GOUT - EPIDEMIOLOGICAL STUDIES ON WORK OUTCOMES, AIRBORNE RISK FACTORS AND TREATMENT PATTERNS

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Cover illustration: The image shows massive aggregation of uric acid crystals viewed under polarised light with 400 x enlargement. Photograph by Marius Lund-Iversen.

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ABSTRACT

The overall aim of the thesis was to describe the contemporary epidemiology and use of urate-lowering therapy (ULT) for gout in the Swedish region of Dalarna, to describe the impact of the disease with regard to sickness absenteeism and to explore potential novel environmental and occupational-related risk factors for gout in the Western Swedish Healthcare Region.

All of the studies used prospectively registered healthcare-, socioeconomic- and administrative data, exploiting the possibility to link individual-level data from different sources with the unique personal identity number that all Swedish residents are given.

In Paper I the incidence rate of gout in Dalarna was 247 cases per 100 000 person-years in 2019, whereas the prevalence in 2018 was 2.45%. Substantial under-use of ULT was found, as 76% of prevalent cases had an indication for ULT, whereas only 24% received treatment. Minor improvements in quality-of-care indicators were demonstrated after the publication of national clinical gout management guidelines in 2016.

Paper II showed that patients with gout had 56% more sickness-absenteeism days than matched population controls and that gout was a predictor for new-onset sickness-absenteeism.

In Paper III we demonstrated a modest association between occupational exposure to inorganic dust and incident gout (odds ratio (OR) 1.12, 95% confidence interval (CI) 1.04 to 1.20).

In Paper IV, we found no association between long-term exposure to residential air pollution and incident gout.

In conclusion, gout is a common and poorly managed condition. Sickness absenteeism is increased among gout patients, which has economic consequences for both the affected individuals and society. Occupational exposure to inorganic dust might increase the risk of gout, whereas long-term exposure to residential air pollution is not a risk factor for gout in the Swedish setting.

Keywords: gout, crystal arthritis, epidemiology

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SAMMANFATTNING PÅ SVENSKA

Gikt uppstår på grund av höga uratnivåer i blodet. De flesta som har höga uratnivåer får aldrig gikt, men hos vissa bildas uratkristaller som ansamlas i leder och mjukdelar. Uratkristallerna utlöser sedan en inflammatorisk reaktion i leden som hos den drabbade yttrar sig med ett giktanfall, den berörda leden (eller lederna) blir röd, varm, svullen och smärtsam. Giktanfallet varar oftast i 7–10 dagar. Det är ofullständigt känt varför bara vissa personer med höga uratnivåer får gikt, därför är det av intresse att studera faktorer som skulle kunna förklara det, såsom yrkes- och miljömässiga faktorer.

Vid obehandlad gikt får en stor andel av patienterna med tiden återkommande giktanfall och en del utvecklar synliga inlagringar av uratkristaller under huden och i mjukdelar kring leder, så kallade tofi. Akuta giktattacker behandlas med symptomlindrande antiinflammatoriska läkemedel, men för att sänka uratnivåerna i blodet och därmed förhindra framtida giktattacker används uratsänkande läkemedel. Svenska behandlingsrekommendationer för gikt publicerades 2016. Svenska och internationella behandlingsrekommendationer poängterar att behandling med uratsänkande läkemedel bör vara målstyrd, dvs läkemedelsdosen ska individanpassas för att uppnå en tillräcklig låg uratnivå, beroende på svårighetsnivå av gikt under 360 µmol/L eller under 300 µmol/L.

Det övergripande syftet med denna avhandling har varit att studera förekomsten av gikt och användning av uratsänkande läkemedel, att undersöka giktsjukdomens påverkan på sjukfrånvaro och att studera yrkes- och miljömässiga riskfaktorer för gikt.

Alla studier i avhandlingen är registerstudier där vi använt anonymiserade uppgifter som registrerats i regionala- och nationella register i samband med rutinsjukvård av individer med gikt, så som diagnoskoder och förskrivna läkemedel. Sådana sjukvårdsdata har kompletterats med uppgifter från nationella register, till exempel information om sjukfrånvaro, yrke, adresskoordinater och utbildningsnivå, för att besvara frågeställningarna.

I delarbete I fann vi en förekomst av gikt på 2.45% i Dalarnas vuxna befolkning. Endast en fjärdedel av giktpatienterna behandlades med uratsänkande läkemedel trots att minst 76% uppfyllde kriterier för att få sådan behandling. Vissa förbättringar vad gäller uppföljning och måluppfyllelse vid uratsänkande behandling sågs efter 2016.

I delarbete II såg vi att personer med gikt i Västra Götaland hade 56% mer sjukfrånvaro jämfört med jämförelsepersoner utan gikt. Gikt ökade dessutom risken för nytillkommen sjukfrånvaro med 45%, efter hänsynstagande till annan samsjuklighet.

I delarbete III fann vi att risken för att få en giktdiagnos var ökad hos individer som hade yrken där man var exponerad för oorganiskt damm. Riskökningen var dock inte längre signifikant när vi i analysen justerade för utbildningsnivå.

I delarbete IV fann vi inga samband mellan långtidsexponering för luftföroreningar och gikt.

Gikt är således en vanlig och underbehandlad sjukdom som har ekonomiska konsekvenser för individen och samhället i form av sjukfrånvaro. Förbättrad implementering av behandlingsrekommendationer behövs. Exponering för oorganiskt damm eller luftföroreningar har en begränsad betydelse för sjukdomens uppkomst.

LIST OF PAPERS

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

I. **Sigurdardottir V**, Svärd A, Jacobsson LTH, Dehlin M. Gout in Dalarna, Sweden – a population-based study of gout occurrence and compliance to treatment guidelines. Scand J Rheumatol. 2022; Published online first: 27 Oct 2022; DOI: 10.1080/03009742.2022.2132055

II. **Sigurdardottir V**, Drivelegka P, Svärd A, Jacobsson LTH, Dehlin M. Work disability in gout: a population-based case-control study. Ann Rheum Dis. 2018;77(3):399-404.

III. **Sigurdardottir V**, Jacobsson LTH, Schiöler L, Svärd A, Dehlin M, Toren K. Occupational exposure to inorganic dust and risk of gout: A population-based study. RMD Open. 2020;6(2).

IV. **Sigurdardottir V**, Svärd A, Jacobsson LTH, Molnar P, Barregård L, Segersson D, Stockfelt L, Dehlin M. Exposure to residential air pollution and risk of gout. Manuscript.

CONTENT

ABBREVIATIONS

ACR	American College of Rheumatology
AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
DECT	Dual-energy computed tomography
EHR	Electronic health record
EULAR	European League Against Rheumatism
FEUA	Fractional excretion of uric acid
GFR	Glomerular filtration rate
GWAS	Genome wide association study
HAQ-DI	Health assessment questionnaire – disability index
HR	Hazard ratio
ICD	International Classification of Diseases
IL	Interleukin
IQR	Interquartile range
MSU	Monosodium urate
MTP	Metatarsophalangeal
NHANES	National Health and Nutrition Examination Survey
NHIRD	National health insurance research database (of Taiwan)
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
NO_x	Nitrogen oxides
OR	Odds ratio
OSA	Obstructive sleep apnoea
PAF	Population attributable fraction
PASI	Psoriasis area severity index
PM_{10}	Particulate matter with diameter <10 μm
$PM_{2.5}$	Particulate matter with diameter <2.5 μm
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SF-36	36 item short form health survey
SU	Serum urate
ULT	Urate-lowering therapy

INTRODUCTION

GOUT – CLINICAL PRESENTATION

Gout is an inflammatory arthritis caused by an immunological response to monosodium urate (MSU) crystals deposited in articular and periarticular structures. MSU crystal deposition and consequently gout preferentially occurs in the extremities, although axial MSU crystal deposition (1) and axial gout has been reported (2). The most common initial presentation of gout is an acute flare of painful monoarthritis in the lower extremity, which completely resolves after 7-10 days and is followed by a symptom-free period (intercritical period) that varies in duration between patients.

In most patients, the first gout flare is a monoarthritis of the first metatarsophalangeal (MTP) joint. The MTP joint is affected in 58-84% of gout patients at some timepoint during the disease course (3-6).

Involvement of the ankle or other joints in the foot, or the knee is seen in 50% and 32% of patients respectively over time, whereas involvement of joints in the upper extremities is less frequent (fingers 25%, elbow 10%, wrist 10%) (4).

As for most diseases, there is a spectrum of gout severity, some patients have infrequent recurrent gout flares, whereas others go on to develop a more chronic form of gout, with frequent flares and an increasing number of affected joints, eventually progressing to a deforming erosive chronic polyarthritis. This later stage of the disease is referred to as tophaceous gout, as it is characterized by visible and palpable subcutaneous depositions of MSU crystals (tophi), microscopically consisting of an inner core of MSU crystals, enclosed by a chronic granulomatous inflammatory response and dense connective tissue (7).

Reports on the natural history of untreated gout are scarce. In a unique report from 1973 by Gutman (8), using data from a cohort of 392 gout patients diagnosed and followed before effective urate-lowering therapy (ULT) was available, it was shown that 29% had tophi 1-5 years after the initial presentation of gout. The proportion of patients with tophi increased to 47%, 61%, 71% and 72% among those alive at 6-10 years, 11-15 years, 16-20 years and >20 years after initial presentation respectively. Among those followed for >20 years, 24% had developed “extensive crippling tophaceous gout”. There was an association between mean serum urate (SU) levels and the development of tophi over time.

GOUT PATHOGENESIS AND RISK FACTORS

Gout pathogenesis is a stepwise process, progressing from normouricemia, to asymptomatic hyperuricemia, MSU crystal formation and deposition, culminating with an inflammatory response to MSU crystals, presenting as clinical gout, which in a proportion of individuals progresses further to tophaceous gout (Figure 1).

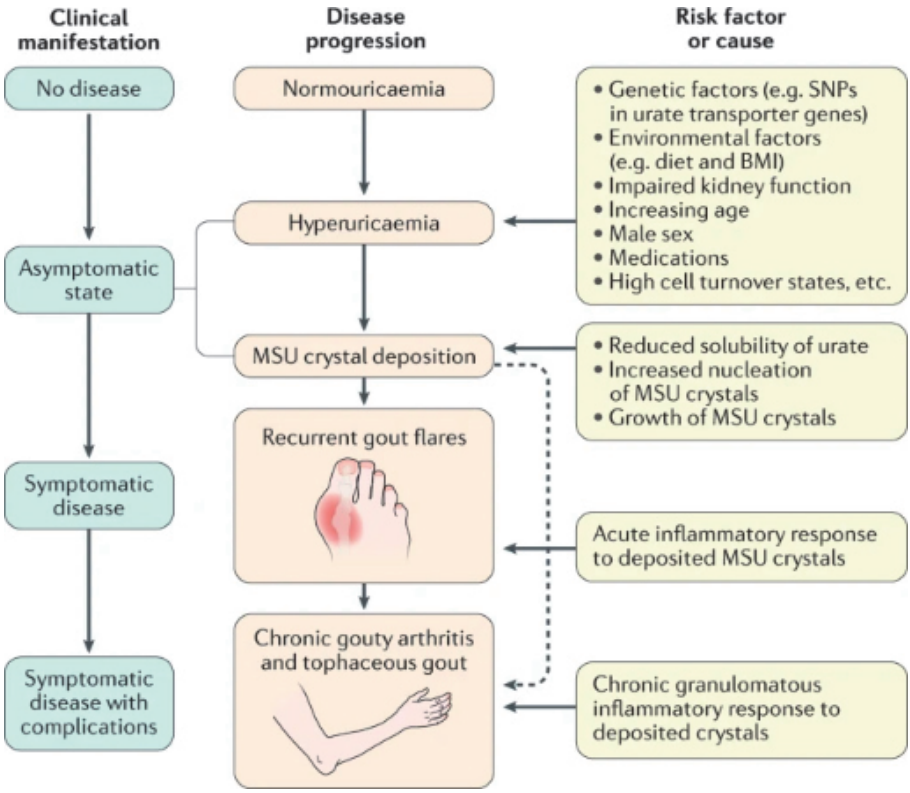

Figure 1. The transition from normouricaemia to clinically evident gout occurs in a number of steps. The first step is the development of hyperuricaemia, which can be caused by various factors, including genetic variants, chronic kidney disease, high body mass index (BMI), medications and dietary factors. In some individuals with hyperuricaemia, monosodium urate (MSU) crystal deposition occurs, and in some individuals with MSU crystal deposition, the clinical manifestations of gout (gout flares, chronic gouty arthritis and tophaceous gout) occur. Factors that contribute to the transition from hyperuricaemia to clinically evident gout are less well understood. SNP, single-nucleotide polymorphism.
Reproduced with permission from Nat Rev Dis Primers. 2019;5.

Hyperuricemia - the main risk factor for gout

Hyperuricemia (commonly defined as SU>405 µmol/L) is the main risk factor for gout, as was recognized already in the 19th century by Garrod (9). Multiple studies have reported the incidence of gout over time as a function of baseline SU levels (10-15). A universal finding across such studies is that even among people with very high SU levels, only a minority develop gout.

In a Swedish cohort study of 33 335 participants, it was shown that the absolute risk (prevalence) of gout was 13.3% for men and 17.7% for women with SU > 405 µmol/L at baseline after 30 years of follow-up (14).

The proportion of people developing gout over a period of 15 years stratified by baseline SU levels was illustrated in a post-hoc analysis by Dalbeth et al of 18 889 subjects from 4 longitudinal cohort studies that were gout-free at baseline (13). Among those with SU ≥ 595 µmol/L at baseline, around 50% were still gout-free after 15 years of follow-up (Figure 2).

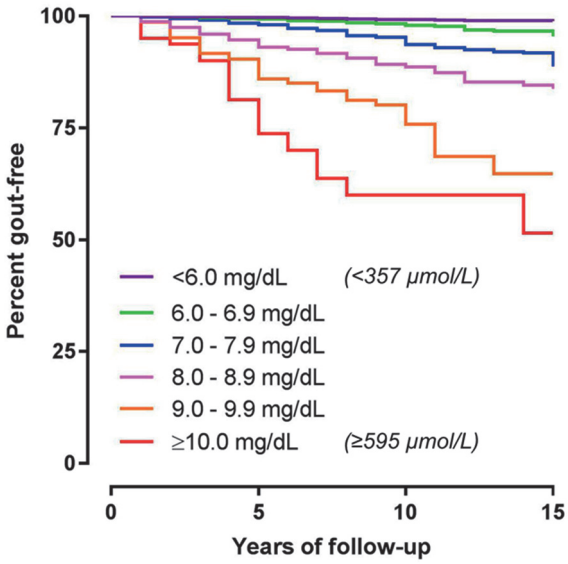

Figure 2. Kaplan-Meier plot showing the percentage of participants who were gout-free over the follow-up period, based on baseline serum urate categories.
Adapted and reproduced with permission from Ann Rheum Dis. 2018;77:1048-52.

Urate levels in serum are dependent on the balance between urate production and excretion and the multitude of factors that can influence this balance (Figure 3).

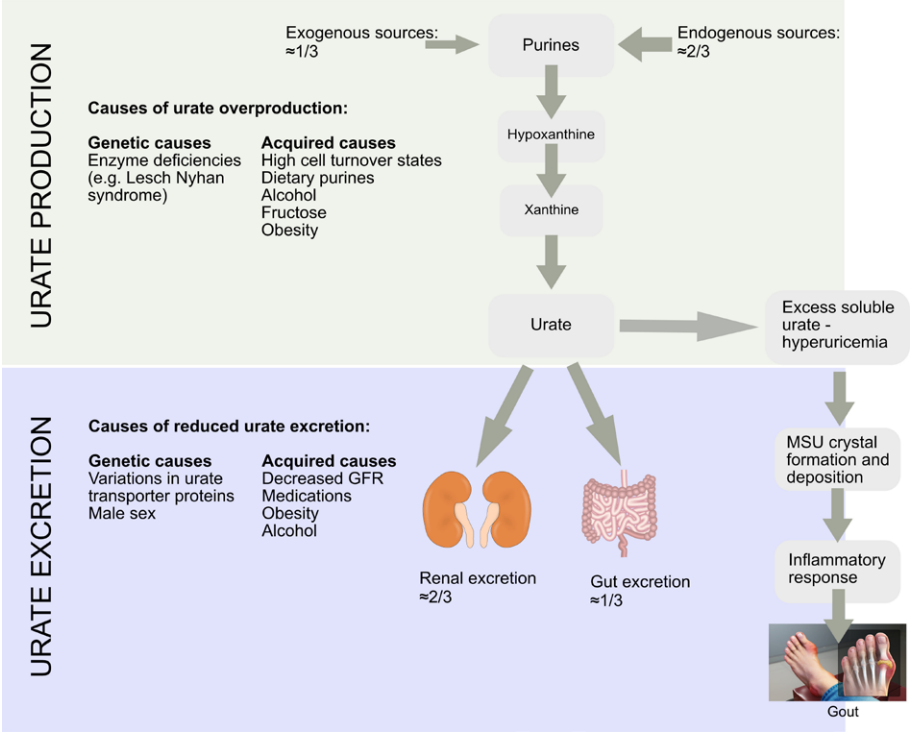

Figure 3. Schematic overview of urate production, urate excretion and its determinants.

Urate production

Due to lack-of-function inducing mutations in the uricase enzyme (which in other species catalyses the breakdown of urate to allantoin), urate is the end product of purine degradation in humans (16, 17).

Ingested dietary purines are often stated to contribute approximately 1/3 of the total purine pool of the body, whereas the remainder is endogenously generated by metabolic- and cell turnover processes that provide substrate (purine nucleoside monophosphate derivatives) to the purine degradation pathway, e.g. when adenosine triphosphate (ATP) is degraded to adenosine monophosphate (AMP) (18-20).

Urate elimination

Urate is eliminated by the kidneys (2/3) and the gut (1/3), these widely stated estimates on the relative contributions of each route originate from experiments in the 1940s-1960s using isotopically labelled urate (21).

Renal excretion

The glomeruli filtrate almost all urate from the blood, but in the end only 3-10% of the filtered urate is excreted in the urine, as most of the filtered load is reabsorbed in the renal tubuli (20). Thus, provided glomerular filtration is adequate, the extent of renal urate elimination is mostly determined by the reabsorption and secretion of urate in the renal tubuli.

Renal excretion of urate can be quantified by calculating the fractional excretion of uric acid (FEUA), i.e. the proportion of filtered urate that is excreted in the urine.

Intestinal elimination of urate

Recently, it has been found that excretion of urate into the intestinal lumen is dependent upon the function of the urate transporter protein ABCG2 (22). Urate that is excreted into the intestinal lumen is metabolized by gut bacteria. Although human tissues do not express functional uricase, it was shown in the 1960s that intestinal bacteria are capable of degrading urate by uricolysis and that approximately one-third of the urate formed daily is degraded and eliminated by the intestinal route (21). Further, it was shown that bacteriostasis with phthalylsulfathiazole, streptomycin and neomycin inhibited the degradation of urate in the intestine (21).

From recent studies there is evidence that the gut microbiota in gout patients differs from that of healthy controls (23, 24), which might influence the capacity for intestinal urate elimination.

Risk factors for hyperuricemia

Genetic factors

Genetic variations in urate transporter proteins

Urate transport in the renal tubuli is regulated by urate transporter proteins that exchange urate for intracellular anions. Genome-wide association studies (GWAS) have identified multiple loci associated with variability in urate

levels, where many have been found to code for such urate transporter proteins (25).

The genes most strongly and consistently associated with variation in SU levels across large GWAS studies are genes that encode the urate transporters GLUT9, URAT1, NPT1 and ABCG2 (26), the last being involved in urate transport in both the gut and kidneys.

Sex
Premenopausal females have lower SU levels than men, the exact mechanism for this is unknown, but as it has been found that females have higher renal urate excretion it is thought to be mediated by an uricosuric effect of oestrogen, a theory that is supported by studies confirming urate-lowering effects of oestrogen therapy (27, 28). Novel findings from a large GWAS study of gout have also implicated genes involved in the regulation of urate production in the prostate as associated with gout (29).

Acquired factors

Chronic kidney disease
SU levels are increased in chronic kidney disease, with the prevalence of hyperuricemia increasing with worsening glomerular filtration rate (GFR) (30). The relationship between the GFR and SU levels is however not as predictable as the relationship between GFR and serum creatinine, which is consistent enough that serum creatinine is used in equations to estimate the GFR, such as the Modification of Diet in Renal Disease (MDRD) Study equation (31) and The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (32). The imperfect association between GFR and serum urate is explained by the fact that when glomerular filtration decreases, compensatory increases in the renal fractional excretion of urate occur (33) and also elimination of urate by the gut can increase, possibly mediated by compensatory increased expression of the ABCG2 transporter in the gut (34, 35).

Medications
Renal excretion of urate is reduced by several medications, most notably by diuretics (36).

Obesity
High body mass index (BMI) is associated with hyperuricemia. In a Japanese longitudinal cohort study with a follow-up of 8 years the hazard ratio (HR) for

incident hyperuricemia was 1.19 (95% confidence interval (CI) 1.04-1.35) per 2.64 kg/m^2 increment of BMI at baseline (37).

Renal urate excretion is reduced in obesity (38). It is often stated in the literature that obesity both increases endogenous urate production and decreases urate excretion. Support for this claim can be found in a case report from 1973 where the urate metabolism of a man with gout was extensively investigated before and after an 18 kg weight loss, finding a decrease in endogenous urate production as well as in increase in renal urate excretion (39).

In a more recent study, changes in SU and FEUA during 180 minutes after an oral inosine load were compared between subjects with BMI<25 (n=48) and subjects with BMI≥25 (n=52) (40). At baseline, SU levels were higher in the BMI≥25 group (320 µmol/L vs 270 µmol/L, p=0.0002), but FEUA was similar between the groups. In response to the purine load, SU increased in both groups, with a larger absolute change in the normal weight group. Conversely, the increase in FEUA was smaller in the overweight group, suggesting that the capacity for increasing the renal clearance of urate in response to dietary purines is reduced in people with above normal BMI (40).

The underlying mechanism of impaired renal urate excretion in obese individuals is unclear but could be mediated by decreased insulin sensitivity and increased insulin concentrations as this enhances renal tubular sodium reabsorption, which in turn decreases renal urate excretion (41). This is supported by an interventional study that showed reductions in SU in overweight subjects with hypertension assigned to either dietary intervention or the insulin-sensitizing agent troglitazone (42). Although only those assigned to the dietary intervention lost weight, SU, insulin concentrations and insulin sensitivity improved to a similar extent in both groups (42).

Overproduction of urate in obesity might contribute to hyperuricemia to some extent, although decreased renal excretion of urate seems to be the most important mechanism for hyperuricemia in obesity. Overproduction of urate in the obese might be explained by increased supply of free fatty acids (e.g. from lipolysis of visceral fat), where further metabolism in the liver provides substrate for the de novo purine pathway, hence enhancing urate production (43) .

Several studies have reported the effect of weight loss on SU and/or FEUA.

An interventional study including 27 severely obese subjects showed decreasing SU and increasing FEUA after weight reduction (38).

In an intervention trial of 12 379 men at high risk for cardiovascular events (79% of participants had a BMI>25 kg/m^2), weight loss in the range of 1 to 4.9 kg, 5 to 9.9 kg and ≥10 kg was associated with reductions in SU of **-7, -19** and **-37 µmol/L** (44).

In the Swedish Obese Subjects study, involving obese subjects who underwent bariatric surgery and controls who were conservatively treated, mean weight loss 2 years after bariatric surgery was 23.4%, this was accompanied by a 14.9% decrease in urate levels from baseline **(≈54 µmol/L)**. The percentage of subjects with hyperuricemia (defined as SU >450 µmol/L) fell from 16% to 4% (45).

In a dietary intervention trial including 13 men with gout and a median BMI of 30.5 kg/m^2 at baseline, a weight loss of 7.7 kg was accompanied by a decline in SU of **100 µmol/L** (46).

Diet

The effect of diet on SU levels is more complex than the purine content of the diet, e.g. fructose exerts effects on SU levels that are not related to purine content, by causing increased degradation of ATP to AMP in the liver (47-49).

In the National Health and Nutrition Examination Survey (NHANES)-III study (50), conducted in 1988-1994, dietary exposures were defined based on data from a food frequency questionnaire administered at home interviews. Participants were then invited to attend examination sessions where blood samples were collected. Effects of individual food items on SU were estimated, with and without adjustment for age, sex, total energy intake, BMI, use of diuretics, β-blockers, allopurinol, and uricosuric agents, self-report of hypertension and gout, serum creatinine level and other food items.

Higher intake of meat and seafood was associated with higher SU levels, whereas the inverse was true for dairy intake (50). In the multiadjusted model, SU was 0.11 mg/dL **(≈6.5 µmol/L)** (95% CI 0.01-0.22) higher for individuals in the highest quintile of meat intake (lowest quintile as reference). For seafood, the SU elevating effect of being in the highest quintile of intake was 0.10 mg/dL (95% CI 0.02-0.18). Individuals in the highest quintile of dairy intake had SU levels that were 0.19 mg/dL **(≈11.3 µmol/L)** lower than those in the lowest quintile, 95% CI 0.09-0.30 (50). Total protein, as % of energy intake was not associated with urate levels.

The multiadjusted difference in SU for the highest quintile of sweetened soft drinks compared to the lowest was 0.42 mg/dL **(≈25 µmol/L)**, 95% CI 0.11-0.73 (51).

Drinkers of >6 cups of coffee per day as compared to non-coffee-drinkers, had 0.36 mg/dL **(≈21 µmol/L)** (95% CI 0.14-0.57) lower SU, tea and non-caffeinated coffee intake was not associated with SU (52).

The effects of fructose on SU levels has been investigated in several randomized controlled trials (RCTs). In one trial including healthy adult men, the administration of 200 g fructose daily for 2 weeks caused an increase in SU of **65 µmol/L** (21% increase from baseline), whereas in the control group, where subjects received the urate-lowering drug allopurinol in addition to fructose, SU decreased with 32% (53). Another trial showed an increase in SU of 12% from baseline after 10 weeks of consuming fructose-sweetened beverages in a daily amount corresponding to 25% of the total energy requirement, whereas in the control group that consumed glucose-sweetened beverages, SU increased by 4% (54).

As opposed to studying the effect of individual diet components, other studies have examined the effect of dietary patterns on SU levels.

Adherence to the Mediterranean diet (as assessed by the MediDietScore) was associated with lower urate levels in a cross-sectional study of 2380 men and women free of cardiovascular and renal disease (55). The magnitude of the effect was a lowering of SU of 0.07 (95% CI 0.01 to 0.13) mg/dL **(≈4 µmol/L)** per quartile increase in MediDietScore, the model was adjusted for age, sex, body mass index (BMI), smoking, hypertension, alcohol intake, coffee intake and insulin resistance (55).

In an interventional study with randomized cross-over design of 103 adults with hypertension or pre-hypertension, the dietary approaches to stop hypertension (DASH) diet reduced SU by 0.35 mg/dL **(≈21 µmol/L)** (95% CI 0.05-0.65) (56).

Alcohol

Apart from beer, alcoholic beverages are not rich in purines (57, 58). Alcohol increases SU levels through several mechanisms. Similarly to fructose, alcohol increases SU by enhancing the degradation of ATP to AMP in the liver, providing increased substrate for the purine degradation pathway. Alcohol also reduces the renal excretion of urate, this is thought to be mediated by an

increased concentration of lactic acid, generated by the metabolism of alcohol, interfering with urate excretion (59, 60).

For total alcohol intake in the NHANES-III, multiadjusted difference of SU between highest quintile and lowest was 0.33 mg/dL **(≈20 µmol/L)** (95% CI 0.21-0.45). This was driven by beer and liquor, whereas wine was not associated with urate levels (61).

Other Disease states associated with hyperuricemia
Hyperuricemia is frequently observed in patients with myeloproliferative or lymphoproliferative diseases (62) and is a hallmark of the tumour lysis syndrome.

SU levels are commonly elevated in psoriasis, in a recent meta-analysis the mean difference in SU between psoriasis patients and controls was 0.99 mg/dL **(≈59 µmol/L)** (95% CI 0.48-1.49) (63). In an Italian case-control study, hyperuricemia was overrepresented in patients with psoriasis compared to matched controls, even after controlling for features of the metabolic syndrome (64). SU levels in psoriasis has been found to associate with disease activity by psoriasis area severity index (PASI) score, indicating that increased turnover of epithelial cells is implicated (64, 65), although the impact of a large improvement in PASI score was only associated with a minor reduction of SU in a post-hoc analysis of pooled data from three placebo controlled RCTs of secukinumab treatment for psoriasis (66).

Patients with obstructive sleep apnoea (OSA) commonly have elevated urate levels (67). Theoretically, tissue hypoxia in OSA could enhance urate production through increased ATP degradation which accompanies tissue hypoxia (19). OSA has been postulated to be an independent risk factor for gout (68, 69). An observational study reported a statistically significant reduction in SU from 8.8 to 6.2 mg/dL after 6 months of continuous positive airway pressure (CPAP) therapy among 32 CPAP-compliant OSA patients (70), whereas a randomized placebo-CPAP controlled trial did not find any effect on SU levels after 3 months (71).

Lead
Lead exposure increases SU levels, this is thought to be primarily due to nephrotoxicity and consequent reductions in GFR, but there is also some evidence from in vitro and animal experiments for the ability of lead to increase urate production (72-74).

Nature or nurture as the cause of hyperuricemia?

The relative importance of genetic and acquired/reversible factors (such as diet, alcohol consumption and obesity) in the causation of hyperuricemia (and consequently gout) is a complex and controversial issue.

That urate levels are to a large extent (45-73%) genetically determined is known from classical twin-studies, where heritability is estimated by comparing phenotypic variation between monozygotic and dizygotic twin-pairs (75-77).

In total, GWAS identified loci have been found to explain 7% of the variability in urate levels (25), i.e. identified genes by GWAS only account for a small part of the heritability of urate levels demonstrated by twin studies.

Probably, some of the heritability unaccounted for lies in uncommon variants not detected by the GWAS methodology (26). Also, it is known that dietary preferences (78), BMI (79) and alcohol consumption (80) are in part genetically determined traits.

A recent meta-analysis of population-based cohorts found that genetics explained 24% of the variability in urate levels whereas none of the studied dietary factors or patterns explained more than 0.3% of the urate variability (81). The authors conclusion, that in contrast with genetic contributions, diet explains very little of the variation in SU levels in the general population, has been harshly criticized, on the basis of the methodology used, i.e. using "variance explained" as an effect measure as opposed to population attributable fraction (PAF) (82). As the explained variance for an exposure in a given set of data is dependent on the variability of the exposure in the data, this means that risk factors that are highly prevalent (i.e. have low variability in the data) will not explain a great deal of variance in the outcome. In contrast, the PAF considers both the effect size and the prevalence of the exposure. A later study by the same authors reported both variance explained and PAFs for genetic, anthropometric and dietary risk factors of hyperuricemia, finding a PAF for hyperuricemia of 20-24% for non-adherence to dietary recommendations, 59-69% for having a BMI > 25 kg/m2 and 57-64% for having the rs12498742 A-allele of the urate transporter protein SLC2A9 (83).

Whether genes or lifestyle factors are the main culprits in causing hyperuricemia (and gout) remains an unresolved issue. From a pragmatic clinical point of view, it seems reasonable to advice the hyperuricemic gout patient to address potential correctable causes of hyperuricemia, such as obesity, poor diet and alcohol consumption, bearing in mind that the urate-

lowering achieved with dietary interventions and weight loss strategies are at best modest even in clinical study settings, in the range of 50-100 μmol/L, which is insufficient to achieve clinical benefits for most patients with gout.

MSU crystal formation and deposition

Obtaining detailed knowledge of the distribution and extent of MSU crystal deposition in the human body has been limited by the fact that MSU crystals are dissolved by formalin (84), and therefore MSU crystals disappear from routine formalin-fixed pathology tissue samples. The demonstration of MSU crystal deposition in tissue samples thus requires fresh frozen or alcohol-fixed samples, although the optimal method to retain MSU crystals in tissue samples has not been determined (85). New imaging techniques capable of demonstrating MSU crystal deposition (dual-energy computed tomography (DECT) and ultrasound) have added much valuable information in recent years.

While hyperuricemia clearly is the main risk factor for MSU crystal formation, as crystallization requires urate concentrations above the threshold for solubility (405 μmol/L at physiologic conditions (37°C, Na^+ concentration 140 mM)) (86), in a majority (58-76%) of individuals with asymptomatic hyperuricemia, no MSU crystal deposits are detected by advanced imaging (6, 87-91). This underscores the notion that elevated urate levels are not sufficient for MSU crystal depositions and gout to develop and strongly implies the existence of risk factors (or protective factors) for gout unrelated to hyperuricemia.

The threshold for MSU crystallization is lowered with decreasing temperatures (92), which is thought to explain the predilection for gout to occur in the peripheral joints where temperature is often considerably below 37°C (93).

In addition, the threshold for solubility of urate is affected by pH (increased at very high and very low pH), the concentration of urate ions in the solution per se as well as the concentration of Na^+ and other ions (92).

In the light of the observation that MSU deposition, gout and osteoarthritis often co-occur in the same joints (94), with exception of the hip, where osteoarthritis but not gout is common, it is interesting that experimental studies have shown that factors derived from cartilage, protein polysaccharides and proteoglycans, can enhance urate solubility, but only when they are structurally intact (95, 96) as this could provide a possible explanation for the tendency of gout to occur in joints with osteoarthritic degenerative changes.

The processes of crystal nucleation and growth of crystals is primarily enhanced by increased concentration of urate, in addition uric acid binding antibodies, globulins, collagen, lead, human serum and synovial fluid have been found experimentally to increase crystal nucleation (92). In vitro evidence has also suggested that acetate, a product of ethanol metabolism (97), and lead (98) can enhance MSU crystallization.

Inflammatory response to MSU-crystals

In the 1960s it was established in human and canine models of gout that the gout flare is caused by an acute inflammatory response to MSU crystals (99, 100).

The acute inflammatory response to MSU crystals in gout is driven by an activation of the innate immune system, where the release of the proinflammatory cytokine interleukin-1β (IL-1β) by monocytes and macrophages leads to the recruitment of neutrophils. The release of IL-1β is dependent on the activation of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)-inflammasome by MSU crystals (101). Inflammasome activation requires two signals; in the first step cells are primed for inflammasome assembly and in the second step, which in the case of gout is triggered by MSU crystals, inflammasome assembly ensues (102).

MSU crystal deposition is not invariably (or at least not immediately) accompanied by an inflammatory response and the progression to clinical gout. This is evident from imaging studies, where MSU deposits have been demonstrated in individuals with asymptomatic hyperuricemia (6, 87-89). Also, it is not unheard of that patients present with tophi without a clinical history of inflammatory arthritis (103).

The gout flare is self-terminating in 7-10 days, a process that has been shown in in vitro and animal models to be dependent on the formation of neutrophil extracellular traps (NETs), which have the ability to degrade pro-inflammatory cytokines (102). During intercritical periods, MSU crystals continue to be present in joints of gout patients and the exact chain of events that initiate the episodic activation of the immune system in response to MSU crystals is not clear (102).

Polymorphisms in the NLRP3 gene and in genes coding for proteins that function as regulators of the NLRP3-inflammasome as well as toll-like-receptor genes have previously been associated with gout (102, 104). The results of a large GWAS-study including 120 282 people with gout have recently been published as a congress abstract (29), with findings of multiple

new gout-associated genetic variants (i.e. genes not associated with urate excretion). The identified genes are involved in regulation of NLRP3 inflammasome activity and autophagy and in addition, genes that are mutated in clonal haematopoiesis of indeterminate potential were identified (29).

Environmental and occupational risk factors for gout

Theoretically, environmental and/or occupational risk factors might operate at all stages of gout pathogenesis, i.e. promoting hyperuricemia, MSU crystallization or the inflammatory response to MSU crystals.

Exposure to lead was historically considered an important risk factor for gout (72). In developed countries, where environmental lead is tightly regulated, blood lead levels (even within the range considered normal) still associate with SU levels and urate excretion (105-109) and one observational cross-sectional study found an association of blood lead levels with prevalent gout (110).

Occupational exposure to dust (such as silica dust and textile dust) has been associated with increased risk of rheumatoid arthritis (RA) (111-114), sarcoidosis (111), systemic sclerosis, systemic lupus erythematosus and dermatomyositis (114) in epidemiological studies. Silica dust has the capacity to activate the NLRP3-inflammasome in vitro (115) and such activation and the resulting increased IL-1β production can lead to increased reactivity of the innate immune system to other stimuli later on, a phenomenon termed "trained immunity" (116). Prior to this thesis occupational exposure to inorganic dusts had not been investigated as a potential gout risk factor in a population-based study.

Some environmental factors, such as ambient temperature, could potentially enhance MSU crystal deposition by altering the solubility threshold for urate. Contrary to what might be expected based on the fact that urate solubility decreases at lower temperatures, epidemiological studies have shown that the incidence rate of gout is increased during the warmer summer months (117) and that higher temperatures were associated with recurrent gout flares (118).

Exposure to ambient air pollution has been associated with both incident hyperuricemia (119) and hospital-diagnosed gout flares (120).

In a time-series study performed in the Korean city Incheon, a weak association between particulate matter <10 μm in diameter (PM_{10}) levels in the preceding week and the daily number of emergency department visits with a gout diagnosis was found (relative risk 1.018 (95% CI 1.008-1.027) per 1 interquartile range (IQR) increment of PM_{10}) (120).

In a study performed in Guangzhou, China which included traffic police officers (119), air pollution exposure was assigned on the basis of working district. The HR for incident hyperuricemia during a 5-year follow-up was 1.46 (95% CI 1.28-1.68) per 10 $\mu g/m^3$ increment of PM_{10} and 1.43 (95% CI 1.26-1.61) per 10 $\mu g/m^3$ increment of nitrogen dioxide (NO_2) (both adjusted for age, body mass index, family history of hyperuricemia, serum creatinine, temperature, and relative humidity).

There is also a Taiwanese study on air pollution and gout (121). The study claims to be population-based, although it is unclear how the study population was defined. The study followed gout-free beneficiaries in the National Health Insurance Research Database (NHIRD) from January 1st 2000 until gout diagnosis, death, withdrawal from the NHIRD or end of study (December 31 2011). The study included 170 318 individuals (which is much less than the 23 million gout-free beneficiaries identified in the NHIRD in 2005 in the report of gout epidemiology in Taiwan by Kuo et al (122)). The study reports a HR for gout of 1.44 (95% CI 1.36-1.53) in the highest quartile of exposure to particulate matter <2.5 μm ($PM_{2.5}$) (with lowest quartile as reference), after adjustment for age, sex, urbanization level, diabetes, hypertension, hyperlipidemia, asthma, chronic obstructive pulmonary disease, coronary artery disease and stroke. Exposure assignment was "based on the clinic sites where beneficiaries received treatment for acute upper respiratory infection (ICD-9-CM code 460)", which might explain the size of the study population, although it is not implicitly stated that only gout-free individuals with an international classification of diseases (ICD)-coded diagnosis of respiratory tract infection were included. If this is the case, the validity of the findings is questionable.

GOUT DIAGNOSIS

The demonstration of MSU crystals in synovial fluid aspirate from an affected joint is still considered the gold standard for gout diagnosis, but diagnostic arthrocentesis is performed in less than 5% of patients diagnosed with gout in primary care in Sweden (123), presumably because the procedure is considered impractical and time-consuming by clinicians.

Thus, most gout patients receive their diagnosis on the basis of clinical history and/or physical examination findings being suggestive of gout. Differential diagnoses include calcium pyrophosphate crystal arthritis as well as other forms of inflammatory arthritis, such as psoriatic arthritis and peripheral spondyloarthritis. In the case of acute monoarthritis with fever, septic arthritis must be considered. Patients that present with late polyarticular gout with tophi

and deformed joints sometimes confuse the clinician as advanced gout can resemble RA with rheumatoid nodules (124).

A diagnostic rule for gout diagnosis in primary care without the use of synovial fluid analysis was developed and internally validated against the gold standard of MSU crystal identification in synovial fluid by Janssens et al (125). It has subsequently been externally validated in secondary care settings (126, 127). The variables included in the rule are:

- Male sex *(2 points)*
- Previous patient-reported arthritis attack *(2 points)*
- Onset within one day *(0.5 points)*
- Joint redness *(1 point)*
- First MTP joint involvement *(2.5 points)*
- Hypertension or ≥ 1 cardiovascular disease *(1.5 points)*
- SU > 5.88 mg/dL (350 µmol/L) *(3.5 points)*

A score of ≥ 8 indicates that gout is very likely (positive predictive value 0.80) whereas a score of <4 indicates that gout is unlikely (negative predictive value 0.97) (8). With scores from ≥4 to <8 synovial fluid analysis is needed for diagnostic certainty.

Classification criteria

The latest gout classification criteria, intended primarily for research purposes, were published in 2015 in a joint effort by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (128).

In addition to clinical and laboratory parameters, the ACR/EULAR gout classification criteria include imaging evidence of urate deposition by ultrasound or DECT (in a symptomatic (ever) joint) as criteria items. Sonographically, MSU crystal deposition on the surface of the articular cartilage in joints is visualized as a hyperechoic enhancement of the superficial margin of the articular cartilage, parallel to the hyperechoic margin of the underlying subchondral bony cortex. This is known as the “double contour sign” (129). DECT relies on the use of two separate x-ray spectra and exploits the fact that materials have different attenuation at different energies (130). Substances with known attenuation properties, such as calcium and urate can then be delineated and color-coded by imaging software, producing reconstructed images where MSU deposits can be visualized (131, 132).

The ACR/EULAR criteria are point-based, with a maximum number of 23 possible points and a cut-off of ≥8 points for classifying an individual as having gout (128).

Historical classification criteria include the Rome criteria from 1963 (133), the NY criteria from 1968 (134) and the ARA criteria from 1977 (135).

Definition of gout in epidemiological studies

Definitions used in epidemiological research are often based on ICD-coded physician diagnosis of gout extracted from healthcare- or administrative databases or on patient/self-reported gout.

Both methods of case ascertainment have their drawbacks. Self-report of gout has been shown to be inconsistent, in a Dutch study only 64% of patients who self-reported having gout at initial inquiry reported having gout when asked again 6 months later (136). In the Atherosclerosis Risk in the Community cohort, 65% of participants that reported gout in 2000 also reported having gout in the 2003 and 2007 questionnaires and of those with a discharge diagnosis of gout or a prescription for a gout medication, only 84% self-reported having gout (137).

When defining gout from ICD-codes in healthcare databases the question of the validity of physician-diagnosed gout arises. To be classified as having gout according to the 2015 ACR-EULAR criteria, the presence of MSU crystals in aspirate from a joint, bursa or tophus is a sufficient criterium. As discussed previously MSU crystal-based diagnosis is rare in clinical practice. In the absence of MSU crystal analysis, detailed information on several clinical characteristics is necessary to fulfil classification criteria, but such information is seldom complete and is in addition difficult to extract from medical records due to their text-based nature. The validity of an ICD-coded diagnosis of gout in the Western Swedish Healthcare Region has been investigated by medical record review (123). The positive predictive value for fulfilling the Janssens diagnostic rule for gout was 42% for patients with one ICD-coded diagnosis for gout in primary care, increasing to 80% for patients with ≥2 ICD-coded diagnoses of gout (123), reflecting the fact that there is more clinical information available in medical records with increasing number of healthcare contacts. Validity of ICD-coded primary care diagnoses of gout has also been investigated by postal surveys designed to collect the clinical information variables of classification criteria, in such studies positive predictive values for the Janssens diagnostic rule ranged from 71-74% (138, 139).

With case definitions based on ICD-codes there is also the possibility of under-ascertainment – individuals with gout might self-manage their condition at home without seeking healthcare and thus are not defined as having gout in healthcare databases or registers.

DESCRIPTIVE GOUT EPIDEMIOLOGY

The prevalence of gout increases with age and is higher for males than females in all age-groups (140). Estimates of incidence and prevalence are consequently affected by the demographics of the population being studied and prevalence can be expected to increase in ageing populations.

One might assume that the local and global incidence and prevalence of a disease as common and well known as gout was a secure statistic. This is however not the case, reports of the descriptive epidemiology of the disease from different parts of the world arrive at different figures which must be interpreted in the light of study-specific case definitions, study populations and study design.

Relatively few studies report secular trends of incidence rate and prevalence. Dehlin et al reported an almost 50% increase in incidence rate between 2005-2015 in the Western Swedish Healthcare Region (141). In Taiwan, both incidence and prevalence of gout decreased between 2005 and 2010 (122). In the UK, incidence and prevalence were stable between 1990-1999 (142), but in a later study by Kuo et al, using the same data source (the clinical practice research datalink) prevalence and incidence increased from 1997-2012 (143). In another UK study, using data from the Royal College of General Practitioners Weekly Returns Service, incidence rate was stable between 1998-2007 (117). In South Korea, incidence and prevalence increased from 2009-2015 (144). In a report from Italy, prevalence increased between 2005-2009, whereas incidence rate was stable (145). From the USA, population-based studies from Rochester Minnesota have reported higher gout incidence in 1995-1996 compared to 1977-1978 (146), with further increases in incidence between 1989-1992 and 2009-2010 (147). In the NHANES surveys, prevalence of gout in the USA was higher in the 2007-2008 survey (148) compared to the NHANES survey of 1988-1994 (149).

Incidence rate

Reported incidence rates of gout range from 0.57 cases per 1000 person-years in a population-wide study from Denmark (150) where gout was defined as an

ICD-coded diagnosis in an inpatient-setting, to 2.8 cases per 1000 person-years reported in the Normative aging study, a USA cohort study that included only males (10). Studies reporting the incidence rate of gout (10, 122, 141, 143-146, 150-153) are summarized in Table 1.

Prevalence

As for studies on incidence rate, case definitions and study methodologies used to estimate prevalence are heterogenous. Prevalence estimates range from 0.76% reported from South Korea (144) to 6.24% reported from Taiwan (122). A summary of studies reporting the prevalence of gout from different countries (122, 141, 143-145, 148, 149, 154-158) is provided in Table 2.

Table 1. Summary of studies reporting the incidence rate of gout. IR=incidence rate (per 1000 person-years)

Country, author	Study design	Subjects	Follow-up	Case definition	IR/ 1000
Denmark, Zobbe	Register	Danish population ≥18 years n≈4500000	1995-2015	ICD-code (secondary care)	0.57
USA, Abbott	Cohort	Age 30-62 years. 45% male. n=5186. Started 1948.	Gout incidence reported after 32 years of follow-up (121308 py of observation)	Clinical history consistent with gout ascertained at study examination – in non-users of diuretics.	0.84
USA, Maynard	Cohort	Age 45-64 years. 43% male. n=11963. Started 1987.	Gout incidence reported in 2012.	Self-reported	0.84
Italy, Trifiro	Register	All persons at risk contributing data to the HSD. n≈1000000	2005-2009	ICD-code (primary care)	0.95
USA, Arromdee	Register	Residents of Rochester, MN, n=?	1977-1978 1995-1996	Physician diagnosis, primary- or secondary care, fulfilling 1977 ACR gout criteria	0.45 0.62
USA, Choi	Cohort	Males, health professionals, age 40-75 years. 100% male. n=47150. Started 1986.	Gout incidence reported after 12 years of follow-up.	Self-reported and fulfilling 1977 ACR survey gout criteria.	1.52
UK, Kuo	Register	All persons at risk contributing data to the CPRD n=4159043 in 2012	1997-2012	READ-code (primary care)	1.77
Sweden, Dehlin	Register	Population of WSHCR, ≥20 years, n=1237935	2005-2012	ICD-code (primary or secondary care)	1.90
South Korea, Kim	Register	Population of South Korea, n=50617045	2009-2015	ICD-code (primary or secondary care)	1.94
Taiwan, Kuo	Register	Population of Taiwan, n=2337132	2005-2010	ICD-code (primary or emergency care)	2.74
USA, Campion	Cohort	Veterans, age 21-81 years. 100% male.n=2046. Started 1963.	Gout incidence reported after 15 years of follow-up (30147 py of observation)	Clinical history consistent with gout ascertained at study examination.	2.80

Table 2. Summary of studies reporting the prevalence of gout.

Country, author	Study period	Case definition, age limit	Study design, sample size	Prevalence % (95% CI)
Taiwan, Kuo	2005-2010	Physician-diagnosed	Register, n=23371362	6.24 (6.23-6.24)
Greece, Anagnostopoulos	2008	Self-reported, Adult population	Cross-sectional survey, n=1705	4.75 (4.41-5.13)
USA , Zhu	2007-2008	Self-reported, ≥20 years	Cross-sectional survey, n=5699	3.9 (3.3-3.4)
NZ, Winnard	2009	Inpatient physician-diagnosed or ULT/colchicine, ≥20 years	Register, n=3047172	3.75 (3.73-3.77)
Spain, Sicras-Mainar	2003-2007	Physician-diagnosed, ≥18 years.	Register, n=96206	3.3 (2.7-3.9)
USA, Kramer	1988-1994	Self-reported, ≥20 years	Cross-sectional survey, n=17017	2.7 (2.3-3.0)
UK, Kuo	1997-2012	Physician-diagnosed, All ages included.	Register, n=4634974	2.49 (2.48-2.51)
Sweden, Dehlin	2002-2012	Physician-diagnosed, ≥20 years	Register, n=1245722	1.80 (1.77-1.82)
Germany, Annemans	2000-2005	Physician-diagnosed, ≥18 years.	Register, n=2402185	1.4 (?-?)
Italy , Trifiro	2009	Physician-diagnosed, ≥18 years.	Register, n=?	0.91 (?-?)
France, Bardin	2013	Self-reported, ≥18 years. Defined as gout by validated questionnaire ≥18 years.	Cross-sectional survey n=10026	3.7 (3.3-4.1) 0.92 (0.74-1.12)
South Korea, Kim	2007-2015	Physician-diagnosed	Register, n=50617045	0.76 (0.75-0.76)

COMORBIDITIES IN GOUT

Patients with gout have a higher burden of comorbidities at diagnosis compared to matched controls (159, 160) and the risk of incident comorbidity after gout diagnosis is also higher than in matched controls (159). The most common comorbidities consistently associated with and overrepresented in gout (renal impairment, cardiovascular disease, obesity and other components of the metabolic syndrome) are conditions that are related to increased urate production and/or reduced excretion of urate, either through effects of the condition itself and/or mediated/exacerbated by the use of diuretics. Other comorbidities that have been identified as overrepresented in gout populations do not have as obvious or well established links to urate metabolism, e.g. hypothyroidism (159) and chronic pulmonary disease (159, 160).

MANAGEMENT OF GOUT

Gout flares are managed by anti-inflammatory medications, such as colchicine, non-steroidal anti-inflammatory drugs, oral- or intraarticular steroids (161).

Gout is prevented by correcting hyperuricemia. Achieving SU levels below the solubility threshold prevents further MSU crystal deposition and with time MSU crystal depositions already formed disappear when sufficiently low SU levels are sustained (162-165), which translates into fewer gout flares and reduction of tophi (166-168).

All gout management guidelines from the major rheumatology societies EULAR (161), ACR (169), the British society for rheumatology (170) and the Swedish national guidelines for gout management (171) recommend treat-to-urate-target ULT for gout patients.

Treat-to-urate-target explicitly means dose titration of a urate-lowering agent to achieve a prespecified target SU, which requires regular monitoring of SU.

In 2017 the American College of Physicians published guidelines for the management of gout that differ substantially from ACR and EULAR guidelines in that they do not recommend treating to a urate target or monitoring SU in ULT-treated gout patients (172). The rationale for this was the absence of high-quality evidence (i.e. RCTs) evaluating the benefits and potential harms of a treat-to-target based ULT approach compared to both no ULT/placebo and compared to fixed-dose ULT.

The older ULTs still in use today, both allopurinol and the uricosurics (probenecid, benzbromarone), were introduced decades ago, at a time when placebo-controlled RCTs with clinical outcomes were not required for the authorization and marketing of new drugs (173). The newer ULTs, febuxostat and lesinurad (the latter now discontinued in Sweden) were introduced on the basis of RCTs with allopurinol and/or placebo in varying doses as control in the case of febuxostat (166, 174-176) or as add-on therapy on top of allopurinol or febuxostat with placebo as control in the case of lesinurad (177, 178). The primary outcome in the febuxostat- and lesinurad-trials was the proportion of patients achieving an SU below a predefined target. The length of the trials was 6-12 months. As flare frequency tends to increase during the first 6 months of ULT due to mobilization of urate deposits, showing clinical benefits of ULT requires trials of longer duration.

This means, as the American College of Physicians noted, that there is an absence of RCTs showing clinical benefits (i.e. reduction of gout flares) of treat-to-urate-target ULT, both as compared to no ULT and as compared to a fixed dose of ULT. Such trials, at least placebo-controlled long-term ULT trials in gout, are unlikely to see the light of day for ethical reasons. There is however an RCT that showed clear clinical benefits of nurse-led care (which was treat-to-urate target based) versus usual care (GP-led care) (168). After 2 years, 96% of patients randomized to nurse-led care were taking ULT compared to 56% of patients randomized to usual care, 95% vs 30% of patients had SU<360 µmol/L and 8% vs 24% of patients had 2 or more flares during year 2 of the study (168). There is also evidence for clinical benefits of treat-to-urate target ULT in gout from an open label extension study including patients from two RCTs of febuxostat versus allopurinol (166) and from observational studies (179, 180). On the basis of this evidence combined with the clear understanding that SU levels above the saturation point are necessary for MSU deposition and gout to occur there is widespread consensus in the rheumatology community regarding the treat-to-urate-target strategy for ULT in gout (181, 182).

Urate-lowering effects of dietary interventions

The effect of dietary interventions on SU has been investigated in multiple trials, most are small, uncontrolled and of short duration and few have included gout patients. In most of the trials where a clinically relevant and significant SU lowering effect was achieved, participants also lost significant weight.

Although significant weight-loss (whether through dietary interventions or bariatric surgery) can have a substantial effect on SU in obese patients with

and without gout, in most patients with gout, urate-lowering medications are necessary to achieve the target SU-levels recommended in clinical guidelines. The absolute change from baseline in SU achieved in dietary intervention trials (38, 46, 183-192) is shown in Figure 4.

Urate-lowering effects of ULT

In Sweden the available ULTs are the xanthine oxidase inhibitors allopurinol and febuxostat and the uricosuric agent probenecid. The uricosuric agent lesinurad was available for a few years but was withdrawn in 2020. Benzbromarone can be prescribed with special licensing. Allopurinol is the first line ULT according to Swedish guidelines for gout management (193).

In the FACT trial (174), 760 gout patients with hyperuricemia (mean baseline SU of 585 µmol/L) were randomized 1:1:1 to febuxostat 80 mg, febuxostat 120 mg and allopurinol 300 mg. The change from baseline in SU at 52 weeks was -261, -301 and -192 µmol/L respectively (Figure 4), and 72%, 77% and 35% of patients achieved a SU <6.0 mg/dL at the final study visit.

For probenecid, data on urate-lowering effects was reported from a retrospective observational study carried out in New Zeeland (194).

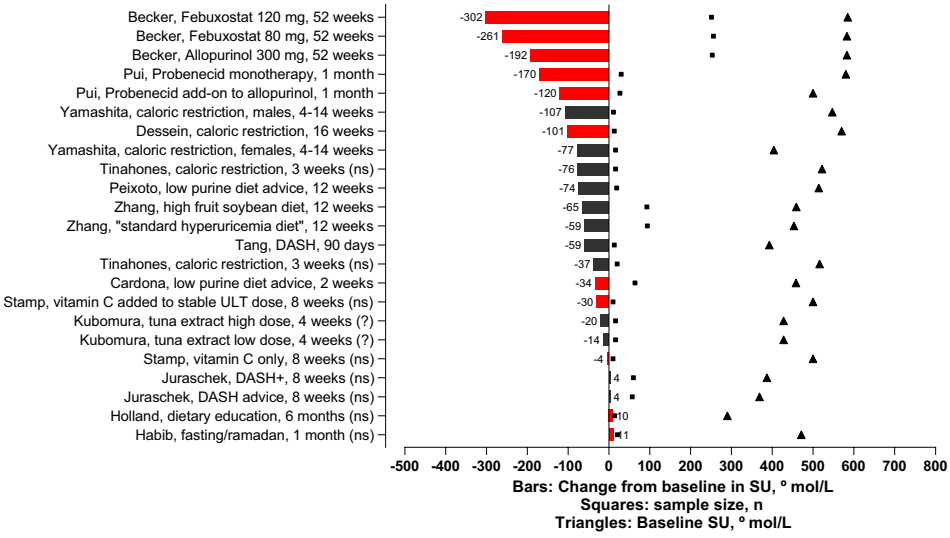

Figure 4. SU lowering effects of ULT and SU lowering achieved in dietary intervention trials. Red bars signify studies including gout patients. Bars: change from baseline in SU, µmol/L. Black squares: sample size. Black triangles: baseline SU, µmol/L. The labels on the y-axis are "Author, intervention, timepoint of endpoint SU assessment", where change from baseline in SU was not statistically significant this is shown with (ns).

Indications for urate-lowering therapy in gout according to current clinical guidelines

Clinical guidelines recommend ULT for all gout patients that have had >1 gout flare and for patients with certain risk factors already after the first flare. A summary of the recommendations regarding ULT for gout in the ACR (169) and EULAR (161) guidelines is summarized in Table 3. Swedish national guidelines (193) are consistent with the EULAR guidelines.

Table 3. Summary of recommendations for ULT in gout according to EULAR and the ACR.

	EULAR Recommendations (161)	**ACR Guideline** (169)
Published	2016	2020
Indication for ULT	All patients with recurrent flares. All patients with tophi, urate arthropathy and/or renal stones. After first flare / close to first flare if: • Age <40 years • SU >480 µmol/L • Comorbidities*	All patients with >1 flare. After first flare / close to first flare if: • CKD stage ≥3 • Renal stones • SU ≥9 mg/dL (535 µmol/L)
Target values for SU	<360 µmol/L <300 µmol/L for patients with ”severe gout” (until crystal dissolution is achieved).	<6 mg/dL (=357 µmol/L)
Titration recommendation	Starting dose 100 mg daily. Dose increase every 2-4 weeks with 100 mg until target achieved.	Starting dose 100 mg (consider lower dose if renal impairment). Titration recommended to occur over “weeks/months”.
Second line ULT if target not reached with allopurinol (or intolerance)	Probenecid, as second-line or add-on therapy. Febuxostat (no preference in guidelines for probenecid or febuxostat).	Febuxostat. Pegloticase for severe gout if target not reached with xanthine oxidase inhibitors and/or probenecid.
Recommendations for patients with renal impairment	Allopurinol maximum dosage should be adjusted to creatinine clearance. “Because the dose recommendations in renal disease may slightly differ across countries, the task force recommends to follow the local Summary of Product Characteristics.”	Recommendation to use FDA approved dosing.

*Renal impairment, hypertension, ischemic heart disease, heart failure
EULAR: European League Against Rheumatism. ACR: American College of Rheumatology. ULT: urate-lowering therapy. SU: serum urate. FDA: The United States Food and Drug Administration.

Treat-to-urate target quality indicators in observational studies

Proportion of patients with gout receiving ULT
A recent systemic review reported that the pooled prevalence of gout patients receiving ULT, from 30 studies, was 52% (95% CI 45% to 59%) (195). As only a few of the included studies attempted to assess the proportion of included patients with an indication for ULT (196-202), interpreting the degree of undertreatment is difficult.

Adherence to and persistence with ULT
Poor adherence to and persistence with ULT among gout patients is a global problem, with only around 50% of ULT users receiving regular uninterrupted therapy (195).

SU testing
Monitoring SU is a necessary component of the treat-to-urate target strategy. The pooled prevalence of any SU testing among ULT-treated gout patients in 19 observational studies was 53% (95% CI 40% to 65%), whereas the pooled prevalence of SU testing after initiation or change of ULT was 44% (95% CI 36% to 52%) (195).

Dose titration of allopurinol
In a report from a UK primary care centre, including 112 gout patients in total, 31% of ULT-treated patients had dosage adjustments (196).

Achieving SU target
The pooled proportion (from 20 studies) of ULT-treated gout patients reaching an SU target ≤ 360 μmol/L was 34% (95% CI 28% to 41%) (195).

HEALTH-RELATED QUALITY OF LIFE AND DISABILITY IN GOUT

Acute gout (gout flares) impacts health-related quality of life and physical function due to pain and the constitutional symptoms related to flares. Chronic tophaceous gout has additional effects due to tophi and destructive changes in joints. In addition, gout patients often have comorbidities that also contribute to decreased quality of life and disability. Tophi are strongly related to erosive joint changes (203), which in turn predict disability (204).

Health-related quality of life in gout patients has mostly been measured in studies by generic instruments, such as the 36-item short form health survey (SF-36) (205). Gout-specific instruments developed in the context of clinical trials exist (gout assessment questionnaire (GAQ) (206), GAQ2.0 (with subscale gout impact scale (GIS)) (207)) but due to concerns about their validity they have not received endorsement by the outcome measures in rheumatology (OMERACT) gout working group (208, 209).

As measured by SF-36, gout has a significant impact, independent of comorbidities, on health-related quality of life in several studies (210-212), although in a population of US veterans, decreased health-related quality of life in gout patients was explained by comorbidities and sociodemographic characteristics (213).

There are few studies reporting physical disability in gout. In a study of 110 patients with uncontrolled gout (70% of patients had tophi), mean health assessment questionnaire disability index (HAQ-DI) was 1.0 indicating mild to moderate disability (210), whereas in a survey including gout patients identified in Italian primary care (2% of patients had tophi), the mean HAQ-DI among 1184 respondents was 0.51 (214). In a Mexican cohort of 206 gout patients (37% had tophi), mean HAQ-DI was 0.59, indicating mild disability (215). In a cross-sectional study of gout patients seen at a rheumatology department in the Netherlands during one year (n=126, 48% with tophaceous gout), the mean HAQ-DI was 0.63, indicating mild disability (216).

WORK DISABILITY / SICKNESS ABSENTEEISM

Sickness absenteeism from the labour market encompasses situations where individuals, because of sickness, are absent from the labour market, either during transient periods or permanently.

Sickness or the sick-role as a concept refers to the social role that is taken on by or given to an individual with (or sometimes without) disease and/or illness. Disease is a condition that medical science can diagnose, whereas illness is the subjective experience of symptoms by the individual (217).

In research, data on sickness absenteeism can be self-reported or be collected from employers registers or from insurance companies or public insurance offices (218). In countries with national social security registers, such as Sweden, individual level data on reimbursed sickness absence can be collected from official registers, avoiding recall bias.

Predictors of sickness absenteeism in general

From official Swedish statistics it is well known that sickness absenteeism associates strongly with age, sex and place of residence and these variables are often treated as confounders in sickness absenteeism research.

In Sweden, the number of sickness absence days compensated with sick-leave or disability pension benefits per insured individual increases with increasing age for both men and women but levels off in the age category 60-64 years for women. Women have more sick leave days per insured individual in all age categories than men (Figure 5). Some of the excess absenteeism among women compared to men on the population level is explained by pregnancy-related diagnoses (219). Sickness absenteeism is of greater magnitude in rural communities compared to urban settings, which is thought to be driven by labour market conditions being harder and selection bias, i.e. that healthy individuals without work impairment would be more likely to relocate to urban areas (219).

Studies that have addressed the association between marital status and the presence of children at home with sickness absenteeism have arrived at conflicting results, whereas change in marital status, whether due to divorce or death of a spouse, seems to be associated with an increase in absenteeism (219).

It is well established that socioeconomic status, whether measured by educational level, occupational level or income, is inversely associated with sickness absenteeism. Studies that have attempted to explain the social gradient in sickness absenteeism have shown (to a varying degree) that the association between socioeconomic status and sickness absenteeism is attenuated by adjusting for conditions of the work environment and health behaviours (220, 221).

Regarding work environments, there is a myriad of observational studies showing statistical associations with sickness absenteeism e.g. for physically demanding work and low control over the working situation (219).

For lifestyle factors, there is also ample evidence for statistical associations between e.g. alcohol consumption, smoking, being overweight and having a sedentary lifestyle with sickness absenteeism, but interpretation of such findings is complicated by problems of reverse causality and confounding (219).

The characteristics of social insurance systems, such as the level of compensation and waiting days and conditions of the labour market (unemployment rate) are associated with sickness absenteeism. When unemployment rates are low, sickness absenteeism tends to increase (219).

Previous sickness absenteeism is a strong predictor of future sickness absenteeism (222, 223)

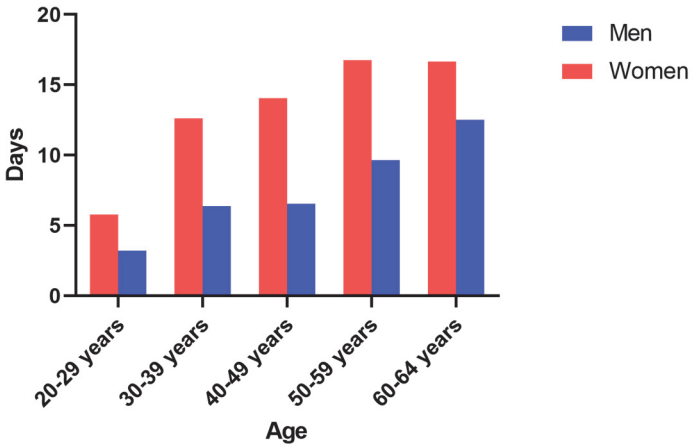

Figure 5. Mean yearly sick-leave days in Sweden 2021 per insured individual, stratified by age category and sex (transient sickness periods of shorter duration than 14 days not included). Source: https://www.forsakringskassan.se/statistik/statistikdatabas#!/

Sickness absenteeism in gout

Sickness absenteeism in gout has not been studied extensively. In an observational study from the USA of 81 gout patients with symptomatic crystal-proven gout and uncontrolled hyperuricemia, 78% reported at least 1 work day lost due to a gout flare during 12 months of observation. The mean annual work day loss was 25 days (224).

In a study from the USA of 249 020 employees, individuals with an ICD-coded gout diagnosis (n=1171) had 14.39 days of sickness absence whereas employees without gout had 9.83 days of sickness absence during 1 year (225).

Another study, also from the USA, found that among employees with gout, the number of sickness absence days was related to the number of gout flares (226).

A cross-sectional study from the Netherlands reported an annual sickness-absence of 9.6% among employed gout patients (n=30) (216).

AIM

The overall aim of the thesis was to describe the contemporary epidemiology and ULT treatment patterns of gout, the impact of the disease with regard to sickness absenteeism and to examine possible environmental and occupational-related risk factors for gout, by using prospectively registered data from healthcare- and administrative registers in Dalarna and the Western Swedish Healthcare Region.

SPECIFIC AIMS

Paper I

- To describe the incidence rate of gout in 2014 to 2019 in Dalarna and prevalence in 2018.
- To assess the proportion of prevalent cases with an indication for ULT and the proportion of prevalent cases receiving allopurinol in 2014 to 2019.
- To evaluate and compare 2-year persistence on allopurinol for patients with gout initiated on allopurinol in 2013 to 2015 compared to 2016 to 2018, i.e. before and after publication of national Swedish gout treatment guidelines.
- To evaluate and compare healthcare provider compliance to treat-to-target oriented principles in the management of gout with allopurinol before and after publication of national treatment guidelines.

Paper II

- To describe the extent of sickness absenteeism among gout patients in relation to matched population controls and to analyse predictors of new-onset sickness absenteeism.

Paper III

- To evaluate occupational exposure to inorganic dust as a predictor of gout

Paper IV

- To evaluate long-term exposure to residential air pollution as a predictor of gout.

METHODS

Ethical approval

Ethical approval for paper I was granted from the Ethical Review Board of Uppsala, Sweden, approval number 2015/435 and 2015/435/1. For papers II-IV ethical approval was granted from the Ethical Review Board of Gothenburg, Sweden, approval number 347/13. As all data were derived from healthcare- and administrative registers, individual participant consent was not needed according to Swedish law.

PAPER I

Background setting

The study was conducted in the Region of Dalarna, Sweden. Dalarna is a geographical and administrative Swedish region. The total population of the region was 287 676 people on December 31st 2020 (227), (3% of the total population of Sweden).

Dalarna is sparsely populated with 10.3 inhabitants per km^2, compared to Sweden as a whole (25.5 inhabitants per km^2 and the Western Swedish Health Care Region (72.9 inhabitants per km^2) (227). More than 80% of the inhabitants in Dalarna live in small towns, ranging in size from 200 to 45 000 inhabitants (227), the remainder live in rural settings.

The population of Dalarna is older than the total Swedish population, with proportionally more people in older age-groups (Figure 6).

Healthcare is organized into primary care, consisting of more than 20 primary care units and secondary out- and inpatient care concentrated to four hospitals located in the largest towns of Falun, Mora, Avesta and Ludvika (Figure 7).

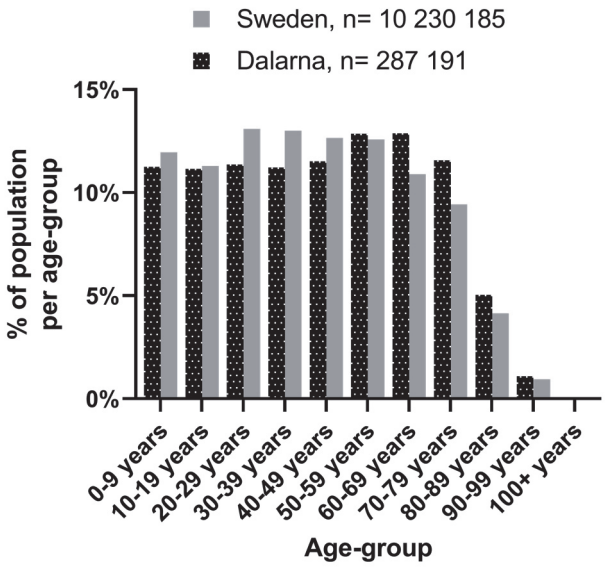

Figure 6. The proportion of inhabitants per age-group in Dalarna compared to Sweden.

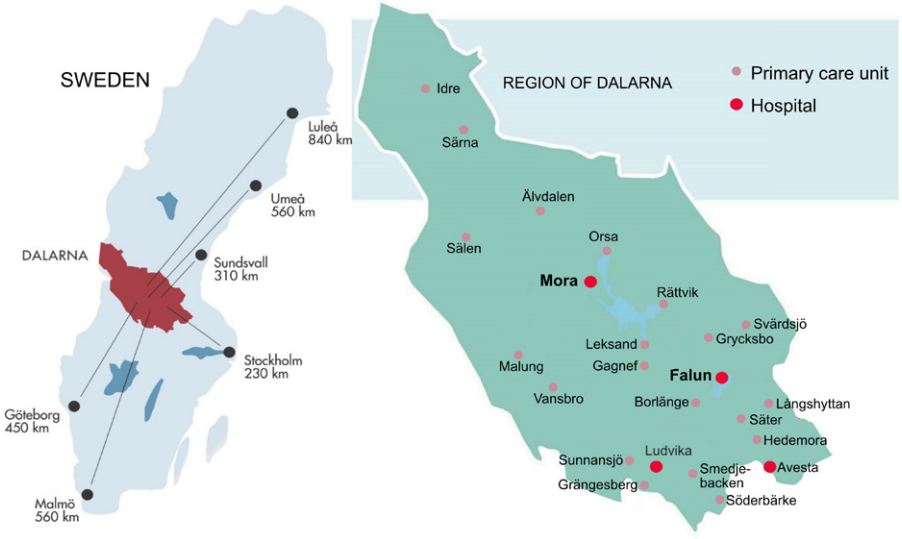

Figure 7. Map of Sweden to the left with Dalarna illustrated in red. To the right a map of Dalarna with locations of primary care units and hospitals.

Case definition

All individuals, aged 20 years and above, that received an ICD-SE or ICD-10 coded diagnosis of gout during the years 2000-2020 in the region were included in the study database.

The ICD-SE is an abbreviated version of the ICD-10 that was in use in primary care until 2013.

The ICD-codes used for case definition and the number of individuals identified per code (code at first gout diagnosis) are shown in Table 4.

Table 4. Diagnostic classification codes used for identification of gout patients and number of individuals identified per code

Code	Classification system	n*
M10.0 Idiopathic gout	ICD-10	2279
M10.1 Lead-induced gout	ICD-10	0
M10.2 Drug-induced gout	ICD-10	26
M10.3 Gout due to impairment of renal function	ICD-10	8
M10.4 Other secondary gout	ICD-10	16
M10.9 Gout unspecified	ICD-10	2081
M10- Gout	ICD-10-SE (used in primary care until 2013, also known as KSH97-P)	5880
Total:		**10290**

* n refers to number of individuals with the corresponding code at the first/earliest identified gout diagnosis.

Data sources and data collection

The main data source of the study was output data from the two electronic health record (EHR) systems that were in use in the region during the study period. Data from the EHR-system in use in specialized outpatient care and inpatient care from 2000-2012 could not be extracted for the study. The availability of data is shown in Figure 8.

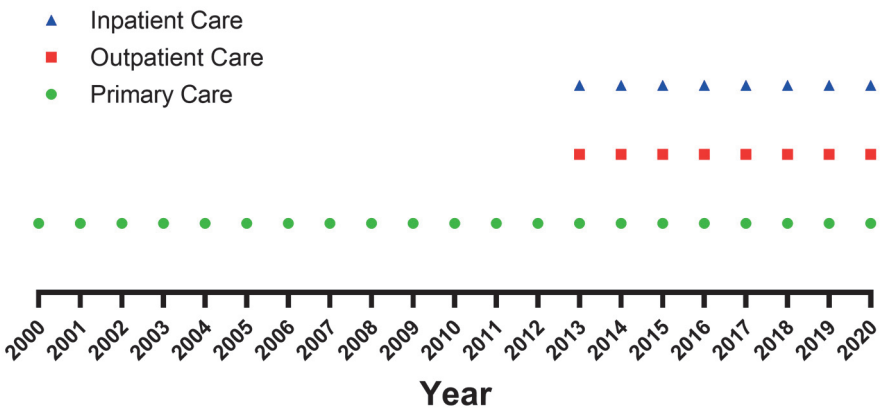

Figure 8. Availability of data from different parts of the healthcare system.

In the first step of data collection, all individuals with an ICD-coded gout diagnosis were identified. We then extracted data on prescriptions for gout-related medications (allopurinol, probenecid, febuxostat and colchicine) and results of laboratory tests (SU, serum creatinine, synovial fluid urate crystals) during the whole study period for the identified cases.

With the exception of date of death, which was collected from the total population register (RTB), all study data was extracted from the EHR systems. The structure of the study database is presented in Figure 9.

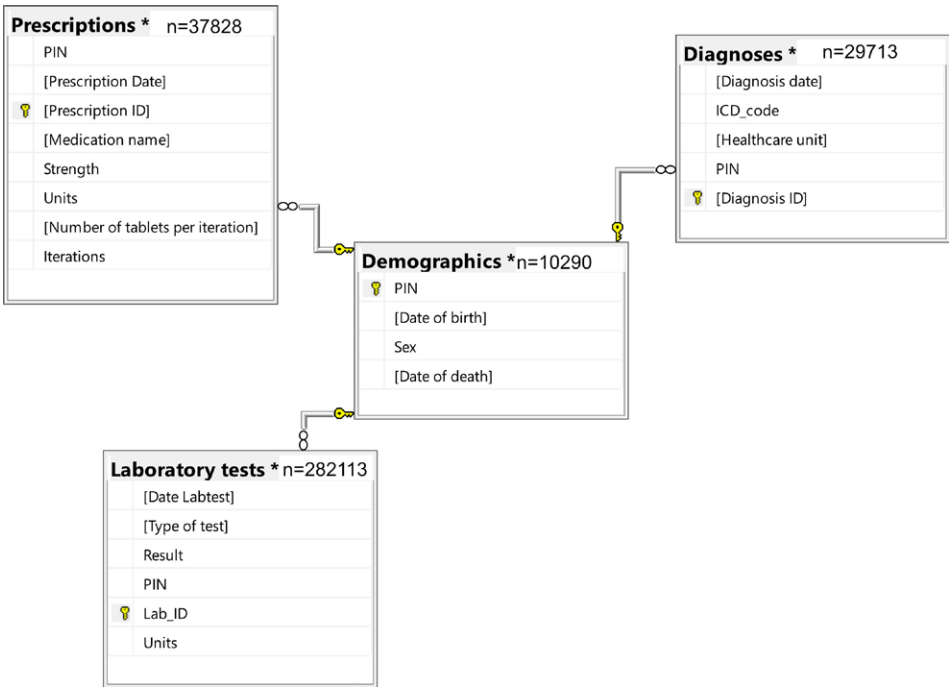

Figure 9. Diagram of the database structure. The database consists of 4 tables, Demographics, Diagnoses, Laboratory tests and Prescriptions. All posts in all tables were identified with an encrypted personal identification number (PIN) to enable linkage of data between tables. The "ns" refer to the number of posts in each table. In total 10 290 individuals with a gout diagnosis were identified, these individuals had 282 113 lab tests (serum urate, serum creatinine, synovial uric acid crystals), 37 828 prescriptions for allopurinol, febuxostat, probenecid and colchicine and 29 713 instances of gout diagnoses during the period of data collection from 2000-2020.

Study population

The study population for the analysis of incidence and prevalence consisted of all individuals, aged 20 years and above, that were residents of Dalarna (n=222 803 in 2018).

For the analysis of compliance to clinical treatment guidelines, gout cases that were prescribed allopurinol for the first time in 2013-2018 were selected.

Statistical Methods

Continuous variables were presented as means and standard deviations or medians and IQR depending on the distribution of data.

Differences in baseline characteristics and treat-to-target related outcomes between time period 2013-2015 and time period 2016-2018 were tested with student's t-test or Mann-Whitney two sample rank sum test for continuous variables depending on the distribution of data and chi-square test for categorical variables. All tests were two-sided and p-values <0.05 were considered statistically significant.

R (package 'dsr') was used for analysis of incidence and prevalence. Rates were standardized to the Swedish population in 2018 using the direct method.

Linear regression with year as independent variable was used to test for linear time trend of proportion of prevalent cases on allopurinol.

Survival analysis with Kaplan-Meier curves and log-rank test was used for the analysis of persistence on allopurinol. 95% confidence intervals for directly standardized incidence rates were derived on the assumption of a Poisson distribution.

PAPER II, III AND IV

Background setting and population

Studies II-IV were performed using data from the Western Swedish Healthcare Region (WSHCR). The total population of the WSHCR was 1 734 443 on December 31st 2020, corresponding to 17% of the total Swedish population.

Data sources

Western Swedish Healthcare Register (VEGA)

VEGA holds data on all healthcare contacts in the region since 2000, including dates of visits and diagnoses. VEGA was used for identification of gout cases and to retrieve information on selected comorbidities.

Total Population Register

The total population register (RTB) was used to collect information on yearly residential addresses (paper IV). It also provided information on migration and date of death (paper II-III).

The RTB was also used for identification of matched controls.

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

LISA is a register that is updated annually and administered by Statistics Sweden. LISA integrates data from multiple national registers, including the social security-, occupational- and educational registers. It was used to retrieve information on educational level (papers II-IV), work-loss days end employment status (paper II) and occupation (paper III).

Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register has data since July 1st 2005 on all dispensations of prescribed drugs at Swedish pharmacies. Information from the Swedish Prescribed Drug Register was used to determine treatment with allopurinol (papers II-IV) and diuretics (papers III-IV).

Incident Gout Case definition

All individuals, aged 20 years and above, that had received an ICD-coded diagnosis of gout by a physician in primary- or secondary healthcare in 2000-2016 were defined as cases.

Cases were defined as incident at the first occurrence of an ICD-code for gout, provided there was no history of allopurinol treatment before that date.

Papers II-IV included different subsets from the total pool of identified incident gout cases in 2000-2016 (Table 5)).

Study design, study populations, definitions of exposure and main outcomes

Studies III-IV are nested case-control studies using density-based sampling of controls. Up to 5 controls were matched to each case on the basis of age, sex and residence on municipality level at the index date (date of first occurrence of an ICD-coded gout diagnosis). Controls were assigned the same index date as their corresponding case. A summary of the case definitions, data sources, exposures and outcomes is provided in Table 5. In paper II and III, all cases identified were included whereas in paper IV only cases (and controls) resident in the municipalities of Gothenburg and Mölndal were included, as air pollution exposure data was only available for this area.

Statistical methods

The difference between cases and controls in number of work-loss days (sick leave and disability pension) was assessed by analysis of variance (paper II).

To determine predictors of absenteeism among cases and controls separately we used logistic regression (paper II).

Conditional logistic regression, taking into account the matched design of the studies, was used to test the association between the outcome of >90 days of work absenteeism and incident gout (paper II), occupational exposure to inorganic dust and incident gout (paper III), and exposure to residential air pollution and incident gout (paper IV). Odds ratios (OR) were presented with 95% confidence intervals.

In the analysis of predictors for new-onset absenteeism (paper II), we adjusted for known gout-related comorbidities associated with absenteeism and for known socioeconomic predictors of absenteeism, low level of education, previous unemployment and previous work disability (i.e. ≥2 years before the year of identification), as socioeconomic variables were also associated with gout in the data.

When analysing the association between occupational exposure to inorganic dust and gout (paper III), the main model was adjusted for obesity and alcohol use disorder which are known gout-related comorbidities and these were also associated with occupational exposure to inorganic dust in the data. A secondary model was also adjusted for educational level, which as a proxy for socioeconomic status, is related to both gout and mediates the choice of occupation.

In paper IV, the main model is unadjusted. In a sensitivity analysis, the model was adjusted for cardiovascular- and renal disease which have been associated with air pollution exposure in epidemiological studies and are known gout-related comorbidities.

Table 5. Methods at a glance. EHR: Electronic health record. RTB: Total population register. WSHCR: Western Swedish healthcare region. VEGA: Western Swedish healthcare register. LISA: Longitudinal integration database for health insurance and labour market studies. T2T: treat-tot-target.

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Design	Population-based cohort of all identified gout cases	Matched case-control (1:5)	Matched case-control (1:5)	Matched case-control (1:5)
Setting	Dalarna	WSHCR	WSHCR	Gothenburg/Mölndal
Data sources	EHR. RTB.	VEGA, LISA, RTB, Swedish prescribed drug register.	VEGA, LISA, RTB, Swedish prescribed drug register.	VEGA, LISA, RTB, Swedish prescribed drug register.
Study population	Incidence & prevalence: Incident gout cases (≥20 years of age) identified in 2000-2020, n=10280 Persistence with allopurinol and T2T outcomes: Cases initiated on allopurinol in 2013-2018, n=1709.	Incident gout cases 2003-2009 and matched population controls, age 30-62 years at index date, n=4571:22482	Incident gout cases 2006-2012 and matched population controls, age 30-65 years at index date, n=5042:20682	Incident gout cases 2006-2016 in Gothenburg/Mölndal and matched population controls, n=6959:34085
Exposure definition		For predictor analysis, predictors were defined by ICD-codes. Socioeconomic predictors were defined from the LISA register.	Occupational codes (LISA) in 5 years prior to index year – classified by job exposure matrix as exposed / not exposed.	Gaussian dispersion model of air pollution applied to geocoded residential addresses in 5 years prior to index year
Main outcomes	Incidence 2014-2019. Prevalence 2018. 2-year persistence on allopurinol and T2T-outcomes.	Work-loss days (descriptive) Predictors for new onset absenteeism.	Occupational exposure to inorganic dust (descriptive). Association of exposure to outcome of incident gout	Exposure to residential air pollution (descriptive). Association of exposure to outcome of incident gout.
Statistics	Descriptive. Kaplan-Meier survival analysis. Linear regression.	Descriptive. Conditional logistic regression. Logistic regression.	Descriptive. Conditional logistic regression.	Descriptive. Conditional logistic regression.

RESULTS

PAPER I

Incidence and prevalence

This paper is based on data from the Swedish region of Dalarna. In total 10290 individuals with ≥1 ICD-coded gout diagnosis during 2000-2019 were identified.

The incidence rate, standardized to the Swedish population in 2019 ranged from 221 to 247 cases per 100 000 person-years in 2014-2019 (Figure 10).

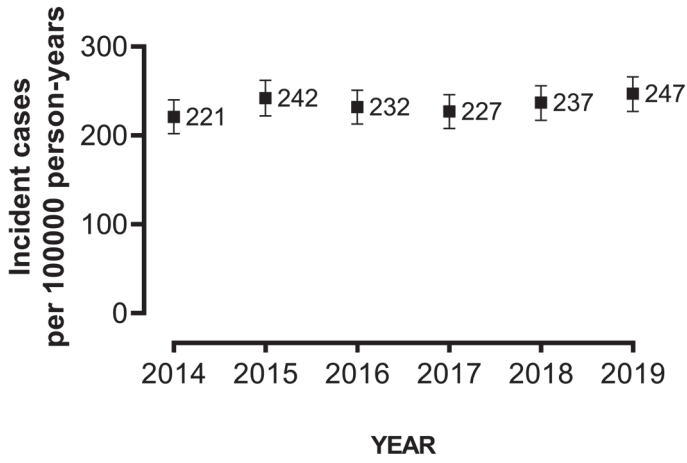

Figure 10. Incidence rate of gout in Dalarna, Sweden, per 100 000 person-years with 95% confidence intervals, standardized to the Swedish population in 2019.

Incidence rate (per 1000 person-years) from 2014 to 2019 is shown in Figure 11, along with previously published incidence rates from studies from other countries (122, 143, 144) that also identified cases from healthcare registers and reported secular trends.

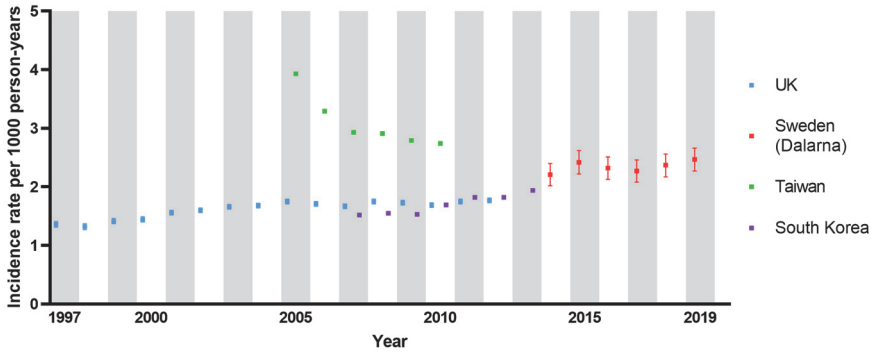

Figure 11. Secular trends in incidence rate of gout per 1000 person-years in Sweden (Dalarna), the UK (from Kuo CF, Ann Rheum Dis. 2015;74:661-7), Taiwan (from Kuo C-F, Arthritis Res Ther. 2015;17:13), South Korea (from Kim J-W, Rheumatol Int. 2017;37:1499-506).

Total prevalence in Dalarna as well as prevalence stratified by age and sex group was determined at the end of 2018. By December 31st 2018 there were 6200 prevalent gout cases that were alive and residing in the region, whereas the total population (age >20 years) was 222 803, which gave a crude prevalence of 2.78% (95% CI 2.71% to 2.85%) and a standardized prevalence of 2.45% (95% CI 2.39% to 2.51%).

Prevalence of gout in 2018, stratified by age and sex and in total is illustrated in Figure 12. Prevalence was lower among females compared to males in all age-groups.

Prevalence increased slightly between 2014 and 2018, from 2.07% to 2.45% (Figure 13).

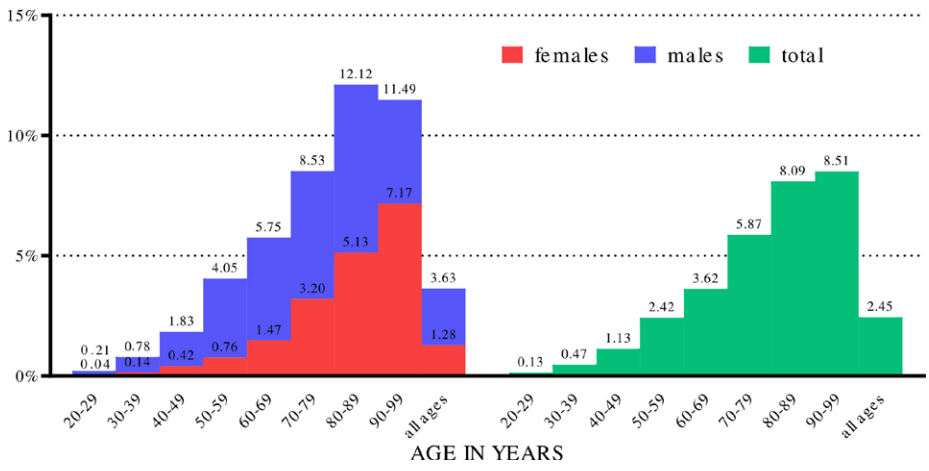

Figure 12. Prevalence of gout by age and sex in 2018, as well as total standardized prevalence in all age-groups combined. Numbers above bars are %

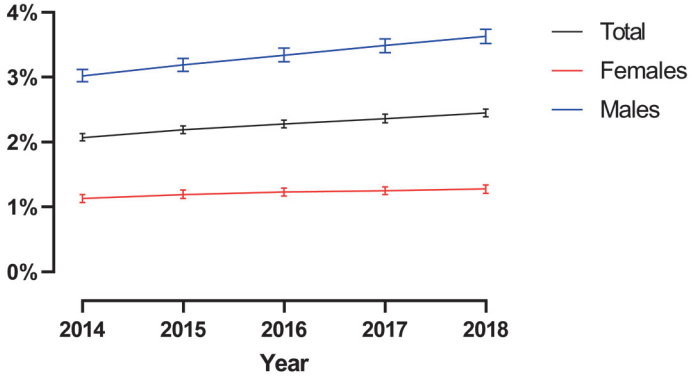

Figure 13. Secular trends in prevalence of gout, in total and for males and females separately. Prevalence is standardized to the Swedish population in 2018 at all time-points.

Indications for urate-lowering therapy among prevalent cases in 2018

Among the 6200 prevalent gout cases in 2018, 76% fulfilled one or more of the indications for ULT, i.e. history of more than one flare of gout, SU >480 µmol/L, renal impairment or age under 40 years at diagnosis (Figure 14).

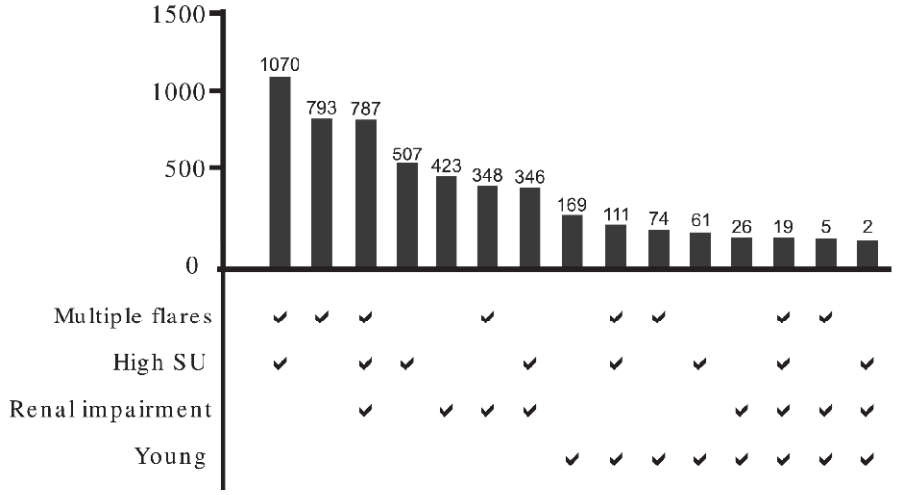

Figure 14. Indications for urate-lowering therapy among prevalent cases in 2018. Among the 6200 cases, in total 4741 (76%) fulfilled criteria that should lead to initiation of ULT. Check-marks indicate conditions that were present for the patients in each bar. Numbers above bars are the number of patients.

Proportion of prevalent cases on allopurinol

During the years 2014-2018 the proportion of prevalent cases with at least one prescription for allopurinol during the same year ranged from 21-24%, while the proportion with an indication for ULT ranged from 76-77% (Table 6).

Among those with ongoing allopurinol treatment, more than 90% had an indication for ULT. Among those with no ongoing allopurinol and no history

of allopurinol treatment (47-49%), the proportion with an indication for ULT ranged from 59-66% (Table 6).

Table 6. Prevalent cases per year by allopurinol treatment status (ongoing in the same year, previous allopurinol treatment or never allopurinol) and proportion per category with an indication for ULT.

	2014	**2015**	**2016**	**2017**	**2018**
Total cases, n (%*)	5001 (100)	5334 (100)	5649 (100)	5921 (100)	6200 (100)
-thereof with ULT indication, n (%**)	3843 (77)	4085 (77)	4306 (76)	4534 (77)	4741 (76)
Ongoing allopurinol, n(%*)	1035 (21)	1156 (22)	1272 (23)	1422 (24)	1519 (24)
-thereof with ULT indication, n(%**)	955 (92)	1073 (93)	1209 (95)	1345 (95)	1452 (96)
Previously treated with allopurinol, n (%*)	1531 (31)	1565 (29)	1594 (28)	1620 (27)	1659 (27)
-thereof with ULT indication, n (%**)	1336 (87)	1394 (89)	1424 (89)	1456 (90)	1492 (90)
Never treated with allopurinol, n (%*)	2345 (47)	2613 (49)	2783 (49)	2879 (49)	3022 (49)
-thereof with ULT indication, n (%**)	1552 (66)	1618 (62)	1673 (60)	1733 (60)	1797 (59)

* % of the total number of prevalent cases.
** % of cases in category.
ULT: urate lowering therapy.

Persistence on allopurinol and guideline compliance

For patients that were initiated on allopurinol in 2016-2018, persistence at 2 years was 45%, compared to 39% for those starting allopurinol therapy in 2013-2015, log-rank p=0.031 (Figure 15).

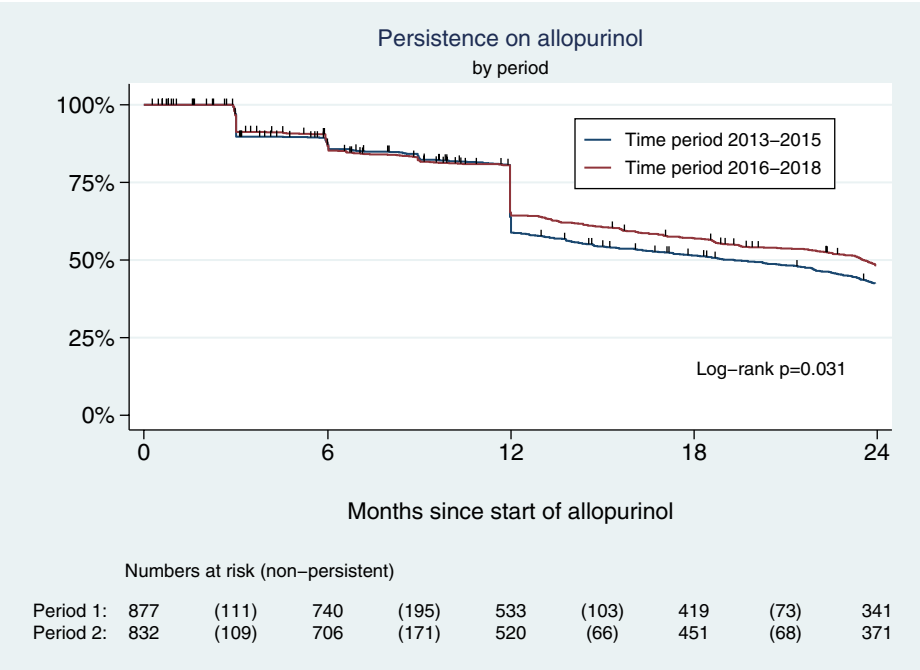

Figure 15. Persistence on allopurinol for patients starting allopurinol in 2013-2015 compared to those starting in 2016-2018. Tick marks indicate individuals censored because of death.

Measures of guideline compliance are presented in Table 7.

Table 7. Outcomes related to guideline compliance / treat-to-target approach, comparison between gout patients initiated on allopurinol in 2013-2015 vs. 2016-2018.

	2013-2015, n=877	**2016-2018, n=832**	**p**
Baseline SU test performed, n (%)	677 (77)	699 (84)	<0.001
Received no subsequent allopurinol prescription, n (%)	269 (31)	208(25)	0.009
≥1 follow-up SU test within 3 months after starting allopurinol, n (%)	319 (36)	419 (50)	<0.001
Number of SU tests during follow-up, mean (SD)	1.63 (2.18)	2.08 (2.40)	<0.001
Follow-up SU ≤ 360 µmol/L ever, n (%)	266 (30)	378 (45)	<0.001
Mean change from BL to lowest follow-up SU, µmol/L (95% CI of difference)	-178 (-166 to -189)	-183 (-173 to -193)	NA
Dose titration of allopurinol, n (%)	183 (21)	291 (35)	<0.001
Daily dose of allopurinol in mg prescribed during follow-up, median (IQR)	111 (148)	185 (177)	<0.001
Subsequently prescribed febuxostat and/or probenecid after becoming non-persistent with allopurinol, n (% of non-persisters)	12 (2)	17 (4)	0.033

PAPER II

Work-loss days due to sickness absenteeism

This paper included gout cases and controls from the Western Swedish Healthcare Region. Descriptively, the number of work-loss days was 56% higher for gout cases compared to controls, in the index year (year of first gout diagnosis) and in the three years thereafter (Figure 16).

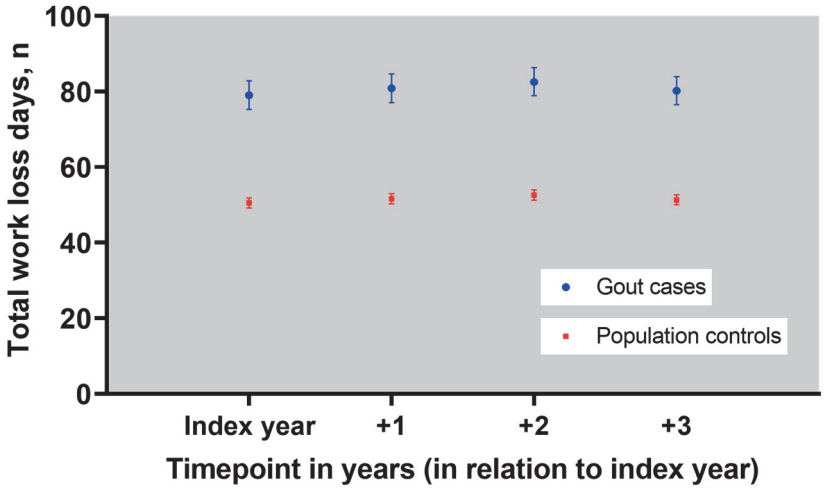

Figure 16. Mean total work-loss days per year (i.e. due to sick-leave and disability pension combined) for gout cases and population controls. Error bars indicate 95% confidence intervals. Adapted from: Ann Rheum Dis. 2018;77(3):399-404.

Predictors of new-onset absenteeism

In the subset of cases and controls with no sick leave or disability pension days in the year preceding the index year, gout was significantly associated with new-onset sickness absenteeism (defined as >90 work-loss days in the year after the index year), OR (95% CI 1.45 (1.21-1.74) (Figure 17).

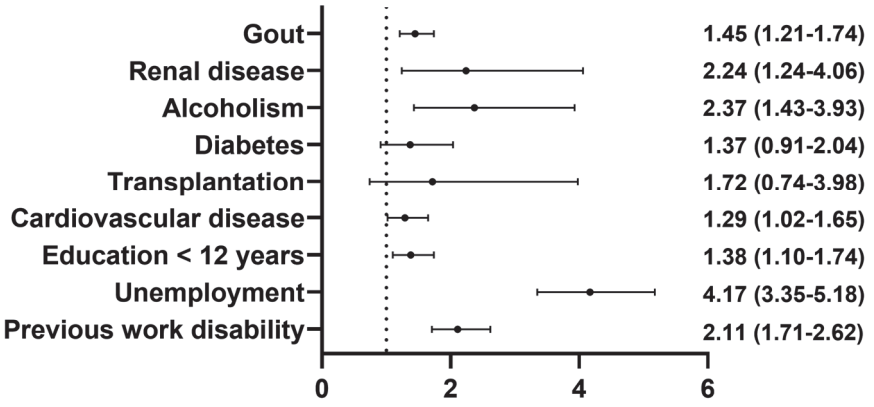

Figure 17. Predictors for new-onset work-disability (>90 days of work-loss). Odds ratios with 95% confidence intervals. Adapted from: Ann Rheum Dis. 2018;77(3):399-404.

PAPER III

Occupational exposure to inorganic dust among gout cases and controls

This paper included gout cases and controls from the Western Swedish Healthcare Region. Descriptively, 30.1% of the gout cases compared to 28.2% of the controls had occupations exposed to inorganic dust in the 5 years prior to the index year (p=0.006).

Association of occupational exposure to inorganic dust to incident gout

In the unadjusted analysis, exposure to inorganic dust was associated with incident gout, OR 1.12, 95% CI 1.04 to 1.20).

In the models adjusted for obesity and alcohol use disorder (model a) and obesity, alcohol use disorder and level of education (model b) the association between inorganic dust exposure and incident gout was diminished (Figure 18).

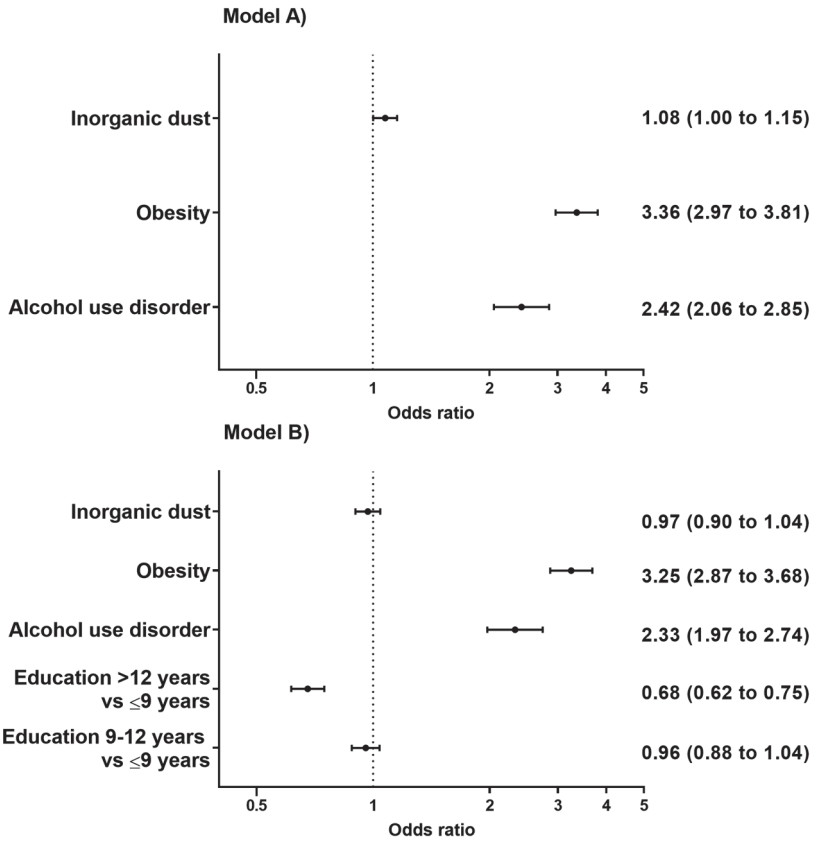

Figure 18. Odds ratios with 95% confidence intervals for the association between occupational exposure to inorganic dust and incident gout. Model A) adjusted for obesity and alcohol use disorder. Model B) in addition adjusted for educational level. Reproduced with permission from RMD Open. 2020;6(2).

PAPER IV

Residential air pollution exposure levels among gout cases and controls

This paper included cases and controls resident in the Gothenburg and Mölndal area of the Western Swedish Healthcare region. Residential air pollution exposure levels were similar between cases and controls (median lag 1-5 exposure of 7 $\mu g/m^3$, 14 $\mu g/m^3$ and 24 $\mu g/m^3$ for $PM_{2.5}$, PM_{10} and nitrogen oxides (NO_x) respectively).

Association of residential air pollution levels to incident gout

There were no significant associations found between air pollution exposure and incident gout for any of the studied exposures or time windows (Table 8), nor in stratified analyses by age, sex, comorbidity status or educational level (Table 9).

Table 8. Unadjusted and adjusted odds ratios for the outcome of gout. Per 1 IQR increment of the exposures. Lag 1-5: mean exposure during the 5 years prior to the index year. Lag 1: mean exposure during the year before the index year.

Exposure / time window	**OR (95% CI) Unadjusted**	**OR (95% CI) Adjusted for renal and coronary heart disease**
PM_{10} lag 1-5	0.96 (0.92 to 1.01)	0.97 (0.93 to 1.02)
PM_{10} lag 1	0.96 (0.92 to 1.01)	0.97 (0.93 to 1.01)
$PM_{2.5}$ lag 1-5	0.95 (0.89 to 1.02)	0.97 (0.91 to 1.04)
$PM_{2.5}$ lag 1	0.97 (0.92 to 1.02)	0.98 (0.93 to 1.04)
NO_X lag 1-5	0.96 (0.83 to 1.00)	0.96 (0.93 to 1.00)
NO_X lag 1	0.95 (0.91 to 0.99)	0.96 (0.92 to 1.00)

IQR for PM_{10} lag 1-5=2.57
IQR for $PM_{2.5}$ lag 1-5=1.92
IQR for NO_X lag 1-5=14.30

IQR for PM_{10} lag 1=2.76
IQR for $PM_{2.5}$ lag 1=1.49
IQR for NO_X lag 1=13.18

Table 9. Unadjusted odds ratios for the outcome of gout per 1 IQR increment of the exposures, stratified by subgroups.

Subgroup	PM_{10} lag 1-5	$PM_{2.5}$ lag 1-5	NO_X lag 1-5
Sex			
Males	0.95 (0.93 to 1.03)	0.98 (0.90 to 1.07)	0.97 (0.93 to 1.02)
Females	0.93 (0.86 to 1.00)	0.88 (0.78 to 1.00)	0.93 (0.87 to 1.00)
Educational level			
<9 years	0.95 (0.86 to 1.05)	0.90 (0.77 to 1.06)	0.95 (0.88 to 1.04)
9-12 years	1.03 (0.95 to 1.11)	1.01 (0.89 to 1.15)	1.03 (0.96 to 1.11)
≥12 years	0.93 (0.83 to 1.04)	0.97 (0.81 to 1.16)	0.90 (0.82 to 1.00)
Medical history			
Any comorbidity	0.99 (0.94 to 1.05)	1.02 (0.93 to 1.12)	0.98 (0.93 to 1.03)
No comorbidity	0.93 (0.85 to 1.02)	0.88 (0.76 to 1.02)	0.92 (0.86 to 1.00)
COPD	1.19 (0.85 to 1.68)	1.26 (0.72 to 2.19)	1.12 (0.81 to 1.55)
Renal disease	0.87 (0.63 to 1.21)	1.03 (0.60 to 1.75)	0.76 (0.56 to 1.05)
Hypertension	0.98 (0.91 to 1.05)	1.00 (0.90 to 1.12)	0.96 (0.91 to 1.03)
Obesity	1.06 (0.78 to 1.43)	1.14 (0.70 to 1.84)	1.02 (0.74 to 1.40)
Congestive heart failure	1.00 (0.84 to 1.20)	1.10 (0.81 to 1.49)	1.00 (0.86 to 1.16)
Coronary heart disease	1.05 (0.91 to 1.21)	1.05 (0.83 to 1.32)	1.04 (0.92 to 1.18)
Atrial fibrillation	0.85 (0.72 to 1.01)	0.77 (0.58 to 1.01)	0.89 (0.77 to 1.04)
Diabetes mellitus	0.95 (0.79 to 1.14)	0.97 (0.72 to 1.29)	0.91 (0.77 to 1.08)
Alcoholism	0.76 (0.45 to 1.28)	0.79 (0.34 to 1.82)	0.72 (0.44 to 1.19)
Thromboembolism	1.12 (0.79 to 1.57)	1.33 (0.76 to 2.35)	1.03 (0.76 to 1.40)
Psoriasis	0.98 (0.51 to 1.86)	1.49 (0.50 to 4.44)	0.83 (0.49 to 1.41)
Peripheral vascular disease	1.12 (0.55 to 2.28)	0.69 (0.17 to 2.76)	1.06 (0.61 to 1.83)

IQR for PM10 lag 1-5=2.57
IQR for PM2.5 lag 1-5=1.92
IQR for NOx lag 1-5=14.30

DISCUSSION

PAPER DISCUSSIONS

Paper I

In this study we described recent trends in gout incidence and prevalence in Dalarna, Sweden. The prevalence of gout (standardized to the Swedish population) was 2.45% (95% CI 2.39% to 2.51%) in 2018. This is higher than prevalence figures previously reported from other Swedish regions, Dehlin et al reported a prevalence of 1.80% in the Western Swedish Healthcare Region in 2012 (141) and Kapetanovic et al a prevalence of 1.79% in Southern Sweden in 2013 (228). That gout seems to be more frequent in Dalarna could be related to an increased prevalence of obesity in the region compared to the rest of Sweden (229), as obesity is a well established risk factor for hyperuricemia and gout. It is also possible that the study design, with a long period of data collection, including cases diagnosed in primary care from year 2000 and onwards in the prevalence estimate, could have contributed to higher prevalence figures, the period of data collection in the study from the Western Swedish Healthcare Region was 11 years and in the study from Skåne it was 16 years.

Based on available register data we concluded that at least 76% of prevalent cases did have an indication for ULT. As we did not have information on the presence of comorbidities, tophi and radiographic destructive changes in joints, the proportion with an indication for ULT could be even higher. Although the vast majority of prevalent patients had an indication for ULT, only 21-24% were on treatment in 2014-2018. This is much lower than the pooled prevalence of ULT in gout of 52% found by a recent meta-analysis (195). Much of this discrepancy is in all likelihood explained by the long period of case ascertainment in our study, enabling us to include all identified gout cases in the region during up to 20 years (2000-2019) in the denominator. Other register-based studies with a similar length of data collection have arrived at estimates more similar to ours. Kuo et al (122), with a data collection period of 16 years (1995-2010), found that in Taiwan, 23% of prevalent gout cases in 2010 were on ULT. In the UK, Kuo et al reported that 38% of prevalent gout cases in 2012 were on ULT, the study included cases identified during a period of 16 years (from 1997-2012) in the denominator (143). Dehlin et al, with a period of case identification of 11 years (2002-2012), found that in the Western Swedish Healthcare region, 42% of prevalent cases were dispensed ULT in 2012 (141).

Although use of ULT was clearly suboptimal in the region, those that did receive ULT did so for valid reasons, with at least 90% having an indication for ULT.

We also analysed compliance to treat-to-target quality indicators among patients initiated on ULT in 2013-2015 compared to 2016-2018, i.e. after the publication of national guidelines for gout management. There was a small improvement in patient persistence on allopurinol at 24 months for those starting treatment in the latter period. There were also minor improvements in healthcare provider compliance with treat-to-urate-target based management of gout.

The study confirms that gout is a common disease and that management is suboptimal. Objective confirmation of the deficiency in gout management is important to guide future interventions intended to improve management of gout and outcomes for gout patients.

Paper II

In this large population-based study, we found that in the index year (year of first gout diagnosis) and for the 3 following years, patients with gout had 56% more sickness absenteeism days than age- and sex-matched controls. In absolute numbers, gout patients had a mean of 81 yearly sickness absenteeism days, whereas controls had a mean of 52 days. Subgroup analysis confirmed that gout had an independent influence on work-loss days, not explained by an increased burden of comorbidities. In addition, gout was an independent predictor of new-onset work-disability.

The absolute number of yearly sickness absenteeism days in our study was much higher than in a previous study from the USA that reported the number of sickness absenteeism days for employees with and without gout (225), but the relative difference between gout cases and controls was similar, emphasizing the fact that the magnitude of sickness absenteeism is highly dependent on the cultural- and social setting.

According to our study, sickness absenteeism is not as pronounced among patients with gout compared to among patients with newly diagnosed RA in Sweden. Neovius et al found that in the 3 years after first RA diagnosis, patients had a mean of 130 sickness absenteeism days (230). Sickness absenteeism in RA was at its highest in the first year after RA-diagnosis and then decreased, although it remained twice as high as among controls (230). This is contrary to our findings, where sickness absenteeism among gout patients was at a similar level during the whole 3-year period after first

diagnosis. A possible explanation for this is that, in contrast to patients with RA, most patients with gout do not receive structured treat-to-target oriented care.

Our confirmation that gout is a disease that influences sickness absenteeism and has economic consequences for individuals and the society is of clinical relevance, although indirectly, as it should be an incentive on the macro-level to improve the management of gout.

Paper III

Previous epidemiological research has implicated occupational exposure to dust (specifically silica- and textile dust) as a risk factor for RA (111-113, 231, 232) and sarcoidosis (111). In the case of RA, as associations have been more consistent for seropositive than for seronegative RA, researchers have speculated that silica exposure could induce an immunological response to citrullinated antigens, which would explain the increased risk for seropositive RA among the silica-exposed.

Unlike RA, gout is not a disease with features of pulmonary involvement nor is it associated with smoking (233, 234). In view of the lack of association between smoking and gout, the idea that exposure to other inhalants, such as inorganic dust, would increase the risk of gout perhaps does not seem immediately plausible. However, silica dust, like MSU crystals, can act as a trigger of NLRP3-inflammasome activation (115). Such activation can lead to increased reactivity of the innate immune system to other stimuli (such as MSU crystals) later on, a phenomenon termed “trained immunity” (116), providing a possible biological explanation for an association between dust exposure and gout.

In this paper we found a modest association between occupational exposure to inorganic dust and incident gout in an unadjusted model and after adjusting for ICD-code defined obesity and alcoholism. The association was diminished when the model was further adjusted for educational level.

Paper IV

There have been reports linking exposure to air pollution to gout. Of note, all such studies on associations between air pollution and gout (and hyperuricemia) have been performed in Asian settings, where ambient air pollution levels are approximately 3-4 times higher than in Sweden.

In this paper we showed that long-term exposure to residential air pollution, at the levels present in Scandinavian settings, was not a predictor of gout.

LIMITATIONS

In all of the papers there is the possibility of misclassification of gout cases, as cases were identified on the basis of ICD-codes for gout. There is also the possibility of under-ascertainment of gout cases (selection bias towards more severe cases of gout), as people with gout that do not seek healthcare for their condition are not identified and thus not included in the studies.

A limitation of paper I is the lack of data from specialized in- and outpatient care during 2000-2012. Estimates of incidence rate and prevalence for this time period are thus based solely on data from primary care, i.e. patients that received a gout diagnosis in specialized care only are not captured and some of the patients identified as incident in the 2000-2012 data could potentially have received a prior diagnosis of gout in specialized care. We therefore chose to present incidence rate and prevalence figures for the period 2014-2019.

In paper II, there is the issue of work-loss periods shorter than 14 days not being captured by register data, as they are reimbursed by the employer and not registered in the social security register. Because most gout flares resolve within 14 days, it is possible that the effect of gout on sickness absenteeism is truly larger than what was demonstrated by our study.

Generalizability of the descriptive results in paper II can be questioned, work-loss days are highly dependent on the setting, all residents in Sweden are eligible for sick-leave and disability pension compensation in case of disease affecting work ability transiently or permanently. The nature of the social security system is likely to influence the number of work-loss days (which were in the range of 5-fold higher than reported from the USA), but the finding of a significant difference between gout cases and matched population controls can not be explained by the accessible and universal Swedish social security.

In paper III, misclassification of exposure is a possibility. Exposure assignment was based on job exposure matrices (JEM) applied to the occupational codes that are reported to the occupational register (mostly by employers). The validity of occupational codes reported to the register has not been comprehensively investigated. Exposure classification by JEMs is an established method in occupational medicine population/register-based research. Using JEMs enables exposure assignment based on job titles / occupational codes in situations where directly measuring individual

occupational exposures is impossible. The drawback of the method is that it does not account for the heterogeneity of exposure within job titles, as all individuals with a given job title are classified as either exposed or non-exposed. There is however no reason to believe that misclassification would be of unequal magnitude for cases and controls in our study, so any bias introduced should be non-differential.

Misclassifications of the covariates adjusted for, obesity and alcoholism, is also a possibility. When defining obesity and alcoholism by ICD-codes there is also in all likelihood grave under-ascertainment of these conditions.

The findings can also be questioned on the basis of unmeasured confounding. When we adjusted our model for educational level the association between inorganic dust exposure and gout was no longer evident. Educational level is a marker of socioeconomic status, is associated with obesity and gout and strongly connected to the choice of occupation. Possibly, associations between gout and occupational exposure to inorganic dust found in this paper are explained by unmeasured confounding, which is rectified by adjusting for socioeconomic status. However, adjusting the model for educational level might also be considered over-adjustment, in the sense that it adjusts for an upward mediator (education) of the variable of interest (inorganic dust).

In Paper IV, there is also the possibility of unmeasured confounding, but even so, the finding of a null-association is in all likelihood valid, it is difficult to imagine any potential unmeasured negative confounder that would bias the unadjusted OR towards 1.00. In addition, known risk factors for gout are not plausibly related to residential address in the Gothenburg setting. In paper IV exposure definition was based on yearly addresses (November 1st each year), meaning that exposure estimates are not correct for individuals who moved during the year.

CONCLUSION

The incidence rate of gout in Dalarna in 2014-2019 varied from 221 to 247 cases per 100000 person-years in 2014-2019 (standardized to the Swedish population in 2019).

Prevalence increased during the study period, the prevalence in 2018 was 2.45% (95% CI 2.39% to 2.51%) (standardized to the Swedish population in 2018).

During 2014-2018, only 21-25% of prevalent gout cases were being treated with allopurinol, even though at least 76% were found to have an indication for ULT.

Two-year persistence on allopurinol was poor, but slightly better for patients that were initiated on allopurinol after the publication of national gout management guidelines in 2016, 45% compared to 39%.

Management of gout with allopurinol as assessed by treat-to-target quality indicators improved somewhat in Dalarna after 2016, although compliance to management guidelines remained suboptimal.

Gout patients had 56% more sickness absenteeism than matched population controls and among subjects with no absenteeism in the year before the index year, gout was a predictor of new-onset absenteeism.

Occupational exposure to inorganic dust was associated with incident gout after adjustment for obesity and alcoholism, an association that was diminished when the model was adjusted for educational level.

Long-term exposure to residential ambient air pollution did not predict incident gout.

FUTURE PERSPECTIVES

The quality of gout care is clearly suboptimal. By using the diagnostic and laboratory data entered into electronic health care records and the data generated by electronic prescribing, it would be entirely possible to monitor the incidence and prevalence of gout and its management continuously in real-time. Such real-time monitoring could be used to assess the effect of interventions intended to improve management. Interventions to improve management could include automatic prompts by the electronic health record system, e.g. a suggestion to order a follow-up SU-test when a urate-lowering medication is prescribed or prompts to review the ULT dose when an off-target SU value is detected for a patient with a gout diagnosis. Future studies could investigate the acceptability to clinicians of such automatic reminders/prompts and the effects on quality of care in gout. Other possible interventions that could improve gout management and should be studied include at-home urate monitoring by devices measuring SU in capillary blood samples, this could be combined with e-health solutions providing automated feedback to the patient on dose-titration of ULT based on patient-supplied SU-values.

We have showed that sickness absenteeism is increased in gout patients compared to matched controls. Sickness absenteeism is highly dependant on socioeconomic factors, but some of the increased absenteeism seen in gout patients could be related to poorly managed gout. Future prospective studies that examine the effect of optimized gout treatment on sickness absenteeism and/or retrospective studies examining sickness absenteeism in relation to the severity of gout would be of interest.

Regarding environmental exposures, experimental studies that address potential effects on urate metabolism, MSU-crystallization and the inflammatory response to MSU-crystals are needed. Regarding occupational exposures and their associations with gout it could be of interest to examine other exposures than inorganic dust, such as exposure to lead and/or other heavy metals historically associated with gout.

Although long-term exposure to air pollution was not associated with gout in our study, future studies should examine the association between short-term variations in air pollution and gout.

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