denburg et al., 2011) A more conservative definition for acute attacks was used in this study to improve specificity, requiring a gout diagnosis and the prescription of anti-inflammatory agents in the same consultation to fulfil the definition for an 'acute attack'. Therefore the estimates of cumulative probability of further attacks were lower in this study than a previous large series, which found 62% of untreated gout patients had attack within one year.(Yu and Gutman, 1961) Furthermore the prevalence of urolithiasis and tophi was lower than other reported rates.(Kramer et al., 2003, Alvarez-Nemegyei et al., 2005, Khanna et al., 2012b, Richette et al., 2013) Therefore collectively the cumulative probability of fulfilling ULT indication is more likely to be under rather than over estimated in this study and the estimate may be considered conservative.

In conclusion, the majority of gout patients are eligible for ULT at or shortly after initial diagnosis. A discussion concerning ULT with patients in the very early course of gout is therefore warranted as part of the recommended full explanation of gout, its outcomes and its management.

CHAPTER 6. Familial aggregation of gout and relative genetic and environmental contributions: a nationwide population study in Taiwan

6.1 Introduction

Gout is the most common inflammatory joint disease (Choi et al., 2005b, Annemans et al., 2008, Zhu et al., 2011, Winnard et al., 2012) with an impact on morbidity (Abbott et al., 1988, Krishnan et al., 2006, Sheane and Cunnane, 2007) and premature mortality.(Choi and Curhan, 2007, Krishnan et al., 2008, Kuo et al., 2010a) The disease is heritable, as suggested by familial clustering of the disease;(Mituszova et al., 1992, Blumberg, 1965, Emmerson, 1960, Hauge and Harvald, 1955, Smyth et al., 1948a, Smyth et al., 1948b, Grahame and Scott, 1970, Copeman, 1964, Cobb, 1971, Reginato et al., 2012) however, the existence of many known risk factors, such as male gender, increasing age,(Arromdee et al., 2002, Mikuls and Saag, 2006) obesity,(Choi et al., 2005a) chronic renal impairment,(Edwards, 2008), hypertension,(Bhole et al., 2010b, Choi et al., 2005a) long-term use of diuretics(Hueskes et al., 2012) and certain diets with high purine(Choi and Curhan, 2005) and alcohol,(Choi et al., 2004a) also supports a strong environmental contribution. Currently, the balance between genetic and environmental contributions is unclear.

High heritability of hyperuricaemia, (Wilk et al., 2000) the main driver of urate crystal deposition and the development of gout, has led to efforts to identify susceptibility genes. A large familial segregation study has demonstrated significant heritability for

hyperuricaemia(Wilk et al., 2000) and specific genetic associations, particularly genes involved in renal urate clearance, have been identified that mechanistically might explain genetic susceptibility to hyperuricaemia.(Vitart et al., 2008, Kolz et al., 2009, Dehghan et al., 2008a, Kottgen et al., 2013) Despite the strong evidence supporting a genetic contribution to hyperuricaemia, studies concerning the relative contributions of genetic and environmental factors to gout are rare. A complex segregation analysis conducted in aborigines in Taiwan showed a substantial genetic component for gout(Wang et al., 2004) but a recent classic twin study, with 514 all-male twin pairs in the US, paradoxically found significant heritability for hyperuricaemia but not for clinical gout.(Krishnan et al., 2012) In addition, efforts have largely failed to identify susceptibility genes to gout beyond genes controlling serum urate concentration, thus questioning the role of genetic factors in gout.(Kottgen et al., 2013)

Therefore for this thesis the first nationwide population-based study was undertaken to estimate the degree of familial aggregation of gout and the extent to which heritability and a common familial environment might each account for familial aggregation. This was undertaken in Taiwan because firstly, Taiwan has the one of the highest reported gout prevalence worldwide(Lin et al., 2000) and secondly, there is an established nationwide health insurance database containing sufficient demographic, family history, and medical data on the entire Taiwanese population to allow these questions to be addressed.

6.2 Methods

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number 101-2178C).

6.2.1 Source of data

The primary data source came from National Health Insurance Research Database (NHIRD), which contained registration information and original claims data on all beneficiaries of NHI in Taiwan since its establishment in 1995. All entries for an individual are linked by a unique personal identifier assigned to each Taiwanese resident, which allows accurate linkage of records from the registration files and from the original claims data. Before release for research, personal identifiers are de-identified to ensure confidentiality.

The registry of beneficiaries, one of the registration files, contains details of demographics, residence, kinship relationships, occupation categories, insurance status and insurance amount of all beneficiaries of NHI. Claims data on all outpatient visits, inpatient care and pharmacy dispensing were recorded in specific datasets with information such as dates of events, medical diagnoses, medical expenditure, and details of prescriptions, operations, examinations, and procedures.

6.2.2 Study population and classification

The study population consisted of all NHI beneficiaries (11,360,576 men; 11,283,172 women) in 2004, representing 99.8% of the total population of Taiwan at the end of 2004.(Directorate General of Budget) Enrolled individuals were classified according to the affection status of gout of their first- and second-degree relatives who were registered in the NHI before 2004.

6.2.3 Identification of cases with gout

The primary case definition of gout was having a physician recorded diagnosis of gout (International Classification of Diseases, Ninth Revision [ICD-9] code: 274.x) together with at least one prescription containing gout-specific medications (colchicine, benzbromarone, allopurinol, probenecid, sulfinpyrazone) at either an outpatient or emergency visit during 2000–2004. An alternative definition, used for sensitivity analysis, was having two outpatient or emergency visits with a physician recorded diagnosis of gout during 2000–2004. An identical case definition of gout was used for all individuals and their relatives.

6.2.4 Identification of first- and second-degree relatives and family ascertainment

The registry of beneficiaries specifies relationships between the insured person who pays the fee and his/her dependents, allowing parent-offspring relationships and spouses to be identified directly. Among 28,402,865 individuals registered with the NHI during 1996 to 2010, 21,009,551 pairs of parent-offspring relationships were identified. Full siblings were

identified as individuals who shared the same parents. Twins were full siblings who have the same date of birth (±1 day). Second-degree relatives were ascertained based on the aforementioned relationships. These links allowed the identification of 4,191,274 families spanning 2–5 generations.

6.2.5 Demographics and socioeconomic information

Socioeconomic factors were also examined, including residence, occupations and income levels, to reflect population stratification with the aboriginals (with significantly higher prevalence of gout (Liu CY, 2006)) and Han people in Taiwan.

The residence for each individual was assigned as one of 369 towns or districts in Taiwan, each classified as urban, suburban or rural. Because of the high prevalence of gout in Taiwanese aborigines, (Chou and Lai, 1998) 55 towns/districts with a predominant aboriginal population (according to the Council of Indigenous People) were categorised as aboriginal areas, regardless of the corresponding urbanisation levels. Occupations were classified into 5 categories: (1) civil servants, teachers, military personnel and veterans; (2) non-manual workers and professionals; (3) manual workers; (4) other and (5) the unemployed/dependents. Income levels were approximated based on the payroll-related amount, which was determined by the payroll of the employees and civil servants and the business income of employers. Income levels were categorised into sex-specific income quartiles.

6.2.6 Threshold liability model

This model assumes a normally distributed liability of disease resulting from a large number of unspecified genes and environmental factors, each with small and additive influences. The liability of the affected individuals is greater than a critical threshold, the value of which can be determined with the information of the disease prevalence in the affected and the general population. The familial transmission is the function of the difference of normal deviation of the threshold from the mean liability between individuals with affected relatives (T1) and the normal population (T0). Since the environmental factors such as diet and alcohol consumption may be shared by family members, a common environmental component may substantially contribute to familial transmission, in addition to heritability. To separate the effects of genes and common environment, individuals with affected spouses were used as controls since a spouse shares the family environment but not the genes with their partner and his/her biological relatives. Assuming that there is no inbreeding or assortative mating effects, the magnitude of the spouse relative risk (RR) provides an estimate of the importance of the familial environment. (Rice, 2008) Therefore, the heritability is the function of the difference of normal deviation of the threshold from the mean liability between individuals with affected relatives (T1) and individuals with affected spouses (Ts).

6.2.7 **Statistical analysis**

The prevalence of gout was calculated for the general population and for individuals who had an affected spouse and/or affected relatives. Any individual fulfilling the case definitions of gout was defined as a prevalent case. For prevalence of gout in individuals with affected first- and second-degree relatives, age and sex were taken into account and age- and sex-standardised prevalence (95% confidence interval [CI]) was determined. The standard population used was the general population of Taiwan in 2004.

The degree of familial aggregation of gout was estimated using the RR, which was calculated as the adjusted prevalence ratio between individuals with affected relatives and the entire population of Taiwan in 2004.(Risch, 1990) The marginal Cox proportional hazard model with an equal follow-up time for all subjects with robust sandwich estimate, (Lin, 1994, Lee and Chia, 1993) adjusted for age, place of residence, income, occupation and family size, was used to optimise the estimate of the RR. Because case clustering within a family may occur, the robust sandwich estimate was used when calculating confidence bounds.(Lin, 1994) The RR was estimated for individuals with different family relatives affected with gout, including first- and second-degree relatives affected and for the number of affected first-degree relatives (father, mother, son, daughter, brother, sister).

The standard ACE model was used to examine the influences of additive genetic (A), common environmental factors shared by family members (C) and non-shared environmental factors (E) accounting for variance in a phenotype (P). This model can be expressed as:

$$\sigma_P = \sigma_A + \sigma_C + \sigma_E$$

where $\sigma_p = total\ phenotypic\ variance$; $\sigma_A = additive\ genetic\ variance$; $\sigma_c = common\ environmental\ variance$; and σ_E = non-shared environmental variance.

The heritability was defined as the proportion of phenotypic variance that is attributable to genetic factors and can be expressed as $\frac{\sigma_A}{\sigma_p}$ and the familial transmission was expressed as$\frac{\sigma_A+\sigma_C}{\sigma_p}$, which is the sum of heritability and common environmental variances.

The polygenic liability model was used to calculate both measures (Falconer, 1967, Reich et al., 1972, Reich et al., 1979) and the sibling RR, spouse RR and the prevalence of gout in the general population (p) were used to calculate the familial transmission and the heritability, which were expressed as:

$$\text{Familial transmission} = \frac{\mathrm{T_0} - \mathrm{T_1} \times \sqrt{1 - \left({\mathrm{T_0}}^2 - \mathrm{T_1^2}\right) \times \left(1 - \frac{\mathrm{T_0}}{\mathrm{i}}\right)}}{\mathrm{a_R} \times [\mathrm{i} + \mathrm{T_1^2} \times (\mathrm{i} - \mathrm{T_0})]}$$

$$\text{Heritability} = \frac{T_s - T_1 \times \sqrt{1 - \left({T_s}^2 - T_1^2\right) \times \left(1 - \frac{T_s}{i}\right)}}{a_R \times [i + T_1^2 \times (i - T_s)]}$$

where T0 =Φ^(-1) (1-p); Ts = Φ^(-1) (1-spouse RR×p); T1 = Φ^(-1) (1-sibling RR×p); p = prevalence of gout in the normal population); aR: the additive genetic relationship between the relatives, for full sibling, aR = 0.5; i = z/p; z, the height of the standard normal curve pertaining to gout prevalence, and , standard normal cumulative distribution function.(Wray and Gottesman, 2012)

Therefore the common environmental component was the difference between familial transmission and heritability. Since the epidemiologic and clinical features of gout are sexually dimorphic and hence equal genetic variances in both sexes may not hold true, (Ober et al., 2008) Sex-specific familial transmission and heritability were estimated using respective sex-specific populations.

All analyses were performed for both primary and alternative case definitions of gout. A 2-sided p value 0.05 was considered statistically significant. All analyses were performed using SAS 9.3 (SAS institute, Cary, NC).

6.3 Results

6.3.1 Gout prevalence in individuals with affected family members versus the general population

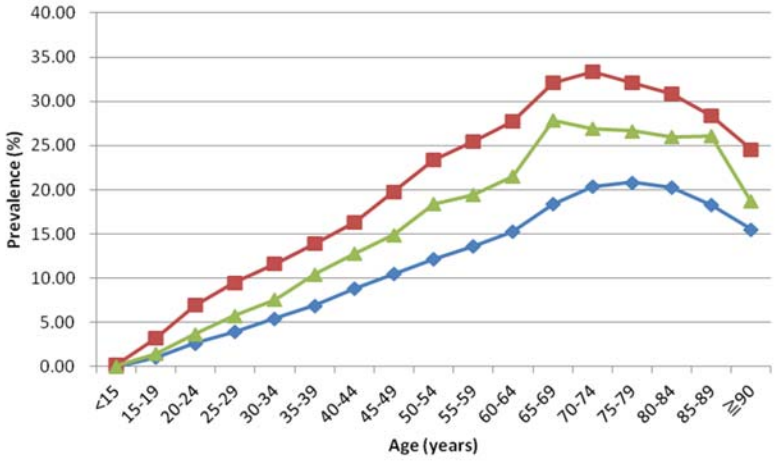
The study identified 802,765 men and 242,294 women with gout in 2004 giving a crude prevalence of gout of 4.62% (95% CI, 4.61%–4.63%) (Table 3-1). Men had a significantly higher prevalence (7.07%, 95% CI, 7.05%–7.08) than women (2.15%, 95% CI, 2.14%–2.16%). There were 1,663,904 individuals with at least one affected first-degree relative and 604,468 individuals with at least one affected second-degree relative. The standardised prevalence of gout in individuals with affected first- and second-degree relatives were 13.37% (95% CI, 13.35%–13.39%) and 10.05% (95% CI, 10.03%–10.06%) in men and 4.16% (95% CI, 4.15%–4.18%) and 3.01% (95% CI, 3.00%–3.02%) in women respectively. Figure 3-1a and 3-1b show age- and sex-specific prevalence of gout in men and women which at all ages is higher in individuals with affected first-degree relatives than in those with second-degree relatives and the general population.

Table 6-1 Demographic characteristics and gout prevalence of the study population by gender and relatives' affected status of gout

	Men		Women	
	≥1 affected relatives (n = 879,852)	General population (n= 11,360,576)	≥1 affected relatives (n = 784,052)	General population (n = 11,283,172)
Age (years) (mean ± standard deviation)	29.8 ± 18.4	34.9 ± 20.8	30.0 ± 19.8	35.2 ± 20.5
Gout (%)	10.79	7.07	3.13	2.15
Place of residence (%)				
Urban	60.16	57.53	61.39	59.40
Suburban	30.86	32.15	29.39	30.39
Rural	5.75	7.49	5.75	7.40
Aboriginal	3.23	2.83	3.47	2.81
Income levels (%)				
Quartile 1	24.27	27.68	24.49	27.77
Quartile 2	25.37	27.52	26.44	30.18
Quartile 3	22.20	19.60	18.79	16.84
Quartile 4	28.16	25.20	30.28	25.21
Occupation (%)				
Dependents of the insured individuals	41.07	34.49	49.97	42.39
Civil servants, teachers, military personnel and veterans	5.25	4.39	4.09	3.04
Non-manual workers and professionals	30.53	29.33	27.17	25.81
Manual workers	14.50	20.28	12.52	21.57
Other	8.65	11.51	6.25	7.19

Foot note: Income levels (in new Taiwan dollars [NTD]): Quartile1, 0 to 16500 NTD (both genders); Quartile 2, 16,501 to 19,200 NTD (both genders); Quartile 3, 19,201 to 33,300 NTD (men) and 19,201 to 28,800 NTD (women); Quartile 4, higher than 33,301 NTD (men) and higher than 28,801 NTD (women).

(a)



(b)

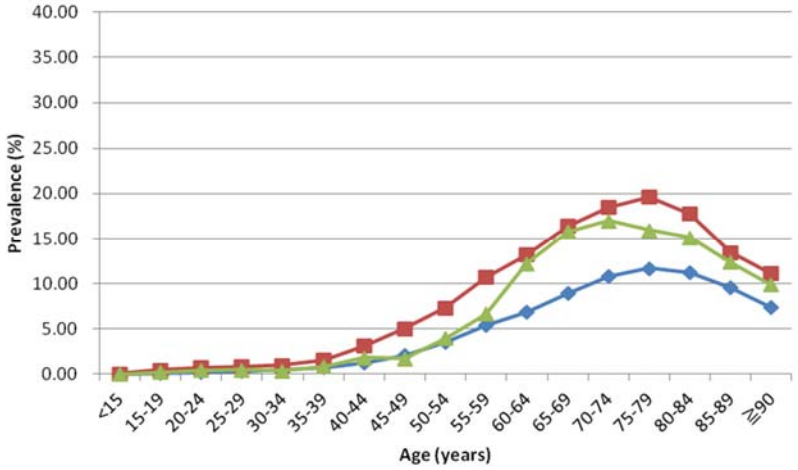


Figure 6-1 Age specific prevalence of gout in men (a) and women (b) according to the affection status of relatives (red, individuals with affected first-degree relatives; green, individuals with affected second-degree relatives; blue, the general population).

6.3.2 Family exposure and risk of gout

The risk of gout was significantly higher in individuals with affected first-degree relatives than in the general population, the RRs being 1.91 (95% CI, 1.90–1.93) in men and 1.97 (95% CI, 1.94–1.99) in women (Table 3-2). Individuals with affected second-degree relatives also had an increased risk of gout, albeit significantly lower than those with affected first-degree relatives, with RRs of 1.27 (95% CI, 1.23–1.31) in men and 1.40 (95% CI, 1.35–1.46) in women. Figure 2 shows that individuals with an affected twin had the highest risk, followed by individuals with an affected sibling, then individuals with an affected offspring and finally individuals with an affected parent. Same-sex twins had the highest RR, being higher in female-female twin pairs than male-male twin pairs. The RRs for gout in individuals with any category of affected second-degree relative (Table 3-3) were lower than RRs in those with affected first-degree relatives (Figure 3-2). The RRs also increased with the number of affected first-degree relatives. Compared with the general population, individuals with one, two or three or more categories of affected first-degree relatives had RRs (95% CIs) of 1.87 (1.86–1.89), 3.22 (3.15–3.29) and 4.96 (4.64–5.30), respectively. This trend was more prominent in women (figure 3-3).

Familial aggregation of gout was evident not only in individuals with affected biological relatives, but also in those with affected spouses. The RRs were 1.66 (1.65–1.68) in men with an affected wife and 1.65 (95% CI, 1.64–1.67) in women with an affected husband.

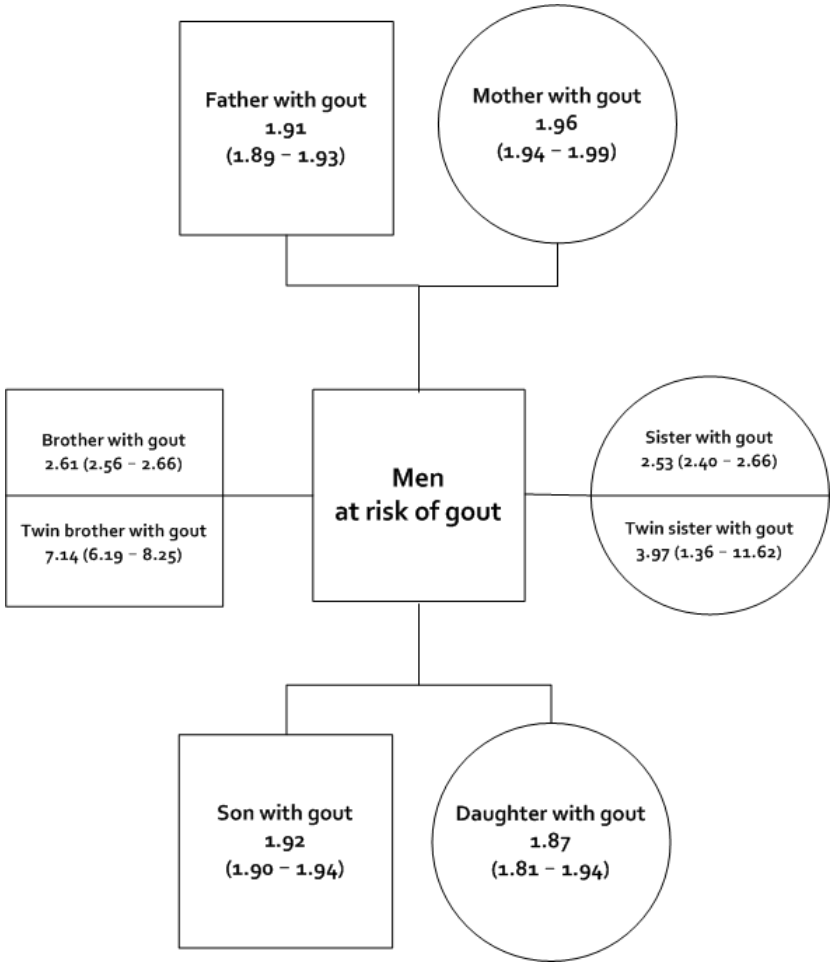
Table 6-2 Sensitivity analysis on the relative risk of gout among individuals with affected first- and second-degree relatives using alternative case definition for gout

Affected first- and second-degree relatives	Men at risk		Women at risk	
	RR	95% CI	RR	95% CI
Parent				
Father	1.77	1.75–1.79	2.15	2.13–2.18
Mother	1.83	1.81–1.85	1.94	1.85–2.03
Offspring				
Son	1.83	1.82–1.85	1.87	1.84–1.89
Daughter	1.79	1.73–1.85	2.34	2.24–2.44
Sibling				
Brother	2.43	2.38–2.47	2.03	1.93–2.14
Sister	2.35	2.23–2.47	3.82	3.19–4.57
Twins				
Twin brothers	6.60	5.72–7.62	2.90	0.73–11.62
Twin sisters	3.66	1.2–10.69	38.23	14.81–98.72
Grandparent				
Grandfather	1.08	1.03–1.14	1.08	0.92–1.27
Grandmother	1.20	1.14–1.27	1.21	1.04–1.41
Grandchild				
Grandson	1.22	1.16–1.28	1.39	1.33–1.46
Granddaughter	1.35	1.17–1.55	1.47	1.27–1.70
Uncle or aunt				
Uncle	1.21	1.13–1.29	1.00	0.80–1.26
Aunt	1.11	0.90–1.36	0.76	0.34–1.70
Nephew or Niece				
Nephew	1.34	1.26–1.42	1.04	0.85–1.28
Niece	1.34	1.09–1.64	0.81	0.36–1.80

Table 6-3 Relative risk of gout among individuals with affected second-degree relatives in comparison with the general population in Taiwan in 2004

Affected second-degree relatives	Men at risk		Women at risk	
	RR	95% CI	RR	95% CI
Grandparent				
Grandfather	1.18	1.12–1.25	1.29	1.10–1.51
Grandmother	1.31	1.25–1.37	1.45	1.24–1.68
Grandchild				
Grandson	1.25	1.20–1.31	1.45	1.39–1.52
Granddaughter	1.39	1.21–1.59	1.54	1.33–1.78
Uncle or aunt				
Uncle	1.32	1.24–1.40	1.19	0.96–1.45
Aunt	1.21	0.98–1.48	0.91	0.41–2.03
Nephew or Niece				
Nephew	1.42	1.34–1.51	1.16	0.95–1.41
Niece	1.42	1.16–1.74	0.90	0.41–2.00

(a)


Father with gout
1.91
(1.89 – 1.93)
Mother with gout
1.96
(1.94 – 1.99)
Brother with gout
2.61 (2.56 – 2.66)
Twin brother with gout
7.14 (6.19 – 8.25)
Men
at risk of gout
Sister with gout
2.53 (2.40 – 2.66)
Twin sister with gout
3.97 (1.36 – 11.62)
Son with gout
1.92
(1.90 – 1.94)
Daughter with gout
1.87
(1.81 – 1.94)

(b)

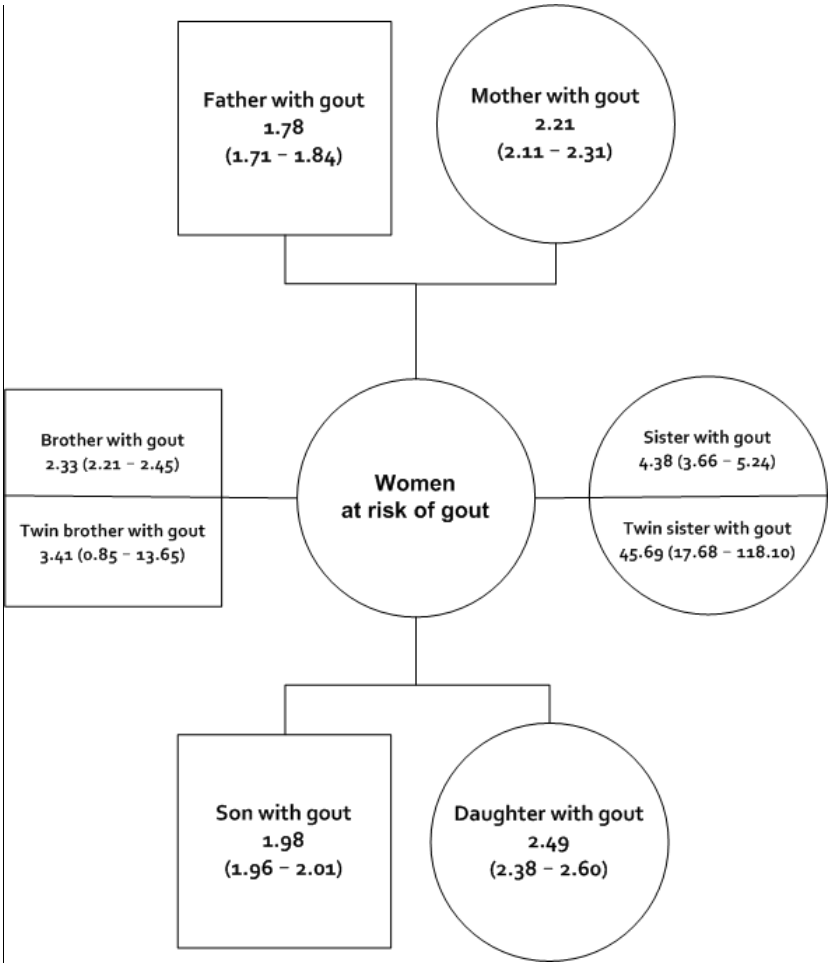


Figure 6-2 Relative risks (95% confidence interval) of gout among (a) men and (b) women with affected first-degree relatives (square, male; circle, female) in comparison with the general population in Taiwan in 2004.

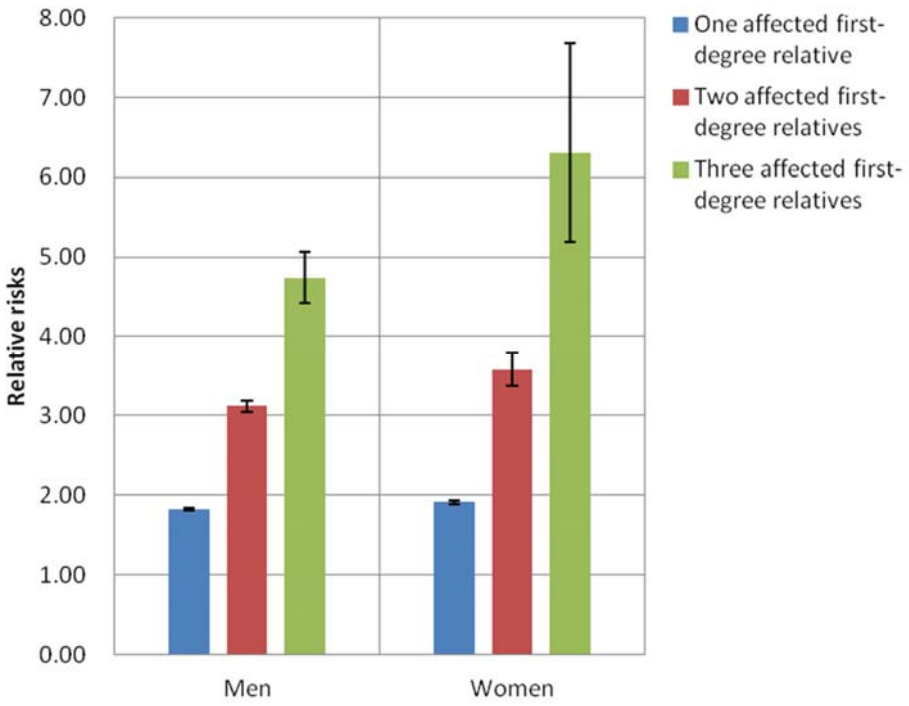


Figure 6-3 The "dose-response" relationship between the numbers of affected first-degree relatives and relative risk of gout (blue: one; red: two; green: three first-degree relatives).

6.3.3 Relative contributions of genetic, common and non-shared environmental factors

To separate the influences of genes and environment, heritability and familial transmission were calculated. In men, heritability was 35.1% (95% CI, 34.1%–36.0%) and familial transmission was 63.2% (95% CI, 61.8%–64.7%); whereas in women, they were 17.0% (95% CI, 15.0%–19.0%) and 35.5% (95% CI, 33.1%–37.8%) respectively. Figure 3-4 shows the relative contributions of genetic (heritability), common environmental and non-shared environmental components to the phenotypic variances of gout.

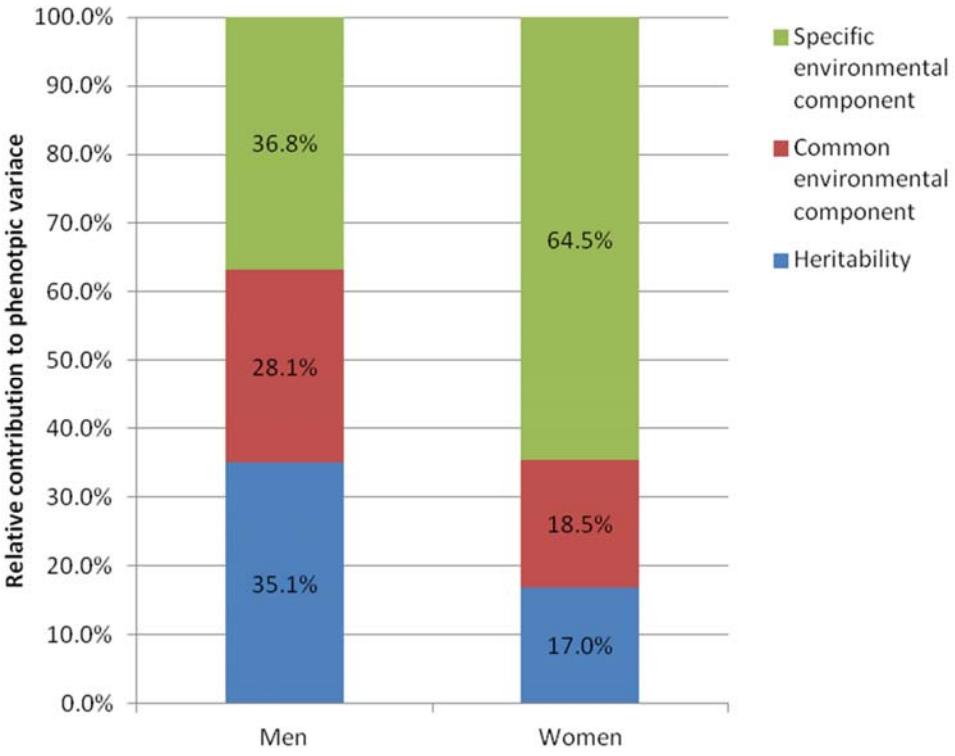


Figure 6-4 Relative contributions of heritability (blue), common environmental (red) and specific environmental factors (green) to phenotypic variation of gout.

6.3.4 **Sensitivity analysis**

The alternative case definition of gout was used for the sensitivity analysis. The results were very similar to those of the primary analysis (please see table 3-4, Figure 3-5, 3-6).

Table 6-4 Sensitivity analysis of adjusted relative risks of gout according to family exposure, age, place of residence, income levels and occupations, using primary and alternative gout case definition.

Risk factors	Adjusted relative risks (95% confidence interval)	
	Men	Women
Age-adjusted model		
Affected relatives of gout		
No relative affected	1	1
≥1 affected relatives	1.92 (1.91–1.93)	1.91 (1.89–1.93)
Multivariate-adjusted model		
Affected relatives of gout		
No relative affected	1	1
≥1 affected relatives	1.91 (1.90–1.93)	1.97 (1.94–1.99)
Place of residence		
Urban	1	1
Suburban	1.00 (1.00–1.01)	1.05 (1.04–1.05)
Rural	1.03 (1.02–1.04)	1.10 (1.09–1.12)
Aboriginal	1.34 (1.33–1.36)	1.58 (1.55–1.61)
Income levels		
Quartile 1	1	1
Quartile 2	1.14 (1.13–1.16)	1.03 (1.02–1.05)
Quartile 3	0.98 (0.97–0.99)	1.05 (1.03–1.07)
Quartile 4	1.10 (1.09–1.11)	0.95 (0.94–0.97)
Occupation		
Dependent	1	1
Civil servants, teachers and military servicemen	1.14 (1.13–1.16)	0.64 (0.62–0.66)
Non-manual workers and professionals (%)	0.98 (0.97–0.99)	0.73 (0.72–0.74)
Manual workers (%)	1.13 (1.13–1.14)	1.08 (1.07–1.09)
Other (%)	1.10 (1.09–1.11)	1.01 (0.99–1.02)

Footnote: adjusted for age and family size. All RR estimates were statistically significant ($p<0.01$).

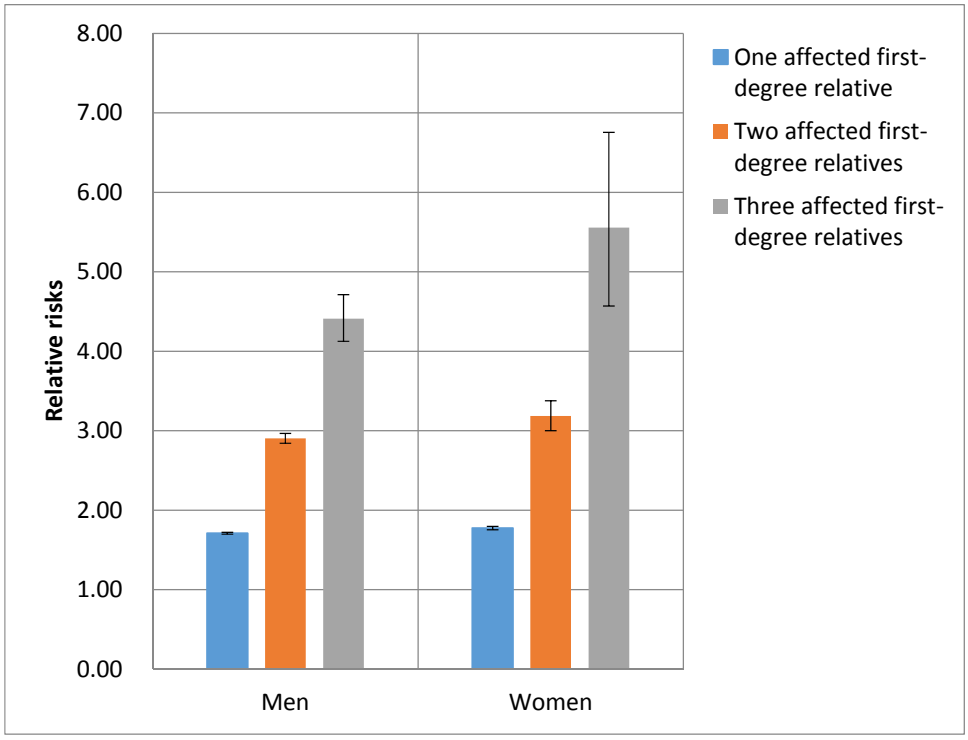


Figure 6-5 The "dose-response" relationship between the numbers of affected first-degree relatives and relative risk of gout using alternative case definition of gout.

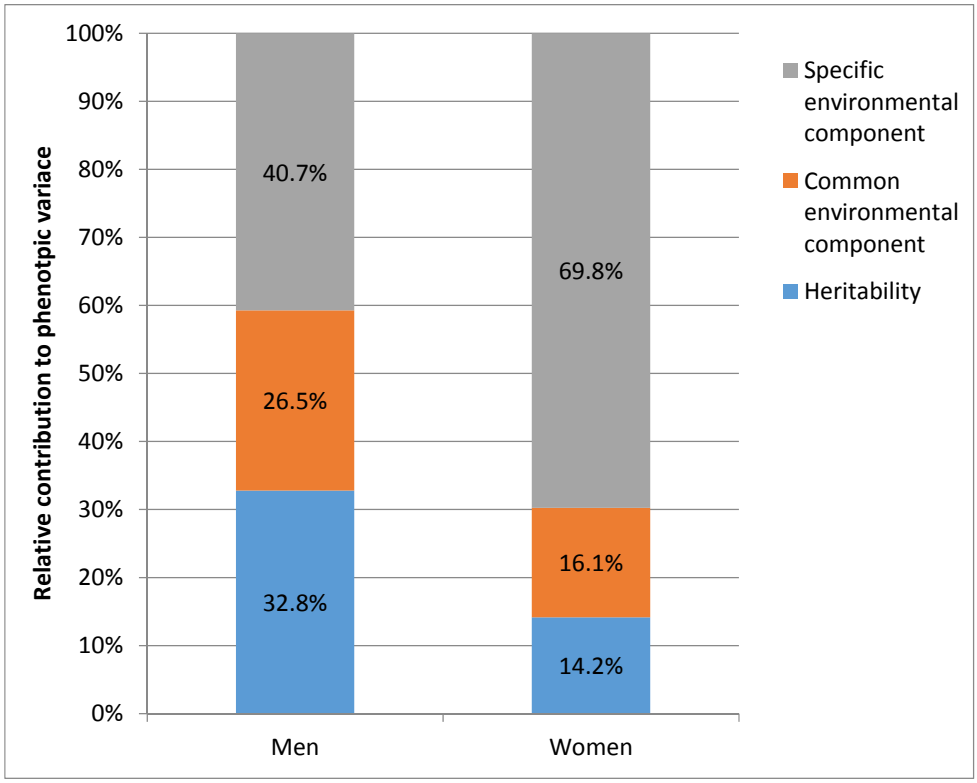


Figure 6-6 Relative contribution of heritability (blue), common environmental (red) and specific environmental factors (green) to phenotypic variation of gout, using alternative case definition of gout.

6.4 Discussion

This nationwide population study has confirmed familial aggregation of gout by demonstrating a greater prevalence and RR of gout for individuals with affected family members compared to the general population. The risk of gout is increased more by having affected first degree relatives than having affected second degree relatives and appears “dose-dependent” in that the risk increases with the number of affected relatives. These results confirm the long-held belief that gout clusters within families and supports an important contribution of common familial factors in predisposing to the development of gout.

However, biological relatives tend to share similar environmental and lifestyle risk factors in addition to genes; and both may contribute to familial aggregation. Therefore the risk associated with having a spouse who has gout was examined on the assumption that any increased risk from this predominantly reflects predisposition from environmental and lifestyle factors common to family members. The relative contributions from this were found to differ between men and women, but overall it appears that genetic factors play a smaller, but still substantial, role than environmental factors in the aetiology of gout. The findings are consistent with the relative paucity of gout susceptibility genes identified by genome-wide association studies in comparison with greater number of genes associated with risk of hyperuricaemia, which had a greater heritability.(Vitart et al., 2008, Kolz et al., 2009, Dehghan et al., 2008a, Kottgen et al., 2013)

Consistent with previous studies, the findings of this study provide strong evidence to support the existence of familial aggregation of gout.(Mituszova et al., 1992, Blumberg, 1965, Emmerson, 1960, Hauge and Harvald, 1955, Smyth et al., 1948a, Smyth et al., 1948b, Grahame and Scott, 1970, Copeman, 1964, Cobb, 1971) However, current evidence concerning the relative contributions of genetic and environmental exposures to gout susceptibility is limited. A complex segregation study conducted in the aborigines of Taiwan supported the existence of a substantial genetic predisposition to gout but no heritability estimate was reported.(Wang et al., 2004) In contrast, one recent study of 253 monozygotic and 261 dizygotic North American male twin pairs found a significant heritability for hyperuricaemia (49.6%) but surprisingly, given that chronic hyperuricaemia is the key mechanism for urate crystal formation, no heritability (0%; 95% CI, 0%–61.8%) for gout.(Krishnan et al., 2012) Nevertheless, the current whole population study provides several lines of evidence to support the existence of genetic predisposition to gout. Firstly, the data on twin pairs showed significantly different risk profiles in same-sex twin compared to the opposite-sex twins. Although lack of information on zygosity prevented the calculation of heritability based on twin data, the higher RR shared by same-sex (partly monozygotic) twins compared with opposite-sex (exclusively dizygotic) twins supports a genetic contribution. Secondly, using the spouse as an indicator of shared environmental risk, the heritability estimate was 35.1% in men and 17.0% in women. Therefore, although not the sole explanation for familial

aggregation, genetic factors, in addition to environmental influences, do contribute to the development of gout.

It has long been observed that men are significantly more likely to have gout than women.(Cea Soriano et al., 2011, Mikuls et al., 2005b) In addition, onset of gout is later in women.(De Souza et al., 2005) The cause of this sexual dimorphism is not clear. One explanation is the uricosuric effect of oestrogen which results in lower serum urate levels in premenopausal women.(Adamopoulos et al., 1977) Therefore, prevalence of gout is generally low in premenopausal women and increases dramatically after the menopause.(Hak et al., 2010) Different exposures to environmental risk factors may also contribute to the sex-difference. For instance, dietary calorie intake and alcohol consumption are lower in women than men in Taiwan according to a national nutrition survey.(Lin et al., 2003b, Wu et al., 2011) This current study shows that familial transmission and heritability are both significantly higher in men. These findings suggest that genetic and common environmental factors are the main predisposing factors to gout in men, but not in women. Therefore, the sex difference can be partly attributed to different contributions from family factors. Further study is needed to confirm this finding.

There are several limitations to this study. Firstly, it was confined to Taiwan so results may not be generalisable to other settings. Secondly, the NHIRD is primarily a health insurance database that contains limited information on criteria for clinical diagnosis. There were no data on

potential confounding factors so the interactions between family history and other confounders and their independent contributions to the risk of gout could not be examined. Further, the analysis of relative genetic and environmental contributions was based on the multifactorial liability model and the results are subject to assumptions so should be interpreted with caution. However, the published data on other disease such as schizophrenia (Wray and Gottesman, 2012) support the validity of this model. Finally it was not possible to examine the effects of assortative mating, whereby spouses are more similar for a phenotype than they would be if mating occurred at random in the population. If this assortment is not negligible, a biased estimation of relative genetic and environmental contributions may The main strengths of this study include the use of data from the entire population of approximately 23 million individuals and systematic methods to identify and ascertain first- and second-degree relatives, which allow very precise estimation of prevalence and RRs of gout with minimal selection bias. The virtually complete identification of gout cases and the use of consistent case definitions for individuals at risk and their relatives ensured the absence of information bias. Furthermore, prospectively recorded data for diagnosis, for construction of family relationships and for ascertaining socio-economic information were utilised, thus minimising recall bias and other errors associated with self-reporting.

The present study provides quantitative estimates both of familial RR and heritability for gout in an entire population of Taiwan. The results of this study confirm the clinical belief that gout clusters within families and that both genetic and environmental components contribute to its aetiology. Studies of familial risk in other populations are required to determine the generalisability of these findings to other populations.

CHAPTER 7. Burden of comorbidities and all-cause mortality in patients with incident gout: a nationwide population study in the UK

7.1 Introduction

Current clinical guidelines and recommendations endorsed by the European League against Rheumatism (EULAR),(Zhang et al., 2006a) American College of Rheumatology (ACR)(Khanna et al., 2012a) and British Society of Rheumatology (BSR)(Jordan et al., 2007) agree on the importance of comorbidity on gout management but only discuss diseases that are recognised to be pathophysiologically related to gout. In addition, the indications for ULT are generally recommended only for patients with high urate load (such as the presence of tophi or urolithiasis) or with other comorbidities such as poor kidney function. Although a focus on comorbidities that are causally related to or are seen as complications of gout is understandable, many gout patients are 'complicated' by multiple comorbidities that may or may not be related directly to gout and as such management decisions are often difficult since these recommendations and guidelines do not give any specific guidance in these scenarios.

Accumulating evidence suggests that comorbidity is epidemic in gout.(Zhu et al., 2012, Annemans et al., 2008, Richette et al., 2013) For instance, a recent large study found that only 12% of prevalent cases were considered to be isolated gout without significant associated

comorbidities.(Richette et al., 2013) However, previous studies have only included limited categories of comorbidities and have not examined the timing of comorbidity occurrence relative to gout diagnosis. If many or most gout patients suffer comorbidity at diagnosis and the risk continues to increase afterwards, current management paradigms should be changed, for example, strategically treating gout and comorbidity as a single entity, rather than managing them separately. Therefore, by using data representative of the general population of UK from the CPRD, this study aimed to examine the burden of comorbidity at the time of first diagnosis of gout and the subsequent accumulation of comorbidities after diagnosis and to compare this to the risk of new comorbidities in non-gout controls.

7.2 Methods

This study was a case-control study with both retrospective and prospective observations using data from the CPRD. It was hypothesised that gout has a higher burden of comorbidity at the time of first diagnosis and that the risk of comorbidity would continue to rise after the diagnosis of the disease.

7.2.1 Data source

Please refer to section 2.3.1

7.2.2 Definition of incident gout

Read codes were used to identify incident gout patients from the CPRD between 1997 and 2005. To be eligible as an incident gout patient, participants had to have no evidence of gout and no prescription for ULT (mostly allopurinol) prior to the time of diagnosis (index date) and to have at least a three-year registration prior to the index date.(Cea Soriano et al., 2011) The case definition was based on physician-diagnosis using 18 Read codes indicative of incident gout (please refer to table 2-3). The validity of gout diagnosis in the CPRD has been validated in a previous study.(Meier and Jick, 1997)

7.2.3 Selection of controls

From a base population of CPRD participants who had an active registration from 1997 to 2005, one control per incident case who had no record of gout and no prescriptions of ULT in the CPRD was selected. Control patients were matched to incident gout patients on a 1:1 basis by year of birth, gender, general practices and year of first continuous registration at this CPRD practice. The same index date was assigned to each of the matched controls. As with incident gout patients the matched controls had at least three years of registration prior to the index date.

7.2.4 Study period

Three periods were defined to assess comorbidity: one from 10 years prior to diagnosis, one from one year prior to diagnosis and one from diagnosis to the earliest date of occurrence of comorbidity, death, transfer out or end of study (31 December 2013), whichever came first. Prevalence of comorbidity assessed in the 10-year and 1-year periods prior to diagnosis was estimated. The Charlson comorbidity index at diagnosis was based on results from the 10-year period. Cumulative probability of all-cause mortality was estimated using the index date as the origin and the disease course in years after diagnosis as time scale.

7.2.5 Comorbidity of interest and mortality

Gout was defined as the index disease in this study and Feinstein's definition was utilised for comorbidity, specifically "Any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study".(Feinstein, 1970) General health status was measured by the Charlson co-morbidity index. This index summarises 17 diagnostic categories (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes mellitus [DM], DM with chronic complications, renal diseases, any malignancy [including leukaemia and lymphoma], metastatic solid tumour and human immunodeficiency virus [HIV] infection) to represent one's health status and has been shown to be a useful predictor for mortality.(Charlson et al., 1994) Deyo et al produced a validated version for use with the ICD-9 based database,(Deyo et al., 1992) which was the basis of the validated Read code version.(Khan et al., 2010b) I calculated the Charlson score for each study person at baseline by adding scores assigned to each specific diagnosis. In addition, other comorbidities were incorporated, including anaemia, cardiac arrhythmias, depression, hypertension, hypothyroidism, multiple sclerosis, neurological diseases, psoriasis, psychosis, urolithiasis and valvular heart disease. The definitions of these

conditions were also based on physician diagnosis recorded as Read codes. The Charlson comorbidity index was categorised as (1) 0, 1-2, 3-4 and ≥ 5 scores and (2) 0 and ≥ 1 score.

Mortality was based on the recording in the main database. The CPRD has developed an algorithm to identify death and date of death for deceased participants. In order to validate the recorded death and death date in CPRD, data were requested from the death registration from the Office of National Statistics for all patients registered between 2004 and 2006 who had consented to participate in the linkage scheme, which covered the period between 1st January 1998 and 10th January 2012. Overall, there were 3,522,601 participants from practices who had consented to the linkage scheme in this period. Data on cause of death were only available from these practices. Of these, 209,154 participants were identified as deceased by the CPRD but according to death registration, 197,139 participants had died. As shown in table 7-1, the sensitivity, specificity, positive predictive value and negative predictive value of a CPRD recorded death were 0.99, 0.99, 0.93 and 1.00, respectively. The CPRD recorded death dates were identical to that recorded in death registration in 89.0% of deceased patients identified by both CPRD and death registration. The difference between recorded dates of death was less than 3 months in 98.5% of deceased patients. Therefore the recording of death and death date in the CPRD is generally consistent with death registration.

Table 7-1 Performance of CPRD recorded death

CPRD	Death registration		Total	PPV	NPV
	recorded	Not recorded			
Recorded	195,047	14,107	209,154	93.3%	
Not recorded	2,092	3,311,355	3,313,447		99.9%
Total	197,139	3,325,462	3,522,601		
Sensitivity	98.94%				
Specificity		99.6%			

Footnote: PPV, positive predictive value; NPV, negative predictive value.

7.2.6 **Statistical analysis**

The prevalence of a specific comorbidity was calculated using the number of people diagnosed with a given comorbidity during the past 10-year or one-year period before the index date as the numerator and the number of incident gout patients or matched controls as denominators. Odds ratios (OR) and 95% confidence intervals (CI) were used to estimate the association between gout and each co-existing medical condition. Conditional logistic regression was used to adjust for age, gender, index year, BMI categories, smoking status and alcohol consumption. Kaplan–Meier

plots were used to estimate the cumulative probability of each comorbidity and all-cause mortality for people with incident gout and those without. Only people at risk for a given comorbidity were considered for the prospective analysis. Hazard ratio (HR) and 95% CI were calculated for mortality by Cox proportional hazards model. The HRs were adjusted by age, gender, index year, BMI categories, smoking status and alcohol consumption. For all-cause mortality all comorbidities were adjusted at index date. All statistical analyses were performed using SAS statistical software, version 9.3.

7.3 Results

During 1997 to 2005, 31,138 incident gout patients were identified with a mean age of 60.5 ± 14.5 years and approximately three quarters being men. They were 1:1 matched to 31,138 controls with the same age and sex structure (Table 7-2). The odds of developing gout increased significantly with BMI, alcohol consumption and smoking. Both unadjusted and adjusted estimates gave similar results.

Table 7-2 Characteristics of incident gout patients and controls. Values are numbers (percentages) unless stated otherwise.

	Incident gout (n = 31,138)	Controls (n = 31,138)	Unadjusted odds ratios (95% CI)	Adjusted odds ratios (95% CI)[a]
Age (years)				
<50 years	7,560 (24.28)	7,581 (24.35)	NA	NA
50-59 years	6,842 (21.97)	6,891 (22.13)	NA	NA
60-69 years	7,194 (23.10)	7,135 (22.91)	NA	NA
≥70 years	9,542 (30.64)	9,531 (30.61)	NA	NA
Gender				
Men	22,803 (73.23)	22,803 (73.23)	NA	NA
Women	8,335 (26.77)	8,335 (26.77)	NA	NA
BMI (kg/m^2)				
<18.5	171 (0.55)	427 (1.37)	0.63 (0.53–0.76)	0.62 (0.52–0.75)
18.5 – 24.9	6,013 (19.31)	9,505 (30.53)	Reference	Reference
25.0 – 29.9	12,474 (40.06)	10,624 (34.12)	1.86 (1.78–1.93)	1.88 (1.80–2.00)
≥30	10,385 (33.35)	5,247 (16.85)	3.13 (2.99–3.28)	3.20 (3.05–3.35)
Unknown	2,095 (6.73)	5,335 (17.13)	0.62 (0.59–0.66)	0.62 (0.58–0.66)
Smoking				
Non-smoker	8,454 (23.01)	7,165 (23.01)	Reference	Reference
Current smoker	4,517 (14.51)	3,402 (10.93)	1.13 (1.07–1.19)	1.14 (1.08–1.20)
Ex-smoker	14,331 (46.02)	13,665 (43.89)	0.90 (0.86–0.92)	0.85 (0.82–0.89)
Unknown	3,836 (12.32)	6,906 (22.18)	0.47 (0.45–0.50)	0.45 (0.43–0.47)
Alcohol consumption (units/week)				
Never/ Ex-drinker	2,951 (9.48)	3,307 (10.62)	Reference	Reference
Current 1-9	13,776 (13776)	13,872 (44.55)	1.11 (1.05–18)	1.15 (1.09–1.21)
Current ≥10	8,551 (27.46)	4,712 (15.13)	2.03 (1.91–2.16)	2.17 (2.04–2.31)
Unknown	5,860 (18.82)	9,247 (29.70)	0.71 (0.70–0.75)	0.74 (0.70–0.79)

Footnote: a. adjusted by age, gender and index year

7.3.1 Retrospective observation

At index date, the proportion of people having no comorbidity in the Charlson comorbidity index was significantly lower in the incident gout patients than in the controls. In a multivariate logistic regression model adjusted for age, sex, index year, BMI class, smoking status and alcohol consumption in the 10-year period before the index date, ORs (95% CIs) were 1.34 (1.28–1.40), 1.72 (1.57–1.88) and 1.99 (1.66–3.39) for Charlson comorbidity index categories 1-2, 3-4 and ≥5 scores ($p_{trend} < 0.001$), respectively. The analysis restricted to diagnoses recorded in the one-year period prior to the index date had a similar pattern of ORs.

As shown in Table 7-3, all diseases in the cardiovascular and genitourinary systems were associated with a higher risk of incident gout. Among them, renal diseases (OR, 5.41) and congestive heart disease (OR, 3.99) were associated with the greatest risk of incident gout. In addition, solid malignancy, leukaemia and lymphoma (OR 1.21), hyperlipidaemia (OR 1.74), hypothyroidism (OR 1.42), chronic pulmonary diseases (OR 1.23), osteoarthritis (odds ratio 1.20), anaemia (odds ratio 1.32) and psoriasis (odds ratio 1.22) were also positively associated with incident gout in adjusted models in both the 10-year and one-year periods, while only multiple sclerosis (odds ratio 0.53) was negatively associated with incident gout. Interestingly, both

uncomplicated and complicated DM were not significant risk factors for incident gout and even showed a slight negative association in the logistic regression model in the 10-year period.

Table 7-3 Comorbidities present 10 years and 1 year before index date. Figures are number (percentage) of subjects and odds ratios (95% confidence intervals).

	10 year period before index date				1 year period before index date			
	Cases	Controls	Unadjusted OR	Adjusted OR[a]	Cases	Controls	Unadjusted OR	Adjusted OR[a]
Charlson comorbidity index categories								
0	20,597 (66.15)	23,382 (75.09)	Reference	Reference	26,414 (84.83)	27,888 (89.56)	Reference	Reference
1-2	8,436 (27.09)	6,536 (20.99)	1.55 (1.47–1.63)*	1.29 (1.22–1.36)*	4,318 (13.87)	3,024 (9.71)	1.54 (1.48–1.60)*	1.34 (1.28–1.40)*
3-4	1,680 (5.40)	1,008 (3.24)	1.94 (1.63–2.31)*	1.53 (1.27–1.85)*	365 (1.17)	206 (0.66)	2.07 (1.90–2.25)*	1.72 (1.57–1.88)*
≥5	425 (1.36)	212 (0.68)	2.28 (1.33–3.90)*	2.01 (1.11–3.61)*	41 (0.13)	20 (0.06)	2.56 (1.16–3.03)*	1.99 (1.66–3.39)*
Neoplasms								
Solid malignancy, leukemia and lymphoma	1,391 (4.47)	1,127 (3.62)	1.25 (1.15–1.36)*	1.21 (1.10–1.32)*	351 (1.13)	272 (0.87)	1.30 (1.11–1.52)*	1.26 (1.06–1.49)*
Metastatic solid tumors	22 (0.07)	21 (0.07)	1.08 (0.58–1.91)	1.00 (0.52–1.92)	4 (0.01)	8 (0.03)	0.50 (0.15–1.66)	0.70 (0.87–2.68)
Circulatory system								
Hypertension	10,820 (34.75)	5,563 (17.87)	2.78 (2.67–2.90)*	2.17 (2.07–2.27)*	4,229 (13.58)	2,107 (6.77)	2.35 (2.21–2.49)*	1.83 (1.72–1.95)*
Cardiac arrhythmias	2,200 (7.07)	938 (3.01)	2.58 (2.38–2.80)*	2.47 (2.27–2.62)*	637 (2.05)	259 (0.83)	2.54 (2.19–2.94)*	2.28 (1.95–2.67)*
Cerebrovascular disease	1,471 (4.72)	960 (3.08)	1.58 (1.45–1.72)*	1.43 (1.31–1.57)*	323 (1.04)	209 (0.67)	1.56 (1.31–1.86)*	1.39 (1.15–1.68)*
Congestive heart failure	1,709 (5.49)	458 (1.47)	4.38 (3.91–4.91)*	3.99 (3.54–4.49)*	482 (1.55)	118 (0.38)	4.43 (3.59–5.47)*	4.00 (3.20–5.00)*
Myocardial infarction	1,420 (4.56)	726 (2.33)	2.04 (1.86–2.24)*	1.79 (1.62–1.98)*	183 (0.59)	120 (0.39)	1.53 (1.22–1.93)*	1.34 (1.04–1.73)*
Peripheral vascular disease	921 (2.96)	583 (1.87)	1.62 (1.46–1.81)*	1.51 (1.34–1.69)*	211 (0.68)	124 (0.40)	1.72 (1.37–2.15)*	1.55 (1.22–1.98)*
Valvular heart disease	559 (1.80)	230 (0.74)	2.50 (2.13–2.92)*	2.50 (2.11–2.95)*	132 (0.42)	45 (0.14)	3.02 (2.14–4.27)*	2.63 (1.82–3.80)*
Genitourinary systems								
Urolithiasis	295 (0.95)	224 (0.72)	1.32 (1.10–1.57)*	1.22 (1.01–1.48)*	59 (0.19)	34 (0.11)	1.74 (1.14–2.65)*	1.74 (1.09–2.76)*
Renal diseases	715 (2.30)	133 (0.43)	5.51 (4.57–6.65)*	5.41 (4.44–6.58)*	302 (0.97)	42 (0.13)	7.34 (5.30–10.17)*	7.50 (5.33–10.55)*
Metabolic/endocrine disease								
Uncomplicated diabetes mellitus	1,926 (6.19)	1,631 (5.24)	1.20 (1.12–1.28)*	0.87 (0.81–0.94)*	1,275 (4.09)	1,011 (3.25)	1.28 (1.18–1.40)*	0.91 (0.83–1.00)
Diabetes mellitus with complications	329 (1.06)	319 (1.02)	1.03 (0.88–1.21)	0.77 (0.65–0.92)*	141 (0.45)	126 (0.40)	1.12 (0.88–1.43)	0.80 (0.62–1.04)
Hyperlipidaemia	3,172 (10.19)	1,676 (5.38)	2.10 (1.87–2.24)*	1.74 (1.62–1.87)*	805 (2.59)	391 (1.26)	2.15(1.90–2.44)*	1.88 (1.65–2.16)*
Hypothyroidism	1,045 (3.36)	669 (2.15)	1.61 (1.46–1.78)*	1.42 (1.27–1.58)*	273 (0.88)	163 (0.52)	1.69 (1.39–2.06)*	1.51 (1.22–1.87)*
Gastrointestinal and hepatic diseases								
Peptic ulcer disease	577 (1.85)	522 (1.68)	1.11 (0.98–1.25)*	1.08 (0.95–1.23)	60 (0.19)	43 (0.14)	1.11 (0.98–1.25)	1.08 (0.95–1.23)
Mild liver disease	115 (0.37)	68 (0.22)	1.69 (1.25–2.28)*	1.41 (1.02–1.96)*	29 (0.09)	15 (0.05)	1.69 (1.25–2.28)*	1.41 (1.02–1.96)*
Moderate to severe liver disease	22 (0.07)	20 (0.06)	1.10 (0.60–2.02)*	1.05 (0.56–2.00)	5 (0.02)	7 (0.02)	1.10 (0.60–2.02)	1.05 (0.56–2.00)
Chronic pulmonary diseases	3,830 (12.30)	2,886 (9.27)	1.39 (1.32–1.46)*	1.23 (1.16–1.30)*	1,708 (5.49)	1,201 (3.86)	1.39 (1.32–1.46)*	1.23 (1.16–1.30)*
Musculoskeletal & connective tissue diseases								
Osteoarthritis	3,184 (10.23)	2,337 (7.51)	1.46 (1.37–1.55)*	1.20 (1.13–1.28)*	771 (2.48)	490 (1.57)	1.61 (1.43–1.80)*	1.35 (1.19–1.54)*
Rheumatologic disease	1,981 (6.36)	1,751 (5.62)	1.15 (1.07–1.23)*	0.92 (0.86–0.99)*	909 (2.92)	740 (2.38)	1.25 (1.13–1.38)*	0.95 (0.85–1.06)
Neurological and mental disorders								
Dementia	37 (0.12)	74 (0.24)	0.50 (0.34–0.74)*	0.56 (0.37–0.86)*	13 (0.04)	29 (0.09)	0.45 (0.23–0.86)*	0.56 (0.28–1.13)
Hemiplegia	101 (0.32)	83 (0.27)	1.22 (0.91–1.63)	1.19 (0.86–1.64)	16 (0.05)	14 (0.04)	1.14 (0.56–2.34)	1.05 (0.48–2.31)
Multiple sclerosis	27 (0.09)	51 (0.16)	0.53 (0.33–0.84)*	0.53 (0.32–0.88)*	6 (0.02)	18 (0.06)	0.33 (0.13–0.84)*	0.26 (0.10–0.69)*
Other neurological diseases	482 (1.55)	566 (1.82)	0.85 (0.75–0.96)*	0.84 (0.74–0.96)*	117 (0.38)	146 (0.47)	0.80 (0.63–1.02)	0.84 (0.65–1.10)
Psychosis	100 (0.32)	143 (0.46)	0.70 (0.54–0.90)*	0.70 (0.53–0.92)*	23 (0.07)	26 (0.08)	0.89 (0.51–1.55)	0.90 (0.49–1.65)
Depression	3,680 (11.82)	3,135 (10.07)	1.21 (1.15–1.27)*	1.12 (1.06–1.18)*	919 (2.95)	745 (2.39)	1.24 (1.13–1.37)	1.12 (1.00–1.25)
Other comorbidities								
Anaemia	2,608 (8.38)	1,786 (5.74)	1.54 (1.45–1.65)*	1.32 (1.23–1.41)*	503 (1.62)	286 (0.92)	1.80 (1.55–2.09)*	1.58 (1.34–1.85)*
Psoriasis	1,002 (3.22)	728 (2.34)	1.39 (1.26–1.53)*	1.22 (1.09–1.35)*	288 (0.92)	178 (0.57)	1.63 (1.35–1.97)*	1.48 (1.20–1.81)*
HIV infection	7 (0.02)	3 (0.01)	2.33 (0.60–9.02)	1.42 (0.29–6.82)	2 (<0.01)	1 (<0.01)	2.00 (0.18–22.05)	0.90 (0.07–11.09)

Footnote: a. adjusted for age, gender, index year, BMI class, smoking status and alcohol consumption. * p<0.05

7.3.2 All-cause mortality of gout after diagnosis

After diagnosis, mortality at 5-year and 10-years (95% CIs) from any cause was 5.28% (5.02%–5.53%) and 18.49% (18.01%–18.97%) respectively in incident gout patients, compared with 4.45% (4.22%–4.68%; log-rank test, p<0.001) and 15.29% (14.85%–15.73%; log-rank test, p<0.001) in matched controls. On average, 21% excess deaths were observed in people with gout compared to those without gout (HR 1.24, 95%CI 1.18–1.30). After the adjustment for age, sex, index year, BMI class, smoking status, alcohol consumption and all comorbidities at baseline, gout associated with a HR of 1.15 (95% CI, 1.09 –1.22). In a model additionally adjusting for all comorbidity at diagnosis, gout was associated with a HR (95% CI) for all-cause mortality of 1.11 (1.05–1.17; p<0.001).

Table 7-4 Cumulative probability of comorbidity after diagnosis of gout. Figures are probability of incident comorbidity (percentage).

	Cases					Controls				
	At diagnosis	1 year	2 years	5 year	10 year	At diagnosis	1 year	2 years	5 year	10 year
Charlson comorbidity index >0	33.85	37.43	40.51	49.50	62.84	24.91	27.24	29.64	37.20	48.74
Any increase in Charlson comorbidity index	0	3.57	6.66	15.46	26.05	0	2.33	4.73	12.09	21.01
Neoplasms										
Solid malignancy, leukemia and lymphoma	4.47	5.20	6.09	9.80	17.39	3.62	4.19	4.93	8.42	15.21
Metastatic solid tumors	0.07	0.09	0.13	0.52	1.48	0.07	0.08	0.11	0.50	1.49
Circulatory system										
Hypertension	34.75	38.41	41.57	49.59	59.57	17.87	20.29	22.89	29.95	38.71
Cardiac arrhythmias	7.07	8.02	8.95	11.88	16.94	3.01	3.46	4.10	6.10	9.62
Cerebrovascular disease	4.72	5.46	6.16	8.58	12.62	3.08	3.63	4.20	61.3	9.48
Congestive heart failure	5.49	6.04	6.63	8.25	10.84	1.47	1.73	1.99	3.08	4.87
Myocardial infarction	4.56	4.98	5.33	6.72	9.08	2.33	2.61	2.89	4.04	5.71
Peripheral vascular disease	2.96	3.41	3.80	5.03	7.10	1.87	2.16	2.44	3.31	4.80
Valvular heart disease	1.80	2.07	2.38	3.34	5.05	0.74	0.88	1.04	1.60	2.79
Genitourinary system										
Urolithiasis	0.95	1.04	1.13	1.42	1.99	0.72	0.81	0.89	1.11	1.48
Renal diseases	2.30	3.02	3.88	6.93	10.78	0.43	0.56	0.76	1.67	3.32
Metabolic/endocrine disease										
Uncomplicated diabetes mellitus	6.19	7.48	8.75	13.00	20.05	5.24	5.92	6.63	8.70	12.27
Diabetes mellitus with complications	1.06	1.33	1.68	3.27	13.57	1.02	1.26	1.57	2.67	8.67
Hyperlipidaemia	10.19	11.86	13.34	17.22	22.16	5.38	6.32	7.27	10.04	13.78
Hypothyroidism	3.36	3.85	4.35	5.88	7.92	2.15	2.43	2.79	3.97	5.40
Digestive system										
Peptic ulcer disease	1.85	2.10	2.27	2.77	3.54	1.68	1.81	1.94	2.25	2.85
Mild liver disease	0.37	0.47	0.58	1.07	1.96	0.22	0.27	0.32	0.49	0.94
Moderate to severe liver disease	0.07	0.08	0.09	0.19	0.42	0.066	0.08	0.09	0.16	0.33
Chronic pulmonary diseases	12.30	13.32	14.19	16.73	20.62	9.27	10.00	10.68	12.76	16.30
Musculoskeletal & connective tissue diseases										
Osteoarthritis	10.23	11.96	13.50	17.54	23.27	7.51	8.39	9.25	12.01	15.86
Rheumatologic disease	6.36	7.62	8.82	12.06	17.89	5.62	6.35	7.06	8.93	12.02
Nervous system and mental disorders										
Dementia	0.12	0.20	0.32	0.89	2.52	0.24	0.32	0.50	1.31	2.97
Hemiplegia	0.32	0.40	0.45	0.6	0.92	0.27	0.31	0.34	0.47	0.66
Multiple sclerosis	0.08	0.10	-	0.12	0.4	0.16	0.18	0.19	2.03	2.49
Other neurological diseases	1.55	1.84	2.14	3.18	4.84	1.82	2.09	2.42	3.39	5.04
Psychosis	0.32	0.39	0.43	0.62	1.03	0.46	0.50	0.55	0.76	1.15
Depression	11.82	13.13	14.40	18.24	24.05	10.07	11.16	12.26	15.34	20.14
Other comorbidities										
Anaemia	7.97	9.26	10.42	14.63	21.88	5.57	6.28	7.02	9.96	14.76
Psoriasis	3.22	3.55	3.84	4.67	5.86	2.34	2.60	2.86	3.41	4.12
HIV infection	0.02	0..03	0.04	0.04	-	<0.001	-	-	0.02	-

Footnote: a. adjusted for age, gender, index year, BMI class, smoking status and alcohol consumption.

7.4 Discussion

Using a large primary care database in the UK, the risk of existing comorbidity at diagnosis and all-cause mortality following initial diagnosis was examined in incident gout patients compared to matched controls. Overall, a third of newly diagnosed gout patients already had a Charlson comorbidity score ≥ 1, compared to a quarter of matched controls. This is the first study that has attempted to examine a full range of comorbidities including those not listed in the Charlson comorbidity index. The prevalence of hypertension, cardiac arrhythmias, valvular heart disease, urolithiasis, hyperlipidaemia, hypothyroidism, chronic pulmonary disease, osteoarthritis, depression, anaemia and psoriasis were all significantly higher in incident gout patients than controls. Despite other diseases which affect longevity, gout itself causes an additional 11% of deaths in the UK general population. Overall, the burden of comorbidity is very high at diagnosis of gout and the risk of all-cause mortality is also higher in incident gout patients than in the general population independent of comorbidities at diagnosis.

The relationships between index disease and comorbidity are very complex(Valderas et al., 2009) but broadly can be classified into three models: direct causation, associated risk factors and heterogeneity.(Rhee et al., 2004) The association between gout and metabolic syndrome,(Choi et al., 2007, Rho et al., 2005) as well as to the individual components of metabolic syndrome,(Chen et al., 2007a) for instance is consistently reported. Although the relationships

between gout and metabolic syndrome were not measured directly, there were close relationships between gout and the individual metabolic syndrome components such as hypertension, hyperlipidaemia and obesity (increased BMI). The coexistence of gout and the components of metabolic syndrome probably is the result of the close links between hyperuricaemia and insulin resistance, the main driver of gout and metabolic syndrome.(Rathmann et al., 1998, Vuorinen-Markkola and Yki-Jarvinen, 1994) This is a typical model of associated risk factors.(Rhee et al., 2004) The associations between gout and diabetes mellitus are more complex. Both hyperuricaemia and gout are independent risk factors to type 2 diabetes mellitus, (Bhole et al., 2010a, Choi et al., 2008) however, diabetes protects against future risk of gout.(Rodriguez et al., 2010) This study found that the prevalence of diabetes was not increased in gout patients at diagnosis compared to the general.(Rodriguez et al., 2010) These findings collectively suggest a heterogeneity comorbidity model for the association between gout and diabetes mellitus,(Rhee et al., 2004) implying that the effects of risk factors (hyperuricaemia and hyperglycaemia) are in different directions to the risk of index diseases. A direct causation model is more difficult to ascertain(Rhee et al., 2004)but the association between gout and osteoarthritis may represent one such example. In accord with one previous study that reported the co-location of sites of acute attacks of gout and osteoarthritis, (Roddy et al., 2007a) this study found a higher prevalence of osteoarthritis in gout patients at diagnosis. Current mechanistic explanations for osteoarthritis as a risk factor for gout generally focus on heightened propensity

of damaged cartilage in facilitating monosodium urate crystal nucleation.(Wilcox and Khalaf, 1975, Perricone and Brandt, 1978, Pascual and Ordonez, 1998, Simkin, 1977) Conversely urate crystals inhibit the viability of chondrocytes (Chhana et al., 2013) and osteoblasts, (Chhana et al., 2011) therefore contributing to the development of osteoarthritis. Furthermore, a recent study found that uric acid concentration in synovial fluid strongly correlates with synovial concentration of pro-inflammatory cytokines (such as interleukins 1 and 18) and is a marker for osteoarthritis severity.(Denoble et al., 2011) These findings support the reciprocal causation between gout and osteoarthritis.

The mechanism for a positive association between gout and some other comorbidities are less obvious. For example, hypothyroidism was found to be more common in incident gout patients at diagnosis. These data are consistent with some previous limited evidence(Kuzell et al., 1955, Durward, 1976, Erickson et al., 1994) and it is of interest that thyroxin replacement is reported to reverse hyperuricaemia secondary to hypothyroidism.(Giordano et al., 2001, Mooraki and Bastani, 1998) Furthermore reduced glomerular filtration rate is reduced in patients with hypothyroidism (Mariani and Berns, 2012) suggesting an influence of thyroxine on renal urate clearance.(Mariani and Berns, 2012) Another example is anaemia, which was found to be more prevalent in incident gout patients in this study, as it was in the Atherosclerosis Risk in the Communities study.(Maynard et al., 2014) Currently, there is no clear explanation for the association between gout and anaemia, although it may be pertinent that a previous study of

sickle-cell anaemia speculated that increased synthesis of nucleic acids as a result of erythropoietic response could lead to hyperuricaemia.(Reynolds, 1983) Further studies should be undertaken to confirm these mechanistic explanations for positive associations between gout and comorbidities.

Despite the complexity of aetiological associations, clinical implications of comorbidity are simple. We could regard comorbidity as part of the diagnostic process, as a consideration for management decisions and as a flag for prognosis.(Feinstein, 1970) Given that there is a gold standard of gout diagnosis (the recognition of synovial monosodium urate crystals) and that clinical diagnosis is reasonably straightforward,(Zhang et al., 2006b) comorbidity would neither simplify nor complicate the diagnosis of gout. Using comorbidity as a flag of prognosis is widely used clinically, regardless of the index disease. For instance, the Charlson comorbidity index is a widely used index to estimate overall comorbidity burden and to predict mortality.(Charlson et al., 1994) The existence of comorbidity, however, greatly complicates the management of gout and requires special attention in managing gout patients. Currently, EULAR recommendations,(Zhang et al., 2006a) BSR (Jordan et al., 2007) and ACR guidelines(Khanna et al., 2012a) have considered comorbidity as part of initial assessment of gout patients and generally advise clinicians to consider comorbidity that may contribute to, or associate with hyperuricaemia. The comorbidity 'checklist' included obesity, metabolic syndrome, diabetes mellitus, hyperlipidaemia, urolithiasis and chronic kidney diseases. In addition, the management

of chronic hyperuricaemia also partly depends on the existence of comorbidities. For example, current consensus supports the prescription of ULT for patients with evidence of excessive urate load (such as urolithiasis) or with comorbidity that promotes long-standing hyperuricaemia (such as renal disease). However, as the data show, comorbidities with higher absolute and relative risks were not limited to the 'comorbidity checklist' recommended by guidelines. Hypothyroidism and anaemia are two examples that were more common in incident gout patients at diagnosis. Yet screening for thyroid function is not mentioned in any of the guidelines and only the ACR guideline recommends a complete blood cell count for gout patients,(Khanna et al., 2012a) which is mainly to look for myeloproliferative disease rather than anaemia. Therefore, this study supports the case for a comprehensive investigation for comorbidities, including but not limited to 'checklists', as an integral part of initial assessment for gout patients at diagnosis.

There are several limitations to this study. Firstly, there may be some misclassification bias since the identification of gout patients was based on diagnoses made by general practitioners, rather than according to American College of Rheumatology(Wallace et al., 1977) or Rome(Kellgren JH, 1963) classification criteria or to the 'gold standard' of urate crystal identification. Against this, however, is that the validity of gout diagnosis in the CPRD has been investigated and found to be high.(Meier and Jick, 1997) Similarly there may have been some misclassification of comorbidities, although again most of the comorbidities in this study have been validated previously.(Herrett et al., 2010) In addition, there is no reason to suspect a differential

misclassification between gout and non-gout patients. Secondly, differential ascertainment bias between incident gout patients and controls cannot be excluded entirely, even though the estimates based on different length of previous observation produced similar results. Third, the models did not adjust for all potential risk factors for gouty arthritis, such as diet and physical activity, both of which are not routinely recorded in the CPRD. However, this study aimed to provide estimates of disease burden of gout patients both at diagnosis and subsequent to diagnosis, rather than to define causes of gout. Fourthly, the problem associated with multiple testing may arise in this study. However, the main focus of this analysis was to identify exposures and outcomes that are more closely associated with gout. Also, most of the results were interpreted in the light of existing research so the conclusions are unlikely to have been affected unduly by false positive findings. In addition, the sample size of this study is about 62,000 including cases and controls. Even when a Bonferroni correction is applied, which is very conservative when the multiple outcome measures under consideration are not independent, the majority of previously significant results remain so.

In conclusion, the majority of gout patients in the UK already have comorbidity at. All-cause mortality was higher in gout patients and the increased risk was contributed to by both gout itself and by comorbidities to approximately the same degree. This study suggests that a thorough search for comorbidity, including both pathophysiologically related and unrelated conditions.

CHAPTER 8. Effect of allopurinol on all-cause mortality in adults with incident gout: population based retrospective cohort study in the UK

8.1 Introduction

The prevalence of gout is rising worldwide(Roddy et al., 2007b) with a recent estimated prevalence of 2.49% in the UK.(Kuo et al., 2013b) The hallmarks of initial gout presentation are acute pain, swelling, erythema and tenderness in peripheral joints but eventually unremitting arthritis, joint deformity and tophus deposition may develop with long-standing hyperuricaemia.(Zhang et al., 2006b) Patients with gout suffer not only arthritis but also cardiovascular,(Abbott et al., 1988, Krishnan et al., 2006, Choi and Curhan, 2007, De Vera et al., 2010, Kuo et al., 2013c, Chen et al., 2007b) renal,(Yu et al., 2012) metabolic(Choi et al., 2007, Suppiah et al., 2008) and other comorbidities.(Boffetta et al., 2009, Kuo et al., 2012, Kuzell et al., 1955, Durward, 1976, McAdams-DeMarco et al., 2012) Collectively gout and associated comorbidities lead to reduced quality of life(Chandratre et al., 2013) and reduced overall survival.(Kuo et al., 2011, Kuo et al., 2010a, Stack et al., 2013, Kok et al., 2012, Teng et al., 2012, Krishnan et al., 2008, Choi and Curhan, 2007)

Since gout results from chronic hyperuricaemia and the deposition of monosodium urate crystals in peripheral joints and surrounding tissues, the use of ULT which is capable of preventing crystal formation and dissolving existing crystal deposits may potentially 'cure' gout.(Terkeltaub, 2010)

Allopurinol with its primary mechanism of inhibiting the activity of xanthine oxidase is currently the first-line ULT recommended by the National Institute for Health and Clinical Excellence, (Excellence, 2008) the European League against Rheumatism (EULAR) recommendations for gout(Zhang et al., 2006a) and American College of Rheumatology (ACR) guidelines for management of gout(Khanna et al., 2012a). However, only around one-third of gout patients receive allopurinol in the UK,(Kuo et al., 2013b) mainly at a fixed dose of 300 mg which is probably insufficient for most patients. This is despite its reasonable safety profile(Schumacher et al., 2008, Reinders et al., 2009) and probable additional beneficial effects on hypertension,(Agarwal et al., 2013) IgA nephropathy,(Shi et al., 2012) diabetic nephropathy,(Maahs et al., 2013) heart failure,(Harzand et al., 2012) and stroke.(Muir et al., 2008)

One of the barriers to prescription of allopurinol for gout patients is the fear of the potential life-threatening drug reactions or rash with eosinophilia and systemic symptoms (DRESS; previously termed allopurinol hypersensitivity syndrome).(Kim et al., 2013) Whether the balance of these potential benefits and risks can translate to any influence on survival in gout patients remains unclear. Therefore, the present study was undertaken to assess the association between allopurinol use and long-term mortality in patients with gout using CPRD.

8.2 Methods

The study was approved by the Trent Multi-centre Research Ethics Committee (reference number: 05/MRE04/87) and the Independent Scientific Advisory Committee (11-021R). This study was a propensity score-matched landmark study comparing all-cause mortality between patients treated with at least 6 months of allopurinol and those who are not treated with allopurinol or other ULT.

8.2.1 Data source

Please refer to section 2.3.1/

8.2.2 Definition of incident gout

Read codes were used to identify incident gout patients in the CPRD between 1995 and 1999. To be eligible as incident gout patients, participants had to be older than 20 years of age, have no evidence of gout or prescription for ULT (mostly allopurinol) prior to the time of diagnosis (index date) and have at least one-year registration prior to their index date.(Cea Soriano et al., 2011) The case definition was based on physician-diagnosis using 18 Read codes indicative of incident gout (please refer to Table 2--3 for relevant Read codes). The validity of a gout diagnosis in the CPRD has been validated in a previous study.(Meier and Jick, 1997)

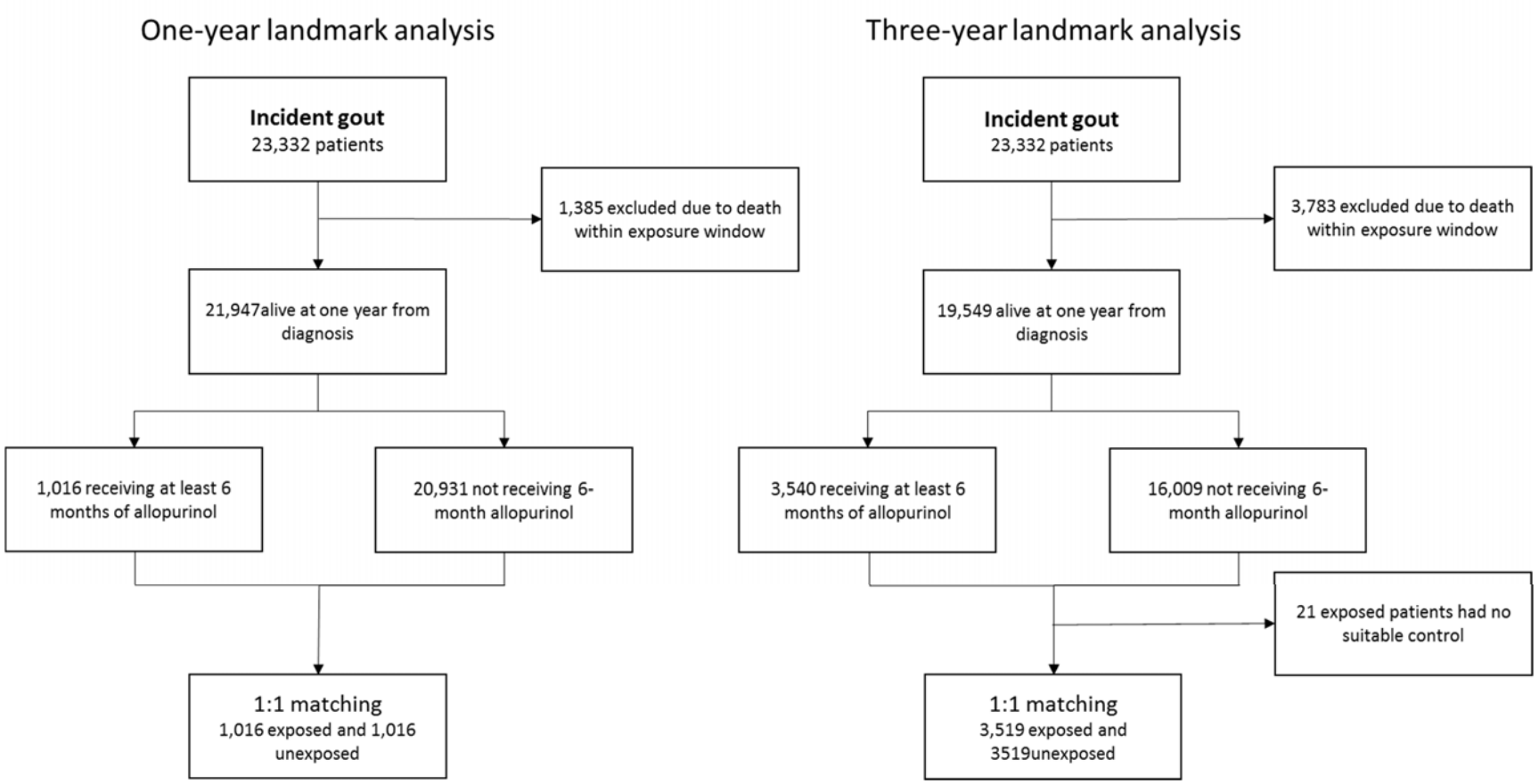
8.2.3 Treatment group assignments

Patients were classified by exposure to allopurinol. A minimal of 6-months prescription of allopurinol was required for assignment of allopurinol exposure. The prescription of allopurinol as the first-line ULT, however, largely lags behind the time of first diagnosis and is given to a minority of people with currently recommended indications for ULT.(Chapter 6;(Roddy et al., 2010) Therefore, the date of completing 6-months of allopurinol use was not necessarily related to the date of diagnosis (cohort entry). In this study, a landmark analysis was used to examine the effect of allopurinol exposure on all-cause mortality.(Dafni, 2011) In a landmark analysis, a fixed time after cohort entry is selected *a priori* for conducting survival analysis. Only patients alive at the date of the landmark are included in the analysis and treatment assignment is based on exposure on landmark date. Exposures are only evaluated between cohort entry and landmark time point (exposure window) and outcome is then evaluated from this landmark time point. Patients with outcomes occurring during exposure are excluded from subsequent analysis to avoid immortal time bias.(Beyersmann et al., 2008)

In this study, the date of initial gout diagnosis was the cohort entry. Two landmark time points were determined *a priori* in this study, specifically at one and at three years after initial gout diagnosis (figure 8-1a). Exposure status was assigned for patients who were alive at landmark dates. Those who had at least 6 months of allopurinol prescription were defined as exposed to allopurinol and those who did not were the unexposed. Patients were followed up until the date

of death, transfer out from a participating CPRD practice, or the 31 December 2013, whichever was earliest (figure 8-1b).

(a)


One-year landmark analysis
Incident gout
23,332 patients
1,385 excluded due to death within exposure window
21,947alive at one year from diagnosis
1,016 receiving at least 6 months of allopurinol
20,931 not receiving 6-month allopurinol
1:1 matching
1,016 exposed and 1,016 unexposed
Three-year landmark analysis
Incident gout
23,332 patients
3,783 excluded due to death within exposure window
19,549 alive at one year from diagnosis
3,540 receiving at least 6 months of allopurinol
16,009 not receiving 6-month allopurinol
21 exposed patients had no suitable control
1:1 matching
3,519 exposed and 3519unexposed

(b)

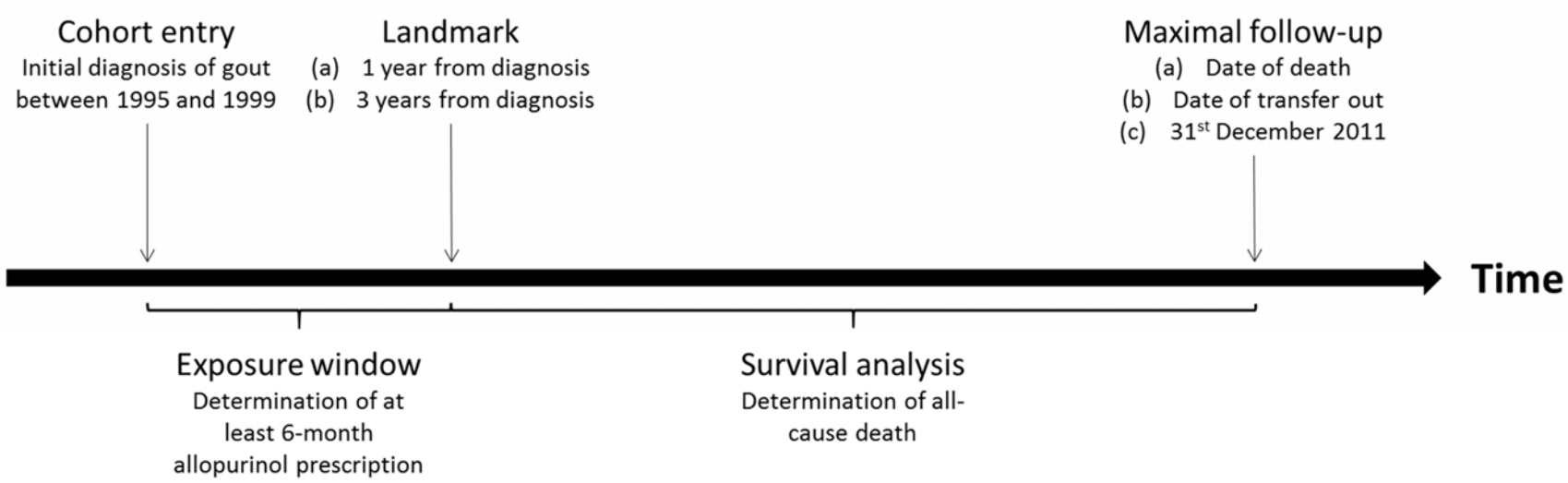


Figure 8-1 Diagram of one-year and three-year landmark analysis (a) decomposition of study population. (b) Details of timeline.

8.2.4 **Covariates**

Covariates included patient characteristics (age, gender, registered general practices, body mass index [BMI]), lifestyle factors (smoking status and alcohol consumption), comorbidities and drug treatment. Only GP records occurring within the 5-year period before initial diagnosis of gout were used to evaluate comorbidities and drug treatment. Comorbidities were grouped into 17 diagnostic categories (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes mellitus [DM], DM with chronic complications, renal diseases, any malignancy [including leukaemia and lymphoma], metastatic solid tumour and human immunodeficiency virus [HIV] infection) for calculation of the Charlson comorbidity index(Deyo et al., 1992, Khan et al., 2010b) and other comorbidities (alcohol abuse, anaemia, cardiac arrhythmias, depression, drug abuse, hip fracture, hypertension, hypothyroidism, multiple sclerosis, neurological diseases, psoriasis, psychosis, urolithiasis and valvular heart disease). The definitions of these conditions were also based on physician diagnoses recorded as Read codes. The specific code lists are available on request. Medications evaluated include aspirin, anticoagulants, anticonvulsants, lipid lowering agents (statin, fibrate and other), antihypertensives (angiotensin converting enzyme inhibitor/angiotensin-receptor antagonist, beta blockers, calcium channel blockers, diuretics and other), nitrates, other cardiovascular medications, insulin, other hypoglycaemic agents, anti-

inflammatory agents (non-steroid anti-inflammatory drugs [NSAIDs], colchicine, corticosteroids), bisphosphonate and vitamin D.

8.2.5 Outcomes

Mortality and date of death were based on the recording in the main CPRD database. The validation of all-cause mortality in CPRD compared with the ONS death registry has been addressed in Chapter 7.

8.2.6 Statistical analysis

Baseline characteristics and event rates were summarized for allopurinol exposure groups as number (percentage) for categorical variables and as median (inter-quartile range) for continuous variables. General health status was measured by the Charlson co-morbidity index. The Charlson score for each study subject was calculated at diagnosis by adding scores assigned to each specific diagnosis. Patient characteristics were compared for patients included in each landmark analysis and those excluded because they died during the exposure window. Binary variables were compared across exposure groups using the Pearson $\chi 2$ test and continuous and ordinal categorical variables were compared using the Wilcoxon rank sum test.

The propensity score matching methods were used to account for confounding by indication. The propensity score for allopurinol use represents the probability that a patient is prescribed (6-

month) allopurinol treatment. Logistic regression models were used to determine a propensity score for receiving at least 6-months of allopurinol prescription during the exposure window. The covariates included were patient characteristics, life style factors, comorbidities and the medications already listed. In the primary analysis the allopurinol exposed patients were matched to unexposed patients in a ratio of 1 to 1 based on the logit of the propensity score using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score.(Austin, 2011b, Austin, 2011a) As a sensitivity analysis, the entire cohort was included and adjusted for raw propensity score.

Kaplan–Meier plots were used to estimate the cumulative probability of survival. The hazard ratio for occurrence of mortality was determined using Cox proportional hazards, accounting for propensity score matching and using robust variance estimation for potential case clustering in practices. Separate analyses were undertaken for different landmarks to examine the effect of different size of exposure window on risk estimates. Also, propensity score adjustment for the entire included cohort was undertaken to compare the mortality risks between users and non-users of allopurinol. All statistical analyses were performed using SAS statistical software, version 9.3.

8.3 Results

8.3.1 Study population

Between January 1995 and December 1999 there were 23,332 incident gout patients (men: 17,197 [73.91%]). Due to transferring out or death, 1,385 patients were excluded from the one-year landmark analysis and 3,783 patients were excluded from the three-year landmark analysis (figure 8-1a). Table 8-1 summarises and compares baseline characteristics between included and excluded patients in the one-year and three-year landmark analyses. In general, those excluded were older and had a higher Charlson comorbidity index. These differences were similar in the one-year and three-year landmark analyses.

Table 8-1 Characteristics of cohort at cohort entry (initial diagnosis of gout. Values are numbers (percentage)

	Entire cohort (n=23,332)	One-year Landmark cohort			Three-year landmark cohort		
		Included patients (n=21,947)	Excluded patients (n = 1,385)	P value	Included patients (n=19,549)	Excluded patients (n=3,783)	P value
Age (years)							
Median (interquartile range)	62 (50—73)	62 (49—73)	73 (60—82)	<0.001	61 (49—71)	72 (58—81)	<0.001
Gender							
Men	17,197 (73.71)	16276 (74.16)	921 (66.50)	<0.001	14628 (74.83)	2569 (67.91)	<0.001
Women	6135 (26.29)	5671 (25.84)	464 (33.50)		4921 (25.17)	1214 (32.09)	
BMI (kg/m2)							
<18.5	162 (0.69)	146 (0.67)	16 (1.16)	<0.001	123 (0.63)	39 (1.03)	<0.001
18.5 – 24.9	4975 (21.32)	4678 (21.31)	297 (21.44)		4142 (21.19)	833 (22.02)	
25.0 – 29.9	8910 (38.19)	8536 (38.89)	374 (27.00)		7846 (40.14)	1064 (28.13)	
≥30	6119 (26.23)	5889 (26.83)	230 (16.61)		5466 (27.96)	653 (17.26)	
Unknown	3166 (13.57)	2698 (12.29)	468 (33.79)		1972 (10.09)	1194 (31.56)	
Smoking							
Non-smoker	2688 (11.52)	2523 (11.50)	165 (11.91)	0.80	2307 (11.80)	381 (10.07)	0.03
Current smoker	1910 (8.19)	1804 (8.22)	106 (7.65)		1588 (8.12)	322 (8.51)	
Ex-smoker	13889 (59.53)	13059 (59.50)	830 (59.93)		11543 (59.05)	2346 (62.01)	
Unknown	4845 (20.77)	4561 (20.78)	284 (20.51)		4111 (21.03)	734 (19.40)	
Alcohol consumption (units/week)							
Never/ Ex-drinker	2525 (10.82)	2299 (10.48)	226 (16.32)	0.07	1992 (10.19)	533 (14.09)	0.35
Current 1-9	8957 (38.39)	8421 (38.37)	536 (38.70)		7461 (38.17)	1496 (39.55)	
Current ≥10	5496 (23.56)	5281 (24.06)	215 (15.52)		4799 (24.55)	697 (18.42)	
Unknown	6354 (27.23)	5946 (27.09)	408 (29.46)		5297 (27.10)	1057 (27.94)	
Charlson comorbidity index							
0	16211 (69.48)	15575 (70.97)	636 (45.92)	<0.001	14365 (73.48)	1846 (48.80)	<0.001
1-2	5916 (25.36)	5384 (24.53)	532 (38.41)		4476 (22.90)	1440 (38.07)	
3-4	1141 (4.89)	947 (4.31)	194 (14.01)		687 (3.51)	454 (12.00)	
≥4	64 (0.27)	41 (0.19)	23 (1.66)		21 (0.11)	43 (1.14)	
Medications							
Aspirin	4188 (17.95)	3750 (17.09)	438 (31.62)	<0.001	3047 (15.59)	1141 (30.16)	<0.001
Statin	105 (4.52)	986 (4.49)	69 (4.98)	0.40)	883 (4.52)	172 (4.55)	0.94
Diuretics	8878 (38.05)	8023 (36.56)	855 (61.73)	<0.001)	6687 (34.21)	2191 (57.92)	<0.001
Insulin	122 (0.52)	103 (0.47)	19 (1.37)	<0.001)	84 (0.43)	38 (1.00)	<0.001
NSAID	17024 (72.96)	16045 (73.11)	979 (70.69)	0.50	14324 (73.27)	2700 (71.37)	0.02

8.3.2 **Matching**

For the one-year landmark analysis there were 21,947 patients who were alive at one year from initial diagnosis of gout. Of these 1,016 patients had at least 6 months of allopurinol prescription. As shown in table 8-2 there were no significant differences in variables included in the propensity score calculation between allopurinol users and non-users after matching, confirming the success of the matching. For the three-year landmark analysis, there were 9,549 patients who were alive three years after their initial diagnosis of gout. There were 3,540 allopurinol users at the three-year landmark. After matching, no significant differences were found in variables for propensity scores (table 8-3). Note that all the aforementioned variables were included to construct propensity score models. Only the selected variables were shown to indicate proper matching for both the one-year and three-year landmark analyses. When compared to all incident gout patients, patients who were prescribed allopurinol tended to be older, have more comorbidities and be on more other medications.

Table 8-2 Comparison of patients exposed or unexposed to allopurinol within one year from initial diagnosis of gout before and after matching. Values are numbers (percentage) unless described otherwise.

	Exposure groups before matching			Exposure groups after matching		
	Allopurinol users (n=1,016)	Allopurinol nonusers (n = 20,931)	P value	Allopurinol users (n = 1,016)	Allopurinol nonusers (n = 1,016)	P value
Age (years)						
Median (interquartile range)	66 (56—74)	61 (49—73)	<0.001	66 (55—75)	66 (56—74)	0.87
Gender						
Men	665 (65.45)	15611 (74.58)	<0.001	665 (65.45)	655 (64.47)	0.64
Women	351 (34.55)	5320 (25.42)		351 (34.55)	361 (35.53)	
BMI (kg/m2)						
<18.5	2 (0.20)	144 (0.69)	<0.001	2 (0.20)	2 (0.20)	0.89
18.5 – 24.9	206 (20.28)	4472 (21.37)		206 (20.28)	223 (21.95)	
25.0 – 29.9	375 (36.97)	8161 (38.99)		375 (36.97)	351 (34.55)	
≥30	352 (34.65)	5537 (26.45)		352 (34.65)	357 (35.14)	
Unknown	81 (7.97)	2617 (12.50		81 (7.97)	83 (8.17)	
Smoking						
Non-smoker	132 (12.99)	2391 (11.42)	<0.001	132 (12.99)	135 (13.29(	0.72
Current smoker	96 (9.45)	1708 (8.16)		96 (9.45)	112 (11.02)	
Ex-smoker	638 (62.80)	12421(59.34)		638 (62.80)	613 (60.33)	
Unknown	150 (14.76	4411 (21.07)		150 (14.76	156 (15.35)	
Alcohol consumption (units/week)						
Never/ Ex-drinker	158 (15.55)	2141 (10.23)	<0.001	158 (15.55)	167 (16.44)	0.80
Current 1-9	435 (42.81)	7986 (38.15)		435 (42.81)	444 (43.70)	
Current ≥10	211 (20.77)	5070 (24.22)		211 (20.77)	188 (18.50)	
Unknown	212 (20.87)	5734 (27.39)		212 (20.87)	217 (21.36)	
Charlson comorbidity index						
0	600 (59.06)	14975 (71.54)	<0.001	600 (59.06)	591 (58.17)	0.84
1-2	330 (32.48)	5054 (24.15)		330 (32.48)	341 (33.56)	
3-4	82 (8.07)	865 (4.13)		82 (8.07)	81 (7.97)	
≥4	4 (0.39)	37 (0.18)		4 (0.39)	3 (0.30)	
Medications						
Aspirin	295 (29.04)	3455 (16.51)	<0.001	295 (29.04)	296 (29.13)	0.96
Statin	94 (9.25)	892 (4.23)	<0.001	94 (9.25)	86 (8.46)	0.53
Diuretics	622 (61.22)	7401 (35.36)	<0.001	622 (61.22)	617 (60.73)	0.82
Insulin	10 (0.98)	93 (0.44)	0.01	10 (0.98)	15 (1.48)	0.31
NSAID	773 (76.08)	15272 (72.96)	0.03	773 (76.08)	789 (77.36)	0.50

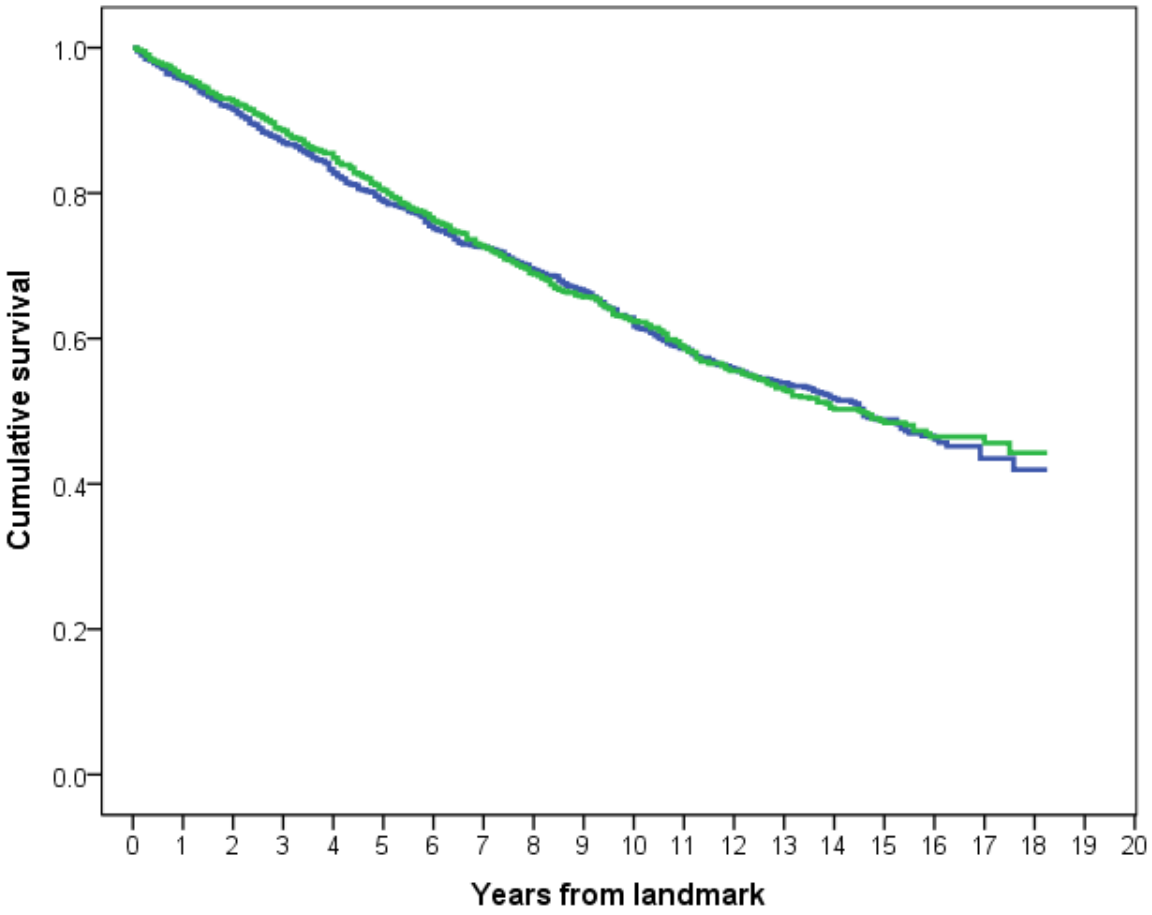
Table 8-3 Comparison of patients exposed or unexposed to allopurinol within three year from initial diagnosis of gout before and after matching. Values are numbers (percentage) unless described otherwise.

	Exposure groups before matching			Exposure groups after matching		
	Allopurinol users (n=3,540)	Allopurinol nonusers (n = 16,009)	P value	Allopurinol users (n = 3,519)	Allopurinol nonusers (n = 3,519)	P value
Age (years)						
Median (interquartile range)	64 (52—73)	60 (48—71)	<0.001	64 (52—73)	63 (51—73)	0.69
Gender						
Men	2530 (71.90)	12085 (75.49)	<0.001	2530 (71.90)	2542 (72.24)	0.75
Women	989 (28.10)	3924 (24.51)		989 (28.10)	977 (27.76)	
BMI (kg/m2)						
<18.5	14 (0.40)	109 (0.68)	0.009	14 (0.40)	16 (0.5)	0.93
18.5 – 24.9	633 (17.99)	3508 (21.91)		633 (17.99)	642 (18.24)	
25.0 – 29.9	1357 (38.56)	6482 (40.49)		1357 (38.56)	1351 (38.39)	
≥30	1205 (34.24)	4248 (26.54)		1205 (34.24)	1202 (34.16)	
Unknown	310 (8.81)	1662 (10.38)		310 (8.81)	308 (8.78)	
Smoking						
Non-smoker	427 (12.13)	1877 (11.72)	0.006	427 (12.13)	426 (12.11)	0.93
Current smoker	273 (7.716)	1312 (8.21)		273 (7.716)	290 (8.24)	
Ex-smoker	2136 (60.70)	9392 (58.62)		2136 (60.70)	2117 (60.16)	
Unknown	683 (19.41)	3426 (21.40)		683 (19.41)	686 (19.49)	
Alcohol consumption (units/week)						
Never/ Ex-drinker	419 (11.91)	1567 (9.79)	0.004	419 (11.91)	425 (12.08)	0.79
Current 1-9	1391 (39.53)	6058 (37.84)		1391 (39.53)	1369 (38.90)	
Current ≥10	820 (23.30)	3979 (24.85)		820 (23.30)	846 (24.04)	
Unknown	889 (25.26)	4405 (27.52)		889 (25.26)	879 (24.98)	
Charlson comorbidity index						
0	2330 (66.82)	12035 (75.18)	<0.001	2329 (66.18)	2341 (66.52)	0.75
1-2	1017 (28.73)	3459 (21.61)		1008 (28.64)	999 (28.39)	
3-4	187 (5.28)	500 (3.12)		176 (5.00)	174 (4.49)	
≥4	6 (0.17)	15 (0.09)		6 (0.17)	5 (0.14)	
Medications						
Aspirin	799 (22.57)	2248 (14.04)	<0.001	785 (22.31)	796 (22.62)	0.75
Statin	263 (7.43)	620 (3.87)	<0.001	255 (7.25)	248 (7.05)	0.75
Diuretics	1778 (50.23)	4909 (30.66)	<0.001	1757 (49.93)	1778 (50.53)	0.62
Insulin	18 (0.51)	66 (0.41)	0.43	18 (0.51)	14 (0.40)	0.48
NSAID	2560 (72.32)	11764 (73.48)	0.16	2544 (72.29)	2549 (72.44)	0.89

8.3.3 Outcomes after matching

The median follow-up was 10 years for both the one-year and three-year landmark analyses. As shown in table 8-4, there were a total of 880 patients in the one-year landmark analysis and 2,546 patients in the three-year landmark analysis who died during the follow-up period. No significant differences were found for overall mortality rate between allopurinol users and non-users in both the one-year and three year landmark analysis. As figure 8-2 shows, there were no differences in Kaplan-Meier survival curves between allopurinol users and non-users in both the one-year (log-rank test p = 0.84) and three-year landmark analysis (log-rank test p = 0.94). Hazard ratios (95% confidence interval) for all-cause mortality were 0.99 (0.87—1.12) in the one-year landmark analysis and 1.01 (0.92—1.09) in the three-year landmark analysis.

a)


Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Years from landmark

(b)

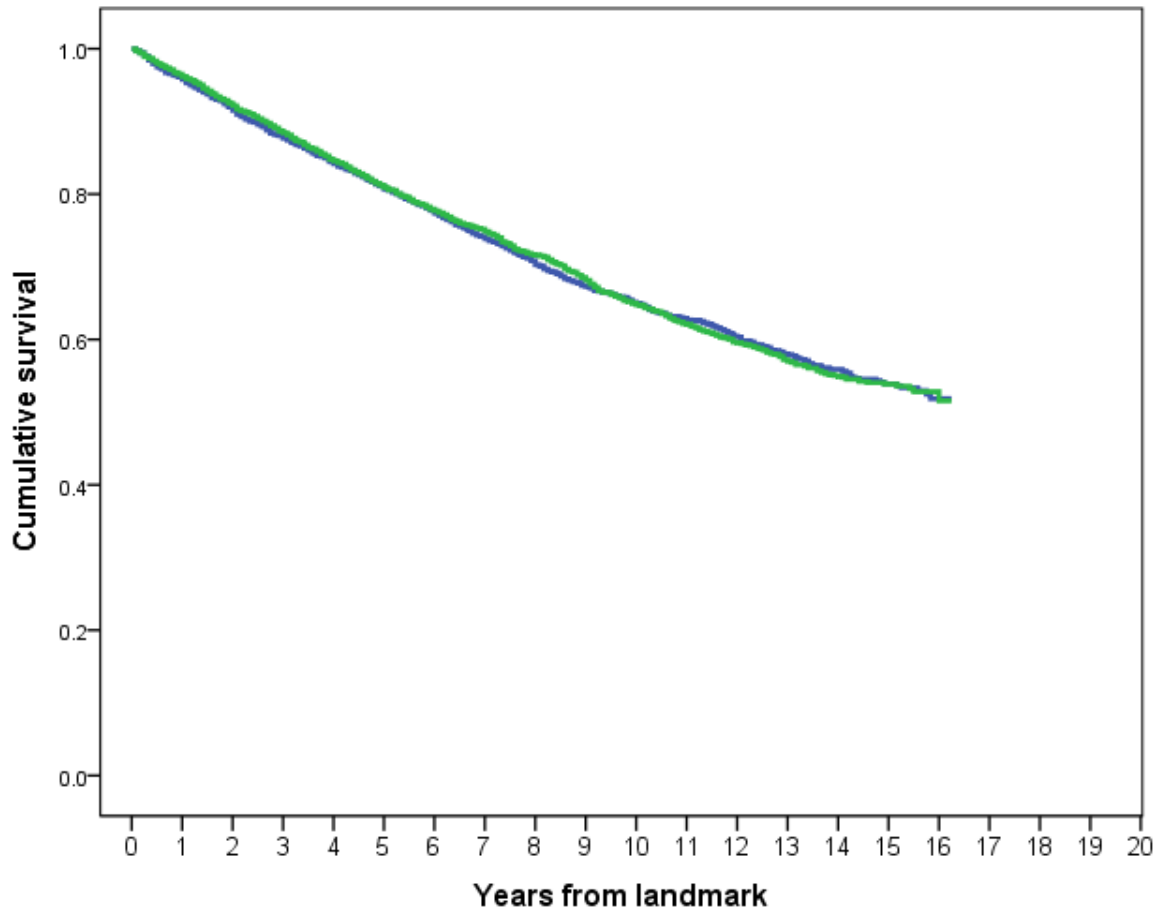


Figure 8-2 Kaplan-Meier survival plot for all-cause mortality in (a) one-year and (b) three-year landmark analysis. Blue line represents allopurinol users and green line represent nonusers.

8.3.4 **Propensity score adjustment analysis**

Similar results to the main analysis were obtained when propensity score adjustment was undertaken for all included patients in both the one-year and three-year landmark analysis. In the one-year landmark analysis, allopurinol was associated with an unadjusted hazard ratio (95% confidence interval) of 1.49 (1.32—1.67) and a propensity score adjusted hazard ratio (95% confidence interval of 1.02 (0.95—1.09) for all-cause mortality. In the three-year analysis, the unadjusted and propensity score-adjusted hazard ratios (95% confidence interval) were 1.35 (1.26—1.44) and 1.05 (0.93—1.20), respectively

8.4 Discussion

This population based study of people with incident gout in the UK found that having at least 6-months use of allopurinol within either one year or three years from initial diagnosis was associated with neither a beneficial nor adverse effect on long-term risk of all-cause mortality in patients who survived to the date of the landmark time point. This study confirms that concern over an increased mortality risk from serious side effects associated with allopurinol is unfounded. This real-world study in primary care in the UK provides reassurance that prescription of allopurinol for at least 6 months as early as one year after diagnosis seems safe in terms of long-term risk of death. Given the many established clinical benefits of allopurinol such neutral effects on all-cause mortality supports the use of allopurinol early in the course of gout to prevent long-term complications secondary to chronic hyperuricaemia.

In this study a well-defined population of incident gout patients was examined to determine whether allopurinol treatment influences all-cause mortality. This study is an observation study based on primary care data in which the date of allopurinol prescription largely lags behind the initial diagnosis of gout, with approximately one in four being treated within 12 months of diagnosis.(Chapters 5 and 6; (Kuo et al., 2013a) Using diagnosis date as an index date to start the follow up for a delayed treatment in a cohort study is prone to immortal time bias.(Weiss et al., 1983) Immortal time is defined as a period of follow-up in which the study outcome cannot

occur,(Levesque et al., 2010) which in this study is the period from the initial diagnosis to the date of completing 6-months of allopurinol. This period does not exist in the non-exposure group. If this issue is not considered, immortal time could confer a spurious survival advantage to the treatment group. Several methods have been devised to avoid this, including using a time-varying model or a landmark analysis as in this study.(Dafni, 2011) With prior knowledge that the cumulative probabilities for ULT prescription in UK primary care were 16.90%, 21.14%, 24.52% and 30.39% at 0, 1, 2, 3 and 5 years from diagnosis (unpublished data from Chapter 6), it was determined a priori that an exposure window of three years could capture over 80% of allopurinol users to prevent misclassification at longer term follow-up. However, because of the landmark analysis design patients who died within the exposure window were not considered in subsequent analysis. As a result 3,783 incident gout patients who died within the three-year exposure window were excluded. These excluded patients were older, had more comorbidities and were taking more prescriptions for other chronic conditions. The inclusion of these patients potentially could have biased the estimates. An analysis based on a shorter period of exposure window (one year), which excluded only one-third of patients compared to the three-year analysis, was also performed and found consistent results. Therefore, the findings of this study are not influenced by the length of the chosen exposure window.

Another important factor that could influence comparison of survival function between patients exposed and unexposed to allopurinol is ‘confounding by indication’, which is the result of non-

random allocation of treatment assignment.(Grobbee and Hoes, 1997) As shown in this study (Table 2 and Table 3) general practitioners tended to prescribe allopurinol for patients with more advanced age, more comorbidity and more polypharmacy. These patients also tended to have higher mortality. Therefore, an unadjusted model demonstrated a higher mortality risk in the allopurinol exposure group. Propensity score matching to balance the probability of being prescribed allopurinol in the exposure window was used to minimise this bias. Propensity score adjustment, as a single variable, was also used for the entire population to examine risk of death between patients exposed and unexposed to allopurinol. Analyses based on both methods produced the same neutral influence of allopurinol on long term risk of all-cause mortality. Therefore, the findings of this study suggest the importance of considering both immortal time bias and confounding by indication to demonstrate treatment effects in an observational study.

Several previous studies have attempted to measure the influence of allopurinol treatment on mortality but have reported conflicting results.(Malek et al., 2012, Wu et al., 2010, Wei et al., 2009, Luk et al., 2009, Struthers et al., 2002, Dubreuil et al., 2014) These studies in general ignored or only in part considered immortal time bias and confounding by indication. Immortal time bias generally causes spurious inflation of beneficial treatment effect due to the guaranteed period of survival in the treatment group by design. Conversely, confounding by indication in general favours the unexposed group because treated patients tend to have a poorer prognosis. For example, Málek et al. reported poorer survival in allopurinol treated patients in a cohort of

acute heart failure patients hospitalised in tertiary care heart centres but noted that allopurinol was an identifier of high-risk patients who obviously had a particularly bad prognosis.(Malek et al., 2012) Similarly Wu et al. found allopurinol users had a poorer prognosis but their survival was no different from untreated patients whose SUA levels were in the highest quintile, implying that allopurinol use serves as a 'surrogate marker' of severe hyperuricaemia.(Wu et al., 2010)

Immortal time bias is more difficult to identify than confounding by indication. For example, Luk et al. reported that allopurinol use was associated with a beneficial effect on mortality in a hyperuricaemic population by comparing survival between users and non-users. However, allopurinol users commenced follow-up from the time of incident allopurinol use (index date), at which time they had survived from the date of first documentation of hyperuricaemia, whereas the follow-up of non-users could have been as early as the date of first documentation of hyperuricaemia. Although they matched the index date between users and non-users, it did not mean that they matched the time from the diagnosis of hyperuricaemia to the index date between the two groups. Allopurinol users were still more likely to have spurious survival advantage because by design they had to survive to the date of incident allopurinol use in order to be assigned as 'cases'. The more recent study by Dubreuil et al, using The Health Improvement Network (THIN) database in the UK, also reported beneficial survival effect related to allopurinol use.(Dubreuil et al., 2014) Their conclusions, however, possibly suffered from immortal time bias because the necessity of allopurinol users to survive from cohort entry (date of hyperuricaemia)

to allopurinol prescription was not required for non-users. The authors used the Greedy matching approach to randomly select a date from the same accrual block (6 months per block) to approximately match the index date between users and non-users. Again, the time to the index date was not matched and the immortal time period is more likely to be longer in the user group due to the delayed allopurinol prescription. In such a situation, the allopurinol users have a survival advantage which has nothing to do with the allopurinol exposure. Therefore without tackling immortal time bias by design (such as using landmark analysis) or explicitly modelling the timing of exposure (such as using time dependent methods) biased estimate can inevitably occur.(Beyersmann et al., 2008) This is a very common bias in cohort studies. For example, the finding suggested 4-year survival advantage for Oscar winners over their less recognised peers(Redelmeier and Singh, 2001) was largely due to immortal time bias and that there was no statistical difference between winners and their peers once this bias was taken into consideration.(Sylvestre et al., 2006) In order to control immortal time bias in the current study a landmark analysis was undertaken which by design implemented a fixed 'exposure window' for both allopurinol users and non-users and therefore avoided inadvertent survival benefits for allopurinol users.(Dafni, 2011) The use of landmark analysis and propensity scores helped mitigate immortal time bias and confounding by indication in this study. Since this study was based on a well-defined cohort of incident gout patients, the results are more applicable to the

full spectrum of gout patients in the primary care setting. Further study should be undertaken for allopurinol use in other settings.

There are potential limitations to this study. Firstly, there is possible misclassification bias since the identification of gout patients was based on diagnoses made by general practitioners, rather than according to American College of Rheumatology(Wallace et al., 1977) or Rome(Kellgren JH, 1963) classification criteria or to the 'gold standard' of urate crystal identification. However, the validity of gout diagnosis in the CPRD has been investigated and found to be high.(Meier and Jick, 1997) Secondly, the use of landmarks at one year and three years means that the findings that allopurinol confers a neutral effect on all-cause mortality only applies to patients who are alive at these two landmarks time points. In addition, the case definition of allopurinol use is a minimal of 6-month prescription of allopurinol. Whether longer allopurinol use confers different effects on all-cause death requires further study. Also, although many factors were included for estimation of propensity score, there may be other unaccounted factors that may influence the probability of a patient with gout being prescribed allopurinol. One possible factor that is hard to measure is the practitioners' knowledge and attitude towards gout management. However, this study did consider general practice variation in the model, which may in part reflect individual practitioner preferences.

In conclusion, this propensity score matched landmark analysis in a population of incident gout patients in the UK primary care setting found a neutral effect on the risk of all-cause mortality from a minimal 6-month allopurinol use at one year and at three years after initial diagnosis of gout on the risk of all-cause mortality. This study provides reassurance for prescription of allopurinol in gout patients early in their disease course to prevent untoward consequences of chronic uncontrolled hyperuricaemia. Further studies should be undertaken for potential effects of allopurinol on mortality in selected patients such as those with chronic heart failure.

CHAPTER 9. Overall Discussion

This thesis focused on the epidemiology of gout in the UK and Taiwan. Based on two nationally representative databases, six different studies were conducted to understand and compare various aspects of gout epidemiology, including ascertainment of gout prevalence and incidence, risk factors, comorbidities, prognosis, mortality and medication use, all of which are of clinical relevance. The main findings are as follows:

1. Gout affects 1 in 40 people in the UK, and 1 in 16 in Taiwan;

2. The disease is more common in men than in women in both nations;

3. It increases with age, starting from age 20 in the UK and earlier in Taiwan;

4. Although the recent prevalence in the UK has increased rapidly, it has remained unchanged in Taiwan;

5. Although the recent incidence in the UK has remained unchanged, it has reduced in Taiwan;

6. Management of gout remains consistently poor in both countries;

7. Gout clusters in families in Taiwan which is related to both genetic predisposition and shared environment;

8. Gout is a signal of many other conditions such as coronary heart diseases, diabetes and renal failure;

9. While gout is associated with increased mortality, allopurinol has a neutral effect on longevity.

Both prevalence and incidence are higher in Taiwan than in the UK. Although it is very difficult to compare prevalence between countries directly, this thesis tries to use similar case definitions and methodology to facilitate comparison. There are still some differences in case definition of gout in the UK and Taiwan studies in this thesis. Among them, the most important one is that the UK study did not restrict length of observation period but the Taiwan study restricted the length to 10 years. The difference in restriction is due to the different database structure between the CPRD and NHIRD. Therefore, the prevalence estimate in Taiwan could be slightly underestimated because patients with gout records 10 years before the index year were not included. On the other hand, this thesis considers gout as a chronic disease. Therefore there is no “exit” of existing gout patients from the prevalent patient pool but as Chapter 4 shows, there is still 16.26% of

gout patients who had no further acute attacks 10 years after initial diagnosis. Whether to include patients with long-term "remission" in prevalence and incidence estimation is a matter of debate. Nevertheless, gout is still the most common inflammatory arthritis even when these patients were excluded from analysis.

Both populations in the UK and Taiwan demonstrate that gout increases with age and is more common in men. In addition, the onset of gout is earlier in men than in women. Gout is very rare in those under the age of 20 years, then increases with age but starts reducing after the age of 80 years. There is no significant rise in gout prevalence in women until 50 years of age, coinciding with the age of the menopause. In men the prevalence of gout increased linearly with age until the age of 80 years. This pattern is consistent in the UK and Taiwan. However, in Taiwan gout incidence in young men increases rapidly with age until the age of 40, which is in contrast to the pattern in the UK. It is clear that the onset age of gout is similar in women in the UK and Taiwan but that the onset age is much earlier in gout patients in Taiwan than in the UK (chapter 5).

The epidemiology of gout shows a substantial regional variation both between and within countries. For example, the prevalence of gout was 2.5 fold higher in Taiwan than in the UK. Several potential factors may account for the obvious differences in gout

epidemiology. Firstly, the ethnic composition is clearly different. The UK population is primarily composed of European descendants and the Taiwan population is a mixture of Han Chinese descendants and indigenous people who are genetically related to gout-laden Pacific Islanders. Secondly, Taiwan has become increasingly socioeconomically westernised in recent years, including marked changes in diet, which could explain the lower prevalence of gout in the 1990s than estimates in the 2000s. Therefore, an increasingly westernised diet in a population with a genetic background that is particularly prone to hyperuricaemia could lead to the current high prevalence of gout in Taiwan.

Although Taiwan has a higher prevalence than the UK, the prevalence in Taiwan appears not to have changed in the past decade. This may be because of the reduction in incidence (less inputs), or improvement of management (more cures). The latter is less likely as there was no clear evidence that the care for gout in Taiwan has been improving, whereas the incidence clearly has reduced. In contrast, although the prevalence in the UK is lower, it keeps rising at a rate of 4% annually. This may be due to both the increase in incidence (inputs) and poor management (less cures). This study found that the management of gout in the UK remains poor.

Within each country, the distribution of gout was also not uniform. The causes of this uneven distribution of gout reflect the regional differences in both genetic/racial and environmental factors. As suggested in Chapter 3, both genetic and environmental factors contribute to the variation in gout occurrence at a population levels but genetic factors account for less than one-third of such variations. Previous genetic studies have documented that the difference in susceptibility to gout is partly controlled by genetic differences. For instance, genetic variation in the ABCG2 gene, encoding a uric acid transporter, is a strong factor in determining gout susceptibility in New Zealand Pacific Islanders and Caucasians, but not in the Māori population.(Phipps-Green et al., 2010) Conversely, polymorphism of SLC2A7 gene have been found to play an important role in the development of gout in Māori, Pacific Island and Caucasian people(Hollis-Moffatt et al., 2009) but not in Han Chinese, Solomon Island(Tu et al., 2010) and Japanese people.(Urano et al., 2010) Given that the indigenous people in Taiwan are genetically related to gout-stricken Polynesians and Oceanic Pacific Islanders, it is not surprising that gout prevalence and incidence were highest in regions where indigenous people cluster. In addition, the prevalence and incidence of alcoholism were very high in indigenous people in Taiwan, (Cheng and Chen, 1995, Lee et al., 2013, Chen and Cheng, 1997) which further increases the risk of gout in these people. Therefore, both genetic and

environmental factors may account for differences in gout epidemiology between Han Chinese and indigenous people in Taiwan.

Despite differing preferences for individual ULT, with uricosuric agents being favoured in Taiwan and allopurinol being almost the exclusive ULT in the UK, the management of gout and prescription of ULT appears to be equally poor in both countries. In general, less than one-third of prevalent gout patients were prescribed ULT. The message that gout patients are managed poorly is reinforced by the finding that most incident gout patient would be eligible for ULT shortly after their diagnosis. An initiative to improve gout management therefore appears warranted. The publication of gout management guidelines is not sufficient, as is evident from the stationary pattern of gout management in both countries despite the publication of national and international guidelines of gout management. Since the prescription of ULT in primary care in the UK appears to be generally random rather than strategic (Chapter 6) strategies focusing on more active GP education to improve interest and quality of gout patient care seem appropriate. One of the practitioner barriers to optimal gout management through use of ULT is the concern over rare but potentially serious adverse drug reaction associated with allopurinol. However, the data presented in Chapter 8 suggests that such a concern is not warranted since allopurinol has a neutral effect on all-cause mortality (Chapter 8).

Comorbidities are commonly present at the time of diagnosis of. These findings support comprehensive screening for comorbidities as part of the routine assessment of incident gout patients. Treatment decisions should take into account such comorbidities for three reasons:

1. Gout-specific drugs may be beneficial or deleterious for patients with comorbidities. Allopurinol has been reported to be beneficial for some cardiovascular diseases, including heart failure, stroke, hypertension and ischemic heart diseases.(Kelkar et al., 2011) However, these beneficial effects need more rigorous clinical scrutiny. Some of the adverse effects of gout-specific drugs are especially toxic to patients with certain comorbidities. NSAIDs for instance, should be avoided in patients with peptic ulcers,(Lanas, 2010) renal(Gooch et al., 2007) and cardiovascular diseases(Trelle et al., 2011) and uriscourics are relatively contra-indicated in patients at risk of urolithiasis.(Perez-Ruiz et al., 2010)
2. Gout-specific drugs may need dose-adjustment in patients with certain comorbidities. For example, adjustment of allopurinol dose according to renal function should be considered in patients with chronic kidney diseases.(Thurston et al., 2013)

3. Gout-specific drugs may have an interaction with other medications. For example, the dose of azathioprine should be reduced one-third in patients receiving allopurinol to prevent severe immunosuppression.(Gearry et al., 2010)

A comprehensive screening for comorbidities at diagnosis in gout patients seem warranted. It should be noted that the majority of gout patients have one or more comorbidities at diagnosis. Therefore, treatment decisions should be based not just on the status of the patient's gout but also on the presence of comorbidities.

This thesis explored the utility of the CPRD and NHIRD for research into gout and demonstrated that both databases are an ideal resource for epidemiological research, especially in terms of providing data on real-life clinical practices in primary care. Both databases are further strengthened by linkage to other sources of information. The CPRD, for instance, has multiple linkages to external data sources, such as the cancer registry and myocardial infarction audit (MINAP). More detailed research on the associations between gout and cancer or myocardial infarction can be performed using these linkages. Similarly, the NHIRD as a claims based database contains extensive information for pharmaco-economic research and in addition comprehensive data on secondary care are

available for all beneficiaries. Therefore hospital treatment and procedures, such as total joint replacement, can be studied reliably using the NHIRD.

Nevertheless a more detailed validation of both the Read and ICD-9 codes for gout could greatly improve the reliability of both the CPRD and NHIRD in gout research. The CPRD has been validated for gout diagnosis, but the only previous study on this was small and involved just 38 gout patients who were prescribed anti-ulcer drugs.(Meier and Jick, 1997) In addition, that study did not examine the accuracy of incident gout diagnosis. Validation of the diagnosis of gout has not been undertaken in the NHIRD. Therefore studies that provide better information on the validity of the entered diagnosis of gout in these databases would be welcomed.

Some important questions have been addressed in this thesis but others still remain. For comorbidities, this study documented broadly that gout patients have higher risk of comorbidities at diagnosis and risk of some comorbidities also increased after gout diagnosis. More detailed studies to confirm and to further explore these associations are required. For example, the association between gout and hypothyroidism is interesting and merits further research. Also gout is associated with a higher risk of osteoarthritis but

whether gout is associated with a higher risk of total knee joint replacement and whether implant survival is shorter in patients with gout has not yet been explored.

The effects of ULT on various outcomes should also be explored further. For example, whether allopurinol decreases the risk of kidney stones in gout patients has not been examined. Also, uricosuric agents increase kidney excretion of urate and theoretically should increase the risk of urolithiasis but there is no firm evidence regarding ULT and urolithiasis. Although allopurinol was found to have a neutral effect on all-cause mortality, whether the relative composition of the causes of mortality changes after the use of ULT in gout patients is unknown.

There are several strengths to the work in this thesis. Firstly, this thesis used large databases that are representative of the general population of the UK and Taiwan, so selection bias is controlled to a minimum. Secondly, the data sources are recorded by general practitioners directly and therefore the results derived reflect the real-world medical practice. The advice and recommendations that follow from the study results could be readily implemented in the first-line care of gout patients. Thirdly, the representativeness of both databases and the similarity of methods used facilitate international comparison of epidemiological parameters. Fourthly, this thesis contains

several novel methodologies, including the use of an administrative database to study population genetics that could potentially facilitate the conduct of similar studies in other diseases.

Several limitations should be noted. Firstly, the case definition of gout in this study is not based on published classification criteria but upon physician diagnosis. Prevalence and incidence estimates could potentially be affected by misclassification. However, several studies have validated the diagnostic codes of gout or the documented accuracy of gout diagnosis in primary care. Nevertheless in general the estimates of gout prevalence and incidence could be slightly overestimated. Misclassification could also affect relative measures to a lesser degree since extensive differential misclassification is less likely to occur. Secondly, both databases are limited by their respective inherent factors such as sampling units, coverage years and the extent of available data. For instance, despite the NHIRD containing data from the entire population of Taiwan, only data in the period between 1995 and 2010 are available. The CPRD is limited by the mobility of the participating patients who can move in and out of registered practices thus limiting available data to periods of active registration. The estimates of prevalence and incidence of both databases therefore are “period” estimates, rather than life time estimates. Thirdly, all the results are conditional on the pattern of medical practices in both

countries. For example, the vast majority of gout patients were under-treated by ULT. Therefore, outcome estimates such as survival reflect a low ULT prescription rate. It would be difficult to extrapolate the results to patients who receive optimal medical care.

In conclusion, the CPRD and NHIRD have been used to successfully address several important epidemiological and clinical research questions. This thesis provides evidence for the current epidemiology of gout in the UK and Taiwan as well as other important aspects including familial aggregation, comorbidities, treatment and mortality of gout all of which address clinically relevant questions. The methodologies established during this thesis lay the foundation for future research in gout using both these electronic databases.

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