The population burden of gout and urate in Western Sweden

Prevalence, incidence, comorbidities, and association with cardiovascular disease

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Gothenburg 2021

Cover illustration by Panagiota Drivelegka

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ISBN 978-91-8009-486-3 (PRINT)
ISBN 978-91-8009-487-0 (PDF)

Printed in Borås, Sweden 2021
Printed by Stema Specialtryck AB

To Marietta, Dimitris, and Nikos

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ABSTRACT

Background: Gout is the most common type of inflammatory arthritis and is associated with several comorbidities and an increased risk of cardiovascular disease (CVD). However, data on the epidemiology and comorbidity patterns of gout in Sweden are scarce, and whether its association with CVD is causal or not, is not clear.

Objectives: This thesis aimed to study: I. The incidence and prevalence of gout, and use of urate lowering treatment (ULT) in Western Sweden in 2012; II. The comorbidity pattern of gout at the time of first diagnosis; III. The association between urate levels and markers of subclinical atherosclerosis; IV. The risk of first-time acute coronary syndrome (ACS) in patients with incident gout, compared to the general population.

Methods: Part I. By using data from the population-based register VEGA, we identified all patients with ≥1 ICD-coded diagnosis of gout at both primary and specialized health care in Western Sweden. Their dispensed prescriptions were identified through linkage with Prescribed Drug Register. Part II. Cases with first ICD-coded gout diagnosis in the period 2006-2012 were matched to population controls on age, sex, and county at first gout diagnosis. We estimated crude, and age-standardized prevalence and prevalence ratios. Part III. Participants of the pilot Swedish CArdioPulmonary bioImage Study (SCAPIS) underwent radiographic investigations for estimation of Coronary Artery Calcification score (CAC), carotid intima-media thickness (CIMT) and carotid plaque score. Their association with urate levels was assessed with logistic regression analysis. Part IV. Cohorts of patients with incident gout and population controls followed prospectively. Incidence rates (IRs), incidence rate ratios (IRRs), and hazard ratios (HRs) were used for risk estimations.

Results: Part I. The prevalence of gout in adults aged ≥ 20 years in 2012 was 1.8% and the incidence was 190 cases per 100,000 person-years. The incidence increased by 50% from 2005 to 2012. Only 42% of gout patients received ULT in 2012. Part II. At the time of first diagnosis, 77% of gout patients had at least one comorbidity, as compared to 56% of the controls. Women with gout were six years older and had higher occurrence of most comorbidities, compared to men. Part III. Serum urate levels >308 μmol/L were associated with the presence of CAC in men (p-value <0.05), but not in women, whereas urate levels were not associated with CIMT or carotid plaques in either men or women. Part IV. Patients with incident gout were at increased risk of first-time ACS, compared to the general population (HR, 1.44; 95%CI, 1.33-1.56). After adjustments for traditional cardiovascular risk factors, this risk was attenuated, but remained significant (HR, 1.15; 95%CI, 1.06-1.25).

Conclusions: Gout has an increasing incidence in Western Sweden, but only a minority of gout patients received ULT. The comorbidity burden at the time of first gout diagnosis is high, particularly in women. Urate may be associated with coronary calcification in men. Gout patients are at increased risk of first-time ACS, which is mainly depending on the underlying comorbidities and, to a lesser extent, on gout itself. Our results imply the importance of improvements in the management of gout and its comorbidities in the Swedish health care system, for increased longevity and better quality of life for these patients.

Keywords: gout, epidemiology, comorbidities, cardiovascular disease

ISBN 978-91-629-486-3 (PRINT)
ISBN 978-91-629-487-0 (PDF)

SAMMANFATTNING PÅ SVENSKA

Bakgrund: Gikt är den vanligaste inflammatoriska ledsjukdomen och är associerad med hög grad av samsjuklighet och en ökad risk för hjärt-kärlsjukdom. Förekomst, behandling och samsjuklighet av gikt i Västra Götaland har inte studerats tidigare, och huruvida det finns orsakssamband mellan gikt och hjärt-kärlsjukdomar, såsom hjärtinfarkt, är inte klartlagt.

Syfte: Syftet med denna avhandling har varit att studera: I. Förekomst av gikt i Västra Götaland och användning av uratsänkande behandling (ULT); II. Förekomst av samsjuklighet vid första giktdiagnosen; III. Association mellan uratnivåer och markörer för ateroskleros i halskärl och kranskärl; IV. Risk för förstagångs akut koronart syndrom (AKS) hos patienter med nydiagnostiserad gikt jämfört med den allmänna befolkningen.

Metoder: Studierna I, II, och IV grundar sig på uppgifterna insamlade från regionala och nationella register. Från Västra Götalands vårdkonsumptionsdatabas utsöktes alla patienter med registrerad giktdiagnos inom primär- och specialistvård, samt de andra diagnoserna som var avsedda att studeras. Kontroller (studie II, IV) utsöktes från befolkningsregistret. Studie III grundar sig på uppgifterna inhämtade från pilotsudien av SCAPIS (Swedish CArdioPulmonary bioImage Study). Patienterna utreddes bland annat med ultraljud av halskärlen och datortomografi av kranskärlen och lämnade blodprov (urat).

Resultat: Studie I. Förekomst av gikt i Västra Götaland 2012 beräknades till 1,8% och incidensen var 190 fall per 100,000 personår. Endast 42% av giktpatienterna hade fått ULT under 2012. Studie II. Patienter med gikt hade en ökad förekomst av samsjuklighet vid den första giktdiagnosen i jamförelse med den allmäna befolkningen. Kvinnor med gikt var äldre och hade högre förekomst av samsjuklighet i jamförelse med män. Studie III. Uratnivåerna var associerade med förekomst av åderförkalkningar i kranskärlen hos män, men inte hos kvinnor. Studie IV. Patienter med gikt hade ökad risk för förstagångs AKS i jamförelse med den allmänna befolkningen.

Slutsats: Gikt har hög förekomst i Västra Götaland, men är otillräckligt behandlad. Förekomst av samsjuklighet är hög bland giktpatienterna, framförallt hos kvinnor. Risken för förstagångs AKS är högre för patienter med gikt i jamförelse med den allmänna befokningen, vilket huvudsakligen beror på de underliggande sjukdomarna men också på gikt i sig, fast i mindre utsträckning. Urat kan vara associerat med åderförkalkningar i kranskärlen hos män. Våra resultat poängterar vikten av förbättrat omhändertagande och

behandling av giktsjukdom och dess samsjuklighet i den Svenska sjukvården för att uppnå en bättre livskvalitet för dessa patienter.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Dehlin M, **Drivelegka P**, Sigurdardottir V, Svärd A, Jacobsson LTH. Incidence and prevalence of gout in Western Sweden. Arthritis Research & Therapy 2016; 18:164

II. **Drivelegka P**, Sigurdardottir V, Svärd A, Jacobsson LTH, Dehlin M. Comorbidity in gout at the time of first diagnosis: sex differences that may have implications for dosing of urate lowering therapy. Arthritis Research & Therapy 2018; 20:108

III. **Drivelegka P**, Forsblad-d'Elia H, Angerås O, Bergström G, Schmidt C, Jacobsson LTH, Dehlin M. Association between serum level of urate and subclinical atherosclerosis: results from the SCAPIS Pilot. Arthritis Research & Therapy 2020; 22:37

IV. **Drivelegka P**, Jacobsson LTH, Lindström U, Bengtsson K, Dehlin M. Incident gout and risk of first-time acute coronary syndrome: a prospective, population-based, cohort study in Sweden. Manuscript.

CONTENT

ABBREVIATIONS

ACR	American College of Rheumatology
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
ATC	Anatomical Therapeutical Chemical Classification system
ATP	Adenosine Triphosphate
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CI	Confidence Interval
CIMT	Carotid Intima-Media Thickness
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
DASH	Dietary Approaches to Stop Hypertension diet
DECT	Dual-Energy Computed Tomography
EULAR	European League Against Rheumatism
GBD	Global Burden of Disease
GWAS	Genome-wide Association Study
HF	Heart Failure

HGPRT	Hypoxanthine Guanine Phosphoribosyl Transferase
HPFS	Health Professionals Follow-up Study
HR	Hazard Ratio
hs-CRP	High sensitivity C-reactive Protein
ICD	International Classification of Disease
IL	Interleukin
IR	Incidence Rate
IRR	Incidence Rate Ratio
LDL	Low Density Lipoprotein
MI	Myocardial Infarction
MR	Mendelian Randomization
MSU	Monosodium Urate
MTP	Metatarsophalangeal
NHANES	National Health and Nutrition Examination Survey
NO	Nitric Oxide
NPV	Negative Predictive Value
NSAID	Non-Steroidal Anti-Inflammatory Drug
PD	Parkinson's Disease
PR	Prevalence Ratio
PRPP	5′-phosphoribosyl 1- pyrophosphate
PPV	Positive Predictive Value

PVD	Peripheral Vascular Disease
RCT	Randomized Clinical Trial
RR	Relative Risk
ROS	Reactive Oxygen Species
SCAPIS	Swedish CArdioPulmonary bioImage Study
SF	Synovial Fluid
SNP	Single Nucleotide Polymorphism
T2T	Treat-to-target
UK	United Kingdom
ULT	Urate Lowering Treatment
US	United States
VSC	Vascular Smooth Cell
XO	Xanthine Oxidase

1 INTRODUCTION

Gout and urate through the ages

With origins in antiquity, gout is among the diseases with the oldest documentation, and one of few times in history when a disease is closely related with lifestyle and social status.

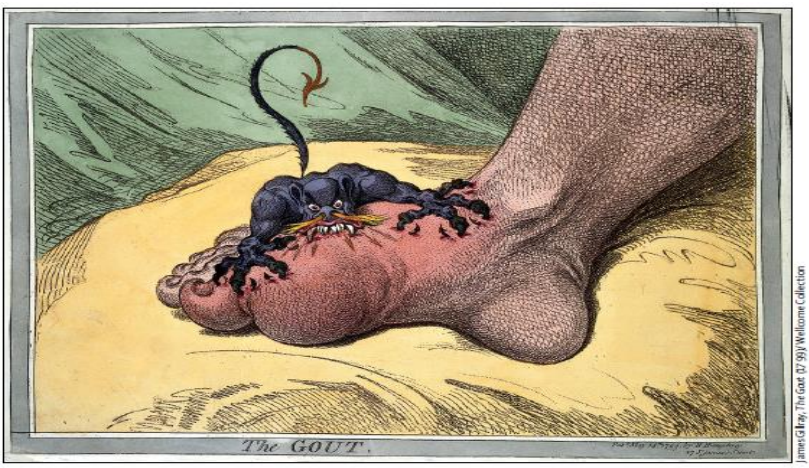
The oldest historical record of urate deposition was found in Egyptian mummy dating back 4,000 years (1). However, a more accurate description of the disease begins with Hippocrates (460-370 BC) (2). His observations about the gout are included in his *Aphorisms,* and 2,500 years later, they are still true: 'Eunuchs do not take the gout nor become bald', 'A woman does not take the gout unless her menses is stopped', 'A young man does not take the gout until he indulges in coitus', 'In gouty affections, inflammation subsides within 40 days' (3). In ancient Greece, gout was called 'podagra', from *pous* meaning a foot and *agra* a seizure, signifying the involvement of the first metatarsophalangeal joint. Hippocrates distinguished gout from the other forms of arthritis and noted an association with a lifestyle, that (at that time) could only be afforded by the wealthy, referring to it as 'the arthritis of the rich'. This perception was hold for centuries, as seen in a comment in the *London Times* in 1900, 'The common cold is well named−but the gout seems instantly to raise the patient's social status' (4). The first description of tophi, which means a loose, porous kind of stone, comes from Galen. The term 'gout', primarily used by the Dominican monk Randolphus of Bocking in the 13th century, was derived from the Latin word *gutta*, meaning a drop, and referred to the humoral theory, that an excess of one of the four 'humors' would 'drop' into a joint and cause pain (4).

In the 17th century, a Dutch biologist Antony van Leeuwenhoek, was the first to describe the crystalline nature of tophi; however, their chemical composition was not known at that time (5). Around the same time, the English physician Thomas Sydenham, also known as 'the English Hippocrates', described in detail the symptoms of the disease based on his own experience, as he suffered from gout. Urate was discovered by the Swedish chemist Carl Wilhelm Scheele in 1776. Eighty years later, Sir Alfred Baring Garrod developed the first chemical test, the 'thread test', measuring urate in urine and serum, and stated that patients with gout have elevated urate levels, which was probably a cause of the disease and not a symptom (6). Sir Archibald Garrod, the son of

Alfred Garrod, suggested in 1931 that gout was a result of ‘inborn errors of metabolism’, introducing the era of molecular medicine.

Treatment of gout is another important chapter in its history. The autumn crocus (Colchicum autumnale), the plant source of colchicine, was used for treatment of joint swelling as early as in 1500 BC, but its first use in the treatment of gout is attributed to the Byzantine physician Alexander of Tralles in the sixth century AD (4). However, Thomas Sydenham rejected all medications that were purgatives and colchicine was not used for about 150 years. Probenecid was initially introduced as an inhibitor of the renal excretion of penicillin in 1950, but later was found to have uricosuric properties and came into the treatment of gout. Perhaps the most important part in the treatment of gout was the development of the first xanthine oxidase inhibitor, allopurinol. George Hitchings and Gertrude Eliot were awarded the Nobel prize in 1988 for the development of allopurinol and six other drugs.

Gout has influenced the history through the ages with many famous personalities included in the list of its sufferers, such as Benjamin Franklin, Thomas Jefferson, Alexander the Great, Leonardo da Vinci, Isaac Newton, John Hunter, and Thomas Sydenham. Franklin was so affected by gout that he was carried by convicts to the Constitutional Convention in a sedan chair (1). In the 21st century gout is no longer the ‘disease of kings’, but the most common inflammatory arthritis, where the role of genetics has become more prominent, and lifestyle seems to have less influence.



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Epidemiology of gout

Gout is the most common inflammatory arthritis worldwide. The prevalence and incidence of gout varies among the studies, probably due to different genetic and environmental factors, gout definitions, geographic locations, different ethnicity groups, and study settings. Furthermore, lack of data from many countries, the long asymptomatic periods between gout attacks, and the fact that not all gout patients seek medical advice, can bias the estimations of the epidemiology of gout and should be considered as limitations of the current available studies.

Prevalence of gout

The prevalence of gout varies a lot between the countries (Figure 1). A meta-analysis of 71 studies published between 1962 and 2012 found a pooled global prevalence of 0.6%, although there was a high level of clinical and methodological heterogeneity between the studies (7).

The highest prevalence of gout has been reported in Oceania, particularly in indigenous people (Maori, Aboriginals). In 2019, the prevalence of gout in Aotearoa New Zealand was 8.5% for Maori, 14.8% for Pasifica peoples, and 4.7% for other New Zealand European (8). Maori and Pasifika peoples develop gout at a younger age (mean age, 39 and 34 respectively), as compared to New Zealand European (mean age, 46) (8). In Australia, the prevalence of gout varies from 4.5-6.8% in studies with a self-reported definition of gout, to 1.5-2.9% in studies based on electronic records or wastewater estimation of allopurinol consumption (9).

The prevalence of gout in North America is also high. The overall prevalence in adults in US according to National Health and Nutrition Examination Survey (NHANES) 2015-2016 was 3.9% (10), whereas in British Columbia, Canada it was 3.8% in 2012 (11).

In Europe, Greece has the highest reported prevalence of gout, 4.75% of the adult population (12). In UK, the gout prevalence in 2012 was 2.49% in the entire population based on register data (13), whereas in Germany it was 1.4% in 2000-2005 (14). In France (15) and Italy (16) the reported prevalence of gout was lower, 0.9% in 2013 and 0.91% in 2009, respectively, whereas the

lowest gout prevalence in Europe has been reported from Portugal (17) and the Czech Republic (0.3% in both countries) (18).

In Sweden, data prior to this thesis were scarce (Figure 1), with only one study reporting a prevalence of 0.55% in Stockholm in 2013-2014 (all ages), based on register data (19). In Norway, using three different methodological strategies (survey of 10,000 people not living in institutions, national reimbursement register for primary care, or national register for specialist care), the reported prevalence of gout in 2012 was varying between 0.09-0.7% in males and 0.02-0.39% in females (20). In Denmark, the prevalence of gout in 1995-2015 was 0.68%, using data from nationwide specialist care register (21).

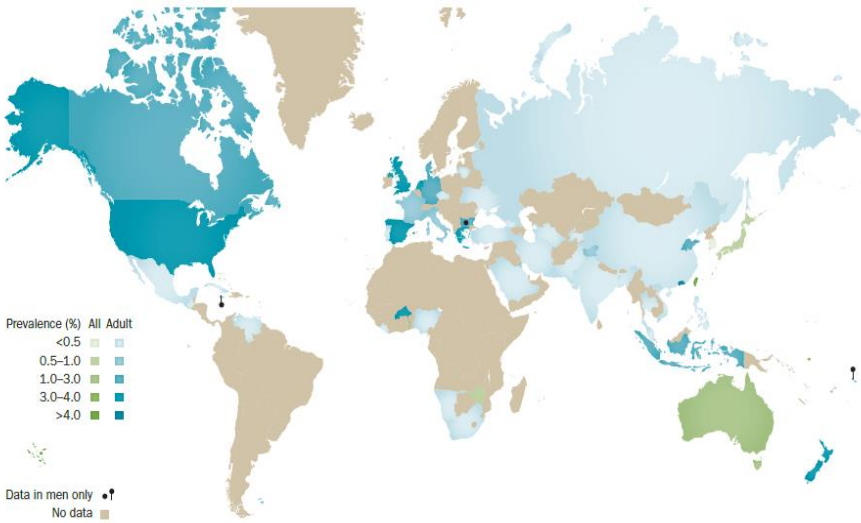


Figure 1. The prevalence of gout across the world until 2015, with no available data for Sweden. Reproduced with permission from Kuo, C.-F. et al. Nat. Rev. Rheumatol. 11, 649–662 (2015).

In Asia, the prevalence of gout is varying with low estimates in China (pooled prevalence of 1.1% in 2000-2014) and South Korea (0.76% in 2015) (22, 23), and higher estimates in Taiwan and Singapore. In Taiwan, the prevalence of

gout was 4.92% in 2004 (24), based on National Health Insurance Research Database, and in Singapore it was 4.1% in the age group 45-74 in 1999-2004 (25). The lowest estimates have been reported in the developing world, although data are scarce (15).

However, in all countries, the prevalence of gout increases with increasing age, and is higher in men than in women (3-4:1) (15). Furthermore, the mean age for gout onset was found to be lower in men than in women (21). Data about differences in prevalence between urban and rural areas have been conflicting, with some studies showing lower risk of gout in rural residents (26), whereas other did not (13, 16).

The prevalence of gout seems to be increasing in many countries. In South Korea, it increased from 0.35% in 2007 to 0.76% in 2015, and they predicted a further increase to 1.66% by 2025 (23). The same trend has been reported from studies in Australia (27) and New Zealand (28). However, the prevalence of gout has remained stable in US in the period 2007-2016, and in Taiwan since 2006 (10, 15).

Incidence of gout

The incidence of gout has been examined by fewer studies (Table 1). Overall, gout incidence is increasing in many countries, is higher in men than in women, and increases with increasing age (15, 29).

In Nordic countries, data on incidence of gout are scarce. In Sweden, the study of Wändell *et al* showed an incidence of 0.16% in Stockholm in 2014 (19). In Finland, a study conducted in 1974 reported an incidence of 12 cases per 100,000 person-years in men and no incident cases in women (30), whereas in Denmark it was 0.58 cases per 1,000 person-years in 2015, based on register data.

Table 1. Incidence of gout in several countries.

Country	Author	Case definition	Study period	Incidence*
New Zealand	Brauer (31)	Self-reported	1962-1974	Men: 9.4 Women: 3.9
US	Abbott (32)	Clinical examination	1948-1980	Men: 1.6 Women: 0.25
	Choi (33)	Self-reported	1986-1998	Men: 1.52
	Elfishawi (34)	Classification criteria	1989-1992 2009-2010	1989-1992: 0.67 2009-2010: 1.37
Canada	Rai (11)	Physician diagnosis	2012	2.90
UK	Kuo (13)	Physician diagnosis	1997-2012	1.77
Italy	Trifiro (16)	Physician diagnosis	2005-2009	0.95
Sweden	Wändell (19)	Physician diagnosis	2014	1.60
Denmark	Zobbe (21)	Physician diagnosis	2015	0.58
Finland	Isomäki (30)	Physician diagnosis	1974	0.06
Taiwan	Kuo (35)	Physician diagnosis	2010	2.74
South Korea	Kim (23)	Physician diagnosis	2015	1.94

*per 1,000 person-years

Definition of gout

Gout is an inflammatory arthritis caused by deposition of monosodium urate crystals (MSU) in the synovial fluid (SF) and other tissues. Elevated urate levels are essential for the development of gout.

Gold standard

Detection of MSU crystals in SF or tophus aspirates has been proposed as the gold standard for the diagnosis of gout, as it has 100% specificity (36). MSU crystals can be detected in both symptomatic and asymptomatic joints, and thus, a diagnosis of gout can be made even during the intercritical period (intercritical gout) (36).

Clinical diagnosis

Arthrocentesis is not always feasible in clinical practices, especially at primary care or emergency departments. In these situations, it is important for the treating physician to be able to identify patients with gout based on common clinical features. Janssens *et al* developed a clinical prediction model for the diagnosis of acute gout based on a limited number of signs and symptoms, and urate levels (Table 2) (37). Validation of this model demonstrated a positive predictive value (PPV) of 0.87 for a score of ≥8 points, and a negative predictive value (NPV) of 0.95 for a score of ≤4 points (38).

Table 2. Janssens model for the diagnosis of gout.

Variable	Points
Male sex	2
Previous patient-reported arthritis attack	2
Onset within 1 day	0.5
Joint redness	1.0
MTP1 involvement	2.5
Hypertension or ≥1 cardiovascular disease*	1.5
Serum urate level > 350 µmol/L (5.88 mg/dL)	3.5

* Angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease.
MTP, metatarsophalangeal

≥ 8 points: high possibility of gout
> 4 to <8: synovial fluid analysis is recommended
≤ 4: low possibility of gout

Imaging

When SF analysis is not possible, and the clinical diagnosis is uncertain, imaging can be helpful in the diagnosis of gout. Detection of tophi or double contour sign by ultrasound have high specificity and sensitivity, although not so high in early gout (36). Another imaging method that has gained attention the last years is dual-energy computed tomography (DECT). Having the identification of MSU crystals as reference, DECT is superior to ultrasound in detection of MSU crystals. However, sensitivity and specificity are also influenced by the disease duration. Since ultrasound is easy to use, has high availability in clinical practices and low cost, the European League Against Rheumatism (EULAR) recommendations prioritized its use over the other imaging techniques (36).

Definitions used in epidemiology

Several classification criteria for gout have been produced to serve as standardized instrument for identification of gout patients and enrollment in studies (39-42). However, these criteria cannot always be applied in epidemiology, due to lack of available clinical or laboratory data. In these situations, gout definitions are often based on physician diagnosis, self-reported data, or data from administrative databases, with great variation and different settings between the studies.

Pathophysiology of gout

There are several stages in the pathophysiology of gout (Figure 2). The first stage is the development of hyperuricemia, defined as elevated urate levels above the solubility limit of 405 μmol/L (6.8 mg/dL) at physiologic temperature and pH. However, only a minority of individuals with hyperuricemia develop clinical evident gout, and the risk has found to be concentration-dependent (43, 44). A previous prospective study in Sweden found that 3.8% of study participants developed gout during the follow-up of approximately 28 years (43).

The next step is formation of MSU crystals, which occurs in three phases: reduced solubility, nucleation, and crystal growth (Figure 2). Solubility is affected by many factors, including temperature, pH, and concentration of

sodium anions (45). In lower temperature, urate solubility is reduced. Laboratory assays showed that at 35°C, crystallization occurs at lower urate levels (360 μmol/L), something that may explain why deposition of MSU crystals occur preferentially at certain locations, such as first metatarsophalangeal (MTP) joint, midfoot, and Achilles tendon, where the temperature is often lower (46). Urate solubility is greater at pH levels ≤6 or ≥10 and minimal at pH 7–8 (45). Among other factors that may favor MSU crystal formation and deposition is osteoarthritis, mainly due to heightened propensity of osteoarthritic cartilage that facilitate crystal formation (47, 48).

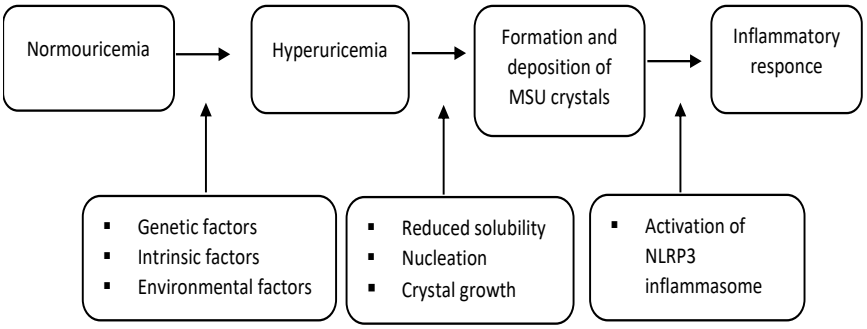


Figure 2. The pathophysiological stages from normouricemia to the development of gout.

Symptoms occur by inflammatory response to MSU crystals which is mediated by the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome. The activation of the NLRP3 inflammasome requires two signals, one signal to upregulate Interleukin (IL)-1β transcription and synthesis of pro-IL-1β, and the second signal (mediated by the interaction of MSU crystals with macrophages) to activate the NLRP3 inflammasome, which processes pro-IL-1β to bioactive IL-1β (Figure 3) (49). Inflammasome-mediated IL-1β release triggers an inflammatory response with vasodilation and recruitment of neutrophils. Neutrophils also have an important role in resolution of gout flares, through the formation of neutrophil extracellular traps (NETs), which contain proteases capable of degrading inflammatory cytokines (49).

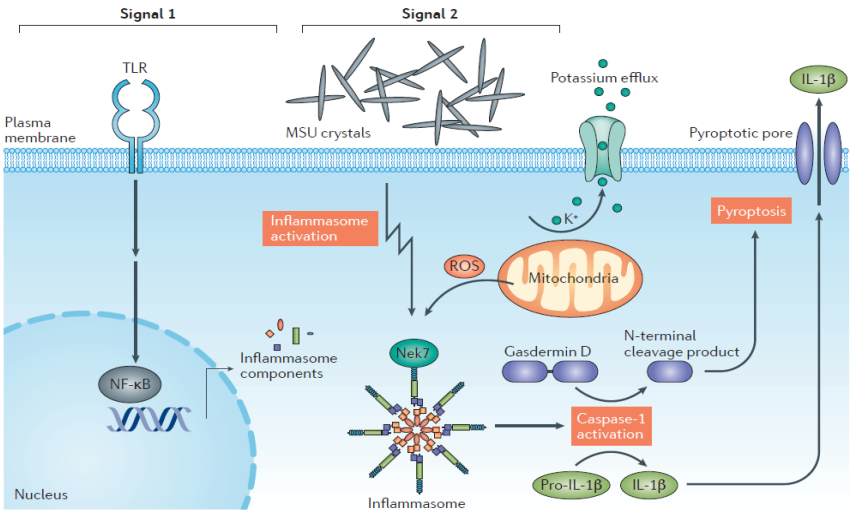


Figure 3. Activation of NLRP3 inflammasome by MSU crystals. Reproduced with permission from Nat Rev Rheumatol. 2017 Nov;13(11):639-647.

TLR, Toll-like receptor; NF-kB, nuclear factor kB; ROS, reactive oxygen species; Nek7, NIMA-related kinase 7

Clinical manifestations of gout

The most typical presentation of gout is acute arthritis with abrupt onset, maximal inflammation and worsening of symptoms within 24 hours, and spontaneous resolution.

The clinical sequence can start from asymptomatic MSU crystals deposition that may precede the onset of gout. Previous studies have shown that ultrasound detected MSU crystal deposition was present in 17-42 % of individuals with mean urate levels >450 µmol/L (8 mg/dL) (50, 51). A previous DECT study found MSU crystal depositions in 24% of individuals with hyperuricemia but without clinical symptoms of gout (52).

Gout attacks are followed by intercritical periods, where most patients are often entirely asymptomatic. However, imaging methods have demonstrated presence of MSU crystals during the intercritical periods, when joints are not

inflamed (53). Microscopy studies have also shown the presence of MSU crystals in previously inflamed joints in patients with gout and persistent hyperuricemia (54). If hyperuricemia persists, MSU crystals may further induce chronic inflammation with structural joint damage, and/or formation of tophi. A recent study showed that levels of proinflammatory cytokines were elevated in the intercritical gout and related to the size of MSU crystals and number of cardiovascular (CV) risk factors, supporting that systemic inflammation is persistent in intercritical gout (55).

The most common affected joints are the first MTP, foot/ankle, knee, and less commonly wrists, elbows, and bursae. Monoarticular involvement in lower limbs is the most common presentation, while polyarticular presentation is less common (56).

Risk factors

The risk factors for the development of hyperuricemia and gout can be categorized into three groups: genetic, intrinsic, and environmental factors. The relative effect of the genetic and environmental contribution is controversial. According to a recent trans-ancestry meta-analysis, the identified single nucleotide polymorphisms (SNPs) explain 7.7% of the serum urate variance, and 17% of serum urate heritability (57), whereas the diet contribution in the general population without gout was found to be much lower (58).

Genetic factors

Urate transporters

Many of the genes, where polymorphisms are associated with urate levels and gout, code for proteins essential to renal urate reabsorption and secretion (Figure 4). Urate levels are mainly regulated by the urate transporters genes SLC2A9 (encoding GLUT9), SLC22A12 (encoding URAT1), ABCG2 (encoding ABCG2), and SLC17A1 (encoding NTP1) in renal tubule, and ABCG2 in the intestine.

Genetic variants for SLC2A9 exert the largest effect on urate levels (59-61) and the effect may be greater in females (62-64). Loss-of-function mutations in SLC2A9 have been associated with renal hypouricemia (65), whereas other

SNPs have been associated with increased urate levels and gout risk (66-68). Furthermore, SLC2A9 alleles have been associated with tophaceous gout (69).

SLC22A12 has an essential role in urate reabsorption, as loss-of-function mutations have been associated with hypouricemia (70-72). However, other SNPs for SLC22A12 have been associated with decreased urate excretion and hyperuricemia (73-75).

ABCG2 polymorphisms have been associated with hyperuricemia and gout (60), and the effect on gout is notably larger than the effect of SLC2A9 (76). In a recent study, ABCG2 polymorphisms were the only SNPs that were associated with early-onset gout in European and Polynesian populations (77).

SNPs for SLC17A1 and SLC17A3, encoding the NPT1 and NPT4 respectively, have been associated with hyperuricemia and gout in some ethnic groups (78).

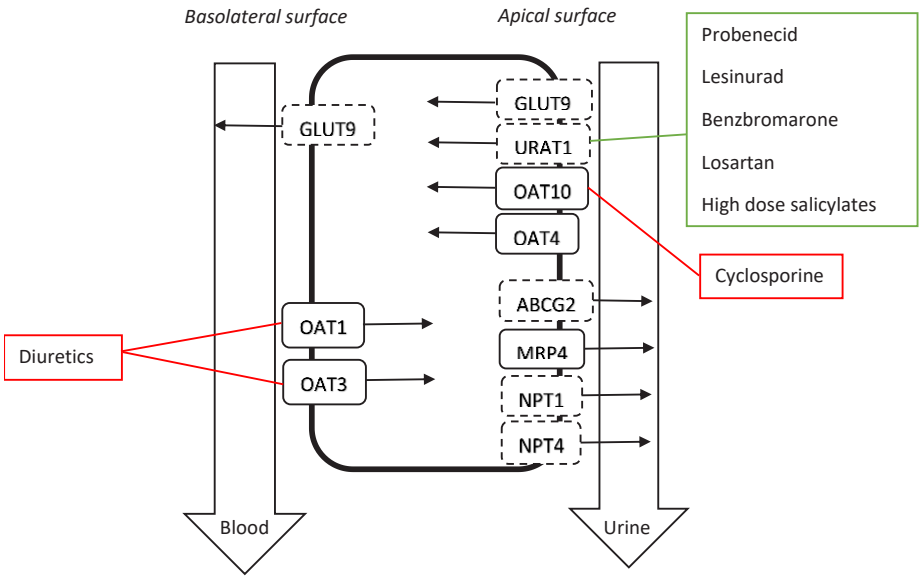


Figure 4. Urate transporters in the proximal renal tubule and the effect of several drugs (the mechanisms are described in detail under 'medications' page 15).

------- *Genetic linkage;* ←— *Urate reabsorption;* —→ *Urate excretion;* —— *Lowering urate levels;* —— *Increasing urate levels.*

Purine metabolism

Overactivity of the PRPP synthetase, which catalyzes the de novo purine synthesis, has been associated with hyperuricemia and gout (Figure 5) (79). As the de novo synthesis is highly energy dependent, purines can be reutilized by the salvage pathway (Figure 5). Complete HGPRT1 deficiency, known as Lesch-Nyhan syndrome, is an X-linked recessive disease causing extremely high urate levels, gout flares, nephrolithiasis, mental retardation, and self-mutilation (80). Partial HGPRT1 deficiency, known as Kelley-Seegmiller syndrome, causes early onset of hyperuricemia and gout, but limited or no neurological symptoms (81).

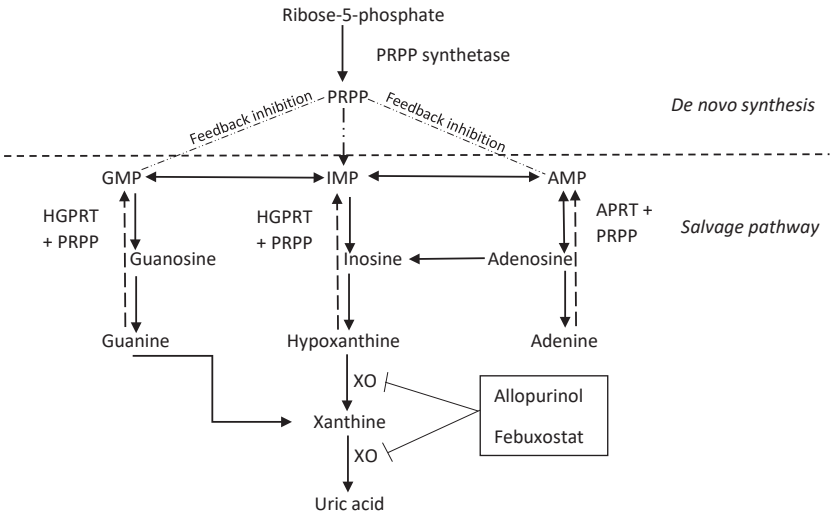


Figure 5. The purine metabolism and the mechanisms of xanthine oxidase inhibitors, allopurinol and febuxostat.

PRPP, 5′-phosphoribosyl 1-pyrophosphate; GMP, guanosine monophosphate; IMP, inosine monophosphate; AMP, adenosine monophosphate; APRT, adenine phosphoribosyl transferase; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; XO, xanthine oxidase

Other

Other identified loci, where polymorphisms have been associated with urate levels, are connected into functional or biochemical pathways, such as carbohydrate metabolism (60, 82). Candidate genes approaches have also

identified associations between gout and genetic polymorphisms in genes that modulate inflammatory responses (CARD8, TLR4, PPARGC1B genes) (49).

Intrinsic factors

Sex

In males, urate levels raise to adult levels after puberty, whereas in females, urate levels are lower and increase substantially around the age of natural menopause (83). This can be attributed to the protective role of estrogens, that enhance the renal urate excretion (84, 85). Hormone replacement therapy has been associated with lower urate levels among postmenopausal women (84, 86). The mean age of gout onset is approximately 10 years later in females than in males, and the prevalence and incidence of gout is higher in men than in women.

Age

Increasing age is strongly associated with increased risk for gout, and many previous studies showed increased prevalence and incidence of gout with increasing age groups (13, 16, 23, 35, 87, 88).

Race/Ethnicity

The prevalence and incidence of gout varies among different ethnic groups and are higher in minorities. These differences suggest the role of genetics in the development of gout, although environmental factors may also have an important role.

Pacific Islanders, Aboriginals in Taiwan, and the Maori population in New Zealand seem to have the highest prevalence of gout in the world. The Maori have also high prevalence of risk factors for gout, such as obesity, diabetes, and hypertension (89). The NHANES 2007-2008 showed a higher prevalence of gout in African Americans than whites (87). The Atherosclerosis Risk in Communities (ARIC) Study showed that black men and women were at increased risk of incident gout, as compared to whites, partly related to higher urate levels, especially in men (90). The prevalence of self-reported gout among the Hmong population in Minnesota was twofold higher than in the general US population (91).

Environmental factors

Medications

A population-based, case-control study from UK demonstrated that past use of loop, thiazide, and thiazide-like diuretics was associated with odds ratios (ORs) of 2.64, 1.70, and 2.30 for incident gout respectively, whereas current use of losartan and calcium channel blockers slightly attenuated the risk (92). Diuretics can inhibit renal transporters OAT1 and OAT3, reducing urate excretion (Figure 4) (93). Cyclosporine may increase urate reabsorption, acting on renal transporter OAT10 (Figure 4) (93). Salicylates in low doses (<300 mg daily) may raise urate levels by acting as exchange substrate at URAT1 transporter, whereas high doses (>300mg daily) inhibit URAT1 and lower urate levels (93). Potassium-sparing diuretics do not affect urate levels. Uricosuric drugs, such as probenecid and lesinurad, are potent inhibitors of URAT1, and thus may decrease urate reabsorption and urate levels (Figure 4) (94). The new anti-diabetic drugs sodium/glucose co-transporter-2 (SGLT2) inhibitors have been shown to reduce urate levels by reducing urate reabsorption (95).

Diseases

Elevated urate levels can be observed in diseases with increased cell turnover, such as hemolytic anemias, sickle cell disease, polycythemia vera, pernicious anemia, thalassemia, and other hemoglobinopathies, but also myeloproliferative and lymphoproliferative diseases, tumor lysis syndrome, solid tumors, rhabdomyolysis, and psoriasis (96).

Toxins

One clinical manifestation of chronic lead toxicity is gout, also known as saturnine gout. Chronic kidney disease (CKD) caused by lead toxicity may result in reduced urate excretion and hyperuricemia (97), whereas there are few studies in literature supporting that lead may also alter purine metabolism and increase urate production (98, 99).

Diet

Alcohol

Ethanol metabolism prompts adenosine triphosphate (ATP) consumption, and thus purine degradation and urate production (100). Guanosine purine load in beer may also increase urate production, as both alcoholic and non-alcoholic

beer increase urate levels (101). Acetate, an ethanol metabolite, can promote MSU crystallization, which may be a possible mechanism on how alcohol consumption can trigger gout flares (102). Greater intake of beer and liquor, but not wine, has been found to increase urate levels (103). The Health Professionals Follow-up Study (HPFS) showed that daily consumption of two or more beers was associated with increased risk of incident gout, whereas wine was not (104). GWAS studies have identified genetic associations with alcohol habits, suggesting that the heritable component of alcohol drinking may contribute to the heritability of urate levels (60).

Purine-rich food

Consumption of red meat, shellfish, and animal protein has long time been proposed to raise urate levels, because of increased purine load. The NHANES study showed that increased urate levels were associated with greater meat and seafood consumption, but not with protein intake (105). In the HPFS, high levels of meat and seafood consumption were significantly associated with increased risk of gout, whereas consumption of purine-rich vegetables and total protein were not (33).

Soft drinks

Sugar-sweetened soft drink consumption has been associated with increased urate levels in a dose-dependent manner (106) and increased risk of incident gout (107).

Dairy products

Low-fat dairy products have been supposed to reduce the risk of developing gout, by lowering urate levels and having anti-inflammatory effects (108, 109). Previous studies have shown a diverse association between diary intake and urate levels (105), as well as risk of incident gout (33).

Coffee and tea

Consumption of coffee may lower urate levels, and the proposed mechanisms are coffee-mediated increased renal urate excretion (110) or reduced insulin resistance (111-113). Furthermore, caffeine is a xanthine and in rats, it was found to be a potent inhibitor of XO (114). In US population, coffee intake was associated with lower urate levels in a dose-dependent manner (115). A modest inverse association was observed between urate levels and decaffeinated coffee, but not with tea (115). Long-term coffee intake was also associated with lower risk of gout (116, 117). A possible causal association between

coffee intake and lower risk of gout is also supported by a Mendelian Randomization (MR) study (118).

Cherries

A recent meta-analysis supported an association between cherry intake and lower risk of gout attacks (119). This effect has been attributed to the anti-inflammatory and antioxidant properties of cherries (120, 121).

Vitamin C

Vitamin C may compete urate for reabsorption via renal urate transporters or may increase renal fractional clearance of urate (122, 123). A meta-analysis of randomized clinical trials (RCT) showed that intake of 500 mg vitamin C per day significantly lowered urate levels (124). The HPFS showed an inverse relation between daily vitamin C intake and urate levels, independent of other risk factors for gout (125).

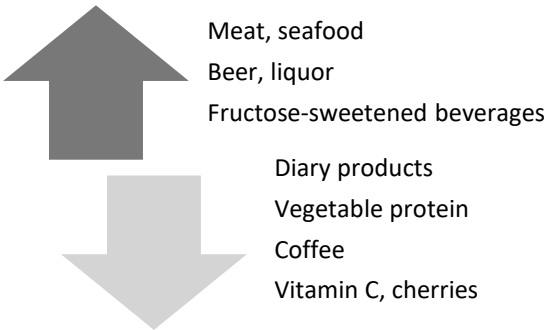


Figure 6. Summary of the effect of diet on urate levels.

Other

The Dietary Approaches to Stop Hypertension diet (DASH) and the Mediterranean diet have been shown to reduce urate levels and risk of gout (126-128). Little is known about the effect of smoking and regular exercise on urate levels and risk of gout. In a murine model of acute gout, low-to moderate intensity exercise could significantly reduce inflammation (129). Chronic smokers had lower urate levels in previous studies, but this was not adjusted for potential confounders (130). Smoking a single cigarette was shown to rapidly reduce antioxidant concentrations in plasma, including urate levels (131).

Gout and comorbidities

Hypertension

Although the relationship between hypertension and hyperuricemia has been studied previously, whether urate has a causal role in the development of hypertension is still unclear. Multiple pathogenetic mechanisms have been proposed, such as reduced nitric oxide (NO) bioavailability, endothelial dysfunction, vascular smooth cells (VSC) proliferation, and activation of the renin-angiotensin system (132-136). In two large meta-analyses, hyperuricemia was associated with higher relative risk (RR) for development of hypertension, independent of other risk factors (137-141). However, hyperuricemia could not predict the development of hypertension in the participants of HPFS study (142).

The association between hyperuricemia and hypertension is more prevalent in primary hypertension (143), and attenuates with increasing age and duration of hypertension. This suggests that the role of hyperuricemia may be of greater impact in early-onset hypertension (144). After renal injury is established and vasoconstriction and inflammation are more consistent, hypertension becomes salt-sensitive and urate-independent (145). Clinical trials reported conflicting results. Treatment with allopurinol in 30 adolescents with newly diagnosed hypertension and hyperuricemia was associated with lower blood pressure (146), whereas another RCT showed that ULT did not lower blood pressure in young adults (147). MR studies showed that urate was not causal for hypertension or cardiometabolic disease (148, 149).

Metabolic syndrome

Patients with gout have a higher prevalence of metabolic syndrome and its components (150). A diagnosis of gout has been associated with higher risk of diabetes type II (151). NHANES reported an 22.2% increase in the prevalence of metabolic syndrome within a decade, and during the same time frame, the prevalence of gout increased by 44.4% and the prevalence of hyperuricemia by 17.6% (87, 152).

A recent MR study showed that hyperinsulinemia may cause hyperuricemia, but not the other way around, and suggested that reducing insulin resistance

could lower urate levels, but lowering urate is unlikely to alter insulin resistance and the cardiometabolic profile (153).

The association between urate and obesity is complex. Obesity induces insulin resistance and is also associated with diet patterns that can also promote hyperuricemia. In a meta-analysis of cohort studies, obesity was found to be an independent risk factor for incident gout (154). Genetically higher BMI, but not waist-to-hip ratio was causally associated with gout in a previous MR study (155). Weight loss has been associated with reduction in urate levels (156-158) and risk of incident gout (159, 160). Furthermore, urate plays a role in lipogenesis, and favors the accumulation of fat in the liver (161).

Renal disease

The association between hyperuricemia/gout and renal disease is bidirectional. CKD seems to be an independent risk factor for the development of gout (159, 162). Gout may also predispose to renal disease via several mechanisms, such as hyperuricemia, systemic inflammation, associated comorbidities, and drugs used for its treatment, for instance nonsteroidal anti-inflammatory drugs (NSAIDs). Furthermore, a cohort study in Western Sweden showed that gout patients had an 60% increased risk of first-time nephrolithiasis, as compared to matched population controls (163).

Neurodegenerative disorders

Three longitudinal studies have examined the association between urate levels and the risk of subsequent dementia. The Rotterdam study showed that increased urate levels were associated with decreased risk of dementia (164). The Prospective Population Study of Women in Gothenburg showed that higher urate levels were associated with lower risk for late-life dementia, Alzheimer's disease, and vascular dementia in women (165). In contrast, the Three-City Dijon study showed that the risk of dementia may be increased with higher urate levels (166). There are also several studies on urate and risk for Parkinson's disease (PD) showing that increased urate levels were associated with lower risk of developing PD (167-169). Decreased risk of PD has also been found in patients with gout, supporting the neuroprotective role of urate (170).

Organ transplantation

Hyperuricemia and gout occur in 5–84% and 7–28% of solid organ transplantations, respectively (171). Apart from the common risk factors for the development of hyperuricemia and gout, including the use of diuretics and impaired renal function, use of cyclosporine plays an important role in transplant recipient population, as it reduces renal excretion of urate (171, 172). Changing from cyclosporine to tacrolimus was found to decrease urate levels (173, 174). Hyperuricemia and gout are more common in transplantation of kidney and heart, compared to liver. Possible explanations could be the lower urate levels before transplantation, lower use of diuretics, and use of lower doses of cyclosporine (175, 176).

Other

Gout has also been associated with macular degeneration (177), erectile dysfunction (178), and cancer, particularly of the urinary tract, digestive system, and lung (179-182). An association between gout and sleep apnea has also been reported, with two cohort studies demonstrating that sleep apnea is an independent risk factor for gout (183, 184).

Cardiovascular disease

Cardiovascular disease (CVD) represents the first cause of death worldwide. Several epidemiological studies have supported the role of urate and gout as independent predictors of CV events. However, their strong association with the traditional CV risk factors makes the link between hyperuricemia/gout and CVD a very debated issue.

Urate: antioxidant and pro-oxidant functions

Urate is a natural antioxidant accounting for two thirds of the total antioxidant capacity in humans (185). However, in elevated levels and depending on the surrounding microenvironment, it can shift from an antioxidant to a pro-oxidant (Figure 7) (186). For instance, it can protect native low density lipoprotein (LDL) against oxidation, but it can also increase the oxidation of already oxidized LDL (187).

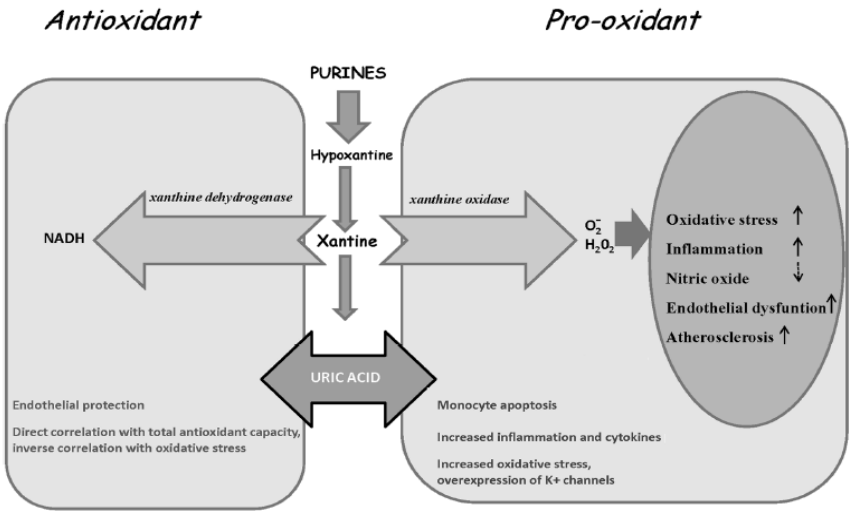


Figure 7. Antioxidant and pro-oxidant functions of urate, depending on concentrations and surrounding microenvironment. Modified from (188). Free copy according to Creative Commons Attribution (CC BY) license.

CVD and hyperuricemia

Subclinical atherosclerotic disease

Many mechanisms have been proposed for the atherogenic role of urate. Urate reduces NO bioavailability, induces endothelial dysfunction, VSC proliferation, and inflammatory response (Figure 7) (189). Endothelial dysfunction favors platelet and leucocyte activation and adhesion, release of inflammatory cytokines, and vessel permeability to oxidized lipoproteins, which can possibly trigger the complex sequence of the atherosclerotic process (190, 191).

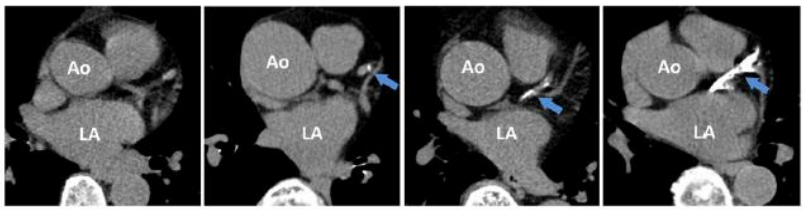
To improve CV risk assessment, interest has been raised for non-invasive imaging techniques that allow early detection of subclinical atherosclerosis. Coronary artery calcification (CAC), carotid intima-media thickness (CIMT), and carotid plaques may be considered as risk modifiers for reclassification of individuals at intermediate risk of CVD and better decision making (192).

CAC

CAC is measured by computed tomography (CT). For the quantification of calcification, the most used scoring is the Agatston score (Figure 8) (193). The extent of the calcification correlates with the extent of total coronary plaque burden, but CAC is not an indicator of the instability of an atherosclerotic plaque (192). CAC has a very high NPV, as an Agatston score of 0 has a NPV of nearly 100% for ruling out significant coronary stenosis (192). According to the 2016 European Guidelines for CVD prevention, CAC may be considered as a risk modifier in individuals at intermediate CV risk (192).

Several studies have examined the association between urate levels and CAC. Higher urate levels predicted the progression of CAC over time in three prospective studies (194-196). Cross-sectional studies have reported conflicting results, with significant association between urate levels and the presence of CAC reported by some (197-202), but not others (203-205).

A) CT images of coronary arteries:



B) Calculation of CAC score (Agatston Method):

Definition of calcified lesion: (1) ≥130 Hounsfield Unit (HU) density
(2) ≥1mm² Area of lesion

Weights assigned to lesion density:

Lesion density	Weight	Lesion Score
130 to <200 HU	1	= Weight × Area of lesion (mm²)
200 to <300 HU	2	
300 to <400 HU	3	
≥ 400 HU	4	

Total CAC Score: Sum of all lesion scores for all coronary CT slices (3mm)

Figure 8. A) CT images with different degrees of CAC. B) Calculation of CAC score according to Agatston method. Free copy according to Creative Commons Attribution License (206).

CIMT

CIMT is measured between the intimal-luminal and the medial-adventitial interfaces of the carotid artery (Figure 9). Many studies have reported that CIMT is an independent predictor of CVD (207-211). However, a meta-analysis showed that the addition of CIMT measurements in the traditional risk scores was of little overall value and unlikely to be of clinical importance (212). Another problem that has arisen is the lack of standardization in definitions and measurements of CIMT. Thus, according to the 2016 European Guidelines for CVD prevention, the use of CIMT as a risk modifier is not recommended.

Many observational studies showed that urate levels were independently associated with CIMT (213-218), whereas others found no significant association (219-222).

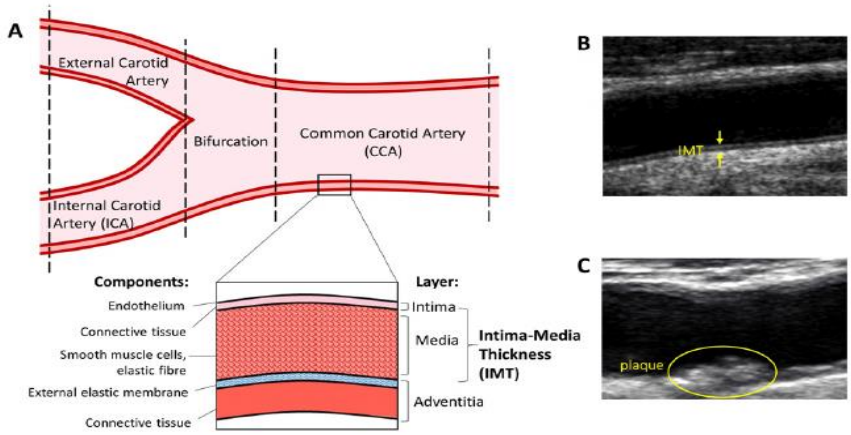


Figure 9. A. The layers of the arterial wall, where intima-media thickness (CIMT) is the distance between the intima and the media-adventitia interface. B. Ultrasound image of the carotid artery; CIMT is the distance between the arrow heads. C. Ultrasound image of plaque in carotid artery. Free copy according to Creative Commons Attribution License (206).

Carotid plaque

Carotid plaque is defined as a focal wall thickening that encroach the lumen by at least 0.5mm, or at least 50% of the surrounding CIMT value, or as having a thickness from the intimal-luminal to the medial-adventitial interface of 1.5mm, according to Mannheim consensus (Figure 9) (223). Plaques are

associated with both coronary and cerebrovascular events and several studies showed that they are a better marker for prediction of future CV events than CIMT. Therefore, the 2016 European guidelines stated that carotid plaque assessment may be considered as a risk modifier in CV risk prediction in some cases (192).

Results from previous studies on the association between urate levels and carotid plaques have been conflicting with an independent association reported in some studies (224, 225), but not in others (226).

Coronary heart disease (CHD)

Many studies have examined the association between hyperuricemia and incident CHD. A previous meta-analysis demonstrated that hyperuricemia was associated with increased risk of CHD morbidity and mortality. Dose-response analysis indicated higher risk of CHD mortality per 1mg/dL increase in urate levels in females, but not significant trend for males (227). Another meta-analysis also showed a significant association between hyperuricemia and CHD incidence/mortality in women, but not in men (228).

In contrast, the Rotterdam study demonstrated no significant association between higher baseline urate levels and risk of myocardial infarction (MI) after adjustment for traditional risk factors (229). In the Reykjavik study and in a combined meta-analysis of 16 prospective studies, urate levels were not an independent predictor of CHD, after adjustments for traditional risk factors (230). MR studies have also failed to demonstrate causal association between urate and CHD or different cardiac events after correction for pleiotropy (231, 232).

Whether ULT has a beneficial effect on CV outcomes is not clear. Treatment with allopurinol was associated with reduced risk of incident MI (233, 234), or risk of all-cause mortality in patients with hyperuricemia and gout in some studies (235), but not in others (236, 237). Among RCTs, the results are still conflicting, with some studies reporting positive CV effect (238, 239), and others negative results (240, 241). A meta-analysis of RCTs reported that treatment with allopurinol was associated with reduced risk of MI and total CV events (242).

CVD and gout

There is growing evidence that gout is an independent risk factor of CVD, and the suggested linking mechanisms also include inflammation apart from hyperuricemia. Low-grade systemic inflammatory response may persist even after an attack resolves or in the absence of symptoms (52, 243, 244).

Inflammation contributes to all stages of atherosclerosis, and also affects the hemostatic mechanisms leading to a pro-coagulant state (245). Several clinical trials aimed to test whether drugs that primarily target inflammation can reduce CV events. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was designed to study whether neutralizing IL-1β with canakinumab in patients with previous MI and elevated levels of high sensitivity (hs)-CRP (≥2 mg/l) would reduce the risk of recurrent CV events beyond standard secondary prevention therapies, and showed a significantly lower rate of recurrent CV events in the treatment group than in placebo (246). Colchicine is another anti-inflammatory treatment, which reduces the mobility of neutrophiles (247), and the crystal-induced activation of the NLRP3 inflammasome (248). The Colchicine Cardiovascular Outcomes Trial (COLCOT) included 4,745 patients who received colchicine or placebo after MI and showed that treatment with colchicine decreased the risk of ischemic events (249).

The association between gout and CVD has been addressed in many studies. The Multiple Risk Factor Intervention Trial showed that patients with gout were at increased risk of MI, after adjustments for other risk factors (250). A population-based study among elderly women demonstrated a higher RR of all MI and non-fatal MI in women with gout, as compared to those without (251). Patients with gout had increased risk of MI, and the RR was slightly higher in men, in a population-based study in Taiwan (252). A retrospective cohort study of primary care patients in the UK showed that women with gout had higher RR of any vascular event, any CHD, and any peripheral vascular disease (PVD), than men with gout (253). A previous meta-analysis of cohort studies, showed that both men and women with gout had an increased risk for non-fatal, but not fatal MI (254).

In contrast, a previous study of 261 gout patients and 522 controls from primary care, showed that gout was not an independent factor for CVD, after adjustments for traditional risk factors (255).

Epidemiological studies have also demonstrated that gout is an independent risk factor for stroke (256), PVD (257), atrial fibrillation (AF) (258), heart failure (HF) (259), and thromboembolism (260).

Mortality

Several studies have examined the mortality in patients with gout. Data from the NHANES I (1971-1975) (baseline) and NHANES I Epidemiologic Follow-up Study (1982-1992) showed that increased urate levels were associated with increased CV mortality (261). The HPFS also reported an excess mortality (all cause and cardiovascular) among men with gout and without prior CHD (262). A study from Taiwan showed that patients with gout had a higher risk of all-cause and CV death, independent of other risk factors (263). A database study in UK, which compared the cumulative mortality rates in gout *vs* non-gout group in the periods 1999– 2006 and 2007– 2014, showed that, whereas mortality rates for rheumatoid arthritis improved over the years, in gout patients they remained unchanged (264). Among the non-CV causes of death, gout was found to be associated with increased risk of mortality due to renal disease, digestive system diseases, and infections, and lower risk of dementia-related mortality (265).

Treatment

The major goal in the management of gout is long-term reduction of urate to below subsaturated levels of 360 μmol/L (6 mg /dL), or 300 μmol/L (5 mg/dL) in patients with severe gout (tophi, gout arthropathy, frequent attacks, nephrolithiasis) (treat-to-target, T2T) (266). ULT include reducing urate production with a XO inhibitor (allopurinol, febuxostat) (Figure 5), enhancing urinary excretion with a uricosuric agent (probenecid, benzbromarone, lesinurad) (Figure 4), or oxidation of urate to allantoin using pegloticase, a recombinant uricase. Febuxostat is a non-purine XO inhibitor, with less complicated dosing than allopurinol. During its development, febuxostat was found to have higher rate of CV events as compared to allopurinol or placebo, which was further investigated with two large-scale, post-marketing RCTs. The CARES trial showed that CV and all-cause deaths were more frequent in febuxostat than in the allopurinol group (267). However, nearly 50% of

participants discontinued the trail and were lost to follow-up, with similar discontinuation rates between the two groups. The FAST trial, published two years later, showed that long-term febuxostat use (median on-treatment follow-up time 1,324 days) was not associated with increased risk of death or serious adverse events compared to allopurinol (268). However, no comparison with placebo group was done in either CARES or FAST trial.

Appropriate ULT reverses and prevents the formation and deposition of MSU crystals (269, 270), the number and size of tophi (270, 271), and improves the quality of life in gout patients (272). Despite many available treatments, the management of gout is still suboptimal (13). Several studies have shown that less than half of patients with gout receive ULT, and the doses are often too low to effectively lower urate levels (14, 273-275). Patients' low adherence to treatment has also been emphasized, as gout is among the chronic diseases with the lowest rate of adherence, ranging between 18-44% (276, 277). This is also affected by a widespread lack of knowledge and misconceptions about the nature of the disease and its treatment among both the patients and the treating physicians (278). A large RCT demonstrated major improvements in clinical outcomes in patients receiving nurse-led gout care according to treatment guidelines, compared to usual care by general practitioners, highlighting the importance of educating and engaging patients in gout management and T2T strategy (279). Finally, an important part in the treatment of gout is the systematical screening for associated comorbidities and CV risk assessment (266).

2 AIM

The overall aim of this thesis was to study the epidemiology and comorbidities of gout in Western Sweden. The specific aims of each part of this thesis are briefly summarized in the following paragraphs.

I. To estimate the prevalence and incidence of gout in Western Sweden in 2012 and the pattern of ULT use.
II. To examine the occurrence of comorbidities in patients with gout at the time of first gout diagnosis, compared to the general population, overall and by sex.
III. To investigate the association between serum urate levels and subclinical atherosclerosis, as reflected in the CAC score, CIMT, and carotid plaque score, in the participants of the pilot trial of the Swedish CArdioPulmonary bioImage Study (SCAPIS).
IV. To investigate the risk of first-time ACS in patients with incident gout, compared to the general population, overall and by sex.

3 PATIENTS AND METHODS

Paper I, II, IV

Ethical approval

Ethical approval for these studies was granted from the Ethical Review Board of Gothenburg, Sweden. Informed consent from the patients was not needed, as the studies were based on register data.

Data sources

Western Swedish Health Care Register (VEGA)

VEGA contains information about all health care contacts, at both primary and specialized health care in Western Sweden from 2000 onwards. Physician diagnoses are registered according to the Swedish version of the International Classification of Disease (ICD) codes. Since 1997, the 10th version of ICD codes (ICD-10) is used in Sweden. VEGA was used to identify the gout cases and retrieve information about all the ICD-coded diagnoses.

Prescribed Drug Register (PDR)

PDR contains information about all dispensed prescriptions at Swedish pharmacies since July 2005, based on the Anatomical Therapeutic Chemical Classification System (ATC). It was used to retrieve information regarding drug prescriptions for gout cases and controls.

Cause-of-death Register

This register contains information about date and cause of death for all deceased residents since 1961. It was used to retrieve information regarding the vital status and the cause of death for gout cases and controls.

Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

This register comprises detailed data on health insurance, parental insurance, and unemployment insurance at the individual level. Data are available from 1990 onwards for all persons aged >16 years who are registered in Sweden on 31 December each year. This register was used to retrieve information about the education level of gout cases and controls. Education data are available in

> 98% of all individuals aged 25-64 years, with an estimated accuracy for highest attained level of education of 85% (280).

Statistics Sweden

It is a government agency that produces official statistics. It was used to identify the control group and retrieve demographic information about gout cases and controls.

Case definitions of gout

Paper I

Three case definitions of gout were used:

a) Liberal case: ≥1 visit with a primary or auxiliary ICD-coded gout diagnosis given by any physician at primary or specialized health care.
b) Base case: ≥1 visit with a primary ICD-coded gout diagnosis given by any physician at primary or specialized health care.
c) Strict case: ≥2 visits with a primary ICD-coded gout diagnosis given by any physician at primary or specialized health care, or ≥1 ICD-coded gout diagnosis given by a rheumatologist.

In a previous validation study, the strict case definition was found to have the highest PPV (>80%) for fulfilling the Netherlands and the Mexico classification criteria (281).

Paper II

Main analysis: liberal case definition

Sensitivity analysis: strict case definition

Paper IV

Main and sensitivity analysis: liberal case definition

Study setting and study populations

Paper I

This study included all individuals aged ≥ 20 years with at least one ICD-coded diagnosis of gout in VEGA in the period 2002−2012 (case definitions discussed in the previous session). ULT treatment in 2012 was defined as having at least one dispensed prescription for allopurinol, febuxostat, and/or probenecid in 2012.

Paper II

Case-control study which included all gout cases aged ≥ 20 years with first ICD-coded diagnosis between 1 January 2006 and 31 December 2012. Each gout case was matched with up to five general population controls on age, sex, and county at the time of index patient's first gout diagnosis (index date) (Figure 10).

Comorbidities were defined as ≥ 1 ICD-coded diagnosis, except for hypertension and obesity, which were defined as ≥ 1 ICD-coded diagnosis or ≥ 1 dispensed prescription of antihypertensive or anti-obesity drugs respectively. Treatment with diuretics was defined as ≥ 1 dispensed prescription of these agents within 6 months prior to first diagnosis of gout.

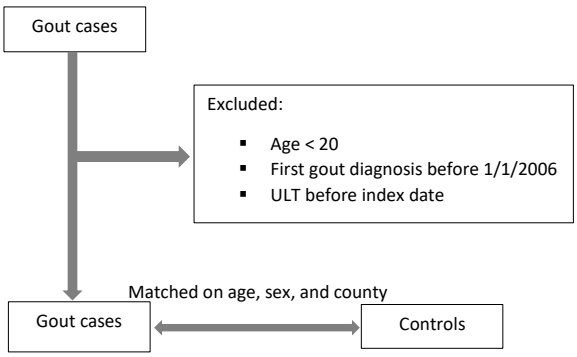


Figure 10. Cases and controls included in the Paper II.

Paper IV

Prospective cohort study. The gout cohort included patients with incident diagnosis of gout in the period 2007-2017 and no prior treatment with ULT or CHD (Figure 11). Each gout case was matched with up to five general population controls on age, sex, and county at index date (control cohort).

The follow-up started at the first gout diagnosis and ended at the occurrence of the outcome, death, emigration, or 31 December 2017, whichever occurred first.

The outcome of interest was first-time MI or unstable angina at discharge from an inpatient unit, or ACS as primary cause of death.

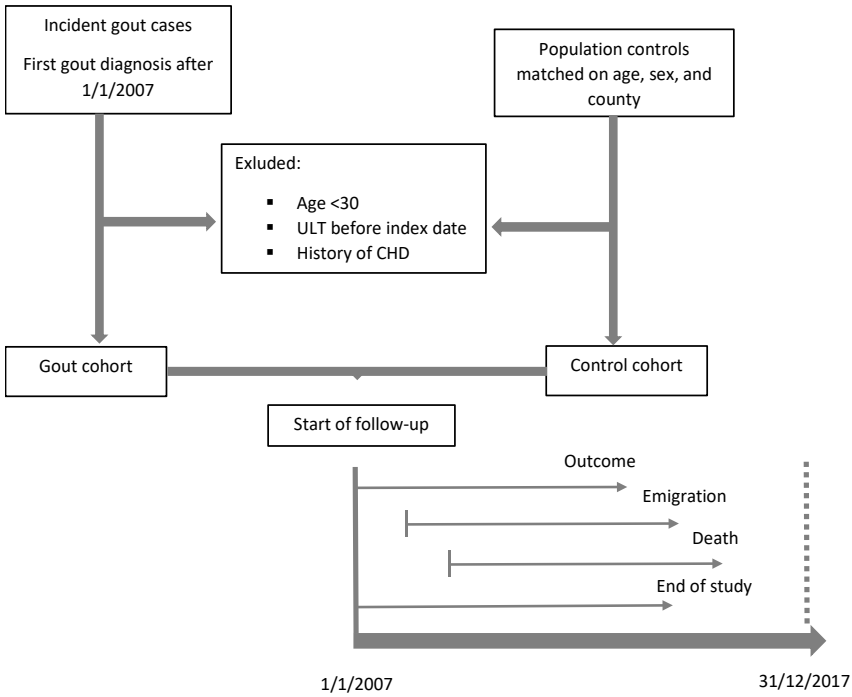


Figure 11. Inclusion and follow-up of cases and controls in the Paper IV.

Statistical analysis

Paper I

The prevalence of gout was calculated with the number of individuals aged ≥20 years with an ICD-coded gout diagnosis by 31 December 2012 as the numerator and the total population of Western Sweden aged ≥ 20 years by 31 December 2012 as the denominator.

The incidence of gout was calculated with the number of incident gout cases aged ≥ 20 years per calendar year as the numerator and the total person-years occurring in the population aged ≥ 20 years in Western Sweden at the same year as the denominator. Trends in incidence of gout in the period 2005-2012 were calculated. For the analysis of trends, an incident case was defined as not having had a diagnosis of gout (liberal case definition) during the preceding three calendar years. To compare incident rates by year, we calculated standardized estimates, using the whole Swedish population aged ≥20 years in 2012 as the standard population. The incidence of gout in 2012 was defined as the number of patients that received a primary or auxiliary diagnosis of gout in 2012, without any recorded gout diagnosis in the previous 10 years.

Paper II

To estimate the association between gout and comorbidities we calculated prevalence, prevalence ratios (PRs) and 95% confidence intervals (CI). We also calculated age-standardized prevalence of comorbidities by sex, using the Swedish population in 2012 as the standard population. Non-overlapping 95% CIs were considered statistically significant for the comparisons.

Paper IV

We calculated incidence rates (IRs), incidence rate ratios (IRRs), and hazard ratios (HRs) crude and with adjustments for age, sex, education level, hypertension, diabetes, hyperlipidemia, obesity, renal disease, HF, cardiomyopathy, psoriasis, chronic obstructive pulmonary disease (COPD), alcoholism, cerebrovascular disease, atherosclerotic disease, cancer, and dispensed prescriptions of cardiovascular drugs and anticoagulants, total and by sex. The IRs were calculated with the number of events as the numerator and person-years at risk as denominator. The IRRs were calculated with the IR for cases as numerator and IR for controls as denominator.

Paper III

Ethical approval

All the participants gave written informed consent on their first visit. Ethical approval for this study was granted by the Ethical Review Board of Gothenburg and the Ethical Review Board of Umea, Sweden.

Study population

This study was conducted on the participants of the SCAPIS Pilot. The total target population for the SCAPIS pilot consisted of 24,502 individuals aged 50-64 years living in the city of Gothenburg. From this population, 2,243 individuals randomly selected from six residential areas (that represented opposite extremes of socioeconomic status) received a written invitation to participate. Totally, 1,111 subjects agreed to participate (50% participation rate). In this study, we excluded individuals with self-reported diagnosis of gout or ULT (N = 3), and individuals with prior history of CVD (N = 68). Finally, 1,040 participants were included.

Study setting

All the participants were asked to respond to a questionnaire which included information about smoking habits, level of education, physical activity, and self-reported health and medication. The levels of creatinine, hs-CRP, and serum urate were measured for all subjects at the study entry.

The CAC score was calculated by measuring the calcium content of coronary arteries with CT, according to the Agatston method. A total score of >0 regarded as positive for the presence of CAC.

The CIMT was calculated by measuring the mean of the intima-media thicknesses of the left and right common carotid arteries, and categorized by percentiles, < 25^{th} percentile, 25^{th}–75^{th} percentile, and > 75^{th} percentile. The CIMT > 75^{th} percentile was considered as positive.

Any sign of carotid plaque on the ultrasound examination (plaque score > 0) was considered as positive for the presence of plaques.

Statistical analysis

We used univariable and multivariable logistic regression models with adjustments for age, smoking, BMI, eGFR, diabetes, dyslipidemia, hypertension, hs-CRP, physical activity level, and education level. CAC score > 0, CIMT > 75^{th} percentile, and plaque score > 0 were used as the cut-off values in the logistic regression models.

4 RESULTS

Paper I

Prevalence

The prevalence of gout in the adult population (aged ≥ 20 years) in Western Sweden in 2012 was 1.8% with the liberal case definition, 1.4% with the base case definition, and 0.5% with the strict case definition.

The prevalence was higher in men in all age groups with a male to female ratio of 3-4:1, which decreased to 2:1 after the age of 70 years (Figure 12).

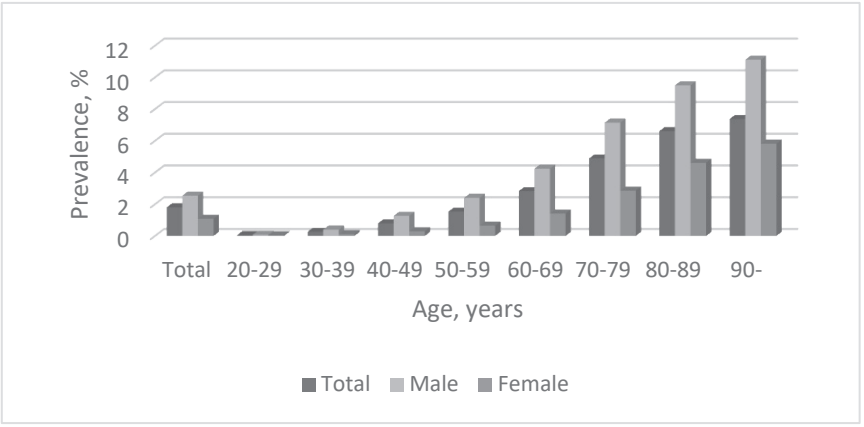


Figure 12. Prevalence of gout in Western Sweden in 2012 by age group, total and by sex. Free copy according to Creative Commons Attribution 4.0 International License (282).

Incidence

The overall incidence of gout in the adult population (aged ≥ 20 years) in 2012 was 190 cases per 100,000 person-years. Incidence was higher in men than in women (267 *vs* 116 per 100,000 person-years). The male to female ratio was > 3:1 in the patients aged <70 years, which decreased to 2-3:1 after the age of 70 years (Figure 13). The incidence of gout increased significantly from 2005 to 2012 by approximately 50%.

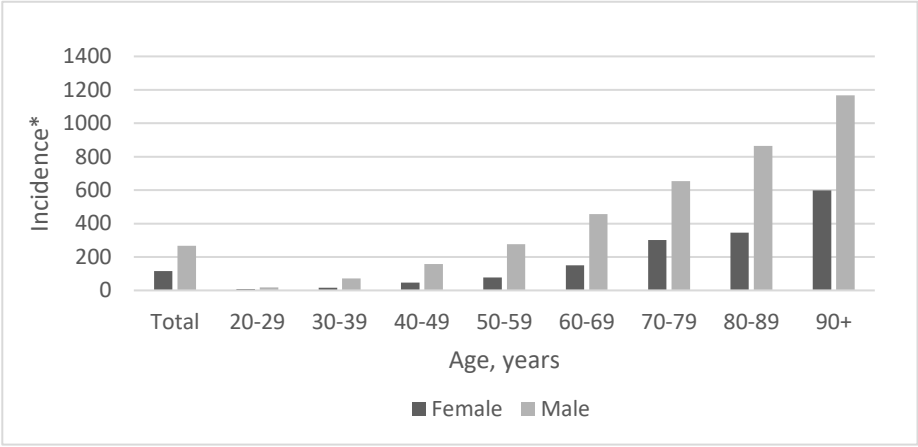


Figure 13. Incidence of gout in Western Sweden in 2012 by age group and sex.
**per 100,000 person-years*

ULT

ULT was prescribed to only a minority of patients with a diagnosis of gout (Figure 14). Most of them were prescribed allopurinol, <2 % probenecid, whereas febuxostat was not used at all in 2012.

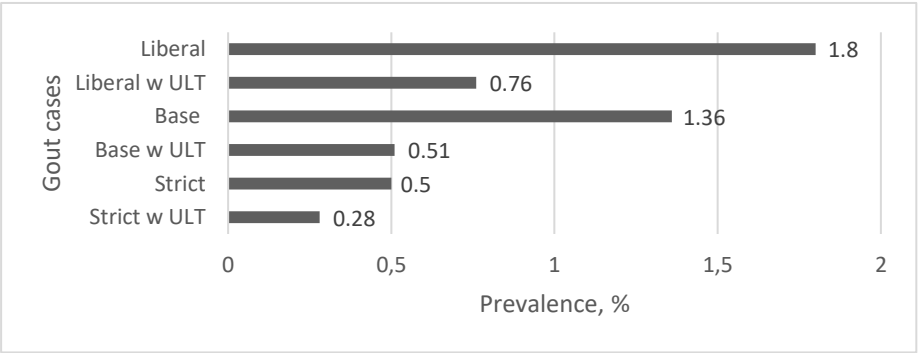


Figure 14. Prevalence of gout and percentage of prescribed ULT, by case definition. Free copy according to Creative Commons Attribution 4.0 International License (282).

Paper II

Gout cases *vs* controls

We identified 14,113 cases (9,513 men) with first diagnosis of gout in the period 2006-2012, which matched to 65,782 controls. Women were approximately six years older than men.

The prevalence of all the examined comorbidities was higher in gout cases than in controls, in total (Figure 15), in men and women (Figure 16). Among gout cases, 76.6% had at least one diagnosed comorbidity at the time of first diagnosis, as compared to 55.7% in the control group.

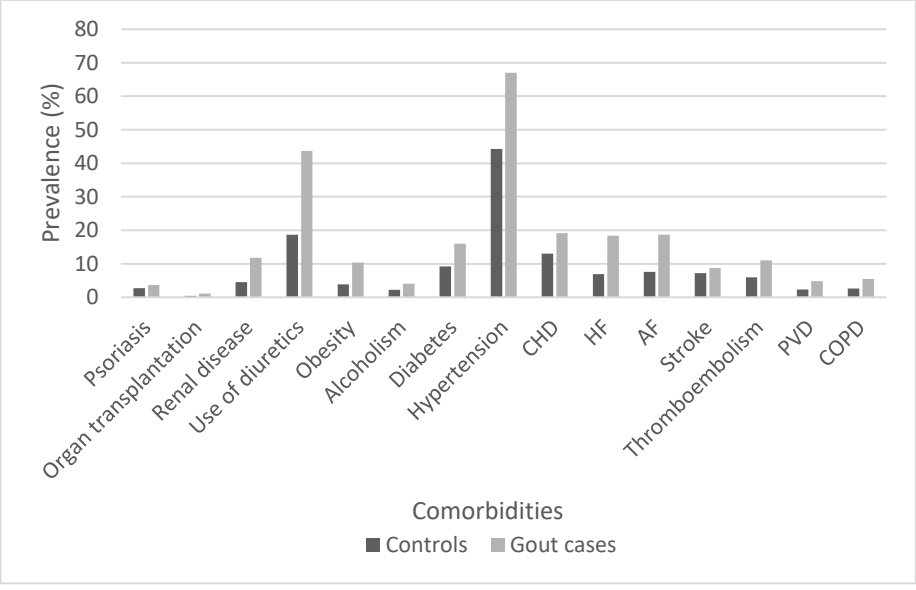


Figure 15. Prevalence of comorbidities in gout cases and controls. CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease

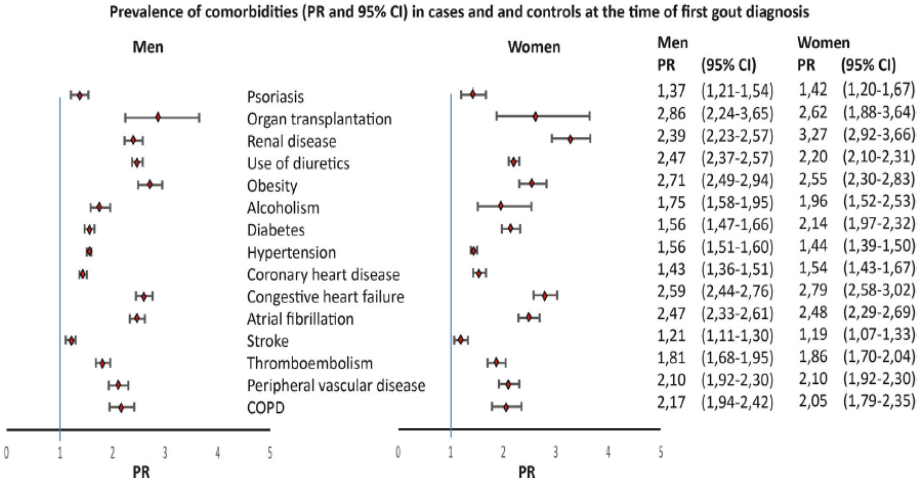


Figure 16. Prevalence ratios (PR) with 95% confidence intervals (CI) for comorbidities in gout cases and controls, by sex. Free copy according to Creative Commons Attribution 4.0 International License (283).

Gout cases

A separate analysis was conducted only for patients with gout. The point prevalence of all examined comorbidities, except for alcoholism, renal disease, and CHD, was higher in women than in men. In men, only diagnosed alcoholism was significantly more common (Figure 17). An age-standardized analysis was conducted because of the higher age of women (71.1 *vs* 65.3) (Table 3). In this analysis, only thromboembolism and COPD were significantly higher in women, whereas CHD, HF, and AF were more frequent in men (Table 3).

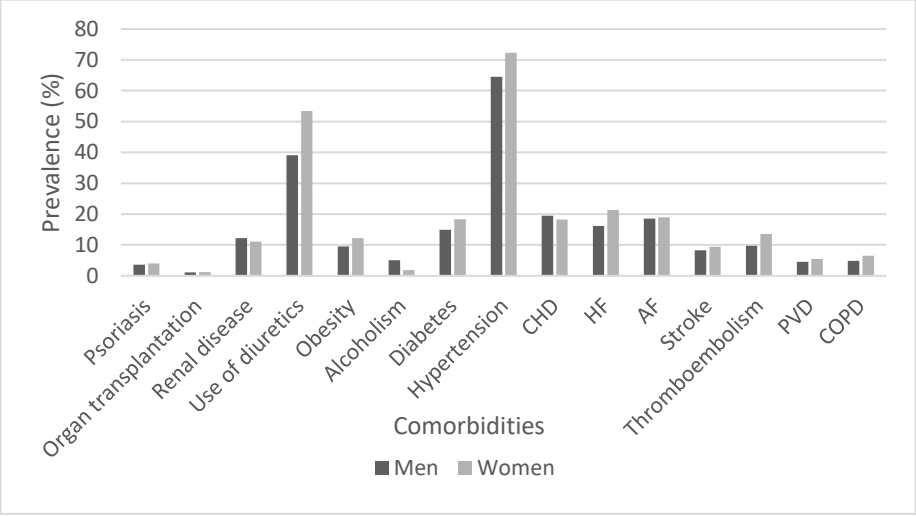


Figure 17. Prevalence of comorbidities in men and women with gout. CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease

Table 3. Age-standardized prevalence of comorbidities in men and women with gout. Free copy according to Creative Commons Attribution 4.0 International License (283).

	Gout cases ($N = 14,113$)			
	Men ($N = 9513$), prevalence (%)	95% CI	Women ($N = 4600$), prevalence (%)	95% CI
Comorbidities suggested to increase SU level				
Psoriasis	3.7	2.8–4.5	3.3	2.6–4.1
Organ transplantation	1.3	0.8–1.8	1.8	0.9–2.6
Renal disease	8.2	7.4–9.0	8.3	6.8–9.8
Use of diuretics	21.9	20.9–22.8	24.1	22.7–25.6
Obesity	10.2	8.9–11.6	12.5	10.8–14.3
Alcoholism	5.5	4.7–6.3	3.5	2.1–4.8
Other comorbidities				
Diabetes	8.7	8.1–9.3	9.9	8.9–10.9
Hypertension	40.1	38.6–41.6	39.4	36.9–41.9
Coronary heart disease	9.4	9.0–9.9	6.4	5.8–7.0
Congestive heart failure	7.7	7.3–8.1	6.6	6.0–7.1
Atrial fibrillation	9.0	8.4–9.5	6.0	5.4–6.5
Stroke	4.1	3.7–4.5	3.3	2.8–3.7
Thromboembolism	5.2	4.8–5.6	6.6	5.8–7.5
Peripheral vascular disease	2.1	1.9–2.3	2.1	1.7–2.5
COPD	2.4	2.1–2.6	3.1	2.6–3.5

CI confidence interval, *COPD* chronic obstructive pulmonary disease, *SU* serum urate

Paper III

CAC

Serum urate levels > 308 µmol/L were statistically associated with the presence of CAC in men ($p < 0.05$), but not in women in multivariable regression analysis (Table 4).

CIMT

Serum urate levels were not associated with CIMT in either men or women in multivariable regression analysis (Table 4).

Carotid plaque

Serum urate levels were not associated with carotid plaques in either men or women in multivariable regression analysis (Table 4).

Table 4. Uni- and multivariable regression analysis for the presence of CAC, CIMT, and carotid plaque in men and women, by quartiles of serum urate. Free copy according to Creative Commons Attribution 4.0 International License (284).

Urate quartiles, µmol/L	Men (*N* = 508)				Urate quartiles, µmol/L	Women (*N* = 532)			
	OR, univariable	*p* value	OR, multivariable	*p* value		OR, univariable	*p* value	OR, multivariable	*p* value
	CAC examined (*N* = 508)[a] CAC+ (*N* = 293)					CAC examined (*N* = 532)[a] CAC+ (*N* = 137)			
31–307, ref	1		1		143–229, ref	1		1	
308–346	1.6 (1.0–2.7)	0.049	2.2 (1.2–4.0)	0.008	230–262	1.0 (0.6–1.8)	0.97	0.8 (0.4–1.6)	0.5
347–391	1.6 (0.9–2.5)	0.08	1.9 (1.0–3.6)	0.04	263–304	1.1 (0.6–1.9)	0.8	1.0 (0.5–1.9)	0.9
392–584	2.0 (1.2–3.4)	0.007	2.3 (1.2–4.4)	0.01	305–702	1.5 (0.9–2.6)	0.2	1.0 (0.5–2.0)	0.96
	CIMT examined (*N* = 436)[a] CIMT+ (*N* = 106)					CIMT examined (*N* = 475)[a] CIMT+ (*N* = 117)			
31–307, ref	1		1		143–229, ref	1		1	
308–346	1.5 (0.8–2.7)	0.2	1.2 (0.6–2.4)	0.5	230–262	1.2 (0.6–2.2)	0.6	1.2 (0.6–2.3)	0.7
347–391	0.9 (0.5–1.7)	0.7	0.7 (0.3–1.4)	0.3	263–304	1.3 (0.7–2.4)	0.4	1.0 (0.5–2.1)	0.9
392–584	1.3 (0.7–2.5)	0.4	0.9 (0.4–1.8)	0.7	305–702	1.6 (0.9–2.9)	0.1	1.0 (0.5–2.2)	0.99
	Carotid plaque examined (*N* = 507)[a] Plaque+ (*N* = 308)					Carotid plaque examined (*N* = 526)[a] Plaque+ (*N* = 268)			
31–307, ref	1		1		143–229, ref	1		1	
308–346	1.6 (0.95–2.6)	0.08	1.8 (1.0–3.2)	0.03	230–262	0.8 (0.5–1.3)	0.4	0.9 (0.5–1.6)	0.7
347–391	1.2 (0.7–1.9)	0.6	1.1 (0.6–2.0)	0.7	263–304	1.1 (0.7–1.7)	0.8	1.3 (0.7–2.2)	0.4
392–584	1.5 (0.9–2.4)	0.1	1.6 (0.9–2.9)	0.2	305–702	0,99 (0.6–1.6)	0.95	1.1 (0.6–2.1)	0.7

[a]The total number of subjects, where CAC score, CIMT, and plaque score respectively, were calculated
CAC+: total CAC score > 0
CIMT+: CIMT > 75th percentile
Plaque+: plaque score > 0

Paper IV

The IRs of first-time ACS are presented in the Figure 18. Gout cases had significantly higher IRs compared to controls (p-value <0.05). The IRs were higher in men than in women in both cohorts (Figure 18).

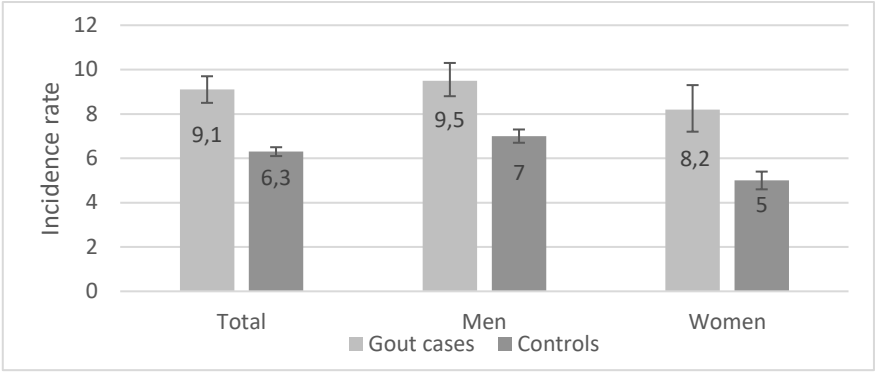


Figure 18. Incidence rates per 1,000 person-years and 95% confidence intervals of first-time ACS in the gout and control cohort, total and by sex.

The results of multivariable Cox regression analysis are presented in Figure 19. After adjustments for age, sex, education level, baseline comorbidities, and dispensed prescriptions, the HRs were significantly increased in total, in men and in women. The HR was higher for women than for men (Figure 19).

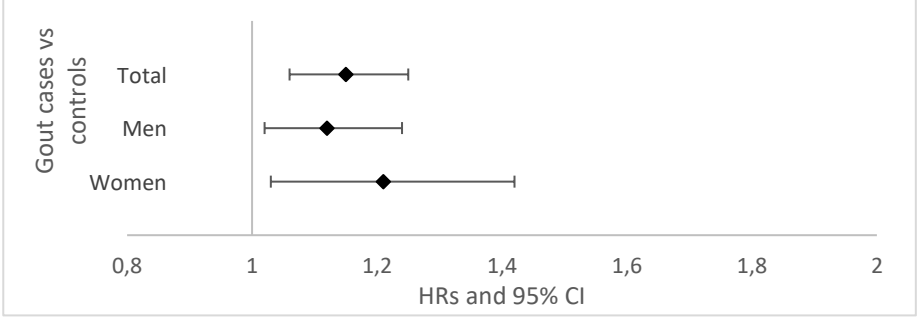


Figure 19. Hazard ratios (HRs) and 95% confidence intervals (CI) for first-time ACS in gout patients compared to controls, with adjustments for age, sex, education level, baseline comorbidities, and dispensed prescriptions.

5 DISCUSSION

Limitations

Systematic errors – Bias

Selection bias

Paper I, II, IV
Cases included in these papers were identified from VEGA, covering all the population living in Western Sweden (Västra Götaland), and both the primary and specialized health care. The controls (Paper II, IV) were drawn from the same population. Furthermore, using register data, the risk of loss-to follow-up is minimized (Paper IV). Thus, selection bias can be considered as a minor concern in these studies.

However, VEGA do not cover the private healthcare providers. The proportion of gout patients in Western Sweden that are exclusively treated by private health care providers is unknown, but according to the National Board of Health and Welfare in Sweden, the proportion of the whole population in Sweden treated by private health care providers is <13% (285). In addition, not all patients with gout seek medical advice. The proportion of these undetected cases is unknown and may differ between the regions and countries. A recent nation-wide study in Spain which used telephone interviews followed by physical examination if suspicion for gout was present, estimated the proportion of undiagnosed cases to 32%; however the response rate was very low (15.2%) (286). The frequency of undiagnosed gout has not been studied in Sweden, and it is not clear if it would have a significant impact on the prevalence estimates.

Paper III
Paper III is a cross-sectional study and factors associated with response and non-response may have led to a degree of bias. In particular, the participation rate was 50%, and a direct comparison between participants and non-participants showed a low participation rate for those born outside Europe, living alone in an area with low socioeconomic status, having a low level of education, finding themselves outside the labor market, or having a low income (287). These differences between the two groups may have led to selection bias

in our study and may limit the generalizability, particularly in the groups that are underrepresented.

Misclassification bias

Paper I, II, IV

The ICD-10 codes for the diagnosis of gout have been validated to five classification criteria (Rome 1963, New York 1966, ARA1977, Mexico 2010, and Netherlands 2010) in a previous study (281). Medical records from two primary care centers and the rheumatology department were reviewed. The study showed that ≥2 ICD-coded gout diagnoses at primary care units and ≥1 ICD-coded gout diagnosis at rheumatology department had high PPVs for fulfillment of Mexico, and Netherlands classification criteria, whereas fulfillment of the three earliest criteria was overall very low.

However, retrieving information of medical records is cumbersome. Essential information for fulfilling classification criteria is likely to be underreported in clinical records or missed during the validation process, although this followed a structured protocol (281). This affects the estimated PPVs and probably underestimates the validity of the ICD-coded diagnoses, since a criterion not found was treated as a negative finding. Aspiration of SF for identification of MSU crystals, which is included in the classification criteria, is rarely performed in both primary and specialized health care, and treatment with colchicine, which is a key criterion in New York criteria, is rarely used in primary care (281). Another limitation regarding the validity of the diagnostic codes for gout is the lack of data from a comparison group representing subjects that are 'truly negative' enabling estimations of the NPVs, sensitivity, and specificity for the ICD-coded diagnoses.

To address the issue of possible misclassification bias in our studies, in Paper I we used three different case definitions of gout for the estimation of prevalence. The demographical characteristics and comorbidities of the gout patients were similar across the different case definitions. In Paper II, we primarily used the liberal case definition, but also conducted a sensitivity analysis using the strict case definition, which showed similar results about overrepresentation of various comorbidities in gout patients compared to controls.

The ICD-10 codes for some comorbidities (cardiomyopathy, thromboembolism, stroke, HF, AF) (Paper II, IV), and the outcome (ACS,

Paper IV) have been validated in the National Patient Register with PPVs between 68% (for cardiomyopathy) and 98% (for MI) (288-292).

For some comorbidities, in particular obesity and alcoholism, there is a risk of underestimation when their definition is based on ICD codes. However, this is probably of the same magnitude in both gout cases and controls.

Detection bias

Patients with gout may have access to healthcare units and potentially check their health care status more often than controls. This may have led to detection bias in Paper II and IV with more frequent recording of comorbidities, due to possible higher healthcare utilization among gout patients.

Residual confounding

In Paper II and IV residual confounding was unavoidable, due to lack of data regarding smoking status, physical activity, and other factors that may have implications on CV risk profile.

Implications

This thesis adds new knowledge on the epidemiology of gout in Western Sweden and its association with comorbidities and CVD. Data on gout in Sweden prior to this thesis are limited with only one previous study from Stockholm (19).

Paper I

This study demonstrates the prevalence, incidence, and ULT pattern of gout in Western Sweden, where previous data are scarce. The estimated prevalence in 2012 according to the liberal case definition was 1.8% in adults aged ≥ 20 years, and the incidence in 2012 was 190 cases per 100,000 person-years. The incidence of gout increased from 2005 to 2012. However, the management of gout was suboptimal in 2012, with only 42% of the prevalent gout cases (liberal case definition) having dispensed prescription for ULT.

A previous study in Stockholm in the period 2013-2014 reported a prevalence of 0.6% overall, 0.83% in men, and 0.28% in women, which is much lower

than the prevalence of gout in our study (19). Data in the previous study were selected for two years, 2013 and 2014, which may have led to underestimation of the prevalence of gout, because of its episodic nature and that not all patients seek medical advice regularly. However, the incidence of gout was similar to our results, 0.15% in 2013 and 0.16% in 2014.

Data from the other Nordic countries are also limited. In Finland, the incidence of gout as reported in a study from 1978 was 12 cases per 100,000 person-years in men, with no incident cases in women (30). These results differ from our estimations, where the incidence was 267 per 100,000 person-years in men and 116 per 100,000 person-years in women, which can be attributed to differences in methodology. The previous study used two selection strategies, the Follow-up Survey of Arthritis, which included 332 patients >16 years with a history of arthritis referred to the hospital by primary care physicians after request, and the Heinola Town Case-finding study, based on physician interviews and review of medical records. The diagnosis of gout was based on typical clinical symptoms or identification of MSU crystals in SF aspiration.

In Denmark, the prevalence of gout among male employees was 1.6% and the incidence 0.4% (293). The differences compared to our results can be attributed to different study methodology and case definition. The previous study included only males aged 40-59 years working in private or public enterprises in Copenhagen that accepted to answer a questionnaire and attend an examination. Gout diagnosis was based on recall information from the participants, in particular typical symptoms that had been regarded and treated as gout by their physicians. A more recent study from Denmark reported a prevalence of 0.68% in adults >18 years in 1995-2015 (21). This is lower than in our study, which can be attributed to the different study setting, as the previous study was based on data from specialist health care.

A previous study from Norway used three difference strategies to estimate the prevalence of musculoskeletal disorders including gout (20). The first one was a survey (based on telephone interviews) of a random sample of 10,000 individuals with exclusion of those living in some institutions, such as retirement homes and orphanages. Thus, the youngest and the oldest age groups were underrepresented. The second one was a national reimbursement register for primary care physicians and the third one was the Norwegian Patient Register containing data from the specialized health care. The reported prevalence was 0.54% in males and 0.39% in females (questionnaire); 0.7% in males and 0.22% in females (reimbursement records); and 0.09% in males and

0.02% in females (specialist care). The different study setting has contributed to the differences in prevalence estimates.

We also found that the proportion of gout patients treated with ULT was low (42%). Similar to our results, Kuo *et al* reported that, among prevalent gout cases in UK in 2012, only 37.6% were being treated with ULT (13). Although the current recommendations advice towards earlier treatment of gout to avoid further elevation of urate levels and deposition of MSU crystals (266), ULT is often underprescribed or underdosed (273, 274). In another study from UK, although 44% of gout patients fulfilled indications for ULT at first diagnosis, only 17% received treatment (275). Another study in Western Sweden showed that only 32% of gout patients received ULT within one year from gout diagnosis, and the majority of those starting (75%) did not persist with ULT within the following two years (294).

Furthermore, patients' adherence to treatment is poor and information about the disease is lacking. Although gout is the only inflammatory arthritis with 'curative' treatment, it is a common problem that it is seldom cured. A large, RCT demonstrated major improvements in achieving the target urate concentrations, flare frequency, presence of tophi, and quality of life in patients receiving nurse-led gout care according to treatment guidelines, compared to usual care by general practitioners (279). These results strongly support the importance of educating and engaging patients in gout management and T2T strategy. Educating the physicians is also important to overcome these barriers and achieve better management of gout (295). Our study suggests that there is large room for improvements in management of gout in the Swedish health care system, improvements that would result into better health quality of life for these patients.

Paper II

This large, population-based, case-control study demonstrates the pattern of existing comorbidities at the time of first gout diagnosis in the period 2006-2012. Overall, 77% of newly diagnosed gout cases had at least one comorbidity, compared to 56% of the controls.

Although many studies have shown a higher occurrence of comorbidities in patients with gout (296-298), there are few population-based studies in Europe (298). Furthermore, the time of comorbidity occurrence in relation to the diagnosis of gout has not always been addressed. Previous studies on sex

differences in the comorbidity pattern of gout included prevalent, and not incident gout cases (299-302).

Detection of existing comorbidities in newly diagnosed gout have important long-term health implications for these patients and should be of major priority. In two previous cluster analyses only 12% (303) and 36% (304) of gout patients respectively were considered to have isolated gout with few comorbidities. Some of the comorbidities associated with gout, including diabetes, ischemic heart disease (IHD), and alcohol use disorders, were reported to be among the leading 30 causes of years lived with disability (YLD), according to the Global Burden of Disease (GBD) Study 2016 (305). According to EULAR guidelines for the management of gout, all gout patients should be screened for associated comorbidities and CV risk factors, and initiation of ULT is recommended close to the first diagnosis for patients with renal impairment, hypertension, IHD, and HF (266). The pattern of comorbidities also has therapeutic implications. For instance, use of NSAID and colchicine should be avoided in patients with severe renal impairment, and in these patients the starting dose of allopurinol should be lower. Uricosuric drugs should be avoided in patients with a history of nephrolithiasis, and these drugs may be less effective in patients with CKD (306).

Our study also showed that all the examined comorbidities, expect for the diagnosis of alcoholism, were or tended to be more frequent in women with gout than in men. However, after standardizing for age, these differences attenuated, and the frequency of CVD was higher in men. A higher comorbidity burden in women with gout than in men has been reported in some previous studies (299, 300). These findings may have implications in the initiation and dose of ULT in women, as obesity, use of diuretics, and renal disease, comorbidities that were more frequent in women, influence urate levels and allopurinol daily maintenance dose. Dose requirements were found to increase by 2-fold to > 3-fold with increasing total body weight and were 1.25–2 times higher in those taking diuretics, whereas renal function had a relatively modest impact on the required allopurinol dose, according to a previous study (307). Taking age into account, the overall comorbidity pattern was similar in men and women supporting that pathophysiological pathways that operate through comorbidities are similar in both sexes. The results from our study suggest that occurrence of comorbidities is high at the time of first gout diagnosis, and comorbidity burden is higher in women, which must be taken into account when initiating ULT.

Paper III

This cross-sectional study investigated the association between urate levels and markers of subclinical atherosclerosis, CAC, CIMT, and carotid plaques, in the participants of pilot SCAPIS. Overall, urate levels >308 μmol/L were significantly associated with the presence of CAC in men, but not in women, after adjustments for traditional CV risk factors. In contrast, urate levels were not associated with CIMT or the presence of carotid plaques in either men or women.

Although urate is a major antioxidant, it can shift to pro-oxidant depending on levels and surrounding microenvironment. Whether increased urate is an independent risk factor that contribute to development of subclinical atherosclerosis is unclear and controversial. Furthermore, whether this would be of different magnitude in men or women, is also unclear. Results from previous observational studies have been conflicting, with some of them reporting a significant association between urate concentrations and CAC (197-202), CIMT (198, 213, 214, 217), or carotid plaques (224, 225), whereas other did not (203-205, 219-222). MR studies failed to show any causal association between urate and CHD or different CV events after correction for pleiotropy (231, 232). There are no previous studies on association between urate levels and subclinical atherosclerosis in Sweden.

Our results imply that urate has different biological effects in men and women or varying effects on different vascular beds or during the different stages of the atherosclerotic process. Further investigation with longitudinal studies to examine association between urate levels and progress av subclinical atherosclerosis is also important. Urate may be a risk factor for subclinical atherosclerosis in men, and this could be taken into consideration in patients at intermediate risk for CVD.

Paper IV

This large, population-based, cohort study investigated the risk of first-time ACS in patients with incident gout compared to the general population in the period 2007-2017. Overall, patients with incident gout were at increased risk of first-time ACS, which remained significant after adjustments for baseline comorbidities and treatment. A sensitivity analysis, where cases and controls with any diagnosed comorbidity were excluded, showed similar results. To our knowledge, there are no other studies in the literature conducted on a population without diagnosed comorbidities.

Our results imply that the risk of ACS in patients with gout is mainly depending on the associated comorbidities, and to a lesser extent, on gout itself. Whether gout is causally associated with CVD or not has been a debated issue in the literature. Observational studies have reported conflicting results, with some of them demonstrating a significant association between gout and CVD (250, 254, 308), whereas other did not (255). MR studies did not support any causal association between urate and CHD (231); however, there are no MR studies on gout and CVD, where additional pathophysiological components, such as inflammation, may alter these results.

In our study, women were found to have higher relative risk of first-time ACS than men (adjusted HR, 1.21 *vs* 1.12). The absolute risk difference was also higher in women than in men (3.2 *vs* 2.5 events per 1,000 person-years). Some previous studies also showed that women with gout had higher relative risk of CVD (253, 256), whereas other studies showed that the relative risk was higher in men (252). Since gout and CVD have historically been considered diseases that primarily affect men, our findings have important implications in clinical practice. The physicians need to pay more attention in optimal gout treatment and optimal CV risk management in women.

According to the GBD study 2017, 17.8 million people globally died of CVD, classifying it as the most frequent cause of death worldwide (309). Except for the traditional CV risk factors, several non-traditional have been identified and should be managed properly. Chronic inflammation is associated with all the stages of atherosclerosis, and hyperuricemia may also contribute to endothelial dysfunction, VSC proliferation, and oxidative stress. Our study highlights the need of optimal treatment of gout to eliminate inflammation and lower urate levels. It also highlights the importance of identification and management of CV risk factors, including even lifestyle factors, as smoking, physical activity, obesity. Systematical screening for CV risk factors is also recommended by the EULAR guidelines, where it is addressed as an integral part of the gout management (266).

6 FUTURE PERSPECTIVES

Overall, this thesis showed that gout has an increasing incidence in Western Sweden during the last decade, but its treatment is suboptimal. Patients with gout have a high burden of comorbidities and are at increased risk of first-time ACS. Urate levels may be associated with coronary artery calcification in men.

As studies on the epidemiology of gout have shown a wide regional variation, further studies from other regions in Sweden are important. Selection of patients using register databases detects only those who have sought medical advice from the health care system, which may lead to underestimation of the prevalence of the disease. Further studies to investigate the proportion of patients with undetected gout are also important for a more accurate prevalence estimation, mainly due to the consequences of the disease in the medical care and society.

Treatment with ULT was found to be suboptimal in 2012, but whether ULT use has increased during the last years is important to study. Implementation of T2T strategies in the Swedish health care system, education of patients and physicians about the disease, and engagement of patients in the gout management are important issues to address in the future to achieve optimal treatment and better quality of life, as demonstrated in previous studies (279, 295).

Previous MR studies examined the association between urate and CVD. It is also important to address in future research if there is any causal association between genetically determined urate levels and subclinical atherosclerosis, as the results from observational studies are conflicting.

Whether ULT has beneficial effect on CV risk remains unclear. Allopurinol is the first line ULT recommended by the EULAR and American College of Rheumatology (ACR) guidelines for the management of gout (266, 310). Allopurinol lowers urate levels, but also inhibits XO and may reduce the production of reactive oxygen species (ROS) and the oxidative stress. A study on whether treatment with allopurinol reduces the risk of first-time ACS in patients with incident gout in Western Sweden is in progress. Moreover, future studies on the effect of T2T strategy on CV risk are also important. Two large, post-marketing RCTs were performed to investigate the association between

treatment with febuxostat and adverse CV events compared to treatment with allopurinol. CARES (267) showed that febuxostat was associated with 49% higher risk of CV mortality compared to allopurinol, whereas FAST trial (268) showed that long-term treatment with febuxostat was not associated with higher risk of CV events compared to allopurinol. However, whether allopurinol and febuxostat are cardioprotective needs to be addressed by future RCTs with placebo group.

Another important question for further research is if gout patients are underdiagnosed or undertreated regarding CV risk factors compared to the general population or other types of inflammatory arthritis. Systematic use of established cardiovascular risk scores is very important, but whether existing scores underestimate the CV risk in patients with gout needs to be examined in the future. A multiplication factor to the CV risk score model for patients with rheumatoid arthritis is already used and it is important to investigate if multiplication factor for patients with gout is needed.

7 CONCLUSIONS

- The prevalence of gout in Western Sweden in 2012 was 1.8% and the incidence was 190 cases per 100,000 person-years.
- The treatment of gout in Western Sweden in 2012 was suboptimal, with only 42% of gout patients having received ULT.
- The comorbidity burden at the time of first gout diagnosis was high, with 77% of gout patients having at least one comorbidity, compared to 56% in the general population.
- The comorbidity burden was higher in women with gout than in men, which may have implications in dosing of ULT.
- Serum urate levels were associated with the presence of coronary artery calcification in men but not in women.
- Patients with gout were at increased risk of first-time ACS, compared to the general population. This risk was mainly explained by the higher occurrence of comorbidities, but there was still a remaining risk that may depend on gout itself.
- Overall, the results of this thesis highlight the importance of improvements in the management of gout in the Swedish health care according to T2T strategy, as well as in CV risk assessment and management of underlying CV factors. Improvements that are going to translate into better quality of life for these patients.

ACKNOWLEDGEMENT

I would like to thank everyone who has contributed to this thesis!

Especially I would like to thank:

All the patients for their invaluable contribution to the studies.

My supervisor Mats. Thank you, Mats, for all help and support during these years! Thank you very much for sharing your knowledge, for always being available to answer my questions, and all the time invested with enthusiasm, wisdom, and patience in helping me to accomplish this journey!

My co-supervisor Lennart. Lennart has been my supervisor since 2012, already before I started working at the Rheumatology Department. Thank you very much, Lennart, for guiding me from my very first steps in research and during all these years! Thank you for all encouragement, support, and valuable advice!

Co-authors, Helena F, Ulf L, Karin B, Vala S, and Anna S. Thank you for the time and effort you have invested and all helpful advice and comments.

Co-authors from SCAPIS group, Göran B, Oskar A, and Caroline S. Thank you for an excellent cooperation.

Tatiana, thank you for all your help with such patience and kindness, and your valuable advice regarding statistical analyses.

My colleagues and the head of the Rheumatology Department at Sahlgrenska University Hospital. Thank you for all good times and support, and for having created a research-friendly work environment.

The Department of Rheumatology and Inflammation Research, and my colleagues at our clinical research group. Thank you for contributing with good advice and valuable comments during our discussions.

My parents, Maria and Giannis, my brother Thanasis, and my friends. Thank you for encouraging me and for always being there whenever I needed.

Last but not least, my husband Nikos and our two children, Marietta and Dimitris. You are the meaning of my life ♡.

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