

Assessing the impact of

GOUT:

validating and understanding outcomes

Assessing the impact of gout: validating and understanding outcomes

Bart Spaetgens



Uric acid crystals

Uric acid crystals are characterized by their needle shape and strong double refraction in polarized light. The image shows massive aggregation of uric acid crystals viewed under polarized light with 400 x enlargement.

BART
Spaetgens

Assessing the impact of gout:

validating and understanding outcomes

© Bart Spaetgens, Sittard, 2017

No part of this book may be reproduced or transmitted in any form or by any means, without prior permission in writing by the author, or when appropriate, by the publishers of the publications.

Layout: Tiny Wouters

Cover design: Jean Scheijen | vierdrie.nl

Production: Ipskamp Drukkers B.V.

ISBN: 978-94-028-0596-3

Financial support by Maastricht University, Dutch Arthritis Foundation (Reumafonds) for the publication of this thesis is greatly acknowledged.

Assessing the impact of gout:

validating and understanding outcomes

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen op donderdag 11 mei 2017, om 12.00 uur.

door

Bartholomeus Pieter Antoinetta Spaetgens

Promotores

Prof. dr. A.E.R.C.H. Boonen

Prof. dr. J.M.J.P. van der Linden

Copromotor

Dr. F. de Vries

Beoordelingscommissie

Prof. dr. R.P. Koopmans (Voorzitter)

Dr. M. Hiligsmann

Dr. T. Janssen, Radboud UMC, Nijmegen en Viecuri MC, Venlo

Prof. dr. M.A.F.J. van de Laar, Universiteit Twente en Medisch Spectrum Twente, Enschede

Prof. dr. C.P. van Schayck

Contents

Chapter 1	General introduction	7
Chapter 2	The Gout Assessment Questionnaire 2.0: cross-cultural translation into Dutch, aspects of validity and linking to the International Classification of Functioning, Disability and Health	23
Chapter 3	Content and construct validity of the Rheumatic Diseases Comorbidity Index in patients with gout	43
Chapter 4	Cost-of-illness and determinants of costs among patients with gout	57
Chapter 5	The importance of 'state-of-the-art' cost-of-illness studies	81
Chapter 6	Health and utilities in patients with gout under care of a rheumatologist	87
Chapter 7	Construct validity of radiographs of the feet to assess joint damage in patients with gout	105
Chapter 8	Risk of infections in patients with gout: a population-based cohort study	115
Chapter 9	Knowledge, illness perceptions and stated clinical practice behaviour in management of gout. A mixed methods study in general practice	131
Chapter 10	Summary and general discussion	147
	Samenvatting	161
	Valorisation	167
	Dankwoord	173
	Curriculum vitae	179

Chapter 1

General introduction

History

Gout is an inflammatory rheumatic disease characterized by acute or chronic arthritis caused by the deposition of monosodium urate (MSU) crystals in the synovial fluid. An acute attack or gout flare is usually monoarticular and affects the first metatarsophalangeal joint (MTP-1) in 56-78% of the first attacks.¹ The earliest documented clinical presentation of the disease has been described by the Egyptians in 2640 BC. Around 400 BC, Hippocrates commented on gout in his writings as 'the unwalkable disease', referring to the severity of the attacks. Also, he was the first to describe the association with lifestyle as he referred to gout as a 'king's disease' or 'arthritis of the rich'.^{2,3} Six centuries later (around 200 AD), Galen was the first to describe a substance later known as MSU depositions (tophi) and also recognized a hereditary trait.⁴ However, the actual term 'gout' was not used until medieval times (1200 AD), when Randolfus of Bocking described it as 'gutta quam podagram vel artritcam vocant', meaning 'the gout which is called podagra or arthritis'. The term gutta ('drop') refers to the belief that the disease was caused by an imbalance in the four humors and the notion of the 'dropping' of a morbid material from the blood in and around the joints.⁵ In 1683, Sydenham, an English physician, also known as the English Hippocrates, who suffered from gout himself emphasized the association of gout with debauchery and he very accurately described an acute gout attack in his book

Tractatus de podagra et hydrope (The Management of Arthritis and Dropsy):
"The patient goes to bed and sleeps quietly until about two in the morning
when he is awakened by a pain which usually seizes the great toe, but
sometimes the heel, the calf of the leg or the ankle... so exquisitely painful as
not to endure the weight of the clothes nor the shaking of the room from a
*person walking briskly therein."*⁶

The presence of (monosodium) crystals in the so-called tophi that appeared in a proportion of patients, were first described in 1679 by Antoni van Leeuwenhoek,⁷ although the chemical composition was unknown at that time. In 1961, McCarty and Hollander showed that the synovial fluid of patients with gout contained crystals composed of MSU.⁸ All this has contributed to the understanding of gout and its pathophysiology.

Epidemiology of gout

Gout is the most common form of inflammatory arthritis worldwide, affecting 2.5% in the UK,⁹ to 3.9% in the United States¹⁰ and numbers are rising in unique populations up to 6.5% (Hmong, USA¹¹), 11.1% (Māori, New Zealand¹²) and 11.7% (Aborigines, Taiwan¹³). The prevalence and incidence of gout were significantly higher in 2012

compared to 1997 with an increase of 63.9% in prevalence and 29.6% increase in incidence respectively.⁹

The prevalence and incidence of gout also rises with age and is more common in men than women, with a male:female ratio ranging from 3:1 to 9:1.^{10,14} Gout therefore emerges as a major public health issue with rising burden of disease.¹⁵ As a part of the Global Burden of Diseases studies 2010,¹⁶ in which gout was estimated for the first time, it was shown that Disability-Adjusted Life Years (DALYs) increased significantly from 1990 to 2010. DALYs capture health loss by assessing the disease burden, combining lifetime lost due to premature mortality and reduced quality of life due to disability. This raise in DALYs might also be attributed or reinforced by a series of factors that can coincide with gout. For example, the ageing population and lifestyle changes enhance comorbidities that might further influence not only the occurrence of gout, but also the disability of patients with gout significantly.

Epidemiological studies have repeatedly shown that gout (and the associated hyperuricaemia) co-exist with a large number of comorbidities, including hypertension (74%), chronic kidney disease >stage 2 (71%), obesity (53%), diabetes (26%), heart failure (11%)¹⁷ and hypercholesterolaemia (72%).¹⁸ Although there is ongoing debate about the causal association between sUA levels and aforementioned comorbidities,¹⁹⁻²¹ there is some evidence that hyperuricaemia causally contributes to worse outcomes in cardiovascular diseases.^{22,23} An alternative explanation could be that lifestyle factors that predispose to hyperuricaemia and gout, also predispose to cardiovascular diseases.²⁴ Despite these frequently mentioned disadvantageous effects, beneficial effects of uric acid have also been described. For example, uric acid concentrations are inversely associated with Parkinson's disease,²⁵ while gout itself is associated with reduced risks of Parkinson's disease and dementia.^{26,27}

Pathophysiology and clinical manifestations of gout

The pathophysiology of gout is well understood. Gout arthritis is induced by deposition of MSU crystals in the synovial fluid and other tissues. Preferentially, MSU crystals are deposited in peripheral joints in the feet, knees, hands and elbows. The crystals form when serum uric acid (sUA) levels rise above the 'saturation point' which is around 0.40 mmol/l.²⁸ The level of sUA is the main risk factor to develop gout.²⁹ Nevertheless, only a minority of individuals with hyperuricaemia develop gout. Therefore, other influencing factors are implied. Environmental (e.g. dietary,³⁰⁻³⁶ alcohol,³⁷ supplements³⁸ and medication^{39,40}), genetic influences⁴¹ and their mutual relationships^{42,43} are now being studied.

Gout can be divided into four clinical stages of disease: hyperuricaemia without urate crystal deposition, urate crystal deposition without gout, crystal deposition with acute

gouty arthritis and advanced gout, which is characterised by chronic gouty arthritis and/or tophi, which represent the accumulation of urate crystal depositions in and around the joints. Both tophi and chronic gouty arthritis can eventually lead to radiographic damage.

Impact of gout

In this thesis, we contribute to the assessment and understanding of the impact of gout to patients and society. Such research is called ‘outcome research’. As any research, also outcome research requires a conceptual framework. According to the conceptual framework proposed within the Outcome Measures in Rheumatology Clinical Trials (OMERACT) working group⁴⁴ two concepts are distinguished when assessing outcome: ‘pathophysiological manifestations’ and ‘impact of health condition’.⁴⁵ The concept of ‘impact of health conditions’ can be subdivided in a number of *outcome areas* (e.g. life impact, economic impact) which are further specified into relevant *outcome domains*. For each selected domain a valid *outcome instrument* is needed to enable measurement of the impact in this domain. Further, it is recognized that other factors, often outside the disease process and therefore called contextual factors, may act on the outcome as confounders, effect modifiers or factors that influence the generalizability of a study.⁴⁵ For example, an important contextual factor in disease management is the environment in which the patient is treated.

OMERACT recommends that rheumatologists, patients and epidemiologists should agree on disease-specific Core Sets of outcome domains, validated instruments, and contextual factors that are (minimally) necessary to capture the impact of diseases within clinical trials. However, outcome assessment is a dynamic process and the choice of core domains or core instruments will vary and improve over time. Continuous research into the complex relationship between pathophysiological and contextual factors, disease manifestations and into validity of measurement instruments will also further contribute to outcome assessment in trials and observational studies.

This thesis addresses a number of knowledge gaps when measuring outcomes in the context of a broader perspective than the clinical trial. We will mainly focus on the measurement of ‘impact of the health condition’, although we will briefly touch upon ‘pathophysiology’ and ‘contextual factors’ as these are sometimes directly related to the disease and might affect study outcomes.

Gout-specific functioning and disability

It is clear that gout with its unpredictable attacks characterized by severe pain and limitations in mobility on the one hand, and chronic joint damage on the other hand,

might have an enormous impact on the life of patients. It is therefore surprising that compared to other diseases, gout received little attention with regard to understand the impact of the disease on different aspects of functioning and disability. Measuring the impact of gout from a patient's perspective is challenging because of the aforementioned heterogeneous manifestations of the disease that need to be captured. Functioning and disability can be measured using generic instruments of which the Short-Form 36 (SF-36), Health Assessment Questionnaire (HAQ) and Health Assessment Questionnaire-disability index (HAQ-DI) are used most often. They also show satisfactory clinimetric properties⁴⁶⁻⁴⁸ and have been endorsed by the OMERACT filter⁴⁴ to measure functioning and disability in gout^{49,50}. Nevertheless, these instruments often lack to adequately measure certain disease-specific aspects related to deteriorated functioning and consequently might be less sensitive to changes (due to progression of disease or treatment).

Therefore a disease-specific questionnaire, the so-called Gout Assessment Questionnaire (GAQ),⁵¹ to measure gout-specific impact across a broad range of areas relevant for patient's health was developed. Next, the GAQ was further adjusted and optimized for use in clinical practice which led to the GAQ2.0.⁵² The application of the GAQ2.0 however is limited by the existence of an English version only. Translation and validation in other languages ensures measurement equivalence of the instrument across languages. Second, availability of a Dutch version of the GAQ2.0 would enhance its application in more cohorts and trials creating additional values for research aiming to understand whether gout-specific impact has an additional value in explaining outcome.

Measuring the impact of comorbidities on health

Currently available research on factors associated with poor functioning and disability in gout indicates that not only the acute arthritis, chronic joint damage, but also the comorbidities have an important impact on functioning and health,⁵³ There are however conflicting data on the magnitude of impact of both gout-specific features and/or comorbidities. There are several studies that showed gout-specific features (tophi, number of flares, pain during a typical attack) are associated with worse health-related quality of life (HRQOL), after adjustment for age, gender, disease duration and comorbidities,⁵⁴⁻⁵⁶ but also studies that showed no difference in HRQOL in those with and without gout after adjusting for comorbidities. As such, these studies concluded that solely the comorbidities were responsible for worse HRQOL.^{48,53} Several explanations for these conflicting studies are postulated. First, there is no consensus whether to call a condition comorbid (co-occurring by chance) or coexistent (thus related to the index disease). Especially in patients with gout, in whom the mutual (causal) relationships between gout and coexistent diseases are very complex. Second, it is possible that different methods to assess comorbidity, such as self-report

questionnaires, structured interviews, physical examinations and medical chart reviews, influence the completeness of data.⁵⁷ Third, it has been shown that different methods to calculate a score (simple comorbidity count vs. weighted scores for every present comorbid condition) lead to different conclusions when correcting for comorbidity.⁵⁸

In the light of the aforementioned problems there seems to be a need for a valid instrument that measures comorbid conditions and adjusts for them whenever appropriate. A potential interesting instrument is the self-reported Rheumatic Diseases Comorbidity Index (RDCI), which was initially developed by Michaud and Wolfe to assess the influence of comorbidity on HRQOL, physical functioning and costs in patients with rheumatoid arthritis.⁵⁹ However, no data on the content or construct validity of the RDCI (or other comorbidity indices) in patients with gout are available. Also, no data on the independent influence of comorbidity (measured by the RDCI) on functioning, disability and healthcare costs are available.

Costs

In the light of the rising burden of disease and the development of new (expensive) pharmacological treatment options, it is important to gain insight into health resource utilization and associated costs incurred by patients with gout. Cost-of-illness (COI) studies are an essential source when developing models for economic evaluations. Moreover, they are of value in identifying which resources drive the costs, and therefore contribute to debates on appropriate or inappropriate healthcare expenditures. As such, COI act as a tool to guide future research to improve efficiency of healthcare.⁶⁰ Classically, COI is divided into direct and indirect costs. Direct costs include those incurred for outpatient visits, emergency department visits, hospitalization, prescribed medication and any additional (laboratory or radiology) services. But also, nonmedical direct costs, such as professional house-hold care and also informal care by family and friends can be included. Indirect costs include those incurred for time absent from work (absenteeism) and productivity loss due to impairment while at work (presenteeism).

To date, only a small number of COI studies provide limited information about patients with gout.⁶¹⁻⁶⁶ First, most of them were insurance database studies with only a limited number of clinical determinants were available. Second, data on direct costs were incomplete, as data on direct costs were only limited to medical and pharmacy costs, while nonmedical direct costs were not estimated. Third, data on indirect costs were scarce and incomplete as only data on absenteeism, but not presenteeism were available. Therefore, it is important to comprehensively investigate direct and indirect costs, including non-medical direct costs and presenteeism, and to investigate which factors (including gout-specific impact and comorbidity) mainly drive the costs of

patients with gout. Eventually, such a study, provides data about the COI in patients with gout, who are likely given innovative medications and care interventions.

Utility

The concept of utility is attractive to compare the impact of diseases or interventions on overall (or global) health across different health conditions. Utility represents the value individuals, either patients or unprejudiced persons from the population, attach to health states. Then, it also serves as the basis to calculate Quality Adjusted Life Years (QALYs).⁶⁷ The basic idea of QALYs is simple, QALYs can be calculated by multiplying utility, which is a single value between zero and one (representing death and perfect health respectively) representing a given health state, by the years lived in that health state. Then QALYs can be incorporated with medical costs to determine the so-called cost per QALY, which is a parameter that can be used in cost-effectiveness analysis.⁶⁷

Several generic patient reported health measures are available, for which an algorithm exists to convert the different health states into the societal value of health. Within these 'indirect societal utility measures', the EuroQol 5-domains instrument (EQ-5D) with EQ-5D visual analogue scale (EQ-5D VAS) and Short-Form 6-dimensions (SF-6D), derived from the Short-Form 36 (SF-36) are the most common-used instruments.^{68,69} Although utility scores of patients should theoretically be similar independent of the approach or instrument used, large differences have been observed.^{70,71} Similar as for costs, it is important to realize which factors drive utility. Especially in a disease in which a large proportion of patients suffer from comorbidities, it could be that utility is mainly influenced by comorbidities and that the contribution of gout-specific impact itself is small. This would have important implications since cost-effective management should mainly address comorbidities, rather than the gouty disease itself. As to date, only two studies have reported on utilities in gout.^{56,72} Currently, there is insufficient knowledge about utility values of patients with gout when compared with the general population, about factors influencing utility values, and on comparability of different instruments assessing utility values.

Joint damage and imaging

Joint damage is considered as an important outcome belonging to the concept of 'pathophysiological manifestations'. The ideal imaging modality would capture all four clinical stages of disease, displaying MSU crystal depositions, acute inflammation, tissue response, bone erosions, tendon involvement and tophi.⁷³ Conventional radiography (XR), ultrasound (US), Computed tomography (CT), Dual-energy computed tomography (DECT) and Magnetic resonance imaging (MRI) are the imaging modalities currently being used to assess gout. All these modalities have different strengths and weaknesses, which depend on whether they are used for diagnosis or disease monitoring. As such, XR for example is inexpensive, widely available and has high

specificity for gout. It is however less accurate than CT, MRI and US for erosions and also characteristic features (tophi, joint space widening) occur later in the disease⁷⁴ or only in the context of severe disease (sclerosis, joint space narrowing (JSN) and ankylosis or subluxation).⁷³

Because of its feasibility however, XR is a potential useful imaging modality for disease monitoring. A quantitative scoring system, scoring erosion and JSN, which is a modified version of the Sharp-van der Heijde developed for scoring structural damage in rheumatoid arthritis,⁷⁵ with good reproducibility, is available to score structural damage in gout.⁷⁶ It is therefore surprising that joint damage is rarely assessed as an outcome in studies on gout.⁷⁷ As such, there are no comprehensive data on the construct validity of radiographic damage scored on XR available. First, it is unclear which pathophysiological features of the disease, contribute to damage on XR. Second, no information on whether radiographic damage is negatively associated with overall functioning and disability is available.

Infection as a comorbidity of gout

A less frequently mentioned comorbidity/outcome in patients with gout is infection or infection-related morbidity. On the one hand, recent literature showed that patients with gout are more likely to be diagnosed with septic arthritis⁷⁸ and vice versa, i.e. patients with septic arthritis often have an underlying inflammatory arthritis of which gout is the most prevalent.⁷⁹ On the other hand, in the relationship between gout and infections, beneficial effects of uric acid have been postulated. An in vitro study showed that peripheral blood mononuclear cells of patients with gout, compared to controls without gout, produced more interleukin-1- β (IL-1 β) when stimulated with MSU crystals.⁸⁰ It was hypothesized that uric acid might have a protective effect in acquiring infections, since it is well established that IL-1 β augments the quality of the host defence between bacteria and viruses.⁸¹ However, to date, the clinical correlate of this concept has not been explored. As such, it would be worthwhile to assess the pathophysiological consequence of this hypothesis in an epidemiologic study.

Management of gout

Although gout is associated with a substantial burden of disease, it is important to mention that gout is a well-treatable disease. In the treatment of gout, a distinction is made between treatment of acute attacks with colchicine, NSAIDs or prednisone, and long-term management with uric acid lowering therapy (UALT). When sUA levels are reduced (and maintained) below 0.30-0.36 mmol/l,^{82,83} further urate crystal joint deposition is prevented and it even leads to dissolution of the existing deposited crystals and tophi.⁸⁴

Despite current guidelines and the fact that gout can be well-treated, standard care for patients with gout is suboptimal.^{85,86} Common barriers of effective treatment are misperception of the disease itself by patients,⁸⁷ but also doctors⁸⁸ which leads to underestimating the importance of prescribing long-term UALT, under-dosing of UALT⁸⁹ and poor adherence to treatment.^{90,91} On the other hand, another study showed that with a 'package of care' including patient education (with full explanation of cause, risk factors and prognosis), lifestyle advices and slow uptitration of UALT more than 90% of patients achieve therapeutic targets.⁹²

As gout in most cases is diagnosed and managed by general practitioners (GPs), treatment usually takes place in primary care.^{83,93} Despite the fact that GPs are the most relevant healthcare professionals when it comes to diagnosing and treating gout, current literature does not provide broad insight into how gout is managed by GPs. Most studies that explored barriers to effective gout management included only a low number of GPs and therefore further studies to gain in-depth insight in how GPs manage the disease are needed.

Outline of the thesis

In this thesis many of the above described knowledge gaps in outcome research in gout are addressed. In chapters 2-7, we describe the validation of different outcome measures and explore their mutual relationships. In **Chapter 2**, reports on the cross-cultural translation and validation of the GAQ2.0, in order to provide a Dutch version of a gout-specific patient-reported outcome instrument to measure functioning and disability with acceptable clinimetric properties. **Chapter 3** describes the validation of the RDCI and modified RDCI (mRDCI) and describes the independent association between comorbidity (using the RDCI/mRDCI) and functioning, disability and healthcare costs. In **Chapter 4**, the costs-of-illness of patients with gout under care of a rheumatologist are comprehensively investigated. Direct and indirect costs, including direct nonmedical costs and presenteeism, are estimated in order to obtain insight in societal costs and to identify main resource utilisation and productivity loss. Furthermore, we determine which are the main contributors to higher costs. In **Chapter 5**, the findings in our study were used to emphasize the importance of cost-of-illness studies as a comment on a systematic review about cost-of-illness study published after ours. In **Chapter 6**, we compare health utility between patients with gout and the general population in the Netherlands, compare utility values assessed by different instruments, and determine which factors influence health utility values. In **Chapter 7**, the construct validity of radiographic damage on XR is investigated. Therefore, as a first step, we explore which pathophysiological features of the disease contribute to damage on XR. Next, the relationship between radiographic damage and functioning and disability is evaluated. The data sources for chapters 2-7 were baseline

data of a cohort of patients with gout who were seen at the outpatient clinic Rheumatology of the Maastricht University Medical Centre. This hospital serves as a university hospital, as well as the only regional hospital. In **Chapter 8**, the hypothesis that uric acid might have a protective effect in acquiring infections is investigated. We use a population-based cohort from the Clinical Practice Research Datalink (CPRD), which is formerly known as the General Practice Research Database, world's largest database of anonymised and longitudinal primary care medical records of 678 general practitioners in the United Kingdom. In this cohort we investigate whether patients with gout acquire fewer community-acquired infections (pneumonia, urinary tract infections) and further explore the role of colchicine and allopurinol. In **Chapter 9**, a mixed methods study is performed among a group of GPs in the province of Limburg, the Netherlands, in order to investigate and understand specific knowledge gaps in diagnosing and treating gout, illness perceptions about the disease, and stated clinical practice of GPs. As such, potential barriers that might affect quality of care in patients with gout can be identified. Finally, **Chapter 10** encompasses a summary and discussion of the main findings from this thesis. Moreover, clinical relevance and some future perspectives are highlighted.

References

1. Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res.* 2011;4:13.
2. Hippocrates, Adams F. *The genuine works of Hippocrates.* New York,: W. Wood and company; 1886.
3. Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. *Arthritis Res Ther.* 2006;8 Suppl 1:S1.
4. Galen C. *Claudii Galeni Opera Omni.* Leipzig: CG Kühn; 1821–33.
5. Pillinger MH, Rosenthal P, Abeles AM. Hyperuricemia and gout: new insights into pathogenesis and treatment. *Bull NYU Hosp Jt Dis.* 2007;65:215-21.
6. Sydenham T. *Tractatus de Podagra et Hydroke.* London: G Kettlby; 1683.
7. McCarty DJ. A historical note: Leeuwenhoek's description of crystals from a gouty tophus. *Arthritis Rheum.* 1970;13:414-8.
8. McCarty DJ, Hollander JL. Identification of urate crystals in gouty synovial fluid. *Ann Intern Med.* 1961;54:452-60.
9. Kuo CF, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis.* 2015;74:661-7.
10. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum.* 2011;63:3136-41.
11. Portis AJ, Laliberte M, Tatman P, et al. High prevalence of gouty arthritis among the Hmong population in Minnesota. *Arthritis Care Res (Hoboken).* 2010;62:1386-91.
12. Stamp LK, Wells JE, Pitama S, et al. Hyperuricaemia and gout in New Zealand rural and urban Maori and non-Maori communities. *Intern Med J.* 2013;43:678-84.
13. Chou CT, Lai JS. The epidemiology of hyperuricaemia and gout in Taiwan aborigines. *Br J Rheumatol.* 1998;37:258-62.
14. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008;58:26-35.
15. Smith E, Hoy D, Cross M, et al. The global burden of gout: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis.* 2014;73:1470-6.
16. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380:2197-223.
17. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med.* 2012;125:679-87 e671.
18. Richette P, Clerson P, Perissin L, et al. Revisiting comorbidities in gout: a cluster analysis. *Ann Rheum Dis.* 2015;74:142-7.
19. Palmer TM, Nordestgaard BG, Benn M, et al. Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts. *BMJ.* 2013;347:f4262.
20. Keenan T, Zhao W, Rasheed A, et al. Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study. *J Am Coll Cardiol.* 2016;67:407-16.
21. Sluijs I, Holmes MV, van der Schouw YT, et al. A Mendelian Randomization Study of Circulating Uric Acid and Type 2 Diabetes. *Diabetes.* 2015;64:3028-36.
22. Kleber ME, Delgado G, Grammer TB, et al. Uric Acid and Cardiovascular Events: A Mendelian Randomization Study. *J Am Soc Nephrol.* 2015;26:2831-8.
23. Mallamaci F, Testa A, Leonardi D, et al. A genetic marker of uric acid level, carotid atherosclerosis, and arterial stiffness: a family-based study. *Am J Kidney Dis.* 2015;65:294-302.
24. Abeles AM. Hyperuricemia, gout, and cardiovascular disease: an update. *Curr Rheumatol Rep.* 2015;17:13.
25. Weisskopf MG, O'Reilly E, Chen H, et al. Plasma urate and risk of Parkinson's disease. *Am J Epidemiol.* 2007;166:561-7.
26. Pakpoor J, Seminog OO, Ramagopalan SV, et al. Clinical associations between gout and multiple sclerosis, Parkinson's disease and motor neuron disease: record-linkage studies. *BMC Neurol.* 2015;15:16.

27. Hong JY, Lan TY, Tang GJ, et al. Gout and the risk of dementia: a nationwide population-based cohort study. *Arthritis Res Ther*. 2015;17:139.
28. Fiddis RW, Vlachos N, Calvert PD. Studies of urate crystallisation in relation to gout. *Ann Rheum Dis*. 1983;42 Suppl 1:12-5.
29. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med*. 1987;82:421-6.
30. Zhang Y, Neogi T, Chen C, et al. Cherry consumption and decreased risk of recurrent gout attacks. *Arthritis Rheum*. 2012;64:4004-11.
31. Choi HK, Willett W, Curhan G. Coffee consumption and risk of incident gout in men: a prospective study. *Arthritis Rheum*. 2007;56:2049-55.
32. Choi HK, Curhan G. Coffee consumption and risk of incident gout in women: the Nurses' Health Study. *Am J Clin Nutr*. 2010;92:922-7.
33. Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA*. 2010;304:2270-8.
34. Zhang Y, Chen C, Choi H, et al. Purine-rich foods intake and recurrent gout attacks. *Ann Rheum Dis*. 2012;71:1448-53.
35. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med*. 2004;350:1093-103.
36. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ*. 2008;336:309-12.
37. Choi HK, Atkinson K, Karlson EW, et al. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet*. 2004;363:1277-81.
38. Choi HK, Gao X, Curhan G. Vitamin C intake and the risk of gout in men: a prospective study. *Arch Intern Med*. 2009;169:502-7.
39. Choi HK, Soriano LC, Zhang Y, et al. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ*. 2012;344:d8190.
40. Bruderer S, Bodmer M, Jick SS, et al. Use of diuretics and risk of incident gout: a population-based case-control study. *Arthritis Rheumatol*. 2014;66:185-96.
41. Merriman TR, Choi HK, Dalbeth N. The genetic basis of gout. *Rheum Dis Clin North Am*. 2014;40:279-90.
42. Dalbeth N, House ME, Gamble GD, et al. Population-specific effects of SLC17A1 genotype on serum urate concentrations and renal excretion of uric acid during a fructose load. *Ann Rheum Dis*. 2014;73:313-4.
43. Dalbeth N, House ME, Gamble GD, et al. Population-specific influence of SLC2A9 genotype on the acute hyperuricaemic response to a fructose load. *Ann Rheum Dis*. 2013;72:1868-73.
44. Boers M, Brooks P, Strand CV, et al. The OMERACT filter for Outcome Measures in Rheumatology. *J Rheumatol*. 1998;25:198-9.
45. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol*. 2014;67:745-53.
46. Khanna PP, Perez-Ruiz F, Maranian P, et al. Long-term therapy for chronic gout results in clinically important improvements in the health-related quality of life: short form-36 is responsive to change in chronic gout. *Rheumatology (Oxford)*. 2011;50:740-5.
47. Taylor WJ, Colvine K, Gregory K, et al. The Health Assessment Questionnaire Disability Index is a valid measure of physical function in gout. *Clin Exp Rheumatol*. 2008;26:620-6.
48. Becker MA, Schumacher HR, Benjamin KL, et al. Quality of life and disability in patients with treatment-failure gout. *J Rheumatol*. 2009;36:1041-8.
49. Schumacher HR, Taylor W, Edwards L, et al. Outcome domains for studies of acute and chronic gout. *J Rheumatol*. 2009;36:2342-5.
50. Singh JA, Taylor WJ, Simon LS, et al. Patient-reported outcomes in chronic gout: a report from OMERACT 10. *J Rheumatol*. 2011;38:1452-7.
51. Colwell HH, Hunt BJ, Pasta DJ, et al. Gout Assessment Questionnaire: Initial results of reliability, validity and responsiveness. *Int J Clin Pract*. 2006;60:1210-7.
52. Hirsch JD, Lee SJ, Terkeltaub R, et al. Evaluation of an instrument assessing influence of Gout on health-related quality of life. *J Rheumatol*. 2008;35:2406-14.
53. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. *Ann Rheum Dis*. 2008;67:1310-6.

54. Lee SJ, Hirsch JD, Terkeltaub R, et al. Perceptions of disease and health-related quality of life among patients with gout. *Rheumatology (Oxford)*. 2009;48:582-6.
55. Alvarez-Nemegyei J, Cen-Piste JC, Medina-Escobedo M, et al. Factors associated with musculoskeletal disability and chronic renal failure in clinically diagnosed primary gout. *J Rheumatol*. 2005;32:1923-7.
56. Khanna PP, Nuki G, Bardin T, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. *Health Qual Life Outcomes*. 2012;10:117.
57. Kieszak SM, Flanders WD, Kosinski AS, et al. A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *J Clin Epidemiol*. 1999;52:137-42.
58. Concato J, Horwitz RJ, Feinstein AR, et al. Problems of comorbidity in mortality after prostatectomy. *JAMA*. 1992;267:1077-82.
59. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2007;21:885-906.
60. Meerding WJ, Bonneux L, Polder JJ, Ket al. Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study. *BMJ*. 1998;317:111-5.
61. Brook RA, Kleinman NL, Patel PA, et al. The economic burden of gout on an employed population. *Curr Med Res Opin*. 2006;22:1381-9.
62. Wu EQ, Patel PA, Yu AP, et al. Disease-related and all-cause health care costs of elderly patients with gout. *J Manag Care Pharm*. 2008;14:164-75.
63. Halpern R, Mody RR, Fuldeore MJ, et al. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. *Curr Med Res Opin*. 2009;25:1711-9.
64. Halpern R, Fuldeore MJ, Mody RR, et al. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. *J Clin Rheumatol*. 2009;15:3-7.
65. Saseen JJ, Agashivala N, Allen RR, et al. Comparison of patient characteristics and gout-related healthcare resource utilization and costs in patients with frequent versus infrequent gouty arthritis attacks. *Rheumatology (Oxford)*. 2012;51:2004-12.
66. Sicras-Mainar A, Navarro-Artieda R, Ibanez-Nolla J. Resource use and economic impact of patients with gout: a multicenter, population-wide study. *Reumatol Clin*. 2013;9:94-100.
67. Gold MR, Stevenson D, Fryback DG. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. *Annu Rev Public Health*. 2002;23:115-34.
68. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208.
69. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21:271-92.
70. Hawthorne G, Richardson J, Day NA. A comparison of the Assessment of Quality of Life (AQoL) with four other generic utility instruments. *Ann Med*. 2001;33:358-70.
71. Brazier J, Roberts J, Tsuchiya A, et al. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ*. 2004;13:873-84.
72. Khanna D, Ahmed M, Yontz D, et al. The disutility of chronic gout. *Qual Life Res*. 2008;17:815-22.
73. Dalbeth N, Doyle AJ. Imaging of gout: an overview. *Best Pract Res Clin Rheumatol*. 2012;26:823-38.
74. Dalbeth N, Milligan A, Doyle AJ, et al. Characterization of new bone formation in gout: a quantitative site-by-site analysis using plain radiography and computed tomography. *Arthritis Res Ther*. 2012;14:R165.
75. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol*. 2000;27:261-3.
76. Dalbeth N, Clark B, McQueen F, et al. Validation of a radiographic damage index in chronic gout. *Arthritis Rheum*. 2007;57:1067-73.
77. Araujo F, Cordeiro I, Ramiro S, et al. Outcomes assessed in trials of gout and accordance with OMERACT-proposed domains: a systematic literature review. *Rheumatology (Oxford)*. 2015;54:981-93.
78. Lim SY, Lu N, Choi HK. Septic arthritis in gout patients: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54:2095-9.
79. Kennedy N, Chambers ST, Nolan I, et al. Native Joint Septic Arthritis: Epidemiology, Clinical Features, and Microbiological Causes in a New Zealand Population. *J Rheumatol*. 2015;42:2392-7.

80. Mylona EE, Mouktaroudi M, Crisan TO, et al. Enhanced interleukin-1 β production of PBMCs from patients with gout after stimulation with Toll-like receptor-2 ligands and urate crystals. *Arthritis Res Ther*. 2012;14:R158.
81. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood*. 1996;87:2095-147.
82. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)*. 2007;46:1372-4.
83. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis*. 2006;65:1312-24.
84. Perez-Ruiz F, Calabozo M, Pijoan JL, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum*. 2002;47:356-60.
85. Mikuls TR, Farrar JT, Bilker WB, et al. Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). *Rheumatology (Oxford)*. 2005;44:1038-42.
86. Harrold LR, Mazon KM, Negron A, et al. Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire. *Rheumatology (Oxford)*. 2013;52:1623-9.
87. Doherty M, Jansen TL, Nuki G, et al. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis*. 2012;71:1765-70.
88. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359:1811-21.
89. Stamp LK, Merriman TR, Barclay ML, et al. Impaired response or insufficient dosage? Examining the potential causes of "inadequate response" to allopurinol in the treatment of gout. *Semin Arthritis Rheum*. 2014;44:170-4.
90. De Vera MA, Marcotte G, Rai S, et al. Medication adherence in gout: a systematic review. *Arthritis Care Res (Hoboken)*. 2014;66:1551-9.
91. Ogdie AR, Hoch S, Dunham J, et al. A roadmap for education to improve the quality of care in gout. *Curr Opin Rheumatol*. 2010;22:173-80.
92. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. *Ann Rheum Dis*. 2013;72:826-30.
93. Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis*. 2006;65:1301-11.

Chapter 2

The Gout Assessment Questionnaire 2.0:
cross-cultural translation into Dutch, aspects
of validity and linking to the International
classification of functioning, disability and health

Bart Spaetgens, Sjef van der Linden, Annelies Boonen

Rheumatology 2014;53:678-685

Abstract

Objectives

The Gout Assessment Questionnaire 2.0 (GAQ2.0) is a disease-specific patient-reported outcome measure for gout that distinguishes five different subscales and comprises overall 31 questions. The aims of this study were to translate the GAQ2.0 into Dutch and to test clinimetric properties.

Methods

Recommendations for translation and cross-cultural adaptation were followed and no cultural adaptations were needed. The resulting Dutch GAQ2.0 was administered to patients registered at the rheumatology outpatient clinic diagnosed with gout. Internal consistency was tested using Cronbach's α , reliability using intraclass correlation coefficient (ICC), content validity by linkage to the International Classification of Functioning, Disability and Health (ICF) and construct validity by correlating the subscales of the GAQ2.0 with the HAQ disability index (HAQ-DI) and 36-item Short Form Health Survey (SF-36).

Results

A total of 126 patients [106 (84%) male, mean age 66.6 years (Standard Deviation (S.D.) 10.4), mean disease duration 11.2 years (S.D. 10.6)] completed a number of questionnaires, including the GAQ2.0, HAQ-DI and SF-36, and underwent a clinical examination. Internal consistency was sufficient (Cronbach's $\alpha = 0.83-0.94$), except for the subscale gout medication side effects (Cronbach's $\alpha = 0.51$). Test-retest reliability was good (ICCs 0.73-0.86) for all subscales, but moderate for the subscale unmet gout treatment need (ICC 0.56). Gout impact subscale scores showed only weak to moderate correlations with HAQ-DI and SF-36, but stronger emphasis on the emotional consequences of gout. Also, it correlated better with gout-specific outcomes such as the number of gout flares and pain.

Conclusion

The Dutch GAQ2.0 shows sufficient evidence of validity to assess disease-specific functioning and health in patients with gout and seems to capture different aspects than those represented in the HAQ and SF-36.

Introduction

Gout is a chronic inflammatory rheumatic disease caused by the precipitation of uric acid crystals in the synovial fluid and tissues.¹ Classically the disease is characterized by acute and transient arthritis of one or more joints, alternating with symptom-free episodes between gout attacks. A subgroup of patients develops frequent and prolonged attacks, and even chronic arthritis can develop. This may be associated with so-called tophi, which represent the accumulation of monosodium urate crystals in and around the joints. Both tophi and frequent gout flares or chronic arthritis can be associated with damage of cartilage, bone, skin and more rarely, other organs.²

It is clear that the disease, with its unpredictable attacks characterized by severe pain and limitations in mobility and possible chronic discomfort due to joint damage, chronic arthritis or tophi, can affect many aspects of health-related quality of life (HRQOL).³⁻⁵

Measuring the impact of gout on HRQOL from a patient's perspective is challenging because of the heterogeneous manifestations of gout that need to be captured. While generic instruments to assess (aspects of) HRQOL might be useful, it is expected that disease-specific questionnaires have a better content validity and therefore discriminative capacity, including sensitivity to change.⁶

Colwell et al.⁷ developed the first disease-specific Gout Assessment Questionnaire (GAQ) to assess the impact of gout across a broad range of areas relevant for patients' health and to be used in the setting of clinical trials. Candidate items were derived from a literature search, expert opinion and a limited number of patient interviews.⁸ A second version of the Gout Assessment Questionnaire (GAQ2.0) was proposed by Hirsch et al.,⁹ after adjusting and optimizing the initial instrument for use in clinical practice. The GAQ2.0 showed acceptable reliability and validity in a community-based patient population and correlated more closely with patient-reported outcome measures of gout (e.g. frequent gout flares) than with the 36-item Short Form Health Survey (SF-36). In a later study, the discriminative ability of the GAQ2.0 according to the severity of gout was explored, which confirmed high scores correlate with more frequent gout attacks and more pain between gout attacks.¹⁰

As such, the GAQ2.0 is the only patient-reported outcome (PRO) measure to assess the impact of gout on functioning and health. However, its application is limited by the existence of an English version only. The availability of versions in other languages could help to fill the gap with respect to a universally accepted disease-specific PRO to assess HRQOL in gout patients.

The purpose of the present study was to develop a Dutch version of the GAQ2.0 by performing a translation according to recommended methods and to assess further clinimetric properties of the Gout Impact Scale (GIS), which is the first section of the GAQ2.0 and represents typical areas of HRQOL that can be affected by gout. Specifically, internal consistency, test-retest reliability, content validity (comparison with the International Classification of Functioning, Disability and Health (ICF),

construct validity with the SF-36 and HAQ and discrimination between groups of gout patients with different disease severity of the GIS were assessed.

Materials and methods

Translation

The translation procedure was performed in collaboration with a reputable company (PharmaQuest, Banbury, UK) in translations of PROs. The translation, review, linguistic validation and cross-cultural adaptation process were performed according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) principles of good practice¹¹ and is consistent with the approach proposed by Beaton as best practice in rheumatology.¹² The forward translation was performed by two qualified native Dutch speakers who are experienced medical translators and speak fluent English. Backtranslation of the Dutch version was performed by two qualified native English speakers who are experienced medical translators and speak fluent Dutch. After this, contact was sought with the developers of the original questionnaire, who approved the preceding steps as well as the final version. Finally, this version was pretested according to the concept of pilot testing and cognitive debriefing. Five patients under rheumatological care in our department were invited to participate. Attention was given to ensure they were native Dutch speakers and represented the spectrum of gender, age (three men, two women, age range 39-78 years), disease (disease duration range and acute intermittent or chronic gout) and education. Participants were first invited to complete the questionnaire. After completion, they were asked to read aloud the instructions, questions and scoring modalities line by line. After each line, they were asked to indicate whether the instruction/item/anchor was clear, were invited to repeat the sentences in their own words and were asked to think aloud while answering the questions. They were probed specifically to comment on whether sentences were unambiguous and whether they would have preferred another wording. Finally, they were asked whether the questions missed aspects of the disease that influence their functioning. These findings were listed and were returned to the translators, who discussed the need for adaptation. Ultimately, no cultural adaptations were necessary. Only minor adjustments in wording, grammar or typography were made. The patients indicated no aspects of their disease that they were missing. Time to complete the questionnaire ranged from 4 to 7 min. The final Dutch version is available as supplementary material, available as Appendix A.

Assessment of clinimetric properties

Patients

A convenience sample of 250 patients that were registered with gout, according to the rheumatologist, in the diagnostic/administrative database of the department of rheumatology between January 2011 and April 2012 were invited by a letter to participate in the study. Patients that signed informed consent received an appointment about 4 weeks later. A random subsample of patients was asked again to complete the GAQ2.0 together with some questions on the recent course of their gout. The principles of the Declaration of Helsinki were followed and the study was approved by the ethics committee of Maastricht University Medical Centre. Prior to the data collection, all participating patients signed the informed consent document.

Assessments

During the study visit, patients were interviewed about demographic characteristics (age, sex, education) and course of disease (symptom and disease duration, number of gout flares last year). Next, they underwent a clinical examination to determine the presence and amount of tophi. Finally, patients completed a series of questionnaires.

Gout Assessment Questionnaire 2.0

The GAQ2.0 is a self-administered questionnaire consisting of 31 questions divided in two sections. First, the so-called GIS evaluates the current impact of gout in five areas: gout concern overall (4 items), gout medication side effects (2 items), unmet gout treatment needs (3 items), well-being during attack (11 items) and gout concern during attack (4 items). All subscales of the GIS are scored separately on a 0 to 100 score, with higher scores indicating a more important impact. The second section asks patients to describe whether they had a gout flare (yes/no) in the last year and to describe on a 6-point Likert scale to what extent the gout affected their quality of life, physical and mental health and pain in the past 4 weeks (1=very poor, 6=excellent). They were also asked to describe on a 10-point numeric rating scale how much pain they experienced due to gout (1=no pain, 10=severe pain) and disease activity (1=no disease activity, 10=severe disease activity). Assessment of the clinimetric properties was limited to the 24 items of the GIS.

Health Assessment Questionnaire

The HAQ is an instrument to assess impairments in physical function in the last 7 days. It was developed for use in RA,¹³ but has been shown to be valid for use in other rheumatic diseases as well, such as gout.¹⁴ The HAQ consists of 20 items across eight categories (dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping and other activities), scored on a 0- to 3-point Likert scale (0=no difficulty,

3 = proposed action cannot be performed without help). The highest score per category is used and divided by 8, resulting in the HAQ-disability index (HAQ-DI) from 0 to 3 (higher score indicates worse physical functioning). A validated Dutch version of the HAQ is available.¹⁵

The 36-Item Short Form Health Survey

The SF-36 is a generic instrument to assess HRQOL over the last 4 weeks. It consists of 36 questions in eight different domains: physical functioning (10 items), role limitation due to physical problems (4 items), bodily pain (2 items), general health perception (5 items), vitality (4 items), social functioning (2 items), role limitation due to emotional problems (3 items) and mental health (5 items).¹⁶ Items are scored on a varying 2- to 6-point Likert scale. The SF-36 also includes a single item measure of health transition or change. The scores are summed per domain and then transformed to a 0-100 score (higher scores = better health). The first four domains can be summarized in the Physical Component Summary (PCS); the last can be summarized into the Mental Component Summary (MCS).¹⁷ A validated Dutch version of the SF-36 is available.¹⁸

Statistical analysis

First, the percentages of missing values per item of the GIS were determined. Floor and ceiling effects were assessed for the total subscales of the GIS, the HAQ-DI and the eight different domains and summed scores of the SF-36 by calculating the percentage of respondents scoring minimum or maximum scores on each scale. Floor or ceiling effects were considered relevant when >15% of the respondents scored worst or best, respectively, on each scale. Internal consistency within each subscale of the GIS was tested using Cronbach's α and the Spearman-Brown prophecy formula to adjust for a 10-item scale. Cronbach's α was acceptable when >0.70 (or >0.80 when adjusted to a 10-item scale).¹⁹

The content of the GAQ2.0 was evaluated by linking the GAQ2.0 to the ICF using the updated ICF linking rules of Cieza et al.²⁰ and comparing the content with the HAQ and SF-36 (that were linked using the same rules). Construct validity was assessed by correlating the scores of the subscales of the GIS with the eight categories of the HAQ-DI and its total score and with the eight domains and summed scores (PCS/MCS) of the SF-36 using Spearman's correlation. Correlations <0.29 were considered small, 0.30-0.49 were moderate and >0.50 were considered large.²¹

Discriminative capacity was tested by determining the differences in GIS scores across clinical characteristics that reflect disease severity: (i) use of uric acid-lowering therapy (UALT); (ii) the presence or absence and amount of tophi [0 tophi (n=82), 1-3 tophi (n=22) and >3 tophi (n=22)]; (iii) gout flares last year (yes/no); (iv) visual analogue scale (VAS) during a typical gout attack and (v) pain between gout attacks using analyses of variance. In order to improve the interpretation we repeated these analyses for the generic measures HAQ and SF-36 (PCS and MCS). We hypothesized that the above-

mentioned characteristics influence GIS scores (e.g. worse GIS scores in patients with tophaceous gout) for disease-specific but not generic instruments. Test-retest reliability was assessed within a 4-week interval between measurements in a sample of 51 patients with stable disease using intraclass correlation coefficients (ICCs). ICCs >0.70 were considered acceptable.²² Stable disease was defined as self-reported stable gout in the past 4 weeks. All statistical analyses were conducted using PASW Statistics 19.0 (IBM, Armonk, NY, USA).

Results

Clinimetric validation

A total of 126 patients [106 (84%) male, mean age 66.6 years (S.D. 10.4), range 42-89 years, mean disease duration 11.2 years (S.D. 10.6)] participated (53% of those were invited), of which 60 (48%) patients had tophaceous gout. Demographic and clinical data are reported in Table 2.1.

Items were missing in 19 (15%) GAQ2.0 questionnaires. Missing items were random, although we postulated that the gout impact (GI) subscale well-being during attack had the most missing items, due to the highest number of items to be scored in the subscale.

Floor (extreme impact/need) and ceiling effects (no problem/need) were negligible for the GIS (floor effects ranged from 0.9 to 5.3% and ceiling effects ranged from 0.0 to 2.6%). Floor effects (high disability) were not observed for the HAQ-DI, while ceiling effects (no disability) were observed in 23.1%. Floor effects for the SF-36 were observed for role limitation due to emotional and physical problems in 18.4 and 37.2% of the patients, respectively, while ceiling effects were also observed in role limitation due to emotional (64%) and physical (35.4%) role problems, but also in the domain social functioning (25.6%).

Internal consistency tested by Cronbach's α was sufficient to excellent ($\alpha=0.83-0.94$) for four of the five GI scales (gout concern overall, unmet gout treatment need, well-being during attack and gout concern during attack) when adjusted to a 10-item scale. The internal consistency of the GIS gout medication side effects was poor ($\alpha=0.51$). Data are shown in Table 2.2.

Test-retest reliability analysis was assessed in a group of 51 of 55 (93%) patients who completed the questionnaire twice within a 4-week interval and who reported their gout had been stable in the past 4 weeks [44 male (80%), mean age 67 years (S.D. 10.0), mean disease duration 11.0 years (S.D. 10.4), 40% tophaceous gout]. The ICCs were sufficient (ICC = 0.73-0.86) for all GISs, except for unmet gout treatment need (ICC=0.56) (Table 2.3), which was only moderate. Further analysis showed 41 of 51 patients scored equal or better in the retest questionnaire for unmet gout treatment need.

Table 2.1 Demographic and clinical data of the 126 patients included in the validation study

Characteristics	
Age, mean (S.D.), years	66.6 (10.4) [42-89]
Male sex, n (%)	106 (84.1)
Education, n (%)	
Low (High school or less)	89 (70.6)
High (College or more)	37 (29.4)
Disease duration, mean (S.D.), years	11.2 (10.6) [0.5-52]
Tophaceous gout ever, yes, n (%)	60 (47.6)
Number of tophi at examination, n=124 (%)	
0	80 (64.5)
1-3	21 (17.0)
4-9	14 (11.2)
10+	9 (7.3)
Flares last 12 months, n=116 (%)	
0	41(32.5)
1-2	46 (36.5)
3-5	23 (18.2)
6-10	12 (9.6)
>10	4 (3.2)
Uric acid lowering therapy, yes, n (%)	86 (68.3)
HAQ-DI, mean, (S.D.) (0-3)	0.6 (0.6)
SF-36, mean (S.D.)	
PCS	39.1 (12.0)
MCS	49.9 (12.3)
Pain	
Typical gout attack, VAS, mean (S.D)	8.6 (1.1)
Pain due to gout, between attacks, n (%)	
None of the time	42 (33.3)
A little of the time	18 (14.3)
Some of the time	31 (24.6)
Most of the time	20 (15.9)
All of the time	15 (11.9)
Gout Impact Scales, mean, (S.D.), [Range]	
Gout concern overall	53.8 (22.4) [0-100]
Gout medication side effects	45.2 (21.3) [0-100]
Unmet gout treatment needs	48.1 (13.8) [0-100]
Well-being during attack	45.0 (11.3) [16-75]
Gout concern during attack	44.7 (22.1) [0-100]

Table 2.2 Internal consistency analysis for Gout Impact Scales

Gout Impact Scale (GIS) (n)	No. items	Cronbach's Alpha	Adjusted Alpha to 10-item scale*
Gout concern overall (116)	4	0.86	0.94
Gout medication side effects (114)	2	0.17	0.51
Unmet gout treatment need (111)	3	0.60	0.83
Well-being during attack (107)	11	0.90	**
Gout concern during attack (116)	4	0.72	0.86

*Adjusted to 10-item scale using Spearman-Brown Prophecy formula. ** Not calculated

Table 2.3 Test-retest reliability (n=51) of the Gout Impact Scales

Gout Impact Scale (GIS)	ICC	95% CI	Significance
Gout concern overall	0.82	0.70-0.90	p<0.001
Gout medication side effects	0.81	0.67-0.89	p<0.001
Unmet gout treatment need	0.56	0.25-0.74	p<0.001
Well-being during attack	0.86	0.74-0.92	p<0.001
Gout concern during attack	0.73	0.53-0.84	p<0.001

Content validity, assessed by linking the constructs within the items of the GAQ2.0 to the categories of the ICF classification (mapping) identified 34 constructs across the 31 items of the GAQ (see Supplementary material, Appendix B) that were linked to 12 ICF categories, while 4 constructs could either not be linked [health condition (number of gout attacks, other health conditions) or could not be specified (overall physical health, overall mental health, quality of life)]. Of these, four ICF categories addressed the component body functions, seven ICF categories the component activities and participation and one category environmental factors. A relatively high number of constructs (n=9) referred to emotional functions (b152) that usually addressed the direct consequence of gout but could also relate to emotions concerning activities [I fear (b152) that I cannot continue my hobbies (d920)]. When comparing the content of the SF-36 and HAQ it is clear that the GAQ addresses no specific limitations in arm use or mobility, does not address vitality and has less emphasis on activities and more emphasis on emotional functions.

Construct validity (Table 2.4) showed that gout concern overall and gout concern during attack showed moderately positive correlations with the HAQ-DI ($r=0.37$ and 0.32 , respectively) and moderately negative associations with the PCS and MCS, respectively ($r=-0.37$). In addition, the GI subscale gout medication side effects correlated moderately with the MCS ($r=-0.34$). For all other subscales, correlations were low.

The discriminative validity (Table 2.5) of the GI subscales could not support the hypothesis that patients with tophaceous gout, with more tophi, with more pain during an attack or on UALT scored worse on any GIS. Importantly, generic measures (SF-36 and HAQ-DI) were unable to discriminate across these measures. On the other hand, and as expected, patients with gout flares last year and patients with more pain between gout attacks had significantly more gout concerns overall and tended to have more unmet gout treatment needs and reported worse physical HRQOL as measured by the SF-36.

Table 2.4 Construct validity Pearson correlations Gout Impact Scales with HAQ-scores, HAQ-DI and SF-36

	Gout Concern Overall	Gout Medication Side Effects	Unmet Gout Treatment Needs	Well-being during attack	Gout Concern during attack
HAQ					
Dressing	0.39**	0.29**	0.15	0.25*	0.28**
Rising	0.37**	0.21*	0.19*	0.10	0.30**
Eating	0.19*	0.16	0.21*	0.16	0.22*
Walking	0.32**	0.24*	0.06	0.14	0.27**
Hygiene	0.24*	0.10	0.07	0.13	0.21*
Reaching	0.26**	0.23*	0.06	0.13	0.21*
Gripping	0.16	0.08	0.13	0.12	0.21*
Activity	0.30**	0.15	0.13	0.09	0.19*
HAQ-DI	0.37**	0.25**	0.16	0.19	0.32**
SF-36					
Physical Function	-0.34**	-0.27**	-0.13	-0.22*	-0.29**
Role Physical	-0.28**	-0.14	-0.01	-0.01	-0.28**
Bodily Pain	-0.53**	-0.31**	-0.29**	-0.02	-0.42**
General Health	-0.43**	-0.37**	-0.23*	-0.03	-0.27
Vitality	-0.44**	-0.32**	-0.19	-0.04	-0.39**
Social Function	-0.40**	-0.32**	-0.24*	-0.11	-0.32**
Role Emotion	-0.19*	-0.27**	0.00	0.08	-0.30**
Mental Health	-0.30**	-0.31**	-0.23*	-0.12	-0.42**
Physical Summary	-0.37**	-0.21*	-0.21*	-0.09	-0.26**
Mental Summary	-0.23*	-0.34**	-0.10	0.01	-0.37**

* p<0.05; ** p<0.01

Table 2.5 Discrimination of Gout Impact Scales across clinical measures

	Uric Acid Lowering Therapy (Y/N)		Tophi (n) 0, 1-3, >3		Flares last year (Y/N)		Pain, gout attack (VAS)		Pain between attacks (VAS)	
	F	p	F	p	F	p	F	p	F	p
GIS										
GCO	1.760	0.177	0.453	0.637	10.873	0.001	1.061	0.386	3.692	0.007
GMSE	0.086	0.917	0.549	0.579	3.422	0.067	1.157	0.335	2.014	0.097
UGTN	0.677	0.510	0.021	0.980	3.400	0.068	0.156	0.978	2.446	0.051
WBDA	0.562	0.572	0.516	0.598	0.083	0.774	0.817	0.540	0.156	0.960
GCDA	2.023	0.137	0.462	0.630	1.123	0.292	0.790	0.559	1.659	0.165
Generic										
SF-36 PCS	2.241	0.142	0.741	0.479	0.436	0.510	1.165	0.332	2.395	0.055
SF-36 MCS	0.002	0.961	0.222	0.802	0.183	0.670	0.420	0.834	0.168	0.954
HAQ-DI	0.291	0.591	1.376	0.257	0.071	0.790	0.695	0.628	1.768	0.147

Discussion

The present study shows that the Dutch version of the GAQ2.0 has aspects of validity that make it worthwhile for further consideration as a disease-specific instrument to assess HRQOL in patients with gout.

Translation of the English version was performed following standard and internationally validated procedures and no cultural adaptations were needed.^{11,12} In further clinimetric testing an important advantage over the commonly used generic measures in gout, namely the lower frequency of either ceiling or floor effects when compared with the HAQ or SF-36, was found. This is important because floor and ceiling effects tend to reduce responsiveness. The higher ceiling effects in the HAQ and SF-36 as found in gout are similar to those reported in the literature.^{14,23,24}

The internal consistency of the different subscales was considered sufficient for all GISs after adjusting for the number of items, except for the two-question subscale (probably explaining the lower Cronbach's α) gout medication side effects. Compared with the internal consistency in the validation study of the English GAQ2.0, Cronbach's α were slightly lower, but still acceptable (>0.80 in the adjusted analyses).

Four-week test-retest reliability was sufficient in all gout impact subscales except for the unmet gout treatment need, which was only moderate, in contrast to the original validation study. Construct validity of all GI subscales showed overall low correlations with the HAQ. Only the gout concern (overall and during attack) GI subscale had moderate correlations with the HAQ-DI (several subscales) and the mental and physical component scores of the SF-36.

As such, the overall disappointing correlations are not surprising, since several subscales of the GIS address concerns with disease while the SF-36 and HAQ-DI address impairments/limitations. In other words, the GIS reflects other aspects of health.

This interpretation is further supported by content comparison using the ICF, which revealed the GIS has a stronger emphasis on emotional functions and less on limitations in functioning (fine hand function, mobility) or physical activities compared with the HAQ and SF-36. It was interesting to notice that the GI subscales tended to discriminate only between patients with and without flares and to a lesser extent with different levels of pain between attacks. Chronic pain and the number of flares likely reflect a worse impact, as was also found by Hirsch et al.¹⁰ In this regard it was surprising the GI subscales did not discriminate between patients with or without tophi, nor the number of tophi. In this respect, the GI subscales were not better or worse than generic measures of HRQOL such as the HAQ and SF-36. Apparently neither the simple presence nor the number of tophi affects patients' HRQOL in our study. This is in line with a recent systematic review by Chandratre et al.²⁵ on HRQOL in gout, who concluded the relationship between tophi and HRQOL was not robust, reporting variable effects (worsening vs. no effects) of tophi on HRQOL.

Limitations of this study were a relatively small sample size recruited in a university rheumatologic clinic, which has resulted in a sample with a high number of patients with tophaceous gout and on ULT, limiting its generalizability to patients with less severe disease. The influence of selection bias on GAQ2.0 validity is difficult to predict. As our study covers the full spectrum of disease, the slight over presentation of worse disease will probably have no important influence on the clinimetric properties.

The sample size likely accounts for the slightly lower Cronbach's α and ICCs as compared with the original validation study. Although we used the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) criteria, we were unable to assess all aspects that are relevant in developing and validating a PRO. In particular, we were unable to assess minimal important change (MIC), minimal important difference (MID) or patient acceptable symptom state. Within the COSMIN criteria, however, no consensus on standards for assessing MIC or MID could be reached.²⁶ Furthermore, there is large variation in the interpretation of these aspects in the literature.²⁷ MID of the GIS was assessed earlier by Khanna et al.,²⁸ showing differences were significantly important when differing between 5 and 8 points per scale.

To the best of our knowledge, the GAQ2.0 is the only disease-specific PRO assessing the impact of gout on functioning and health. PROs are becoming increasingly important in outcome research, because not every aspect of disease can be measured using biomedical findings. This is clearly applicable to gout, with its heterogeneous manifestations (from asymptomatic hyperuricaemia to chronic tophaceous gout). This highlights the need for a disease-specific instrument to understand the impact of gout. In clinical care the GAQ2.0 (and more specifically the GIS) could serve as a screening tool to identify to what extent (and on which subscale) patients experience the impact of gout. Also, as physicians and patients have different views on disease severity and needs, application of the GIS in clinical practice might help to adjust the choice of pharmacological and non-pharmacological interventions to the patients' needs, which in turn could also improve adherence as well as overall health outcome and well-being.²⁹ Ultimately, it may have an effect on health care resource utilization and costs. Having said this, the issue of interpretability of the GAQ2.0, as for any PRO, in clinical practice and its final impact on health and resource utilization needs further exploration.³⁰ In conclusion, the Dutch GAQ2.0 is a gout-specific PRO instrument that measures HRQOL. The GAQ2.0 seems to measure different aspects of health than generic instruments, such as the HAQ-DI and SF-36. It is therefore promising to further explore its predictive value with regard to long-term health outcomes. Our study contributes to the further development and testing of the GAQ2.0 as a promising gap-filling instrument to measure HRQOL.

References

- 1 Richette P, Bardin T. Gout. *Lancet* 2010;375:318-28.
- 2 McQueen FM, Chana A, Dalbeth N. Mechanisms of joint damage in gout: evidence from cellular and imaging studies. *Nat Rev Rheumatol* 2012;8:173-81.
- 3 Khanna PP, Nuki G, Bardin T, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use. Results from a cross-sectional survey. *Health Qual Life Outcomes* 2012;10:117.
- 4 Singh JA. Quality of life and quality of care for patients with gout. *Curr Rheumatol Rep* 2009;11:154-60.
- 5 Brook RA, Kleinman NL, Patel PA, et al. The economic burden of gout on an employed population. *Curr Med Res Opin* 2006;22:1381-9.
- 6 Taylor WJ, Schumacher HR Jr, Singh JA, et al. Assessment of outcome in clinical trials of gout. *Rheumatology* 2007;46:1751-6.
- 7 Colwell HH, Hunt BJ, Pasta DJ, et al. Gout Assessment Questionnaire: initial results of reliability, validity and responsiveness. *Int J Clin Pract* 2006;60:1210-7.
- 8 Boers M, Brooks P, Strand CV, et al. The OMERACT filter for outcome measures in rheumatology. *J Rheumatol* 1998;25:198-9.
- 9 Hirsch JD, Lee SJ, Terkeltaub R, et al. Evaluation of an instrument assessing influence of gout on health-related quality of life. *J Rheumatol* 2008;35:2406-14.
- 10 Hirsch JD, Terkeltaub R, Khanna D, et al. Gout-disease specific quality of life and the association with gout characteristics. *Patient Relat Outcome Meas* 2010;1:1-8.
- 11 Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient reported outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 8:94-104.
- 12 Beaton DE, Bombardier C, Guillemin F, et al. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976)* 2000;25:3186-91.
- 13 Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
- 14 Alvarez-Hernández E, Peláez-Ballestas I, Vázquez-Mellado J, et al. Validation of the health assessment questionnaire disability index in patients with gout. *Arthritis Rheum* 2008;59:665-9.
- 15 Bijlsma JW, Oude Heuvel CH, Zaalberg A. Development and validation of the Dutch questionnaire capacities of daily life (VDF) for patients with rheumatoid arthritis. *J Rehab Sci* 1990;3:71-4.
- 16 Ware JE, Sherbourne CD. The RAND-36 Short-Form Health Status Survey: 1. Conceptual framework and item selection. *Med Care* 1992;30:473-81.
- 17 Ware JE, Kosinski M, Dewey JE. How to Score Version 2 of the SF-36 Health Survey. Lincoln, RI, USA: QualityMetric, 2000.
- 18 Aaronson NK, Muller M, Cohen PD, et al. Translation, validation and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-68.
- 19 Nunnally JC. *Psychometric Theory*, 2nd edn. New York: McGraw-Hill, 1978.
- 20 Cieza A, Geyh S, Chatterii S, et al. ICF linking rules: an update based on lessons learned. *J Rehabil Med* 2005;37:212-8.
- 21 Cohen J, Cohen P, West SG, et al. *Applied Multiple Regression/Correlation Analysis for the Behavioural Sciences*. 2nd edn. Hillsdale, NJ: Lawrence Erlbaum, 2003.
- 22 Fitzpatrick RD, Buxton MJ, Jones DR. Evaluating patientbased outcome measures for use in clinical trials. *Health Technol Assess* 1998;2:1-74.
- 23 Taylor WJ, Colvine K, Gregory K, et al. The health assessment questionnaire disability index is a valid measure of physical function in gout. *Clin Exp Rheumatol* 2008;26:6206.
- 24 Ten Klooster PM, Oude Voshaar MA, Taal E, et al. Comparison of measures of functional disability in patients with gout. *Rheumatology* 2011;50:709-13.
- 25 Chandratne P, Roddy E, Clarson L, et al. Health-related quality of life in gout: a systematic review. *Rheumatology* 2013;52:2031-40.

- 26 Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res* 2010;19:539-49.
- 27 Terwee CB, Roorda LD, Dekker J, et al. Mind the MIC: large variation among populations and methods. *J Clin Epidemiol* 2010;63:524-34.
- 28 Khanna D, Sarkin A, Khanna P, et al. Minimally important differences of the gout impact scale in a randomized controlled trial. *Rheumatology* 2011;50:1331-6.
- 29 Sarkin AJ, Levack AE, Shieh MM, et al. Predictors of doctor-rated and patient-rated gout severity: gout impact scales improve assessment. *J Eval Clin Pract* 2010;16:1244-7.
- 30 Higginson IJ, Carr AJ. How can quality of life measures be used in the clinical setting? *BMJ* 2001;322:1297-300.

Supplementary material

Appendix A: Dutch version of the Gout Assessment Questionnaire GAQ2.0

Vragenlijst over beoordeling van jicht – de impact van jicht (versie 2.0)

Beantwoord alstublieft elke vraag. **Lees elke vraag zorgvuldig door en kies het antwoord dat het beste bij u past.** U kunt de vragen beantwoorden door de *cirkel in te vullen* naast het antwoord van uw keuze.

Sommige vragen in deze vragenlijst gaan over uw jicht in het algemeen en andere vragen gaan alleen over de keren dat uw gewrichten pijnlijk of gezwollen zijn vanwege de jicht. In deze vragenlijst worden twee belangrijke begrippen gebruikt:

Jichtaanval = de tijd dat u pijnlijke of gezwollen gewrichten hebt door jicht. Wanneer een vraag gaat over een jichtaanval, denk dan alleen aan hoe het voor u is als u pijnlijke of gezwollen gewrichten heeft door de jicht.

Jicht in het geheel = keren dat u een jichtaanval hebt **EN** de tijd tussen de aanvallen wanneer uw gewrichten niet pijnlijk of gezwollen zijn door de jicht.

OVER HOE JICHT UW DAGELIJKS LEVEN IN HET GEHEEL BEÏNVLOEDT

1. Geef aan in hoeverre u het eens of oneens bent met elk van onderstaande uitspraken. (Markeer bij elke uitspraak één antwoord)

	Sterk mee eens	Mee eens	Ik weet het niet zeker	Mee oneens	Sterk mee oneens
a. Ik maak me zorgen dat ik binnen het komend jaar een jichtaanval krijg.	☐	☐	☐	☐	☐
b. Ik ben bang dat mijn jicht in de loop van de tijd erger wordt.	☐	☐	☐	☐	☐
c. Ik ben bang dat mijn jicht mijn toekomstige activiteiten zal hinderen.	☐	☐	☐	☐	☐
d. Ik maak me zorgen dat ik door mijn jicht niet van vrijetijdsactiviteiten kan blijven genieten	☐	☐	☐	☐	☐
e. Ik heb last van bijwerkingen van mijn medicatie tegen jicht.	☐	☐	☐	☐	☐
f. Ik ben kwaad als ik een jichtaanval heb.	☐	☐	☐	☐	☐
g. Het is moeilijk om evenementen of activiteiten vooruit te plannen omdat ik een jichtaanval kan krijgen.	☐	☐	☐	☐	☐
h. Ik voel me depressief als ik een jichtaanval heb.	☐	☐	☐	☐	☐
i. Met mijn huidige medicatie kan een jichtaanval (als ik die heb) effectief worden behandeld.	☐	☐	☐	☐	☐
j. Ik mis geplande of belangrijke activiteiten wanneer ik een jichtaanval heb.	☐	☐	☐	☐	☐
k. Ik maak me zorgen over de langetermijneffecten van jichtmedicatie.	☐	☐	☐	☐	☐
l. Mijn huidige medicatie werkt niet goed wat betreft het voorkomen van jichtaanvallen.	☐	☐	☐	☐	☐
m. Ik heb mijn jicht onder controle.	☐	☐	☐	☐	☐

- Ja.
- Nee

--	--	--	--	--	--

- | | De hele tijd
(100%) | Meestal | Een deel van de tijd
(50%) | Een klein deel van de tijd | Nooit
(0%) |
|---|------------------------|-----------------------|-------------------------------|----------------------------|-----------------------|
| Werk verzuimen vanwege uw jichtklachten? | ☐ | ☐ | ☐ | ☐ | ☐ |
| Moeite met werken vanwege uw jichtklachten? | ☐ | ☐ | ☐ | ☐ | ☐ |
| Moeite met hobby's of sociale activiteiten vanwege uw jichtklachten? | ☐ | ☐ | ☐ | ☐ | ☐ |
| Moeite met zelfzorgactiviteiten zoals maaltijden, wassen of uzelf aankleden vanwege uw jichtklachten? | ☐ | ☐ | ☐ | ☐ | ☐ |

- | | | Helemaal niet | Een beetje | Matig | Nogal | Uitermate |
|----|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| a. | Uw stemming? | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. | Uw mobiliteit? | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. | Uw slaap? | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. | Uw normale werk? | | | | | |
| | (zowel werk buitenshuis als het huishouden) | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. | Uw vrijetijdsbesteding? | ☐ | ☐ | ☐ | ☐ | ☐ |
| f. | Genieten van uw leven? | ☐ | ☐ | ☐ | ☐ | ☐ |
| g. | Uw vermogen om te doen wat u wilt? | ☐ | ☐ | ☐ | ☐ | ☐ |

- | Heel slecht | Slecht | Matig | Goed | Heel goed | Uitstekend |
|-------------|--------|-------|------|-----------|------------|
| ○ | ○ | ○ | ○ | ○ | ○ |

Appendix B: Items of the core set acute arthritis, HAQ, SF-36 and GAQ2.0 with the corresponding international classification of functioning, disability and health (ICF) categories

ICF-code	body functions	HAQ	SF-36	GAQ 2.0
Chapter: Mental functions				
b1300	Energy level		4	
b134	Sleep functions			1
b152	Emotional functions		7	15
b1529	Emotional functions, unspecified		1	
Chapter: Sensory functions and pain				
b280	Sensation of pain	1	2	2
Chapter: Neuromusculoskeletal and movement-related functions				
b710	Mobility of joint functions			1
Chapter: General tasks and demands				
d210	Undertaking a single task			2
d220	Undertaking multiple tasks			2
d230	Carrying out daily routine		2	
d240	Handling stress and other psychological demands			1
Chapter: Mobility				
d4100	Lying down	1		
d4102	Kneeling		1	
d4104	Standing	2		
d4105	Bending	1	1	
d429	Changing and maintaining body position,	1		
d430	Lifting and carrying objects		1	
d4300	Lifting	1		
d4305	Putting down objects	1		
d4309	Lifting and carrying, unspecified		1	
d4400	Picking up	1		
d4401	Grasping	1		
d4402	Manipulating	1		
d4403	Releasing	1		
d4452	Reaching	1		
d4453	Turning or twisting the hands or arms	1		
d4458	Hand and arm use, other specified	2		
d4459	Hand and arm use, unspecified		1	
d450	Walking	1		
d4500	Walking short distances		1	
d4501	Walking long distances		1	
d4502	Walking on different surfaces	1		
d4551	Climbing	1	2	
d4559	Moving around, unspecified		1	

ICF-code	body functions	HAQ	SF-36	GAQ 2.0
Chapter: Self-care				1
d5100	Washing bodyparts	1		
d5101	Washing whole body	1	1	
d5202	Caring for hair	1		
d5308	Toileting, other specified	1		
d540	Dressing	2	1	
d5402	Putting on footwear	1		
d550	Eating	2		
d560	Drinking			
Chapter: Domestic life				
d6209	Acquisition of goods and services, unspecified	2		
d6408	Doing housework, other specified	1		1*
d6409	Doing housework, unspecified		1	
d649	Household tasks, other specified and unspecified		1	
d699	Domestic life, unspecified	1		
Chapter: Marjor life areas				
d850	Remunerative employment		1	3*
d859	Work and employment, other specified+unspecified		2	
d920	Recreation and leisure			2
d9205	Socialising		2	
d9209	Recreation and leisure, unspecified		2	
Chapter: Products and technology				
Environmental factors				
e110	Products or substances for personal consumption			3
e1151	Assistive products and technology for personal use in daily living	6		
e1201	Assistive products and technology for personal indoor and outdoor mobility and transportation	4		
Chapter: Support and relationships				
e3	Support and relationships	2		
Other:				
hc	(number of gout attacks)			1
nc	(overall mental health)			1
nc	(overall physical health)			1
pf	(overall quality of life)			1
hc: health condition; nc=not covered; pf= personal factor.				
* 1 item adressed paid as unpaid work				

Chapter 3

Content and construct validity of the Rheumatic
Diseases Comorbidity Index in patients with gout

Bart Spaetgens, José M. A. Wijnands, Caroline van Durme, Annelies Boonen
Rheumatology 2015;54:1659-1663

Abstract

Objectives

Gout has been associated with a large number of comorbidities. As yet, no comorbidity measure has been validated for use in clinical studies in gout. This study aims to evaluate the content and construct validity of the Rheumatic Diseases Comorbidity Index (RDCI) and a gout-specifically modified RDCI (mRDCI) in patients with gout.

Methods

In a cross-sectional sample of 122 patients with gout, data on comorbidities were obtained during an interview, chart review and clinical examination. The data were used to compute the RDCI/mRDCI, a simple comorbidity count, the Charlson Comorbidity Index (CCI) and the Functional Comorbidity Index (FCI). Content and construct validity was explored by assessing Spearman correlations between the two RDCI versions and between RDCI/mRDCI and the other comorbidity indices, as well as demographic and clinical outcomes. In addition, we assessed the independent association between the RDCI/mRDCI and physical functioning (HAQ disability index), physical health (36-Item Short Form Health Survey) and direct healthcare and non-healthcare costs using multivariable regression analyses.

Results

The correlation between the RDCI and mRDCI was 0.86. Correlations between the RDCI/mRDCI and simple comorbidity count, CCI or FCI varied between 0.72 and 0.88. Correlations with generic and gout-specific health outcomes were moderate and weak, respectively, with slightly better results for the mRDCI. Multivariable analyses showed that both the RDCI and mRDCI contributed to the variation in physical functioning, physical health and direct healthcare and non-healthcare costs.

Conclusion

Both the RDCI and mRDCI have appropriate content and construct validity to evaluate the influence of comorbidity on outcome in patients with gout.

Introduction

Gout is a chronic rheumatic disease that causes joint inflammation, joint destruction and physical disability as a result of deposition of uric acid crystals (tophi) in the joints and other tissues. It is suggested that the prevalence of gout is increasing, which is partly attributable to the epidemic of obesity.^{1,2} Epidemiological studies have repeatedly shown that gout is associated with several coexisting diseases, including cardiovascular disease, hypertension, hypercholesterolaemia, chronic kidney disease and diabetes.³⁻⁵ It remains unclear to what extent hyperuricaemia or gout itself contributes to the development of these diseases or whether gout and its coexisting diseases are caused by a common pathophysiological pathway. Further, patients with gout may suffer from comorbidities that are more common in the older population [e.g. cancer, chronic obstructive pulmonary disease (COPD), depression], and probably not related to the pathophysiology of gout.

Gout, its coexistent diseases and the comorbidities that occur by chance have been shown to have an impact on health-related quality of life (HRQOL), physical functioning, costs and even mortality.⁶⁻⁸ However, it is unclear whether gout itself or its comorbidities contribute most to these outcomes. Therefore it is relevant to measure comorbid conditions and adjust for them, whenever appropriate, in clinical research.

To our knowledge, no instrument to measure comorbidity has been validated in gout. The Rheumatic Diseases Comorbidity Index (RDCI) was developed initially by Michaud and Wolfe⁹ as a self-report instrument among patients with rheumatoid arthritis (RA) to assess the influence of comorbidity on HRQOL, functional disability and medical costs. The proposed comorbidity index can be calculated by scoring 11 weighted comorbid conditions. Recently, the RDCI was further validated and the results supported calculation of the comorbidity index based on administrative data.¹⁰

The purpose of the present study was to assess the content and construct validity¹¹ of the RDCI. As the RDCI was not developed for gout, some comorbidities such as kidney disease and obesity, which are prevalent in gout but not included in the RDCI, might be additionally relevant with regard to functional and economic outcomes. Therefore, a modification including coexisting diseases prevalent in gout was developed (mRDCI). Next, we assessed the association of the RDCI/mRDCI with three commonly used comorbidity indices [Charlson Comorbidity Index (CCI),¹² the Functional Comorbidity Index (FCI)¹³ and a simple comorbidity count (COUNT)] and compared the influence of the RDCI/mRDCI on physical functioning, physical HRQOL and direct healthcare and non-healthcare costs.

Methods

Patients

The present study uses data from a cross-sectional study (n=126) of gout patients who were registered in the outpatient rheumatology clinic and agreed to participate. The principles of the Declaration of Helsinki were followed and the study was approved by the ethics committee of the Maastricht University Medical Centre. All participating patients provided signed informed consent.

Data collection

During the study visit, patients completed an interview and underwent a clinical examination in order to obtain demographic data (age, sex, education) and gout-specific characteristics [disease duration, number of gout flares last year, use of uric acid lowering drugs, BMI, presence of tophi (yes/no)]. In addition, the patients completed a series of questionnaires to assess different aspects of health. Generic physical function was assessed using the Dutch version of the HAQ.¹⁴ The HAQ consists of 20 items across eight different categories that can be used to calculate the HAQ disability index (HAQ-DI; range 0-3). Generic HRQOL was assessed with a validated Dutch 36-Item Short Form Health Survey (SF-36).¹⁵ It consists of 36 items across eight different domains, from which the physical component summary (PCS) score (range 0-100) and the mental component summary score (range 0-100) can be calculated.¹⁶ Gout-specific impact on HRQOL was measured by a validated Dutch Gout Assessment Questionnaire (GAQ2.0), and specifically the Gout Impact Scale (GIS), which consists of 24 items across five different subscales (range 0-100), with higher scores indicating a greater impact on HRQOL.¹⁷ Finally, a self-report questionnaire that assessed healthcare resource utilization was used to calculate annual (gout- and non-gout-related) direct (healthcare and non-healthcare) costs per patient.¹⁸

Data on comorbidities (self-reported and confirmed or additionally revealed by the medical records) were assessed to compute the RDCI (range 0-9), the CCI (range 0-33) and the FCI (range 0-18). The mRDCI for gout was developed by including obesity (BMI >30 kg/m²) and kidney disease (defined as a glomerular filtration rate <60 ml/min/1.73 m²) among the comorbidities considered in the RDCI. Several candidate versions of the mRDCI for gout, which differed by the weights attributed to the different comorbidities, were tested and the final version was selected based on the best fit, in terms of strongest correlations with the HAQ-DI and SF-36 PCS. The final mRDCI contains 13 comorbidities, with scores ranging from 0 to 12. Finally, a simple comorbidity count (COUNT; range 0-13), which incorporated all the comorbidities included in the RDCI and its proposed modification, was computed. Additional details regarding the comorbidity indices and the development of the mRDCI are provided in the supplementary data (sections on comorbidity indices and the scoring system) and supplementary Table S3.1, available in Appendix A.

Statistical analysis

Descriptive statistics were used to describe the sample and presented as mean (S.D.) or as median [interquartile range (IQR)] depending on the distribution (skewness) of the data. Spearman correlations were used to calculate the correlations between the comorbidity indices and between the indices and demographics and clinical outcomes. Correlations <0.29 were considered small, 0.30-0.49 moderate and >0.50 were considered strong.¹⁹

The relative contribution of the RDCI and mRDCI to physical functioning (HAQ-DI), the physical component of HRQOL (SF-36 PCS) and direct costs was tested in univariable and multivariable (manual stepwise) linear or logistic (for costs, median as cut-off) regression analyses, after adjusting for age, sex, disease duration and gout-specific characteristics (clinical and GIS). Statistical analyses were performed with SPSS Statistics 19.0 (IBM, Armonk, NY, USA).

Results

Four of the 126 patients were excluded because of incomplete data on comorbidities. The mean age of the remaining 122 patients (84% male) was 66.4 years (S.D. 10.4), with mean disease duration of 11.3 years (S.D. 10.6). Demographic and clinical characteristics are shown in Table 3.1. The mean number (COUNT) of comorbidities was 3.4 (S.D. 1.8), with mean scores for the RDCI and mRDCI of 2.7 (S.D. 1.5) and 4.1 (S.D. 2.3), respectively. The most frequent comorbidities were hypertension [$n=101$ (82.8%)], kidney disease [$n=53$ (43.4%)], obesity [$n=41$ (33.6%)] and myocardial infarction [$n=39$ (32.0%)]. Correlations between the different comorbidity indices were strong; the correlation between RDCI and mRDCI was 0.86, while the correlations between RDCI/mRDCI and COUNT, CCI or FCI varied between 0.72 and 0.88. Weak to moderate positive correlations were found between RDCI/mRDCI (and other indices) and age ($r=0.28$ -0.40), and weak negative associations were found with disease duration ($r=-0.26$ to -0.20). In addition, RDCI/mRDCI (and other indices) correlated moderately with HAQ-DI, SF-36 PCS and direct costs. The mRDCI showed slightly stronger correlations than the RDCI (and all other indices) with HAQ-DI ($r=0.42$ vs. 0.34 - 0.36) and SF-36 PCS ($r=-0.44$ vs. -0.39 to -0.40), but not with direct costs ($r=0.35$ vs. 0.41 - 0.46). As expected, only weak correlations ($r=0.02$ - 0.17) were found between the gout-specific measures (GIS, number of flares) and the RDCI/mRDCI. The results are summarized in Table 3.2.

Table 3.1 Demographic and clinical characteristics of 122 gout patients.

Characteristics	
Age, mean (S.D.), years	66.4 (10.4)
Male sex, n (%)	102 (83.6)
Education, n (%)	
Low (high school or less)	87 (71.3)
High (college or more)	35 (28.7)
Disease duration, mean (S.D.), years	11.3 (10.6) [0.5-52]
Tophaceous gout, n (%)	58 (47.5)
Uric acid lowering therapy, yes, n (%)	86 (70.5)
Gout Flares last 12 months, mean (S.D.)	3.1 (7.5)
HAQ-DI, mean, (S.D.) (0-3)	0.61 (0.57)
SF-36, mean (S.D.) [0-100]	
PCS	39.3 (12.1)
MCS	49.9 (12.3)
Gout Impact Scales, mean, (S.D.), [0-100]	
Gout concern overall	53.8 (22.4)
Gout medication side effects	45.3 (21.3)
Unmet gout treatment needs	48.1 (13.8)
Well-being during attack	45.0 (11.3)
Gout concern during attack	44.7 (22.1)
Direct costs, mean, {median} [IQR], Euros	5686, {1146} [258-5120]
Comorbidities from the RDCI, n (%)	
Pulmonary	20 (16.4)
MI	39 (32.0)
Other heart disease	31 (25.4)
Stroke	7 (5.7)
Hypertension	101 (82.8)
Diabetes	30 (24.6)
Fracture	21 (17.2)
Depression	17 (13.9)
Ulcer	16 (13.1)
Other GI	34 (27.9)
Cancer	14 (11.5)
Comorbidities added to mRDCI, n (%)	
Obesity (BMI>30)	41 (33.6)
Kidney Disease (MDRD<60)	53 (43.4)
Kidney Disease (MDRD<30)	13 (10.7)
Comorbidity indices, mean (S.D.), {median} [IQR]	
Count (number of comorbidities)	3.4 (1.8), {3} [2-5]
Rheumatic Diseases Comorbidity Index [range: 0-9]	2.7 (1.5), {3} [2-4]
Modified RDCI [range: 0-12]	4.1 (2.3), {4} [2-6]
Charlson Comorbidity Index [range: 0-33]	1.9 (1.8), {2} [0-3]
Functional Comorbidity Index [range: 0-18]	2.9 (2.2), {2} [1-4]

In supplementary Tables S3.2-S3.4, available in Appendix A, the results of the univariable and multivariable regression analyses to explore the independent impact of RDCI/mRDCI on generic, disease-specific outcomes and costs are shown. In multivariable analysis, the RDCI and mRDCI were independently, significantly associated with the HAQ-DI, SF-36 PCS and direct costs and had a relevant additional contribution

to variation in the outcomes [about 5.4% (RDCI) and 8.3% (mRDCI) for the HAQ-DI, 11% and 13% for the SF-36 PCS and 4.0% for direct healthcare and non-healthcare costs].

Table 3.2 Construct validity of the comorbidity indices.

	n	COUNT	RDCI	mRDCI	CCI	FCI
COUNT	122	-	0.85**	0.88**	0.74**	0.79**
RDCI	122	-	-	0.86**	0.78**	0.75**
mRDCI	122	-	-	-	0.76**	0.77**
CCI	122	-	-	-	-	0.72**
FCI	122	-	-	-	-	-
Age	122	0.32**	0.28**	0.33**	0.35**	0.40**
Disease duration	122	-0.20*	-0.22*	-0.26**	-0.25**	-0.26**
No. of gout flares last year	122	0.07	0.05	0.07	0.08	0.06
HAQ-DI	114	0.33**	0.34**	0.42**	0.34**	0.36**
SF-36 PCS	107	-0.39**	-0.36**	-0.44**	-0.39**	-0.40**
SF-36 MCS	107	-0.01	-0.13	-0.06	-0.12	-0.15
Direct costs	115	0.31**	0.32**	0.35**	0.41**	0.46**
Gout Impact Scales						
Gout concern overall	116	0.06	0.02	0.07	0.09	0.06
Gout medication side effects	114	0.17	0.16	0.17	0.16	0.16
Unmet gout treatment needs	111	0.09	0.10	0.08	0.15	0.22*
Well-being during attack	107	0.08	0.02	0.03	0.08	0.04
Gout concern during attack	116	0.04	0.05	0.11	0.03	0.11

* $p < 0.05$, ** $p < 0.01$

Discussion

This study showed that the RDCI and mRDCI have good content and construct validity to assess the influence of comorbidity on clinical outcomes in patients with gout. Importantly, the RDCI/mRDCI had substantial additional influences on generic outcomes (HAQ-DI, SF-36) and direct costs in patients with gout, proving the relevance of comorbidities in patients with gout in relation to outcomes.

The mRDCI for gout was developed to include prevalent comorbidities and the clinical phenotype of patients with gout, including obesity and kidney disease. Although the mRDCI for gout showed somewhat superior construct validity compared with the RDCI, this difference was small. In terms of feasibility, one might recommend use of the original RDCI. This has the additional advantage of avoiding inconsistent use and incomparability of data when different instruments are used.

Both the RDCI and mRDCI correlated strongly with other commonly used comorbidity indices, but they have the advantage that they do not include musculoskeletal diseases and therefore have no risk of overadjusting for the index disease (gout). The weak correlations between the RDCI/mRDCI and gout-specific outcomes (tophi, flares, gout impact scales) were as expected and are reassuring since gout-specific outcomes should be independent of comorbidities. This is further supported by the fact that comorbidity as measured with the RDCI/mRDCI provides a substantial additional

contribution to the variance in the multivariable models with the HAQ-DI and SF-36 as outcome measures.

This study is not without limitations. First, patients were recruited from a university hospital, and although it serves as a regional hospital for patients with gout, it is possible that our population represents a severe form of the disease and thus results may not be generalizable to all gout patients. Also, this might be illustrated by the high number of patients with tophaceous gout and somewhat higher number of comorbidities when compared with other studies conducted among patients under the care of a rheumatologist.²⁰ Therefore the validity of the RDCI/mRDCI needs to be further demonstrated in other populations, at least in a population-based sample. Second, because we used cross-sectional data, it was not possible to investigate whether the RDCI/mRDCI will also predict deterioration in physical functioning, HRQOL or future resource utilization. Third, there is an ongoing debate about whether to call a condition comorbid or coexistent (and thus related to the index disease). Especially in patients with gout, it has not yet been clarified to what extent there is a common cause between gout and some of the coexisting diseases, since the mutual relationships are very complex. To overcome this, we considered all diseases as comorbid, acknowledging its possible inaccuracy. Fourth, we were unable to assess adherence to therapy in this study (because of an error in linking patient identification numbers with pharmacy data). Since gout is recognized as a chronic inflammatory disease and not just an acute transient arthritis, it is important to assess the influence of appropriate treatment and adherence to treatment on HRQOL, physical functioning and costs. As adequate disease management may prevent or even resolve chronic tophaceous gout and hyperuricaemia-associated comorbidities, this might have influenced the results. The already complex mutual relationships between gout and comorbidities might be different in adherent vs. non-adherent patients.

In this study, we did not investigate the test-retest reliability of our approach to assess comorbidities. However, a recent publication of the RDCI confirmed validity based on self-report as well as on databaseretrieved approaches, contributing also to the feasibility of the RDCI/mRDCI.¹⁰

In conclusion, the RDCI/mRDCI is the first comorbidity instrument validated for use in gout, providing support for adequate construct validity of the RDCI/mRDCI to measure comorbidity in patients with gout. Comorbidities had a substantial independent influence on generic HRQOL and costs.

References

1. Kuo CF, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74:661-7.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum* 2011;63:3136-41.
3. Robinson PC, Merriman TR, Herbison P, et al. Hospital admissions associated with gout and their comorbidities in New Zealand and England 1999-2009. *Rheumatology* 2013;52:118-26.
4. Seminog OO, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. *Rheumatology* 2013;52:2251-9.
5. Meek IL, Picavet HS, Vonkeman HE, et al. Increased cardiovascular risk factors in different rheumatic diseases compared with the general population. *Rheumatology* 2013;52:210-6.
6. Chandratne P, Roddy E, Clarson L, et al. Health-related quality of life in gout: a systematic review. *Rheumatology* 2013;52:2031-40.
7. Spaetgens B, Wijnands JM, van Durme C, et al. Cost of illness and determinants of costs among patients with gout. *J Rheumatol* 2015;42:335-44.
8. Perez-Ruiz F, Martinez-Indart L, Carmona L, et al. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. *Ann Rheum Dis* 2014;73:177-82.
9. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007;21:885-906.
10. England BR, Sayles H, Mikuls TR, et al. Validation of the Rheumatic Disease Comorbidity Index *Arthritis Care Res* 2015;67:865-72.
11. Boers M, Brooks P, Strand CV, et al. The OMERACT filter for outcome measures in rheumatology. *J Rheumatol* 1998;25:198-9.
12. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
13. Groll DL, To T, Bombardier C, et al. The development of a comorbidity index with physical function as the outcome. *J Clin Epidemiol* 2005;58:595-602.
14. Boers M, Jacobs JW, van Vliet et al. Consensus Dutch health assessment questionnaire. *Ann Rheum Dis* 2007;66:132-3.
15. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-68.
16. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
17. Spaetgens B, van der Linden S, Boonen A. The Gout Assessment Questionnaire 2.0: cross-cultural translation into Dutch, aspects of validity and linking to the International Classification of Functioning, Disability and Health. *Rheumatology* 2014;53:678-85.
18. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-65.
19. Cohen J, Cohen P, West SG, et al. *Applied Multiple Regression/Correlation Analysis for the Behavioural Sciences*. 2nd edn. Hillsdale, NJ: Lawrence Erlbaum, 2003.
20. Scire CA, Manara M, Cimmino MA, et al. Gout impacts on function and health-related quality of life beyond associated risk factors and medical conditions: results from the KING observational study of the Italian Society for Rheumatology (SIR). *Arthritis Res Ther* 2013;15:R101.

Supplementary material

Appendix A: Comorbidity indices and scoring systems

Rheumatic Diseases Comorbidity Index and modification

The Rheumatic Diseases Comorbidity Index (RDCI) (range 0-9) is originally developed as a self-reported questionnaire which is composed of 11 weighted present or past comorbid conditions including pulmonary disorders (asthma/chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), other cardiovascular disease (CV), stroke, hypertension, diabetes, spine/hip/leg fractures, depression, gastrointestinal ulcer, other gastrointestinal disorders (liver problem, gall bladder problem, other stomach problem) and cancer.¹ A recent publication about the validity of the RDCI confirms that both self-report as well as database-retrieved approaches are valid.² This contributes to the feasibility of the index. To calculate the RDCI, the formula is as follows:

$RDCI = 2 \times \text{lung disease} + [2 \times ((MI, \text{ other CV, or stroke})) \text{ or } 1 \times \text{Hypertension}] + 1 \times (\text{ulcer or other GI}) + 1$ for each of the following conditions: diabetes, fracture, depression and cancer.³

We modified the RDCI (range 0-12) by adding kidney disease (eGFR <60 ml/min/1.73m²) and obesity (BMI >30 kg/m² or BMI >35 kg/m²) for which we assigned a weight of 1 and 1 or 2 (dependent on BMI) respectively. This modification is based on the best-fit data, in terms of strongest correlations with HAQ-DI and physical summary score of the SF-36, which were investigated by assessing different weights to all variables. The strongest correlations were found for the index with the following formula:

Modified Rheumatic Diseases Comorbidity Index (mRDCI) = $1 \times \text{lung disease} + [2 \times ((MI, \text{ other CV, or stroke})) \text{ or } 1 \times \text{Hypertension}] + 1 \times (\text{ulcer or other GI}) + 2 \times \text{kidney disease} + 1 \times \text{if BMI} >30 \text{ or } 2 \times \text{if BMI} >35 + 1$ for each of the following conditions: diabetes, fracture, depression and cancer.

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) (range 0-33) is, in contrast to the RDCI, designed to use extracted data from medical records and is composed of 19 weighted comorbid conditions of which the conditions and their weightings are based on the mortality risk.⁴

The formula is as follows:

CCI = 1 point for each of the following conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease or TIA, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease and diabetes without end-organ damage and 2 points for each of the following

conditions: hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, tumor without metastases, leukemia and lymphoma. and 3 points for moderate or severe liver disease and 6 points for metastatic solid tumor and AIDS.

Functional Comorbidity Index

The Functional Comorbidity Index (FCI) (range 0-18) is a self-reported questionnaire, which is composed of 18 comorbid conditions with physical function as outcome of interest.

The formula is simple, as all conditions are weighted as 1:

FCI = 1 point for each of the following conditions: arthritis, osteoporosis, asthma, (chronic obstructive pulmonary disease or acquired respiratory distress syndrome or emphysema), angina, congestive heart failure, heart attack (myocardial infarction), neurological disease (Parkinson's or multiple sclerosis), stroke or TIA, peripheral vascular disease, diabetes (type I or II), upper gastrointestinal disease (ulcer, hernia, reflux), depression, anxiety or panic disorders, visual impairment (eg, cataract, glaucoma), hearing impairment, degenerative disc disease (back disease, spinal stenosis or severe chronic back pain) and obesity.

Table S3.1 Summary of the comorbidity indices

Author	Index	Content	Score	Population ^a	Data Source	Outcome
Michaud, Wolfe ¹	RDCI	11 weighted comorbid conditions	0-9	20,416 RA patients from the US NDB ^b	Self-reported	Mortality, Hospitalisation, Work and functional disability (HAQ-DI) and medical costs
This study:	(m) RDCI	13 weighted comorbid conditions	0-12	122 patients with gout	Self-reported & medical records	Functional disability (HAQ-DI) Direct medical costs SF-36 PCS
Charlson et al. ⁴	CCI	19 weighted comorbid conditions	0-33	685 patients (women) with breast cancer	Medical records	Mortality
Groll et al. ⁵	FCI	18 comorbid conditions	0-18	9,423 Canadian and 28,349 US adults seeking treatment for spine ailments	Self-reported	Physical function (SF-36 PF subscale)

Appendix B: Univariable and multivariable regression analyses for functional disability, physical health-related quality of life and costs

Table S3.2 Uni- and multivariable linear regression analyses to explore impact of comorbidity on physical functioning, measured with HAQ-DI

	Univariable Analysis		Multivariable Analysis			
	B (95% CI)	p	Model 1 RDCI		Model 2 mRDCI	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
RDCI	0.12 (0.06, 0.19)	0.001	0.10 (0.03, 0.16)	0.004	-	-
mRDCI	0.10 (0.05, 0.14)	<0.001	-	-	0.07 (0.03, 0.11)	0.002
CCI	0.10 (0.05, 0.16)	<0.001	-	-	-	-
FCI	0.08 (0.04, 0.13)	0.001	-	-	-	-
Age, years	0.02 (0.01, 0.03)	0.003	-	0.062	-	0.099
Female sex	0.59 (0.31, 0.86)	<0.001	0.49 (0.24, 0.75)	<0.001	0.45 (0.20, 0.71)	0.001
Disease duration, years	-0.01 (-0.02, 0.00)	0.085	-	0.716	-	0.642
Tophaceous gout (yes)	0.19 (-0.02, 0.40)	0.080	0.18 (-0.01, 0.37)	0.055	0.18 (0.00, 0.36)	0.048
UALT (yes)	0.12 (-0.11, 0.35)	0.317	-	-	-	-
Gout concern overall/10	0.10 (0.05, 0.14)	<0.001	0.09 (0.05, 0.13)	<0.001	0.09 (0.05, 0.13)	<0.001
Variance explained by comorbidity, %			5.4%		8.3%	
R ² model, %			32.7%		35.6%	

RDCI: range 0-9, mRDCI: range: 0-12, Comorbidity indices and all variables with a p-value<0.10 were included in the model using stepwise linear regression. RDCI: Rheumatic Diseases Comorbidity Index; mRDCI: modified Rheumatic Diseases Comorbidity Index; CCI: Charlson Comorbidity Index; FCI: Functional Comorbidity Index; HAQ-DI: HAQ disability index; UALT: uric acid lowering therapy.

Table S3.3 Uni- and multivariable linear regression analyses to explore the impact of comorbidity on HRQOL, measured with the SF-36 PCS

	Univariable Analysis		Multivariable Analysis			
	B (95% CI)	p	Model 1 RDCI		Model 2 mRDCI	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
RDCI	-3.00 (-4.47, -1.53)	<0.001	-2.73 (-4.14, -1.33)	<0.001	-	-
mRDCI	-2.32 (-3.22, -1.41)	<0.001	-	-	-2.24 (-3.16, -1.31)	<0.001
CCI	-2.51 (-3.69, -1.34)	<0.001	-	-	-	-
FCI	-2.09 (-3.04, -1.13)	<0.001	-	-	-	-
Age, years	-0.22 (-0.45, 0.01)	0.056	-	0.565	-	0.737
Female sex	-8.25 (-14.41, -2.08)	0.009	-5.85 (-11.38, -0.33)	0.038	-4.20 (-9.84, 1.48)	0.181
Disease duration, years	0.08 (-0.15, 0.31)	0.487	-	-	-	-
Tophaceous gout (yes)	-3.51 (-9.13, 1.12)	0.136	-	-	-	-
UALT (yes)	-5.20 (-10.27, -0.17)	0.043	-5.26 (-9.76, -0.81)	0.021	-4.17 (-8.56, 0.23)	0.063
Gout concern overall/10	-2.08 (-3.11, -1.06)	<0.001	-1.83 (-2.76, -0.89)	<0.001	-1.89 (-2.90, -0.86)	<0.001
Variance explained by comorbidity, %			11.0%		13.6%	
R ² model, %			32.8%		35.4%	

RDCI: range 0-9, mRDCI: range: 0-12, Comorbidity indices and all variables with a p-value<0.10 were included in the model using stepwise linear regression. HRQL: health-related quality of life; RDCI: Rheumatic Diseases Comorbidity Index; mRDCI: modified Rheumatic Diseases Comorbidity Index; CCI: Charlson Comorbidity Index; FCI: Functional Comorbidity Index; SF-36: Dutch Short Form-36; PCS: physical component summary score.

Table S3.4 Uni- and multivariable logistic regression analyses to explore the impact of comorbidity for above median direct costs

	Univariable Analysis		Multivariable Analysis			
	B (95% CI)	p	Model 1 RDCI		Model 2 mRDCI	
			B (95% CI)	p	B (95% CI)	p
RDCI	1.45 (1.10, 1.91)	0.009	1.52 (1.10, 2.09)	0.010	-	
mRDCI	1.32 (1.10, 1.59)	0.003	-		1.31 (1.07, 1.61)	0.009
CCI	1.41 (1.12, 1.78)	0.003	-		-	
FCI	1.50 (1.20, 1.86)	<0.001	-		-	
Age, years	1.04 (1.00, 1.08)	0.052	-	0.180	-	0.200
Female sex	5.97 (1.62, 22.11)	0.007	5.07 (1.27, 20.27)	0.022	4.38 (1.07, 17.88)	0.040
Disease duration, years	0.96 (0.92, 1.00)	0.049	-	0.488	-	0.457
Tophaceous gout (yes)	1.27 (0.61, 2.62)	0.517	-		-	
UALT (yes)	1.74 (0.78, 3.91)	0.177	-		-	
Gout concern overall/10	1.27 (1.06, 1.52)	0.011	1.30 (1.06, 1.58)	0.010	1.29 (1.06, 1.58)	0.013
Variance explained by comorbidity, %			4.0%		4.0%	
R ² model, %			28.1%		28.1%	

RDCI: range 0-9, mRDCI: range: 0-12, Comorbidity indices and all variables with a p-value<0.10 were included in the model using stepwise logistic regression. RDCI: Rheumatic Diseases Comorbidity Index; mRDCI: modified Rheumatic Diseases Comorbidity Index; CCI: Charlson Comorbidity Index; FCI: Functional Comorbidity Index.; UALT: uric acid lowering therapy.

References

1. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2007;21:885-906.
2. England BR, Sayles H, Mikuls TR, et al. Validation of the Rheumatic Disease Comorbidity Index. *Arthritis Care Res*. 2015;67:865-72.
3. Wolfe F, Michaud K, Li T, et al. Chronic conditions and health problems in rheumatic diseases: comparisons with rheumatoid arthritis, noninflammatory rheumatic disorders, systemic lupus erythematosus, and fibromyalgia. *J Rheumatol*. 2010;37:305-15.
4. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-83.
5. Groll DL, To T, Bombardier C, et al. The development of a comorbidity index with physical function as the outcome. *J Clin Epidemiol*. 2005;58:595-602.

Chapter 4

Cost of illness and determinants of costs among
patients with gout

Bart Spaetgens, José M.A. Wijnands, Caroline van Durme, Sjef van der Linden
Annelies Boonen

J Rheumatol 2015;42:335-344

Abstract

Objectives

To estimate costs of illness in a cross-sectional cohort of patients with gout attending an outpatient rheumatology clinic, and to evaluate which factors contribute to higher costs.

Methods

Altogether, 126 patients with gout were clinically assessed. They completed a series of questionnaires. Health resource use was collected using a self-report questionnaire that was cross-checked with the electronic patient file. Productivity loss was assessed by the Work Productivity and Activity Impairment Questionnaire, addressing absenteeism and presenteeism. Resource use and productivity loss were valued by real costs, and annual costs per patient were calculated. Factors contributing to incurring costs above the median were explored using logistic univariable and multivariable regression analysis.

Results

Mean (median) annual direct costs of gout were €5647 (€1148) per patient. Total costs increased to €6914 (€1279) or €10,894 (€1840) per patient per year when adding cost for absenteeism or both absenteeism and presenteeism, respectively. Factors independently associated with high direct and high indirect costs were a positive history of cardiovascular disease, functional limitations, and female sex. In addition, pain, gout concerns, and unmet gout treatment needs were associated with high direct costs.

Conclusion

The direct and indirect costs-of-illness of gout are primarily associated with cardiovascular disease, functional limitations, and female sex.

Introduction

Gout is the most common inflammatory arthritis with a prevalence varying from 1.4% (Europe) to 3.9% (United States).^{1,2} While in the past gout was typically seen as an acute and transient form of arthritis, gout is now also recognized as a chronic disease with a broad variety of manifestations, varying from acute transient attacks to chronic tophaceous gout.^{3,4} Gout and its accompanying hyperuricemia have been associated with a large number of comorbidities, mainly cardiovascular diseases (CVD).⁵ Common risk factors include hypertension, obesity, use of diuretics, and certain lifestyles.⁶⁻¹⁰

In principle, gout is an easily treatable disorder, and timely diagnosis and appropriate treatment may prevent chronic tophaceous gout as well as its associated disability. Parallel with the development of some new (but expensive) pharmacological treatment options and care innovations, interest in the societal costs of gout has increased, including the identification of resources that mainly drive the costs, and the characteristics of patients who incur the highest costs. Cost-of-illness (COI) studies are useful as starting points to debate appropriate healthcare, and for use in economic evaluations. These studies also provide insight into future health expenditure, and where and how to avoid unnecessary costs.¹¹

Currently, only a limited number of studies provide information about healthcare costs in patients with gout, composed of healthcare, as well as non-healthcare consumption (direct medical costs), and costs of productivity loss (indirect costs).¹²⁻²⁰ Even fewer studies have explored the determinants of these costs, because these were insurance database studies in which only a limited number of clinical determinants were available. Further, the majority of the studies were performed in North America, hampering transferability to the European setting because it is well known that healthcare organization strongly influences resource use and costs. This and the fact that, to our knowledge, there is only one European-based COI study in gout highlights the need for more research in a European setting. Finally, to date, no study has assessed resource use and COI of patients with gout under care of a rheumatologist, who are likely given innovative medications and care interventions.

In view of the above, the aims of the current study were, first, to understand resource use and productivity loss among patients with gout attending a rheumatology clinic; second, to estimate average annual direct and indirect costs; and third, to identify the characteristics of patients incurring the highest costs.

Materials and methods

Patients

Our study is a cross-sectional assessment of patients with gout who were seen at the outpatient Department of Rheumatology at Maastricht University Medical Centre, the

Netherlands. The hospital serves as a university centre, as well as the only regional hospital. Patients, registered by the rheumatologist with a diagnosis of gout between April 2011 and April 2012, were sent an invitation letter, and those who agreed to participate were invited for a study visit. The principles of the Declaration of Helsinki were followed and the study was approved by the ethics committee of Maastricht University Medical Centre. Prior to the data collection, all participating patients provided signed informed consent.

Data collection

During a structured interview, data were collected on socioeconomic background (age, sex, highest achieved education), comorbidities (CVD; defined according to the original Framingham definition),²¹ diabetes, chronic kidney disease (defined as glomerular filtration rate <60 ml/min/1.73m²), and asthma or chronic obstructive pulmonary disease (COPD). Moreover, we collected data on the course of gout [duration of disease, number of gout flares last year, and treatment with uric acid lowering therapy (yes/no)]. If applicable, data were verified through the electronic patient file. Next, the patients underwent a physical examination to determine body mass index (BMI) and the presence of tophi (yes/no). Finally, a series of questionnaires was completed.

Health Assessment Questionnaire (HAQ)

The validated Dutch version of the HAQ was included to assess physical function.²² It consists of 20 items across 8 categories (dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping, and other activities) that measure impairments in physical functioning during the last 7 days on a 0-3 Likert scale. The total score is the sum of the highest score per category, divided by 8, and represents the so-called HAQ-Disability Index (HAQ-DI). Higher scores indicate more functional disability.

Gout Assessment Questionnaire, version 2.0 (GAQ2.0)

The GAQ2.0 is a disease-specific, self-administered gout questionnaire consisting of 2 parts with 31 questions overall. Part 1 consists of the Gout Impact Scale (GIS) that assesses the current effect of gout in 5 different subscales: (1) gout concern overall (4 items); (2) gout medication side effects (2 items); (3) unmet gout treatment needs (3 items); (4) well-being during attack (11 items); and (5) gout concern during attack (4 items).²³ These subscales are scored from 0 to 100; higher scores indicate more effect on quality of life.

Part 2 addresses the previous 4 weeks and asks whether patients had experienced a gout flare (yes/no); the extent to which gout affected physical and mental health, quality of life, and pain (1=very poor, 6=excellent); and finally, to rate the level of pain and disease activity attributable to gout (1=no pain, no disease activity; 10=severe pain, severe disease activity). A validated Dutch version is available and was used.²⁴

Healthcare resource use and productivity loss

Healthcare resource use was assessed using a questionnaire on resource use for any health problem in the preceding 6 months regarding (1) the number of consultations with healthcare professionals (general practitioner, rheumatologist, or any other medical specialist); (2) visits to paramedics or exercise therapy; (3) number of days admitted to either a hospital or rehabilitation centre; (4) hours per week care received because of health problems from professional home care; or (5) hours per week help from informal caregivers (family or friends). Productivity loss was assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI) consisting of 6 questions about work productivity in the past 7 days.²⁵ First, subjects were asked whether they were currently employed (Q1). Next, the number of hours missed from work because of health problems (Q2) and for other reasons (Q3) was assessed, as well as the number of hours actually worked in the past 7 days (Q4). Finally, subjects had to indicate to what extent health problems had compromised productivity while working (presenteeism; Q5) or while performing regular activities at home (Q6) on a numeric rating scale (from 0=no problem to 10=health completely prevented me from working). Based on these questions, the percentage of time absent (work time missed because of health problems), the percentage of productivity loss at paid work (presenteeism or work impairment while working), and the percentage of unproductive time because of absenteeism and presenteeism (overall work impairment) were calculated.

Cost estimation

Costs of healthcare resource use and hours of formal/informal help were calculated by multiplying the number of visits or hours by the corresponding unit costs as recommended in Dutch guidelines for economic evaluations in healthcare (Appendix 4.1).²⁶ The costs per resource type were first annualized and then summed to represent the total yearly direct costs per patient. For cost valuation of drug prescriptions, the chronic supplied drugs (data retrieved from the patients' pharmacy) were annualized and costs for each drug were retrieved from the official Dutch website for drug costs.²⁷ Productivity costs were estimated using the friction costs approach as theoretical framework that restricts productivity costs to the time absent during the friction period, which was 23 weeks at the time of our study.²⁸

Hours absent attributable to health in the past week, as indicated in the WPAI, were multiplied by the hourly gross wages, specific for age and sex, and thereafter, annualized to represent the annual indirect costs per patient. In a second analysis, the costs of presenteeism also were included in the indirect costs. Estimates of productivity costs because of presenteeism were based on the WPAI question on the percentage of impaired productivity, which was applied to the hours actually worked per week (% productivity x h worked), and multiplied by hourly gross wages, specific for age and sex, and finally annualized. Annual indirect and total (direct and indirect) costs were calculated twice, by including or excluding costs of presenteeism.

Statistical analysis

First, annual health resource use, costs per resource type, direct, indirect, and total costs of gout per patient were calculated as mean (median) and interquartile ranges (IQR) because of highly skewed data. Patients were divided into a low-cost and high-cost group using the median as cutoff for (1) direct costs, (2) total costs excluding presenteeism, and (3) total costs including presenteeism. Next, logistic regression models were applied. Candidate explanatory variables considered 4 domains: (1) demographics: age, sex, educational level; (2) gout characteristics: disease duration, number of gout flares last year, tophaceous gout (yes/no), use of uric acid lowering therapy (yes/no); (3) comorbidities: BMI, diabetes (yes/no), asthma/COPD (yes/no), kidney disease (yes/no), history of CVD (yes/no); and (4) patient-reported health: HAQ-DI, the GIS, as well as the GAQ2.0 questions about physical and mental health, quality of life, and pain and disease activity.

First, univariable logistic regressions were performed for all candidate variables, and those significantly associated with costs at p value ≤ 0.10 were included in the final backward multivariable models. Before computing multivariable regressions, (multi)collinearity between variables was checked. To enhance interpretability of the regressions, we calculated the marginal effects of the explanatory variables by predicting the probability of total costs above median, holding all other factors at the average value of the total population.

Results

Patients

Altogether, 126 of the 250 patients with gout agreed to participate in our study. The nonparticipating patients did not significantly differ from the participating patients with regard to sex and age. Data were available for all participating patients. Table 4.1 shows that 106 (84%) were male, mean age was $66.6 \pm \text{SD } 10.4$ years, mean disease duration 11.2 ± 10.6 years, and 60 patients (48%) had tophaceous gout.

Health resource use and direct costs

Table 4.2 presents resource use and annual costs per patient. On average, patients visited the outpatient department (rheumatologist or any other medical specialist) 2.9 times (median 2, IQR 1-4) in the preceding 6 months, went to the general practitioner 3.4 times (2, 0-4), to the psychologist 0.5 times (0, 0-0), and underwent 3.7 h (0, 0-0) of physiotherapy. Fifteen patients (12%) had been admitted to hospital for an average of 8 days. For the total population, this resulted in an average of 1.0 day (0, 0-0) in the hospital in the last 6 months. Reasons for hospitalization were CVD ($n=5$), surgery ($n=5$), gout flares ($n=2$), pneumonia ($n=1$), exacerbation COPD ($n=1$), and liver

cirrhosis (n=1). Professional and informal care by family and friends were delivered 0.8 h (0, 0-0) and 2.7 h (0, 0-0) per week, respectively.

Annualized direct costs of gout per patient are on average €5647 (median €1148). Professional home help and informal care by family and friends accounted for 56% of total direct costs. Consultations with healthcare workers (rheumatologist/medical specialist, general practitioner, psychologist, and physiotherapist) accounted for 23% of the direct costs.

Because the overview of drug prescriptions could only be retrieved in a subsample of 56 patients (44%), we calculated these costs only in a subsample. The characteristics of the 56 patients did not differ significantly in age, sex, disease duration, and presence of tophi or CVD when compared to the sample with the medication overview unavailable. In this subsample, the average number of drugs prescribed was 4.6 (median 5) and annualized total medication costs per patient were on average €259 (97).

Table 4.1 Demographic and disease characteristics of the study sample (n=126)

Characteristics	n=126
Age (years), mean $\pm$ SD [range]	66.6 $\pm$ 10.4 [42-89]
Male sex; n (%)	106 (84.1)
Education	
Low (High school or lower)	89 (70.6)
High (College or higher)	37 (29.4)
Disease duration (years), mean $\pm$ SD [range]	11.2 $\pm$ 10.6 [0.5-52]
Tophaceous gout, n (%)	60 (47.6)
No. of gout flares last year, mean $\pm$ SD [range]	3.1 $\pm$ 7.4 [0-25]
Uric acid lowering therapy, n (%)	83 (67.5)
Body Mass Index (kg/m ²), mean $\pm$ SD [range]	29.6 $\pm$ 5.0 [22-47]
Diabetes, n (%)	31 (24.6)
Asthma / COPD, n (%)	14 (11.1)
Kidney disease, n (%)	12 (9.5)
History of cardiovascular event, n (%)	38 (30.2)
Paid work, n (%)	30 (23.8)
HAQ-DI (0-3); mean $\pm$ SD	0.63 $\pm$ 0.58
GAQ2.0 (Gout impact scales: 0-100); mean $\pm$ SD	
Gout concern overall	53.9 $\pm$ 22.4
Gout medication side effects	45.3 $\pm$ 21.3
Unmet gout treatment need	48.1 $\pm$ 13.8
Well being during attack	45.0 $\pm$ 11.3
Gout concern during attack	44.7 $\pm$ 22.1
GAQ2.0: physical health past 4 weeks (1-6)	3.5 $\pm$ 3.9
GAQ2.0: mental health past 4 weeks	2.8 $\pm$ 1.0
GAQ2.0: quality of life past 4 weeks	3.1 $\pm$ 1.0
GAQ2.0: pain past 4 weeks	3.2 $\pm$ 1.2
GAQ2.0: disease activity due to gout (1-10)	4.2 $\pm$ 2.6
GAQ2.0: pain due to gout (1-10)	3.7 $\pm$ 2.6

Table 4.2 Resource utilization, productivity loss (WPAI) and annual costs across the different cost-categories of patients with gout (n=126).

	Patients with resource use, n (%)	Resource use per 6 months	Annual costs (EUR/patient)	Total direct costs, %
Consultation (number of visits)				
Rheumatologist / Other medical specialist	92 (73.0)	2.9 (2) [1-4]	743 (516) [258-1032]	13.1
General practitioner	84 (66.7)	3.4 (2) [0-4]	190 (112) [0-224]	3.4
Psychologist	10 (7.9)	0.5 (0) [0-0]	85 (0) [0-0]	1.5
Therapy (number of visits) ¹	27 (21.4)	3.7 (0) [0-0]	262 (0) [0-0]	4.6
Hospital admissions (days)	15 (11.9)	1.0 (0) [0-0]	1189 (0) [0-0]	21.1
Non-medical resource use (hours/week)	16 (12.7)	0.8 (0) [0-0]	1442 (0) [0-0]	25.6
Household care (professional)	26 (20.6)	2.7 (0) [0-0]	1735 (0) [0-0]	30.7
Informal care by family and friends				
Total direct costs			5647 (1148) [258-5239]	100
	Time, %	Total costs/week (EUR/patient)	Annual costs (EUR/patient)	Indirect costs of total, %
Paid productivity loss				
Absenteeism	9.6 (0) [0-25]	96 (0) [0-34]	4982 (0) [0-1791]	
Presenteeism	26.9 (0) [0-55]	301 (155) [0-436]	15657 (8067) [0-22683] [#]	
Total indirect costs for total group				
Absenteeism			1267 (0) [0-0]	
Presenteeism			3980 (0) [0-0]	
Total Costs:				
Total direct and indirect costs (absenteeism only)			6914 (1279) [258-7543]	18.3
Total direct and indirect costs (absenteeism and presenteeism)			10894 (1840) [314-14467]	48.1

¹ Physiotherapy, occupational therapy or exercise therapy; * Values are mean (median) and [interquartile range], unless otherwise specified; [#] Presenteeism is not calculated in total costs (Friction Cost Approach).

Productivity loss and indirect costs

Table 4.2 presents the percentage of time productivity loss and weekly costs for the 30 patients (24%) with a paid job. Among these, 8 (27%) reported to have incurred at least a 1-h absence attributable to health, but nobody had been absent for full working time.

On average, the proportion of time absenteeism was 9.6% (median 0, IQR 0-25) and average productivity impairment was 26.9% (0, 0-55), resulting in an overall work impairment of 30.6% (10, 0-53).

Annualizing costs of absenteeism resulted in an average of €4982 (median €0) per working patient. Since no patient was absent for the full working time, the data did not

need to be adjusted for the friction period. Averaged over all patients in the sample, this would result in €1267 (€0) per patient per year.

When including costs of presenteeism in productivity costs, these costs amounted to €15,657 (€8067) per year per working patient or €3980 (€0) per patient per year when averaged over all patients.

Total costs

Total annual direct and indirect costs of all patients, excluding presenteeism, amounted to €6914 (median €1279) per patient per year. The proportion of direct costs is 82%. When calculating total annual direct and indirect costs, including presenteeism, the estimate is €10,894 (€1840); the proportion of direct costs is 52%.

Factors associated with higher costs

Results of the uni- and multivariable logistic regression analyses of factors associated with costs above the median are presented in Table 4.3. Multivariable regression for direct costs showed that female sex (OR 5.13, 95% CI 0.87-29.41), CVD (OR 7.50, 95% CI 2.30-24.40), functional disability (OR 3.20, 95% CI 1.05-9.31), unmet gout treatment needs (OR 1.04, 95% CI 0.99-1.09), and pain (OR 1.19, 95% CI 0.97-1.41) were independently related to higher costs. For total costs (excluding presenteeism), multivariable regression analysis revealed that again female sex (OR 4.67, 95% CI 0.85-25.64), CVD (OR 5.67, 95% CI 1.91-16.81), functional disability (OR 3.70, 95% CI 1.34-10.17), and also unmet gout treatment needs (OR 1.04, 95% CI 0.99-1.08) were independently related to higher total costs (excluding presenteeism). The multivariable logistic regression analysis for total costs including presenteeism showed similar results with respect to the role of female sex (OR 5.59, 95% CI 1.05-29.41), CVD (OR 5.09, 95% CI 1.81-14.34), and functional disability (OR 3.38, 95% CI 1.31-8.70). The Nagelkerke R^2 of these multivariable models were 0.48, 0.42, and 0.38, respectively.

Figure 4.1 shows the predicted probability of patients being in the group with higher total costs. As can be seen, women have consistently higher costs compared to men, independent of HAQ-DI and presence of CVD. Within men and women, CVD also consistently increases the probability of higher costs, independent of HAQ. For example, at a HAQ of 1, about 40% and 80% of men have high costs, depending on whether they have CVD, and for women, these proportions would be 65% and 90%.

Table 4.3 Results of univariable and multivariable logistic regression analysis for above median direct and total costs (absenteeism and in/excluding presenteeism) ($R^2=0.48, 0.42, 0.38$ respectively)

Variable	Univariable analysis			Multivariable analysis			Univariable Analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Direct Costs																		
Age (per year)	1.041 (1,003-1,080)	0.032*					1.032 (0,955-1,070)	0.090*					1.007 (0,973-1,042)	0.864				
Sex (female)	5.814 (1,572-21,28)	0.008*	5,128 (0,874-29,41)	0.070			5,814 (1,572-21,28)	0.008*	4,673 (0,848-25,64)	0.077			5,814 (1,572-21,28)	0.008*	5,587 (1,052-29,41)	0.044*		
Education level (high)	1.000	1.000					1.000	1.000					0.718 (0,322-1,599)	0.417				
Body Mass Index	1.029 (0,956-1,108)	0.443					1.039 (0,451-2,218)	0.306					1.090 (1,006-1,181)	0.036				
<i>Gout-specific</i>																		
Disease duration (p.y)	0.958 (0,921-0,996)	0.031*					0.966 (0,931-1,003)	0.070*					0.972 (0,938-1,008)	0.130				
Number of gout flares	1.028 (0,964-1,096)	0.405					1.025 (0,964-1,089)	0.437					1.021 (0,963-1,082)	0.484				
Tophaceous gout (y/n)	1.227 (0,595-2,532)	0.580					1.227 (0,595-2,532)	0.580					1.070 (0,519-2,207)	0.854				
UALT (y/n)	1.884 (0,856-4,146)	0.116					1.689 (0,772-3,698)	0.190					1.231 (0,566-2,677)	0.600				
<i>Comorbidities</i>																		
Diabetes (y/n)	1.916 (0,812-4,519)	0.138					2.327 (0,973-5,568)	0.058*					1.916 (0,812-4,519)	0.138				
Asthma/COPD (y/n)	1.189 (0,374-3,776)	0.769					1.694 (0,520-5,519)	0.302					1.694 (0,520-5,519)	0.382				
Kidney disease (y/n)	1.851 (0,512-6,695)	0.348					1.851 (0,512-6,695)	0.348					1.851 (0,512-6,695)	0.348				
CV events (y/n)	7,181 (2,806-18,38)	0.001*	7,495 (2,301-24,40)	0.001			7,181 (2,806-18,38)	0.002*	5,672 (1,914-16,81)	0.002			3,861 (1,646-9,055)	0.002*	5,089 (1,805-14,34)	0.002*		

Table 4.3 (continued)

	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	Direct Costs	OR (95% CI)	p	Total Costs	OR (95% CI)	p	Total Costs (absenteeism)	OR (95% CI)	p	Total Costs (absenteeism and presenteeism)
<i>Functional disability</i>												
HAQ-DI (0-3)	5.404 (2.422-12.06)	0.001*	3,195 (1,045-9,310)	0.041	5,079 (2,301-11,21)	0.001*	3,696 (1,343-10,17)	0.011	3,949 (1,863-8,374)	<0.001*	3,379 (1,313-8,698)	0.012*
<i>Gout Impact Scales</i>												
Gout concern overall	1.024 (1.005-1.043)	0.011*		^b	1.021 (1.003-1.040)	0.021*		^b	1.012 (0.995-1.029)	0.178	^a	^a
Gout medication side effects	1.017 (0.998-1.036)	0.073*		^b	1.015 (0.997-1.034)	0.107		^a	1.009 (0.991-1.027)	0.332	^a	^a
Unmet gout treatment needs	1.050 (1.014-1.087)	0.006*	1.042 (0.996-1.089)	0.071	1.043 (1.009-1.078)	0.014*	1.037 (0.995-1.081)	0.081	0.998 (0.969-1.028)	0.891	^a	^a
Well being during attack	1.003 (0.970-1.038)	0.843		^a	1.010 (0.976-1.045)	0.579		^a	1.024 (0.990-1.061)	0.164	^a	^a
Gout concern during attack	1.013 (0.996-1.031)	0.142			1.010 (0.993-1.027)	0.255		^a	1.001 (0.984-1.018)	0.914	^a	^a
<i>GAQ2.0 part 2</i>												
GAQ2.0 physical health	1.540 (1.011-2.346)	0.044*		^b	1.461 (0.968-2,204)	0.071*		^b	1.279 (0.865-1,892)	0.217	^a	^a
GAQ2.0 mental health	1.415 (0.962-2,081)	0.078*		^b	1.332 (0.906-1,929)	0.148		^a	1.076 (0.747-1,549)	0.695	^a	^a
GAQ2.0 quality of life	1.518 (1.004-2,296)	0.048*		^b	1.512 (1.001-2,284)	0.049*		^b	1.328 (0.896-1,969)	0.158	^a	^a
GAQ2.0 pain	1.570 (1.107-2,227)	0.011*		^c	1.464 (1.044-2,051)	0.027*		^c	1.264 (0.920-1,737)	0.149	^c	^c
GAQ2.0 disease activity	1.287 (1.100-1,506)	0.002*		^b	1.245 (1.068-1,452)	0.005*		^b	1.109 (0.959-1,282)	0.162	^a	^a
GAQ2.0 pain	1.276 (1.093-1,490)	0.002*	1,191 (0,970-1,411)	0.095	1,240 (1,065-1,443)	0.005*		^b	1,206 (1,039-1,401)	0.014*	^b	^b

* p-value ≤0.10 and therefore included in the multivariable analysis. ^a The variable was not tested in multivariable regression because of a p-value >0.10 in univariable analysis. ^b The variable was not selected during multivariable regression analysis (backward selection); ^c The variable was not tested due to collinearity.

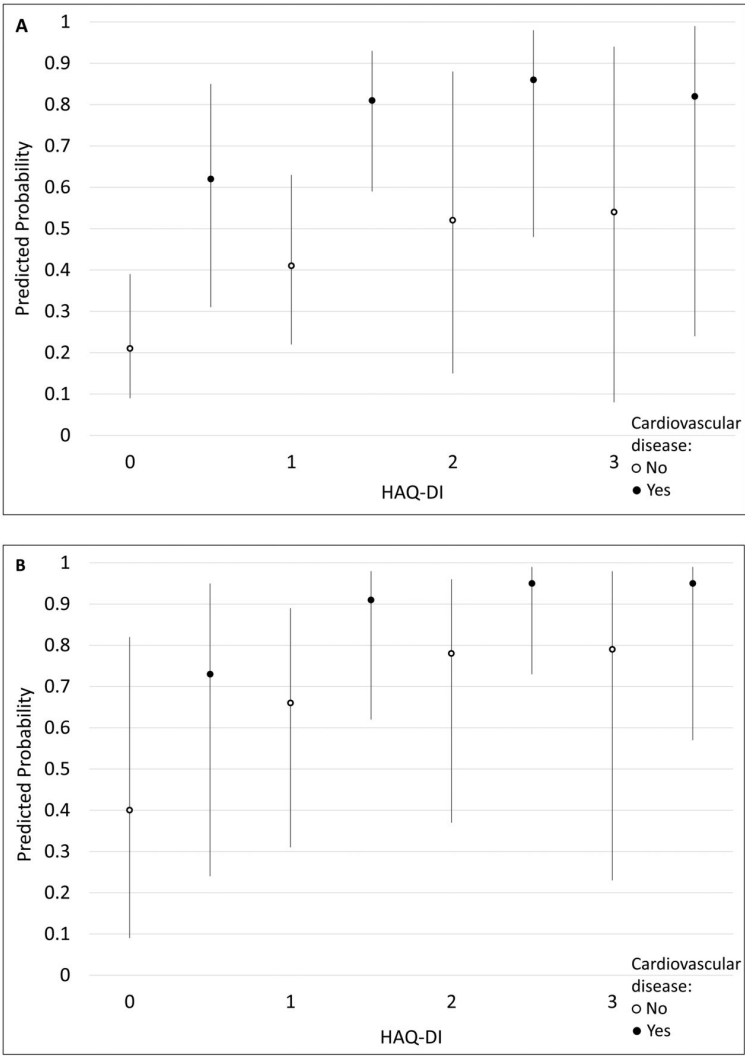


Figure 4.1 (A) Predicted probability (95% CI) of higher-than median total costs for men with gout. (B) Predicted probability (95% CI) of higher-than median total costs for women with gout.

Discussion

To the best of our knowledge, ours is the first COI study in patients with gout based on information on health resource use from patients themselves and simultaneously assessing a large amount of real-world clinical data related to gout and its

comorbidities. Moreover, this is only the second COI study in gout performed in Europe. The annual total (direct and indirect) costs of patients with longstanding gout who are under the care of a rheumatologist were estimated to be on average €6914 or €10,894 per patient when excluding or including costs of presenteeism, respectively. Independent of the approach to value indirect costs, the direct costs were at least 50% of the total amount. The proportion of indirect costs as part of the total COI was lower than classically seen in rheumatoid arthritis (RA) and ankylosing spondylitis (AS). However, this is not surprising because the average age of patients was almost 67 years and consequently, a lower proportion of subjects were currently employed and thus at risk for productivity loss. While a large percentage of patients consulted a general practitioner (66%) or specialists (73%), only 12% was hospitalized, and 13% and 21% of the patients received professional or informal household care, respectively. Notwithstanding, the costs of hospitalization and caregiving were the categories driving the direct costs. Interestingly, factors contributing consistently to both direct and total costs were functional limitations and CVD.

Within the limitation of comparability, the total annual costs (dollars converted to Euros) per patient as reported in 9 prior studies ranged from €2228 (US\$3023) to €18,975 (US\$25,741) for all-cause direct costs, and €68 (US\$92) to €2885 (US\$ 3915) for all-cause indirect costs (Table 4.4).¹²⁻²⁰ While a large variation in the reported all-cause COI was found, our results fall within the higher part of the range. Several factors can explain these findings. First, all studies in the literature report on data from insurance/claims databases, being a case-mix of persons under care of a general practitioner, as well as those referred to specialists. Therefore, these studies likely include more patients with less severe gout than in our study, which can influence direct as well as indirect costs. Second, the categories of resource use that are taken into account for cost calculation varied between studies and are not always described in detail. Different from all other studies, we accounted for formal and (disease-related) informal care by family and friends, which was a large proportion of the direct costs, especially in females. Presumably, the societal roles females play as housewife and/or caretaker explain the higher need for substitution of their tasks by (in)formal caregivers when females are ill. While we assessed only all-cause costs and some of the studies reported all-cause and gout-related costs, it became clear that the vast majority of the costs were not directly related to the gout disease itself. Third, the costs or value of resources were often not provided. Next, the costs are difficult to compare because of large differences in healthcare practices and social security systems between different countries, affecting not only resource use, but also the unit prices of resources. It is of note that in the Dutch healthcare system, formal (and even informal) caregiving are covered under specific indications and that patients incurring sick leave continue to receive 100% of their salary for the entire first year. When costs were reported, as far as could be compared, it could be seen that the Dutch resources were more expensive as compared with the unit prices of other studies. However, it is important to note that the Dutch figures are based on activity-based cost calculation and not tariffs. In these

calculations, a distinction is made between university and non-university hospitals, the first having not only higher overhead costs, but also increased medical personnel time. Last, we have chosen the friction costs method for estimating the indirect costs, taking into account sick leave for the period the sick worker is not replaced. Likely inclusion of costs of work disability [human capital approach (HCA)] would have raised indirect and total costs significantly. However, it is recognized that the HCA overestimates the production losses for society because in case of absence beyond the friction period (23 weeks), someone looking for work will take over the job and productivity loss will stop.²⁸ Further, we performed a scenario analysis including the costs of presenteeism. Presenteeism is an interesting concept that is receiving increased attention. Our data confirm that patients with gout who have paid work experience substantial problems while at work. This is consistent with the findings by Kleinman, et al.²⁹ that showed that employees with gout processed fewer units per hour/year work (although not significantly compared to employees without gout). However, with regard to our data on presenteeism, caution must be used to calculate workplace or societal productivity costs based on self-reported productivity at work. The assumption of a linear association between self-reported reduced productivity and performed production at the workplace might be an overestimation. Research into the true relation between self-reported and actual performed effect is urgently needed.

One point of interest is to compare COI in gout with studies in non-gout inflammatory arthritis.³⁰ Therefore, we compared our results with data from a review on COI in RA and AS. The annual direct costs of gout (€5647 per patient per yr) in our study were between the weighted average from different studies on RA (€6454 per patient per yr) and AS (€3196 per patient per yr). Similarly, the total costs excluding presenteeism in our study were €6914 as compared with €9224 and €4109 per patient per year in RA and AS, respectively.³¹ Interestingly, the relative distribution over the different cost categories in direct costs was similar in gout as in RA and AS. While a high percentage of patients incur ambulatory care visits, opposed to a minority needing a hospitalization or formal/informal care, the latter drive the costs. Also, the factors contributing to costs were partly comparable in gout and RA or AS because worse physical functioning is an important driver of higher costs in each disease.³²⁻³⁴ The important contribution of CVD to the economic consequences in gout is different. The strong association between CVD and costs in our sample was also reported by Sicras-Mainar, et al., who found that costs in patients with gout increased with increasing prevalence of metabolic syndrome.¹⁴ It is well known that CVD brings an enormous economic burden.^{35,36}

To contribute to the further validation of the GAQ2.0, we explored, as part of our analysis, whether the gout-specific GAQ2.0 (and especially GIS) had an additional value in explaining costs compared to generic patient-reported outcomes. Indeed, the subscale “unmet gout treatment needs” and “gout concern” contributed independently to the costs. This association was already suggested by Sarkin, et al.³⁷ and adds to the construct validity of the GAQ2.0.

Table 4.4 Available literature on cost of illness in gout.

	Source and Population	Design and perspective	Cost-categories and method of assessment	Costing method	Direct costs per patient per year	Indirect costs per patient per year
Wu et al 2008 J Manag Care Pharm (14)	Gout patients >65yr N= 11,935 Age (SD): 71.4 (4.5) Male (%): 73.5% USA	Retrospective analyses insurance cohort with matched controls Third party payer	Direct healthcare resources: inpatient, outpatient emergency services, other medical services and pharmacy costs Assessed through claims.	Claims (tariffs) Year of costing: 2005	Direct gout related costs USD 876 Direct all-cause healthcare costs USD 14,734	not calculated
Brook et al 2006 Curr Med Res Opin (15)	Employed gout patients N=1171 Age: 45.9 (0.5) Male (%): 85.0%	Retrospective analyses insurance cohort Mixed payers and societal perspective	Direct healthcare resources: medical and drug-prescription data assessed through claims Indirect costs: sick leave, short and longterm disability and compensation assessed from payment roll	Direct costs: using claims (tariffs) Indirect costs: calculated from employment payroll system (compensation) Year of costing: 2001-2004	Direct gout related costs: USD 124 Direct all-cause healthcare costs USD 3957	Indirect all-cause costs USD 2885 Indirect all-cause costs in controls: USD 1548
Sicras-Mainar et al 2013 Rheumatol Clin (16)	Gout patients >18yr N= 3130 Age (SD) 55.8 (12.2) Male: 81.1% Spain	Retrospective health insurance database (serving 6 primary care centers, 2 hospitals) Mixed payer & societal perspective	Direct healthcare resources: primary care visits, specialist visits, laboratory tests, imaging, drug prescriptions, days in hospital, emergency department visits; assessed through medical records Indirect costs: Sick leave (days disability and job loss); unclear how assessed	Direct healthcare costs: insurance payments (tariffs) 2007 Indirect costs: using minimum wage	Direct all-cause healthcare costs: EUR 2228	Indirect all-cause costs: EUR 68

Table 4.4 (continued)

	Source and Population	Design and perspective	Cost-categories and method of assessment	Costing method	Direct costs per patient per year	Indirect costs per patient per year
Park et al 2012 Clin Ther (17)	Gout patients >18yr with at least 2 serum uric acid levels. N=352 Age: 61.0 (15) Male: 72.4% USA	Retrospective laboratory, pharmacy and medical service claims database	Direct healthcare resources: Days in hospital, emergency department visits, outpatient clinic visits, physician visits and pharmacy visits with number of unique drug prescriptions were obtained from a integrated health delivery system	Direct healthcare costs were estimated using medical and pharmacy claims. Year of costing: 2010	Direct gout related costs: sUA <6 USD 332 sUA 6-9: USD 352 sUA 9: USD 663 Direct all-cause healthcare costs: sUA <6 USD 11,365 sUA 6-9: USD 11,551 sUA 9: USD 14,474	not calculated
Saseen et al 2012 (18)	3 cohorts based on sUA level <6, 6-9, >9 mg/dL are presented Patients with gouty arthritis N= 15,669 Age: 58 yrs (14.1) Male: 77.3% USA	Retrospective medical and pharmacy service claims database	Direct healthcare resources: Number of outpatient visits, emergency department visits and hospitalizations (and days hospitalized), associated diagnostic testing (including laboratory and radiology) and drug prescriptions	Direct health care costs were estimated using medical and pharmacy claims Year of costing: 2005-2010	Direct gout related costs: <3 attacks: USD 210 >3 attacks: USD 889 Direct all-cause healthcare costs: <3 attacks: USD 10,685 >3 attacks: USD 10,913	not calculated
	2 groups based on infrequent vs frequent gout (<3 or >3 attacks)					

Table 4.4 (continued)

	Source and Population	Design and perspective	Cost-categories and method of assessment	Costing method	Direct costs per patient per year	Indirect costs per patient per year
Halpern et al 2009 J Clin Rheum Curr Med Res Opin (19,20)	Patients with gout flares	Retrospective medical, laboratory, pharmacy and enrollment claims database	Direct healthcare resources: no specific resource was presented (but the authors used claims from: physician office, outpatient hospital, emergency department and hospitalization	Direct healthcare costs were estimated using medical, laboratory and pharmacy claims.	Direct gout related costs: sUA <6 USD 259/505 sUA 6-9: USD 477/696 sUA 9: USD 562/677	not calculated
	N= 18,243 Age: 53.9 yrs (13.5) Male: 84.2 % USA		Additional claims for laboratory tests and drug prescriptions	Year of costing: 2002-2004	Direct all-cause healthcare costs: not calculated.	
Lynch et al 2013 Popul Health Manag (21)	3 cohorts based on sUA level <6, 6-9, >9 mg/dL are presented	Retrospective analyses insurance cohort	Direct healthcare resources: Number of outpatient visits, emergency department visits, hospitalizations (and days hospitalized) and drug prescriptions assessed from insurance claims	Direct healthcare costs were estimated using medical and pharmacy claims	Direct all-cause healthcare costs: <3 attacks: USD 9009 >3 attacks: USD 9748	Indirect all-cause costs: <3 attacks: USD 915 >3 attacks: USD 2021 although it is important to mention the difference between <3 and >3 attacks, is mainly the result of the short-term disability (USD 1663 in the last category)
	Employed gout patients total N=3361 2 cohorts based on <3 or >3 attacks are presented <3 attacks: N=3285 Age: 50.2 (0.2) Male: 82.5 % >3 attacks: N=76 Age: 47.3 (1.1) Male: 94.7 % USA		Indirect costs: sick leave, short and longterm disability and compensation assessed from payment roll	Indirect costs were calculated from employment payroll system (compensation)		

Table 4.4 (continued)

	Source and Population	Design and perspective	Cost-categories and method of assessment	Costing method	Direct costs per patient per year	Indirect costs per patient per year
Wu et al 2012 Am J Ther (22)	Patients with refractory gout, defined as >=3 attacks	Retrospective analyses insurance cohort	Number of outpatient visits, emergency department visits and hospitalizations (and days hospitalized), associated diagnostic testing (including laboratory and radiology) and drug prescriptions	Direct healthcare costs were estimated using medical and pharmacy claims	Direct gout related costs: >=3 att: USD 5924 >=6 att: USD 12620	not calculated
	N=679 Age: 50.4 (9.2) Male: 91.5%				Direct all-cause healthcare costs: >= 3att: USD 17,603 >= 6 att: USD 25,778	
	USA					
	they also presented a subgroup, patients with refractory gout >= 6 attacks				Direct all-cause healthcare costs in controls: USD 4312-6891 (2 figures are given, because of matched cohorts)	
	N=195 Age: 49.9 (9.0) Male 90.3%					

We recognize our study has some limitations. First, the sample size was relatively small, which may have influenced our main results. Second, the results cannot simply be generalized to the whole gout population because only patients of a regional outpatient clinic were included. Likely, our sample has higher costs compared to a population-based cohort and the results are only generalizable to patients under care of a rheumatologist. Notwithstanding, the sample represents the full spectrum of disease, ranging from patients visiting the rheumatologist once per year and/or having experienced only one episode of gouty arthritis during their lifetime to patients with severe tophaceous gout. Third, we were not able to calculate medication costs for the whole sample because of an unforeseen error in linking patient identification numbers with pharmacy data. Therefore, medication costs are not included in the estimates of total direct costs. The estimates of total medication costs in the subsample show that the attributable costs are low. The discrepancy between the high average number of drugs purchased and the relatively low prices is probably a result of the generic prescribing in the Netherlands. The role of medication in calculating direct costs is, to date, much less important in gout than it is in other inflammatory rheumatic diseases.³³ However, with an increasing number of costly drugs becoming available or being developed and marketed, this picture might change dramatically in the near future. Our study shows the COI of gout is considerable and comparable to COI in RA and AS. Further, we show that the main contributors of high direct and indirect costs are CVD, functional disability, and female sex. Our study provides useful data about the costs of gout that can be used in further studies on cost-effectiveness of new treatments.

References

1. Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. *Ann Rheum Dis* 2008;67:960-6.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum* 2011;63:3136-41.
3. Richette P, Bardin T. Gout. *Lancet* 2010;375:318-28.
4. McQueen FM, Chana A, Dalbeth N. Mechanisms of joint damage in gout: evidence from cellular and imaging studies. *Nat Rev Rheumatol* 2012;8:173-81.
5. Stamp LK, Chapman PT. Gout and its comorbidities: implications for therapy. *Rheumatology* 2013;52:34-44.
6. Choi HK, Atkinson K, Karlson EW, et al. Obesity, weight change, hypertension, diuretic use and risk of gout in men: the health professionals follow-up study. *Arch Intern Med* 2005;165:742-8.
7. Lin KC, Tsao HM, Chen CH, et al. Hypertension was the major risk factor leading to development of cardiovascular diseases among men with hyperuricemia. *J Rheumatol* 2004;31:1152-8.
8. Krishnan E, Svendsen K, Neaton J. Long term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008;168:1104-10.
9. Hjortnaes J, Algra A, Olijhoek J, et al. Serum uric acid levels and risk for vascular diseases in patients with metabolic syndrome. *J Rheumatol* 2007;34:1882-7.
10. Dalbeth N, So A. Hyperuricaemia and gout: state of the art and future perspectives. *Ann Rheum Dis* 2010;69:1738-43.
11. Meerding WJ, Bonneux L, Polder JJ, et al. Demographic and epidemiological determinants of healthcare costs in Netherlands: cost of illness study. *BMJ* 1998;317:111-5.
12. Wu EQ, Patel PA, Yu AP, et al. Disease-related and all-cause health care costs of elderly patients with gout. *J Manag Care Pharm* 2008;14:164-75.
13. Brook RA, Kleinman NL, Patel PA, et al. The economic burden of gout on an employed population. *Curr Med Res Opin* 2006;22:1381-9.
14. Sicras-Mainar A, Navarro-Artieda R, Ibanez-Nolla J. Resource use and economic impact of patients with gout: a multicenter, population-wide study. *Reumatol Clin* 2013;9:94-100.
15. Park H, Rascati K, Prasla K, et al. Evaluation of health care costs and utilization patterns for patients with gout. *Clin Ther* 2012;34:640-52.
16. Saseen JJ, Agashivala N, Allen RR, et al. Comparison of patient characteristics and gout-related healthcare resource utilization and costs in patients with frequent versus infrequent gouty arthritis attacks. *Rheumatology* 2012;11:2004-12.
17. Halpern R, Mody RR, Fuldeore MJ, et al. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. *Curr Med Res Opin* 2009;25:1711-9.
18. Halpern R, Fuldeore MJ, Mody RR, et al. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. *J Clin Rheumatol* 2009;15:3-7.
19. Lynch W, Chan W, Kleinman N, et al. Economic burden of gouty arthritis attacks for employees with frequent and infrequent attacks. *Popul Health Manag* 2013;16:138-45.
20. Wu EQ, Forsythe A, Guerin A, et al. Comorbidity burden, healthcare resource utilization and costs in chronic gout patients refractory to conventional urate-lowering therapy. *Am J Ther* 2012;19:e157-66.
21. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743.
22. Boers M, Jacobs JW, van Vliet Vlieland TP, et al. Consensus Dutch health assessment questionnaire. *Ann Rheum Dis* 2007;66:132-3.
23. Hirsch JD, Lee SJ, Terkeltaub R, et al. Evaluation of an instrument assessing influence of Gout on health-related quality of life. *J Rheumatol* 2008;35:2406-14.
24. Spaetgens B, van der Linden S, Boonen A. The Gout Assessment Questionnaire 2.0: cross-cultural translation into Dutch, aspects of validity and linking to the International Classification of Functioning, Disability and Health (ICF). *Rheumatology* 2014;53:678-85.
25. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353-65.

26. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. [Guideline for cost-of-illness study: methods and guideline-rates for economic evaluations in health care]. [Book in Dutch] Rotterdam: College voor Zorgverzekeringen; 2010.
27. College voor Zorgverzekeringen. [Drug prescription costs by College voor Zorgverzekeringen]. [Internet. Accessed October 9, 2014. Website in Dutch]. Available from: www.medicijnkosten.nl.
28. Koopmanschap MA, Rutten FF, van Ineveld BM, et al. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995;14:171-89.
29. Kleinman N, Brook R, Patel P, et al. The impact of gout on work absence and productivity. *Value Health* 2007;10:231-7.
30. Boonen A, Mau W. The economic burden of disease: comparison between rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009;4 Suppl 55:112-7.
31. Franke LC, Ament AJ, van de Laar MA, et al. Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol* 2009;4 Suppl 55:118-23.
32. Yelin E, Wanke LA. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum* 1999;42:1209-18.
33. van Jaarsveld CH, Jacobs JW, Schrijvers AJ, et al. Direct cost of rheumatoid arthritis during the first six years: a cost-of-illness study. *Br J Rheumatol* 1998;37:837-47.
34. Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. *Arthritis Rheum* 2002;46:223-31.
35. Leal J, Luengo-Fernandez R, Gray A, et al. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J* 2006;13:1610-9.
36. Youman P, Wilson K, Harraf F, et al. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;21 Suppl 1:43-50.
37. Sarkin AJ, Levack AE, Shieh MM, et al. Predictors of doctor-rated and patient-rated gout severity: gout impact scales improve assessment. *J Eval Clin Pract* 2010;16: 1244-7.

Supplementary material

Appendix A. Costs per unit for contacts with health professionals, admissions in healthcare facilities, non-medical resource use and paid productivity loss

Consultation (number of visits)	Cost per visit (€)
Rheumatologist	129
University Hospital	64
General Hospital	28
General Practitioner	
Other medical specialist	129
University Hospital	64
General Hospital	80
Psychologist	
Therapy (hours of therapy)	Costs per hour (€)
Physiotherapy	36
Exercise therapy	35
Occupational therapy	22
Rehabilitation therapy	110
Admission to care facility (days admitted)	Costs per day (€)
Hospital	
University Hospital	575
General Hospital	435
Rehabilitation Centre	340
Non-medical resource use (hours of help)	Costs per hour (€)
Household care (professional)	35
Informal care by family and friends	12,50
Paid productivity loss (hours of work loss)	Costs per hour of work loss (€)†
	8,76 – 39,13
	adjusted by sex and age categories

Chapter 5

The importance of 'state-of-the-art' cost-of-illness studies. Comment on: The economic burden of gout: A systematic review.

Bart Spaetgens, Annelies Boonen

Semin Arthritis Rheum. 2016;45(4):e9.

We read with great interest the paper on the economic burden of gout by Rai et al.¹ in *Seminars in Arthritis and Rheumatism*. In this meticulously performed systematic review the authors provide complete and useful insight into the current knowledge on the costs-of-illness (COI) in patients with gout. One of their main findings is that the economic impact of the disease is important, but likely still underestimated. Two main reasons are mentioned by the authors. First, in most cases, data on direct costs do not provide a complete picture, as they are limited to the direct medical costs (medical and pharmacy costs), while the direct non-medical costs have as yet not been estimated. Second, data on indirect costs are scarce and incomplete. On this line, only data on productivity loss due to time absent from work (absenteeism), but not on productivity loss due to impairment while at work (presenteeism) were available. Therefore, the authors recommend performing additional research, as both direct non-medical as well as full range of indirect costs are relevant for the total societal COI. In this letter, we wish to point to our recent data that partly respond to the authors' call for additional research. We performed a COI study in Dutch patients with gout under care of a rheumatologist, in which we comprehensively calculated all-cause direct and indirect costs, including (I) direct costs related to non-medical resource use and (II) indirect costs including absenteeism and presenteeism.² We found that 56.3% of the direct costs (46.0% of the total costs) were constituted by the non-medical resource use, representing costs of professional house hold care (\$1981/patient/year (25.6%)) and informal care by family and friends [\$2375/patient/year (30.7%)]. In direct costs of absenteeism and presenteeism were estimated \$1745/patient/year and \$5483/patient/year, being 18.3% and 48.1% of the total COI, respectively. We agree with the authors the substantial costs from formal but also informal care giving should be accounted for in a total cost calculation from a societal perspective, although they cannot simply be transferred to other healthcare systems and other cultures. Secondly, we believe it is indisputable to also include costs related to productivity loss due to impairment while at work, rather than absenteeism only. As such, presenteeism is an interesting and relevant concept of which the potential productivity costs should at least be considered.³ Nevertheless, we believe caution is needed when doing so, as not all presenteeism measures accurately reflect real loss of productivity at the workplace.⁴ In conclusion, we support the authors' conclusion that the overall economic impact of gout is not yet adequately reflected in the current available COI studies and that with these data the societal costs are likely under estimated. By comprehensively investigating direct and indirect costs, including non-medical resource use and productivity loss while at work, (which we show both highly drive the costs), eventually the complete picture becomes visible. Only then, COI studies will be useful for incorporation in economic evaluations and can provide valuable information for policy development and rational healthcare resource allocation.

References

1. Rai SK, Burns LC, DeVera MA, et al. The economic burden of gout: a systematic review. *Semin Arthritis Rheum* 2015;45:75-80.
2. Spaetgens B, Wijnands JM, van Durme C, et al. Cost of illness and determinants of costs among patients with gout. *J Rheumatol* 2015;42:335-44.
3. Tang K, Boonen A, Verstappen SM, et al. Worker productivity outcome measures: OMERACT filter evidence and agenda for future research. *J Rheumatol* 2014;41:165-76.
4. Kessler RC, Maclean JR, Petukhova M, et al. The effects of rheumatoid arthritis on labor force participation, work performance, and healthcare costs in two workplace samples. *J Occup Environ Med* 2008;50:88-98.

Chapter 6

Health and utilities in patients with gout under the care of a rheumatologist

Bart Spaetgens, An Tran-Duy, José Wijnands, Sjef van der Linden, Annelies Boonen
Arthritis Care & Research 2015;67:1128-1136.

Abstract

Objectives

To compare limitations in health between Dutch patients with gout and the general population and to determine factors influencing societal and patient values for health as assessed with different utility approaches.

Methods

A cross-sectional study was done among 110 patients with gout under the care of a rheumatologist, with patients completing the EuroQol 5-domain instrument (EQ-5D), the EQ-5D visual analog scale (EQ-5D VAS), and the Short Form 6-dimensions health survey (SF-6D). Scores on EQ-5D domains were compared with age- and sex-matched general population data. Agreement between utility measures was assessed using the intraclass correlation coefficient (ICC). Mixture modeling was used to assess factors associated with the different approaches to assess utility.

Results

Compared to the general population, gout patients reported more limitations in mobility (66% vs. 12%), self-care (24% vs. 8%), daily activities (49% vs. 24%), and pain (76% vs. 45%), but equal anxiety/depressive symptoms (18% vs. 19%). For patients with gout, utilities were reduced: the mean, median, and interquartile range, respectively, were 0.74, 0.81, and 0.69-0.84 for EQ-5D, 0.69, 0.67, and 0.59-0.81 for SF-6D, and 66, 70, and 57-77 for EQ-5D VAS. ICC agreement between each pair of utilities was only moderate (0.52-0.59). Only minor differences were seen in the type of variables associated with each utility approach, with worse Health Assessment Questionnaire scores, cardiovascular disease (CVD), gout concern, and gout pain consistently associated with lower utility. The strength of contribution of these variables, however, differed among the 3 approaches.

Conclusion

Patients with gout experience substantially impaired health compared to the general population. Although absolute values of utility varied between instruments and perspectives, functional disability, CVD, and higher gout impact contributed to utility independently of which instrument was used.

Introduction

Gout is a chronic inflammatory rheumatic disease manifesting itself through a varying disease spectrum, comprising recurrent acute arthritis, chronic arthritis, and tophaceous gout. Gout causes pain and functional disability that become irreversible when joint damage due to inflammation and/or deposition of tophi progresses. In addition, gout is associated with a number of comorbidities, such as obesity, hypertension, cardiovascular disease (CVD), and chronic kidney disease.^{1–3} Both articular manifestations and extraarticular comorbidities contribute to the impact of gout on overall health-related quality of life (HRQOL) of patients.^{4–6}

As a part of the Global Burden of Diseases initiative in 2010, it was reported that gout-related disability-adjusted life years (DALYs) increased significantly between 1990 and 2010.⁷ As the prevalence of gout may not have increased substantially,⁸ this rise in DALYs might be attributed both to the ageing population and to lifestyle changes that enhance coexisting comorbidities, which might influence disability significantly.

Parallel with the rising burden of gout, a broad range of initiatives emerged to improve outcomes, such as the development of new urate lowering drugs, recommendations to treat to a specific (low) uric acid target, and programs to enhance medication adherence.⁹ A key element in the evaluation of such initiatives is the extent to which they improve overall health and DALYs or quality-adjusted life years (QALYs). Assessing health is not only important from the patient perspective, but also from the societal perspective, as both provide essential information for health care providers, health care insurers, and policy makers when deciding on priorities and resource allocation in times when budgets are increasingly restricted.¹⁰

In the context of decision making, utility is considered to be the appropriate approach to assess value for health.¹¹ A health utility is a cardinal measure of HRQOL and represents the strength of a person's preference for a health state. By consensus, a utility is summarized into a single value between 0 and 1, representing death and perfect health, respectively. Importantly, utility values for health states can be elicited from the perspective of the patients themselves (i.e., those who experience the disease) or the general population (i.e., those who are able to judge objectively and are not prejudiced when comparing and choosing between health states).¹²

Although the concept of the utility is attractive because it can be used to compare the impact of disease or interventions on health, independent of the specific condition, obtaining values of utility is challenging, as the different approaches that have been developed have shown different results.^{13,14} The most commonly used and feasible health utility instruments are the EuroQol 5-domain instrument (EQ-5D)¹⁵ and the Short Form 6-dimensions health survey (SF-6D; derived from the Short Form 36 health survey [SF-36]).¹⁶ These indirect approaches are very attractive, since the health state surveys can be completed by patients, and publicly available algorithms are available to compute societal values (utilities) for the health states.¹⁷ In addition, the EQ-5D visual analog scale (EQ-5D VAS) is available as part of the EQ-5D instrument.

It displays the patient valuation of health on a 0-100 vertical rating scale and thus represents a direct utility value from the patient's perspective.

In gout, several studies have addressed HRQOL,¹⁸ but only 2 studies have reported on utilities.^{4,19} The first study compared scores of 2 indirect societal health utilities (EQ-5D and SF-6D) and 2 direct patient utilities (time trade off and standard gamble) and reported important differences. Some univariable comparisons across specific patient characteristics were presented, but no extensive analyses were performed to understand clinical variables contributing independently to utility. In the second study, only the SF-6D was reported, but multivariable analyses were performed and revealed that flares and self-reported tophi independently contributed to worse utility after adjusting for age, sex, disease duration, and (according to a sensitivity analysis) comorbidities. However, the independent influence of comorbidities was not shown. Lastly, no data are available that discuss the impact of gout on health compared to healthy subjects of the same age and sex.

In this study we first compared the health of patients with gout with that of the general population in The Netherlands and next explored utility as well as factors influencing utility, assessed by different approaches and perspectives. We hypothesized that 1) patients with gout have lower HRQOL compared to population controls for all domains except for mental health, 2) different instruments and perspectives to assess utility provide different values, and 3) in addition to Health Assessment Questionnaire (HAQ) score, comorbidities as well as concerns about gout always contribute to utility but with a stronger influence of gout concerns in the patient perspective.

Patients and methods

Patients attending an outpatient rheumatology clinic between April 2011 and April 2012 and registered with a diagnosis of gout were invited to participate in this cross-sectional study, which comprised an extensive clinical examination, chart review, and questionnaire survey. The study followed the principles of the Declaration of Helsinki and was approved by the ethics committee of the Maastricht University Medical Centre. Prior to collection of the data, all participating patients provided written informed consent.

Data collection

During the study visit, demographic and clinical data on age, sex, disease duration, number of gout flares in the previous year, and current treatment with uric acid lowering therapy were collected. Chronic kidney disease was defined as glomerular filtration rate <60 ml/minute/1.73m². The presence of CVD (consistent with the Framingham definition²⁰ comprising coronary artery disease, stroke, peripheral artery disease, or heart failure) and diabetes mellitus was based on self-report during the

interview, as well as on information about medication and/or previous medical history as found in the pharmacy's output, if available. During a clinical examination, the presence of tophi and body mass index were assessed. Finally, the patients completed a series of questionnaires: the HAQ^{20,21} to assess physical functioning, the Gout Assessment Questionnaire 2.0 (GAQ2.0)²² to reflect gout-specific impact on functioning and health, the EQ-5D to assess utility, which included EQ-5D VAS, and the SF-36,²³ which allowed calculating the health utility with SF-6D.^{16,24} Validated Dutch versions were available for all of these questionnaires.²⁵⁻²⁸

HAQ

The HAQ consists of 20 items, using a Likert scale to assess impairments in physical functioning during the previous 7 days across 8 domains. The total score is the sum of the highest score per category, divided by 8, and represents the HAQ disability index (range 0-3). Higher scores indicate more functional disability.

GAQ2.0

The GAQ2.0 consists of 2 parts and 31 items. The first part, the gout impact scale, determines current impact of gout in 5 subscales: gout concern overall (4 items), gout medication side effects (2 items), unmet gout treatment needs (3 items), well-being during attack (11 items), and gout concern during attack (4 items). The scores range 0-100, with higher scores indicating stronger impact on quality of life. In the second part, patients report whether they had gout flares (yes/no) and to what extent gout affected physical and mental health, quality of life, and pain in the previous 4 weeks on a 6-point Likert scale (where 1=very poor and 6=excellent). The last 2 questions address the level of pain or disease activity due to gout (where 1=no pain, no disease activity and 10=severe pain, severe disease activity).

Instruments to assess utility

The EQ-5D asks about problems in the previous week with mobility, self-care, daily activities, pain, and anxiety/depression. Each domain is scored on a 1-3 scale (where 1=no problems, 2=some/moderate problems, and 3=severe problems). The resulting health states can be converted using country-specific scoring functions into a single utility index. Because the conversion functions were derived from studies in the general population, EQ-5D utilities represent the societal perspective.²⁹ The Dutch EQ-5D utility, which was used for the current analyses, ranges from -0.33 (worst health) to 1.00 (perfect health).²⁵

The SF-36 consists of 36 questions across 8 different domains (physical functioning, role limitation due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems, and mental health) to measure HRQOL over the previous 4 weeks.²³ Items are scored on a Likert scale

(range 2-6). Similar to the EQ-5D, a preference weighted value or utility conversion tool is available, the SF-6D, based on 11 items from 6 dimensions.^{24,30} This conversion formula is also derived from the general population, and therefore the SF-6D utility represents the societal value of health. In contrast to the EQ-5D, no countryspecific conversion tools are available.

The EQ-5D VAS represents the patient perspective of utility, as patients directly evaluate their current health state on a 0-100 vertical rating scale (where 0=worst imaginable health state and 100=best imaginable health state). To convert this score into a classic utility value between 0 and 1, the original values are divided by 100.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the study sample. Frequency of moderate and severe limitations (2 or 3 score) on the EQ-5D health domains of the patients with gout were compared with the frequencies in the general Dutch population, using indirect standardization to achieve the same distributions for age (5 categories) and sex. For each pair of the 3 utility approaches considered, first the level of absolute agreement was calculated using single-measure, 2-way random effects and intraclass correlation coefficients (ICCs), and then Bland-Altman plots were used to visualize the distribution of the difference against the mean utility.³¹

As EQ-5D and SF-6D have a highly skewed, multimodal, and right-bounded distribution, the mixture modeling approach, as proposed by Hernandez Alava et al., was used to understand which factors were associated with each of the 3 utilities.³² Given the number of observations (n=110) and number of potential explanatory variables, we decided that the maximal number of latent classes (ordered subcategories within the range of utility values that likely have different relations with the explanatory variables) should not exceed 4. Therefore, we fitted mixture models to data with different numbers of latent classes (to a maximum of 4), assuming a normal distribution of utility within each class. We determined the optimal number of latent classes based on Akaike's information criteria (AIC)³³ and the similarity of the classes, i.e., if 2 or more classes had the same parameters, they could be pooled.³⁴ Since 2 latent classes turned out to be the best, we assumed a binomial logit mode for the probability of the latent class membership and fitted a logistic regression model to the nominal data representing the 2 classes. Conditional on a specific class, we fitted a linear regression model to the actual values of health utility within each class.

Because of the large number of collected explanatory variables (as discussed in data collection), the power of detecting significant effects might be reduced when all variables are included in the multivariable analyses. Therefore, only the variables that remained as candidates after univariable analyses were included in the multivariable analyses: age, sex, disease duration, HAQ score, gout concerns (overall and during attack), presence of tophi, number of gout flares in the previous year, and a history of

CVD. These remaining variables were tested for collinearity and correlation and further selected for the final model using a stepwise manual procedure based on AIC and likelihood ratio tests. For each linear regression model, we checked the assumption of normality distribution and heteroscedasticity of the residuals using the Shapiro-Wilk and studentized Breusch-Pagan tests, respectively. All the statistical analyses were performed using the R program.³⁵

Results

Patients

Sixteen of the 126 patients (13%) who participated in this study were excluded from analysis because of incomplete data from the EQ-5D and SF-6D (missing questionnaires, $n=9$; multiple missing items in SF-36, $n=7$). The characteristics of the 110 gout patients contributing to the current analyses are presented in Table 6.1. Those who were excluded due to missing data were somewhat older (mean age 71.4 versus 65.9 years; $p=0.048$).

Health compared to the general population

Figure 6.1 shows the percentages of patients with moderate or severe problems in the 5 domains of the EQ-5D: 65.6% (mobility), 23.8% (self-care), 49.2% (daily activity), 75.6% (pain), and 17.9% (anxiety/depression). These percentages are substantially higher than those of the age- and sex-matched general population for mobility (12.4%), self-care (7.7%), daily activity (24.1%), and pain (44.8%), but not for anxiety/depression (19.1%). The mean EQ-5D VAS in the gout patient group was 66.1 (median 70.0, interquartile range [IQR] 59.7–75.3), which is substantially lower than that of the age and sex-matched general population (mean 79.5).

Table 6.1 Characteristics of the 110 gout patients.

Characteristics	n=110
Age (years), mean $\pm$ S.D. [range]	65.8 $\pm$ 10.5 [42-89]
Male sex; n (%)	94 (85.5)
Disease duration (years), mean $\pm$ S.D. [range]	11.4 $\pm$ 10.8 [0.5-52]
Tophaceous gout, n (%)	50 (45.5)
No. of gout flares last year, mean $\pm$ S.D. [range]	3.1 $\pm$ 7.8 [0-25]
Currently on uric acid lowering therapy, n (%)	77 (70.0)
Body Mass Index (kg/m ²), mean $\pm$ S.D. [range]	29.8 $\pm$ 5.0 [22-47]
Diabetes, n (%)	26 (23.6)
Chronic kidney disease, n (%)	11 (10.0)
Cardiovascular disease, n (%)	34 (30.9)
HAQ-DI (0-3); mean $\pm$ S.D.	0.63 $\pm$ 0.58
GAQ2.0 (Gout impact scales: 0-100); mean $\pm$ S.D.	
Gout concern overall	53.9 $\pm$ 22.4
Gout medication side effects	45.3 $\pm$ 21.3
Unmet gout treatment need	48.1 $\pm$ 13.8
Well-being during attack	45.0 $\pm$ 11.3
Gout concern during attack	44.7 $\pm$ 22.1
GAQ2.0: physical health past 4 weeks (1-6)	3.5 $\pm$ 3.9
GAQ2.0: mental health past 4 weeks	2.8 $\pm$ 1.0
GAQ2.0: quality of life past 4 weeks	3.1 $\pm$ 1.0
GAQ2.0: disease activity due to gout (1-10)	4.2 $\pm$ 2.6
GAQ2.0: pain due to gout (1-10)	3.7 $\pm$ 2.6
EQ-5D, mean $\pm$ S.D.,(median) $\pm$ [IQR]	0.74 $\pm$ 0.23 (0.81) $\pm$ [0.69-0.84]
SF-6D, mean $\pm$ S.D.,(median) $\pm$ [IQR]	0.69 $\pm$ 0.13 (0.67) $\pm$ [0.59-0.81]
EQ-5D Visual Analog Scale (VAS), mean $\pm$ S.D.,(median) $\pm$ [IQR]	66.1 $\pm$ 15.4 (70) $\pm$ [57-77]

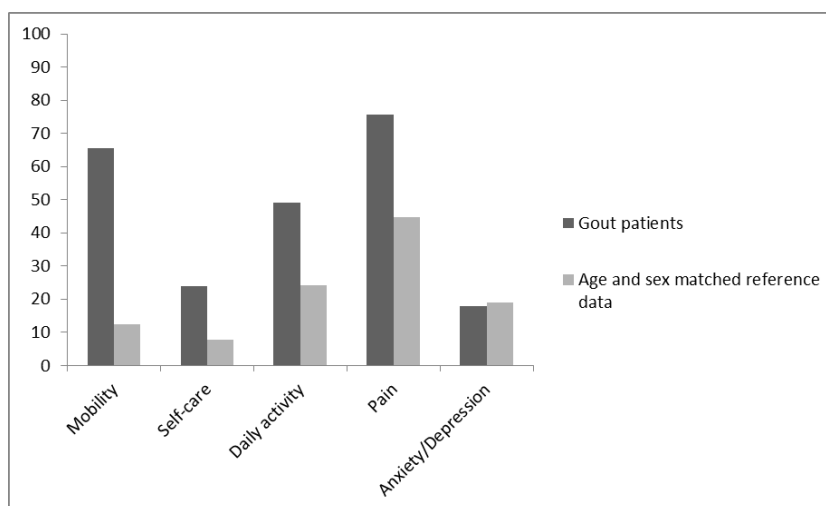


Figure 6.1 Percentage of patients with gout reporting moderate or severe problems compared to the age- and sex-matched general population.

Utilities and agreement between utilities

For patients with gout, the mean, median, and IQR, respectively, were 0.74, 0.81, and 0.69-0.84 for EQ-5D; 0.69, 0.67, and 0.59-0.81 for SF-6D; and 66, 70, and 57-77 for EQ-5D VAS. As shown in Figure 6.2, utility values for EQ-5D, SF-6D, and EQ-5D VAS were non-normally distributed and showed a bimodal pattern.

Only moderate agreement was observed between the utility instruments, with ICC 0.52 (95% confidence interval [95% CI] 0.32-0.67) between EQ-5D and SF-6D, 0.55 (95% CI 0.35-0.69) between EQ-5D and EQ-5D VAS, and 0.59 (95% CI 0.45-0.71) between SF-6D and EQ-5D VAS. Figure 6.3 shows the Bland-Altman plots for each comparison of utilities. The mean $\pm$ SD difference between both societal utilities (EQ-5D minus SF-6D) was 0.07 $\pm$ 0.16, between patient and societal utility (EQ-5D VAS minus EQ-5D) 0.08 $\pm$ 0.18, and for EQ-5D VAS minus SF-6D -0.02 $\pm$ 0.13. The lower and upper 95% limits of agreement were quite large, -0.24 to 0.39 for both societal utilities (EQ-5D minus SF-6D), -0.28 to 0.44 for EQ-5D VAS minus EQ-5D, and -0.27 to 0.22 for the difference between patient and societal utility (EQ-5D VAS minus SF-6D).

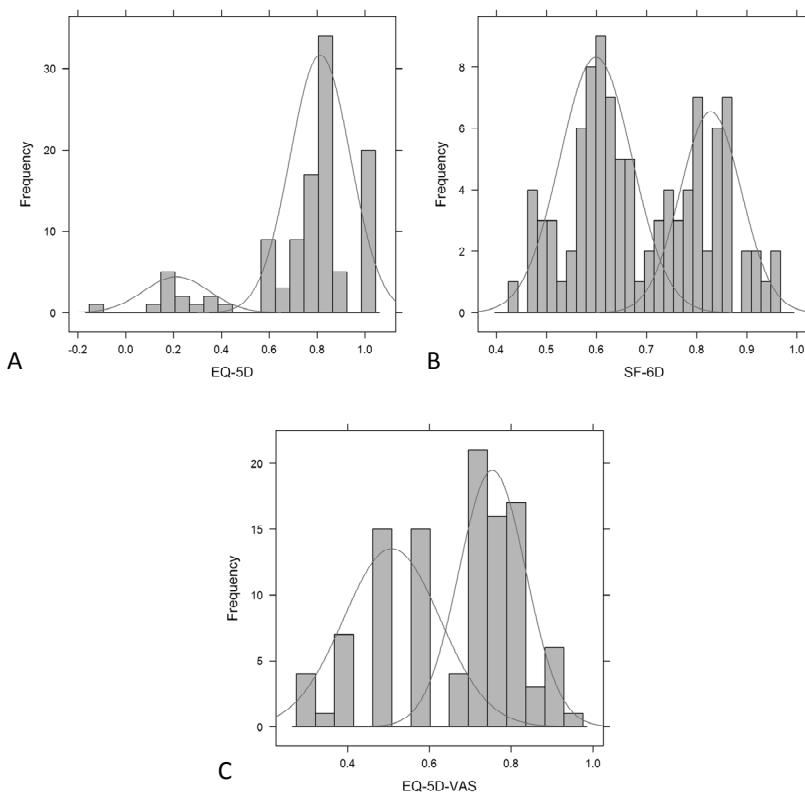


Figure 6.2 Observed distributions and the 2-class normal fitted overlying curve after applying mixture modeling. A, EuroQol 5-domain instrument (EQ-5D). B, Short Form 6-dimensions health survey (SF-6D). C, EQ-5D visual analog scale (EQ-VAS).

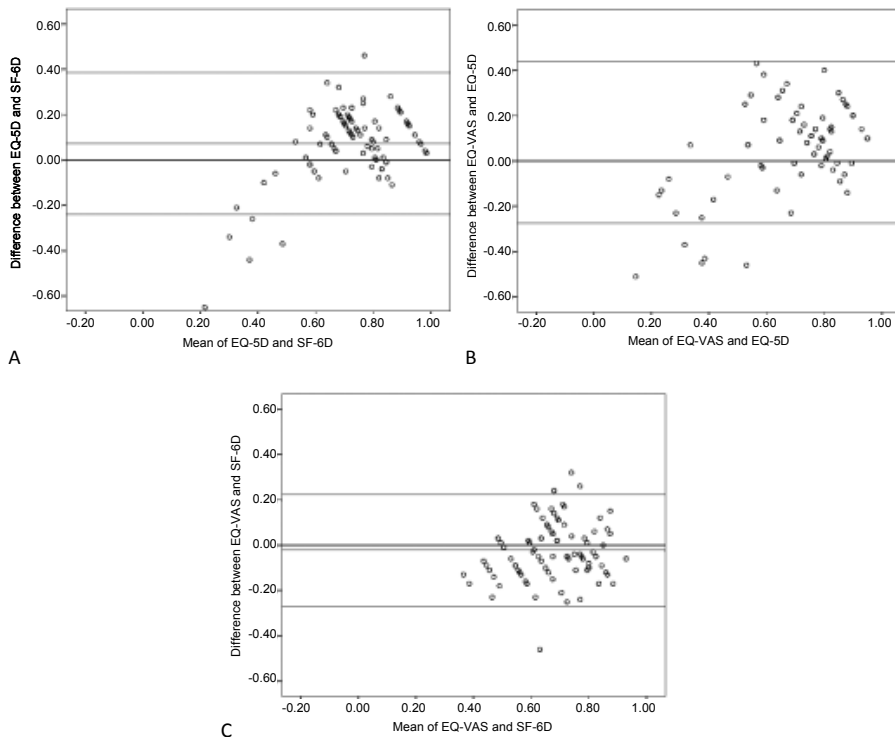


Figure 6.3 Bland-Altman plots to explore agreement between EuroQol 5-domain instrument (EQ-5D) and Short Form 6-dimensions health survey (SF-6D) (A), EQ-5D visual analog scale (EQ-VAS) and EQ-5D (B), and EQ-VAS and SF-6D (C). Perfect agreement is represented by the black line ($y = 0$). The 3 grey lines represent mean difference, and mean $\pm 2 \times \text{SD}$ difference between the utility scores.

Variables explaining utilities

First, to check whether the mixture modeling approach outperformed standard linear regression, we performed a confirmatory analysis that showed the assumptions of normality and homoscedasticity of the errors in any linear model for the latent classes were satisfied. Also, the mixture models outperformed the standard 1-class linear models, as they had lower AIC and mean absolute errors, indicating better fit.

The mixture analysis classified 12 and 98 observations in the first (worse health) and second (better health) class of EQ-5D and EQ-5D VAS and 31 and 69 observations in the first and second class for SF-6D, respectively. The expected probabilities of class membership were 11% and 89% for class 1 and 2, respectively, of EQ-5D, 31% and 69% for class 1 and 2 of SF-6D, and 13% and 87% for class 1 and 2 of EQ-5D VAS. Mean utility scores for class 1 and 2 were 0.19 and 0.81, respectively, for EQ-5D, 0.58 and 0.73 for SF-6D, and 0.42 and 0.69 for EQ-5D VAS. Table 6.2 shows the logistic regression analysis

to determine which factors affect probability of class membership. HAQ score significantly affected the probability of class membership for EQ-5D, and gout concern during attack affected the probability of class membership for EQ-5D VAS, although the latter was not significant ($p=0.08$). For SF-6D, no significant factors affected probability of class membership.

Table 6.2 Explanatory variables and parameter estimates of statistical models for the 3 approaches for health utility of patients with gout.

Explanatory variable		Estimate (SE)	p-value
<i>EQ-5D</i>			
<i>Logistic model:</i>			
Probability of class membership (using class 1 as baseline)			
	(Intercept)	3.667 (0.688)	<0.001
	HAQ	-1.833 (0.576)	0.001
<i>Linear model</i>			
Latent class 1	No significant coefficient estimates		
Latent class 2	CVD	-0.043 (0.019)	0.030
	HAQ	-0.120 (0.019)	<0.001
	Gout Concern Overall	-0.015 (0.004)	<0.001
	GAQ pain	-0.007 (0.004)	0.090
<i>SF-6D</i>			
<i>Logistic model</i>			
Probability of class membership (using class 1 as baseline)			
No significant coefficient estimates			
<i>Linear model</i>			
Latent class 1	CVD	-0.033 (0.014)	0.021
	HAQ	-0.076 (0.016)	<0.001
	Gout Concern Overall	-0.015 (0.003)	<0.001
	Gout Concern Attack	-0.010 (0.003)	0.002
Latent class 2	HAQ	-0.121 (0.013)	<0.001
	Gout Concern Overall	-0.011 (0.004)	0.004
	GAQ pain	-0.008 (0.004)	0.040
<i>EQ-VAS</i>			
<i>Logistic model</i>			
Probability of class membership (using class 1 as baseline)			
	(Intercept)	3.330 (0.834)	<0.001
	Gout Concern Attack	-0.247 (0.143)	0.083
<i>Linear model</i>			
Latent class 1	Age	0.005 (0.001)	0.004
	Female sex	-0.167 (0.034)	0.001
	Gout Concern Overall	-0.025 (0.006)	0.002
Latent class 2	CVD	-0.107 (0.017)	<0.001
	HAQ	-0.066 (0.020)	0.002
	GAQ pain	-0.017 (0.005)	<0.001

Table 6.2 also shows that further linear regressions of each class of the EQ-5D could not find significant explanatory variables to account for variation in utility within latent class 1, while CVD, HAQ score, and overall concern with gout were significantly, negatively related to EQ-5D in class 2. For SF-6D, within class 1, CVD, HAQ score, and gout concerns, and in class 2, HAQ score, gout concerns, and pain were significantly associated with variation in SF-6D. For the EQ-5D VAS, within class 1, age, female sex, and more gout concerns, and within class 2, CVD, HAQ score, and pain were significantly associated with variation in EQ-5D VAS.

To improve overall interpretability of the results of the mixture models, a calculator was developed based on the regression coefficients, which enables understanding the influence of changing specific variables. Of specific interest was the question to what extent CVD, the only comorbid disease retained in the model, would have a net contribution to utility. Using the calculator, it was easy to see that at HAQ scores of 0 and 3, the expected EQ-5D values in patients with or without CVD were -0.04 and -0.01, respectively, holding values of other factors constant. For EQ-5D VAS and SF-6D, the expected values in patients with and without CVD were, respectively, -0.08 and -0.01, irrespective of HAQ score. For potentially insightful examples based on the calculator, see Supplementary Material, Appendix A.

Discussion

This study indicates a great burden of disease for patients with gout under the care of a rheumatologist, as we found that a strikingly higher number of patients experienced limitations in all areas of health considered by the EQ-5D, except for the domain anxiety/depression, than in the age and sex-matched general population. Further, patients with gout indicate a significantly worse overall health utility assessed by EQ-5D VAS compared to population controls.

When exploring the value for health utilities by comparing different approaches and perspectives, we first found that different methods provide different utility values. Only moderate agreement between EQ-5D, SF-6D, and EQ-5D VAS was found, as can be seen in the Bland-Altman plots (Figure 6.3). While the average difference between the instruments was not great, differences in scores for individuals with health states at both ends of the scale could be very large and reach 0.65 in the most extreme case. This difference is huge when considering the small range of the utility scales. The discrepancy could not be simply attributed to the difference in patient (EQ-5D VAS) and societal (EQ-5D and SF-6D) perspectives, as the difference between both societal utilities was also large. While the aspects of health considered in the instruments differs somewhat, the problem mainly stems from the difference in the mathematically possible range of the scales. For example, in our study, negative values as low as -0.11 (indicating a health state worse than death) for EQ-5D were found, while the lowest values for SF-6D and EQ-5D VAS were 0.43 and 0.30, respectively. Differences in utility

between approaches have been shown in one other study in gout⁴ and in several other diseases.³⁶

When incorporating utilities in economic modeling, understanding which variables contribute to utility is important, because in the development of models, the clinical outcomes are mapped on (or linked to) health utilities.³⁷ Consistent with our hypothesis, we found that HAQ score, comorbidity (CVD), and several gout-specific characteristics contributed to all assessments of utility. In contrast to our hypothesis, the presence of tophi or number of gout flares was not associated with worse utility in our study. In the literature, one other study found that the presence of tophi as well as gout flares (>4 per year) was associated with worse utility (SF-6D) after adjusting for age, sex, time since diagnosis, and (in an additional analysis) comorbidities.⁴ Differently from the previous study, we included gout concerns from the GAQ2.0, which likely captured the negative influence of tophi and attacks. Older age and male sex were associated with better health utility only in the patient perspective (EQ-5D VAS), illustrating that when patients evaluate their overall health status, they are implicitly influenced by their age and sex. This influence is not explicitly reflected in the scores of the major health domains represented by EQ-5D and SF-6D.

Despite overall consistency in factors contributing to the 3 utility approaches, the role and level of contribution differed substantially. The influence of HAQ score was especially strong on EQ-5D utility, where HAQ score importantly influenced the probability of belonging to the group with worse utility. This stronger influence of functional disability on EQ-5D can be explained by the content of the EQ-5D, of which the domains mobility, self-care, daily activity, and pain are likely to be affected by diseases associated with functional disability. Not surprisingly, and as can be seen in Figure 6.1, these domains were most frequently affected by gout. In the direct patient perspective (EQ-5D VAS), gout concerns had a stronger influence on the chance that a patient would belong to the group with worse utility, which reflects the fact that patients implicitly weigh their needs and concerns when assessing utility. Lastly, of the comorbidities explored, only the presence of CVD influenced utility significantly. The absolute influence was somewhat stronger on the EQ-5D VAS and EQ-5D when compared to SF-6D. The overall absolute impact of comorbidity, however, as illustrated by the calculator was not stronger than the influence of HAQ score or aspects of gout impact. Our findings that both comorbidity, as well as gout itself, independently contribute to lower utility values add fuel to the ongoing debate about whether comorbidities or the disease itself explain health outcomes, including HRQOL and utility.

Some limitations of this study need to be addressed. First, patients were recruited from a single centre and all patients were under the care of a rheumatologist. Therefore, generalizing our results to all patients with gout is not possible. Nevertheless, our patients represent the full spectrum of disease, varying from one episode of gouty arthritis to severe tophaceous gout. Moreover, as insight in utilities is especially relevant for calculating QALYs and use in economic evaluations, innovative

pharmacologic and nonpharmacologic treatments were (and probably will be) developed specifically for this group of patients.

Second, the small sample size is an important limitation that led to a somewhat imbalanced distribution over the latent classes, making it more difficult and more uncertain to investigate factors that influence health utility in the particular smaller latent classes. We used a stepwise method to choose the preselected (among univariable associated) explanatory variables, making it possible to investigate explanatory factors in depth, despite the small sample size. However, in stepwise regression not all the subsets of variables are considered, and the results depend on the order of the variables that are added in the forward steps, especially when the predictors are highly correlated with each other. In our study, the degree of correlation between the explanatory variables was low to moderate and collinearity did not occur. Nevertheless, it is likely that some of the explanatory variables (for example CVD and HAQ score) are probably not completely independent from each other. Furthermore, we expected that the influence of the order of variable entry on the variable selection would be small.

Third, self-report of comorbidities might have resulted in misclassification. However as self-report was assessed during an interview (and not solely using a questionnaire), and as the comorbidities of interest have been shown less liable to inaccuracy, we think misclassification could be limited.^{38,39} Finally, this is a cross-sectional study and therefore knowledge about how utility values change over time in patients with gout could not be obtained. As our sample included patients with a broad range of disease durations, this knowledge might have provided tolerable estimates of the course of patient-reported health outcomes.⁴⁰ However, disease duration did not influence health utility in our sample. Notwithstanding, information about sensitivity to change and differences in factors that are associated with change is important when it comes to utilities, as differences may lead to different interpretations of health status and might influence decisions of policy makers and health care insurers.

In summary, patients with gout report substantially impaired health when compared to the general population. Functional disability and CVD, as well as gout-specific characteristics, are the main independent contributors to utility, regardless of which method was used. Altogether, the burden of gout should not be underestimated any longer. The finding that the burden of gout cannot be merely attributed to gout-related comorbidity but also to the gouty disease itself requires specific attention, as gout is at least partly an avoidable disease.

References

1. Choi HK, Atkinson K, Karlson EW, et al. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Intern Med* 2005;165:742–8.
2. Choi HK, Soriano LC, Zhang Y, et al. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ* 2012;344:d8190.
3. Stamp LK, Chapman PT. Gout and its comorbidities: implications for therapy. *Rheumatology (Oxford)* 2013;52:34–44.
4. Khanna PP, Nuki G, Bardin T, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: results from a crosssectional survey. *Health Qual Life Outcomes* 2012;10:117.
5. Perez-Ruiz F, Herrero-Beites AM. Evaluation and treatment of gout as a chronic disease. *Adv Ther* 2012;29:935–46.
6. Singh JA. Quality of life and quality of care for patients with gout. *Curr Rheumatol Rep* 2009;11:154–60.
7. Smith E, Hoy D, Cross M, et al. The global burden of gout: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1470–6.
8. Wijnands JM, Viechtbauer W, Thevissen K, et al. Determinants of the prevalence of gout in the general population: a systematic review and meta-regression. *Eur J Epidemiol* 2015;30:19–33.
9. Rees F, Hui M, Doherty M. Optimizing current treatment of gout. *Nat Rev Rheumatol* 2014;10:271–83.
10. Doward LC, Gnanasakthy A, Baker MG. Patient reported outcomes: looking beyond the label claim. *Health Qual Life Outcomes* 2010;8:89.
11. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull* 2010;96:5–21.
12. De Wit GA, Busschbach JJ, De Charro FT. Sensitivity and perspective in the valuation of health status: whose values count? *Health Econ* 2000;9:109–26.
13. Hawthorne G, Richardson J, Day NA. A comparison of the Assessment of Quality of Life (AQoL) with four other generic utility instruments. *Ann Med* 2001;33:358–70.
14. Brazier J, Roberts J, Tsuchiya A, et al. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ* 2004;13:873–84.
15. Centre for Health Economics. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
16. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271–92.
17. McCabe C, Brazier J, Gilks P, et al. Using rank data to estimate health state utility models. *J Health Econ* 2006;25:418–31.
18. Chandratne P, Roddy E, Clarson L, et al. Health-related quality of life in gout: a systematic review. *Rheumatology (Oxford)* 2013;52:2031–40.
19. Khanna D, Ahmed M, Yontz D, et al. The disutility of chronic gout. *Qual Life Res* 2008;17:815–22.
20. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982;9:789–93.
21. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003;30:167–78.
22. Hirsch JD, Lee SJ, Terkeltaub R, et al. Evaluation of an instrument assessing influence of gout on health-related quality of life. *J Rheumatol* 2008;35:2406–14.
23. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical Care* 1992;30:473–83.
24. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care* 2004;42:851–9.
25. Lamers LM, Stalmeier PF, McDonnell J, et al. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Nederlands tijdschrift voor geneeskunde* 2005;149:1574–8. In Dutch.
26. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055–68.

27. Boers M, Jacobs JW, van Vliet Vlieland TP, et al. Consensus Dutch health assessment questionnaire. *Ann Rheum Dis* 2007;66:132–3.
28. Spaetgens B, van der Linden S, Boonen A. The Gout Assessment Questionnaire 2.0: cross-cultural translation into Dutch, aspects of validity and linking to the International Classification of Functioning, Disability and Health. *Rheumatology (Oxford)* 2014;53:678–85.
29. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53–72.
30. Kharroubi SA, Brazier JE, Roberts J, et al. Modelling SF-6D health state preference data using a nonparametric Bayesian method. *J Health Econ* 2007;26:597–612.
31. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–10.
32. Hernandez Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. *Value Health* 2012;15:550–61.
33. Akaike H. Factor analysis and AIC. *Psychometrika* 1987;52:317–32.
34. Fleisch F. FlexMix: a general framework for finite mixture models and latent class regression in R. *J Stat Software* 2004;11:1–18.
35. The R Core Team. R: a language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2013.
36. Joore M, Brunenberg D, Nelemans P, et al. The impact of differences in EQ-5D and SF-6D utility scores on the acceptability of cost-utility ratios: results across five trial-based cost-utility studies. *Value Health* 2010;13:222–9.
37. Brazier JE, Yang Y, Tsuchiya A, et al. A review of studies mapping (or cross walking) non-preference-based measures of health to generic preference-based measures. *Eur J Health Econ* 2010;11:215–25.
38. Kriegsman DM, Penninx BW, van Eijk JT, et al. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly: a study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol* 1996;49:1407–17.
39. Okura Y, Urban LH, Mahoney DW, et al. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004;57:1096–103.
40. Rupp I, Boshuizen HC, Roorda LD, et al. Course of patient-reported health outcomes in rheumatoid arthritis: comparison of longitudinal and cross-sectional approaches. *J Rheumatol* 2006;33:228–33.

Supplementary material

Appendix A. Predicted utility values of patients with gout for EQ-5D, EQ-VAS and SF-6D using mixture modeling approach

Patient	Age	Sex	HAQ	CV-event	GCO	GCDA	GAQ-pain	Expected value EQ-5D	Expected value EQ-VAS	Expected value SF-6D
1	50	M	0	No	2	2	3	0.92	0.77	0.81
2	50	M	1	No	4	4	5	0.69	0.66	0.67
3	50	M	1,5	Yes	2	5	2	0.57	0.58	0.64
4	70	F	2	Yes	6	6	7	0.38	0.45	0.51
5	70	F	2,5	Yes	7	7	8	0.27	0.40	0.43
6	70	F	3	Yes	8	8	10	0.22	0.34	0.35

The results of this calculation should be interpreted within the limits of the model, which weighs the negative effects of the explanatory variables to calculate utility values.

GCO: gout concern overall, GCDA: gout concern during attack.

Chapter 7

Construct validity of radiographs of the feet to assess joint damage in patients with gout

Bart Spaetgens, Caroline van Durme, Casper Webers, An Tran-Duy, Thea Schoonbrood, Annelies Boonen

J Rheumatol 2017;44:91-94

Abstract

Objectives

To investigate construct validity of radiographic damage of the feet in gout.

Methods

Radiographs of the feet were scored using the Sharp-van der Heijde method. Factors associated with damage were investigated by a negative binomial model. Contribution of damage to health by linear regressions.

Results

Age, disease duration, serum uric acid and tophi were associated with being erosive and erosion score. Tophi were associated with joint space narrowing. Erosions were associated (β :0.47, 95% CI:0.09-0.84) with physical function, but damage was not associated with overall physical health.

Conclusion

Our results support construct validity for radiographs of the feet when assessing joint damage in gout.

Introduction

Gout is worldwide the most prevalent inflammatory arthritis.¹ It is therefore surprising that outcome research in gout is more limited when compared to other rheumatic diseases. To fill this gap, the Outcome Measures in Rheumatology (OMERACT) gout working group, reached consensus on outcome domains that should be measured in clinical trials and studies in gout and proposed instruments to measure domains.² With joint damage being endorsed as a core outcome domain, joint imaging was proposed as instrument.³

To date, radiographic damage measured by conventional radiography (XR) is still considered a feasible approach to measure joint damage because of its widespread availability, low patient burden and easy scoring method. For scoring XR damage, a highly reliable scoring method, namely, the gout-modified Sharp-van der Heijde score (SvdH-mG) is available.⁴ The SvdH-mG includes the same joints in hand and feet of the SvdH system for rheumatoid arthritis, plus the distal interphalangeal joints of the hand. Joints are scored for erosions and joint space narrowing (JSN), each reflecting features that can be distinguished on XR.⁵

While XR has intuitively high face validity to assess joint damage in gout, no comprehensive data on the construct validity of radiographic damage are available. Construct validity addresses the ability of the instrument to measure the 'construct' it intends to measure. Although construct validity of XR to measure joint damage is supported by comparisons of damage scores assessed by other imaging modalities,⁶ there is only one study (n=20) that assessed whether radiographic damage was associated with functioning.⁷ It was shown that radiographic damage on XR had impact on hand function. Another aspect of construct validity can be found in the expectation that a series of biological factors that reflect the disease process (such as serum uric acid (sUA) or tophi) would be associated with radiographic damage as it is generally assumed that joint damage is the resultant of progressive accumulation of uric acid. Bringing together more pieces of evidence that radiographic damage relates in expected directions with physical function and biological factors, would add confidence in the construct validity of XR and enhance the systematic inclusion of XR in any gout trial.

Therefore, the aim of this study was to evaluate the construct validity of radiographic damage in the feet by exploring which biological factors of gout contribute to radiographic damage and by investigating the relationship between radiographic damage and health outcomes.

Materials and methods

Patient population

Data from patients with gout were obtained from a cross-sectional study of 126 patients attending the outpatient clinic of rheumatology at the Maastricht University Medical Centre (MUMC), which serves as a regional hospital for patients with gout. During the study visit, comprising a structured interview and clinical examination, demographic and disease characteristics were assessed, including disease duration, sUA level, use of uric-acid lowering therapy (ULT), location and number of clinical tophi, and confirmation of number of self-reported gout flares (past year). Bases on physician confirmed comorbidities, the Rheumatic Diseases Comorbidity Index (RDCI) was calculated.⁸ Physical function was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI; range 0-3) and physical health using the physical component score of the Short-Form-36 (SF-36 PCS).^{9,10} Plain radiographs of the feet were obtained as part of standard clinical care within one month before or after the study visit. The principles of the Declaration of Helsinki were followed and the study was approved by the ethics committee of the MUMC.

Radiographic damage

The radiographs were independently scored by two trained and experienced rheumatologists (CvD, TS) blinded for the clinical characteristics and for each other's score. Radiographs were scored using the SvdH-mG assessing erosions in MTP I-V and IP I (score 0-10 per joint; 0-5 per articular surface) and JSN (score 0-4 per joint) resulting in a maximum combined score of 168 for both feet.⁵ Intra- and interobserver ICCs (two-way mixed, average measures) were calculated for erosion-, JSN-, and total damage scores separately.

Statistical analysis

The sample characteristics are presented as mean (SD) or median (IQR) depending on the distribution of the data. To explore biological factors associated with radiographic damage, a negative binomial regression (NB) and a zero-inflated negative binomial regression (ZINB) were performed for JSN- and erosions score respectively, as data were non-normally distributed with overdispersion (for JSN) and an excess of zeros (for erosions). In the multivariable models, age and sex were included by default, and the remaining variables were added using manually forward selection ($p < 0.05$). To explore the relative contribution of JSN and erosions to HAQ-DI and SF-36 PCS, linear regressions analyses, adjusted for age, sex, disease duration and comorbidities were performed. Data were analysed using IBM SPSS statistics v19.0 and Stata Release 12 (for NB and ZINB).

Results

Study population

Eighty-one patients with gout (81/126; 64.3%) had radiographs and were included. The demographic and clinical characteristics are presented in Table 7.1. No patient had an acute gout flare at the time of the study visit. The patients contributing to the current analyses did not differ significantly from the 45 patients with no radiographs with regard to age, sex, use of ULT or presence of tophi.

Table 7.1 Baseline characteristics.

Characteristics	n=81
Age (years)	66.4 (10.5)
Male sex; n (%)	65 (80.2)
Body Mass Index (kg/m ²)	29.4 (4.6)
Disease duration (years)	11.1 (10.0)
No. of gout flares last year, median [IQR]	1 [0 to 3]
Currently on uric acid lowering therapy, n (%)	57 (70.4)
Uric acid level (mmol/l)	0.40 (0.13)
Uric acid level <0.36 mmol/l, independent of ULT, n (%)	38 (46.9)
Tophaceous gout, n (%)	38 (46.9)
Number of tophi, mean, (median) [IQR]	2.0 (0) [0 to 2]
RDCl (0-9), mean (median) [IQR]	2.8 (3) [2 to 4]
Gout-modified SvdH-score foot	
Total (0-168), mean, (median)	5.1 (4.5)
[IQR]	[1.5 to 7.5]
Erosion (0-120), mean, (median)	1.6 (0.5)
[IQR]	[0.0 to 2.0]
JSN score (0-48), mean, (median)	3.5 (3)
[IQR]	[1.0 to 5.3]
HAQ-DI (0-3)	0.65 (0.59)
SF-36 PCS (0-100)	38.7 (11.9)
SF-36 MCS (0-100)	49.2 (12.7)

Values are expressed as mean (SD) unless stated otherwise. DCI: Rheumatic Disease Comorbidity Index, SvdH-score: Sharp/van der Heijde-score, JSN: Joint Space Narrowing, HAQ-DI: Health Assessment Questionnaire – Disability Index, SF-36 PCS: Short Form-36 Physical Component Score, SF-36 MCS: Short Form-36 Mental Component Score.

Radiographic damage

The ICCs (95% CI) for intraobserver reliability (of 10 radiographs) for erosion-, JSN-, and total scores were 0.98 (0.95-0.99), 0.87 (0.57-0.96) and 0.96 (0.87-0.99) for observer 1 and 0.92 (0.72-0.98), 0.71 (0.20-0.92) and 0.88 (0.60-0.97) for observer 2, respectively. For interobserver reliability the total sample ICCs (95% CI) for erosion-, JSN-, and total scores were 0.94 (0.90-0.96), 0.85 (0.76-0.90) and 0.93 (0.90-0.96).

Seventy-one patients (71/81, 87.7%) had radiographic damage, of which thirty-eight (46.9%) had erosions (score>0.5) and 63 (77.8%) had JSN (score>0.5). Median [IQR]

erosion, JSN and total SvdH-mG scores were 0.5 [0-2], 3.0 [1.0-5.3] and 4.5 [1.5-7.5] respectively for the entire group.

Factors associated with radiographic damage

Table 7.2 shows the final model of the NBREG and ZINB regression analyses. Older age and having not reached the sUA target level (i.e. sUA <0.36 mmol/l) were significantly associated with the chance of being erosive. Older age, longer disease duration and higher number of clinical tophi were positively associated with erosion scores. Presence of clinical tophi was associated with having more JSN.

The contribution of radiographic damage to outcome

In Table 7.3, the results of the uni- and multivariable regression analyses to explore the impact of radiographic damage on HAQ-DI and SF-36 PCS are shown. In multivariable analysis, higher erosion scores were significantly associated with higher HAQ-DI, although contribution to the variation in outcome (+6.0% after adjustment) was limited. The multivariable analysis of SF-36 PCS revealed no significant influence of erosions or JSN.

Discussion

The current study further supports the construct validity of radiographic damage of the feet when assessing outcome in gout. First, patients who were older, had longer disease duration, had not reached the sUA target level, and had more tophi were more likely to be erosive or to have more erosions. In addition, patients with tophaceous gout had higher JSN scores. Second, radiographic damage showed an association with physical function assessed by HAQ, but not with overall physical health measured by the SF-36.

The finding that age, disease duration, sUA level and tophi were associated with radiographic damage was recently also reported by Dalbeth et al., who found that sUA level, tophi but also disease duration were at least moderately associated with radiographic damage of hands and feet.¹¹ A study showing that profound reduction of sUA levels lead to improvement of the SvdH-mG (erosion) score, further supports the role of sUA and clinical tophi in the pathophysiology of erosions.¹²

Table 7.2 a) Multivariable Zero-Inflated Negative Binomial regression analysis exploring determinants of erosive disease in patients with gout, b) Multivariable Negative Binomial regression analysis exploring determinants of joint space narrowing (JSN) in patients with gout.

	Multivariable regression Being non-erosive*				Multivariable regression Erosion-score (count) [‡]			
	B	OR [†]	95% CI (OR)	p-value	B	Exp(β) [‡]	95% CI (Exp(β))	p-value
a)								
Age (years)	-0.15	0.86	0.74 to 0.99	0.036	0.05	1.06	1.02 to 1.09	0.002
Sex (female)	3.36	28.80	0.87 to 955.74	0.06	0.50	1.65	0.72 to 3.75	0.23
Disease duration (years)					0.04	1.04	1.01 to 1.07	0.018
Amount of tophi (n)					0.07	1.07	1.03 to 1.12	0.001
sUA ≤0.36mmol/l (yes/no)	4.39	80.53	1.25 to 5192.79	0.039				
b)								
Age (years)	#	#	#	#	0.01	1.01	0.99 to 1.02	0.63
Sex (female)	#	#	#	#	-0.13	0.88	0.55 to 1.39	0.58
Tophaceous gout (yes/no)	#	#	#	#	0.57	1.76	1.23 to 2.53	0.002

*Logistic model, predicting being non-erosive (the amount of erosions being a 'certain zero'). [†]Negative binomial model, predicting expected count. [‡]Factor change in odds for one unit increase in the independent variable. [‡]Factor change in expected count for one unit increase in the independent variable.

Table 7.3 Uni- and multivariable linear regressions exploring the impact of radiographic damage on physical functioning and health-related quality of life, measured with HAQ-DI and SF-36 PCS.

	HAQ-DI				SF-36 PCS			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
Erosion score (per 10 points worsening)*	0.52 (0.10 to 0.94)	0.016	0.47 (0.00 to 0.94)	0.05	-2.20 (-11.36 to 6.96)	0.63	-2.88 (-13.67 to 7.90)	0.59
JSN score (per 10 points worsening)*	0.02 (-0.45 to 0.49)	0.93	-0.25 (-0.74 to 0.24)	0.31	4.54 (-5.25 to 14.33)	0.36	6.08 (-5.07 to 17.23)	0.28
R ² model, %				27%				14%
Variance (R ²) explained by radiographic damage scores, %				2.4%				0.0%
				0.0%				1.6%

*Tested separately in multivariable analysis. HAQ-DI: Health Assessment Questionnaire – Disability Index, SF-36 PCS: Short Form 36 Physical Component Score. Multivariable analyses are adjusted for age, sex, disease duration and comorbidity (calculated by the Rheumatic Diseases Comorbidity Index).

On the other hand, radiographic damage was not consistently associated with health outcome in our study. A reason for the inconsistent and at most moderate (for HAQ-DI) association might be the fact the natural course of gout is difficult to capture, as radiographic damage seems reversible with ULT. Another explanation might be the overall low scores of radiographic damage, but this is likely the clinical reality of unselected patients under care of a rheumatologist, as observed damage scores are in line with those reported in other studies by patients not selected for trials.¹³ Further, self-reported HAQ-DI and SF-36 might insufficiently capture lower limb impairments. Especially SF-36, a health related quality of life instrument, is strongly influenced by different aspects of health such as vitality. Last but not least, it is known that patients with slowly progressive disease, as is the case for chronic gout can often adapt to impairments, indicating reference shift.¹⁴

We recognize that this study is not without limitations. First, the sample size is small and patients were recruited from a university hospital, although for patients with gout it serves as a regional hospital. Although this would not hamper the internal validity, it might be possible that the relation between radiographic damage and health outcomes is stronger in selected subgroups with more severe disease. Second, only radiographs of the feet were obtained in standard clinical care, as clinical manifestations occur most frequently in the feet. Third, we need to be cautious when interpreting our results, since joint damage scored with SvdH-mG, might be attributable to osteoarthritis rather than gout, especially since both diseases often occur together.¹⁵ The study by Dalbeth et al.¹¹ showed that JSN, was the imaging feature least associated with crystal deposition (assessed using dual-energy CT). Therefore, we believe that JSN, present in both gout and osteoarthritis lacks discriminative validity and might be reconsidered in the future. Nevertheless, our study convincingly confirmed that the SvdH-mG is a highly reproducible method to score radiographic damage. Finally, this is a cross-sectional study and therefore knowledge about how radiographic damage evolves over time could not be obtained.

In conclusion, our findings support the construct validity of XR to evaluate joint damage in gout. Together with the wide-spread availability, low patient burden and low costs, this suggests a role for XR to monitor joint damage in patients with gout. More research is still needed to understand whether in clinical practice, information on XR would influence currently recommended treatment strategies.

References

1. Wijnands JM, Viechtbauer W, Thevissen K, et al. Determinants of the prevalence of gout in the general population: a systematic review and meta-regression. *Eur J Epidemiol.* 2015;30:19-33.
2. Schumacher HR, Taylor W, Edwards L, et al. Outcome domains for studies of acute and chronic gout. *J Rheumatol.* 2009;36:2342-5.
3. Grainger R, Dalbeth N, Keen H, et al. Imaging as an Outcome Measure in Gout Studies: Report from the OMERACT Gout Working Group. *J Rheumatol.* 2015;42: 2460-4.
4. Dalbeth N, Clark B, McQueen F, et al. Validation of a radiographic damage index in chronic gout. *Arthritis Rheum.* 2007;57:1067-73.
5. Dalbeth N, McQueen FM. Clarification of the modified radiographic damage scoring method for gout. *J Rheumatol.* 2012;39:874; author reply.
6. Durcan L, Grainger R, Keen H, et al. Imaging as a potential outcome measure in gout studies: A systematic literature review. *Semin Arthritis Rheum.* 2016;45:570-9.
7. Dalbeth N, Collis J, Gregory K, et al. Tophaceous joint disease strongly predicts hand function in patients with gout. *Rheumatology* 2007;46:1804-7.
8. Spaetgens B, Wijnands JM, van Durme C, et al. Content and construct validity of the Rheumatic Diseases Comorbidity Index in patients with gout. *Rheumatology* 2015;54:1659-63.
9. Boers M, Jacobs JW, van Vliet Vlieland TP, et al. Consensus Dutch health assessment questionnaire. *Ann Rheum Dis.* 2007;66:132-3.
10. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol.* 1998;51:1055-68.
11. Dalbeth N, Aati O, Kalluru R, et al. Relationship between structural joint damage and urate deposition in gout: a plain radiography and dualenergy CT study. *Ann Rheum Dis.* 2015;74:1030-6.
12. Dalbeth N, Doyle AJ, McQueen FM, et al. Exploratory study of radiographic change in patients with tophaceous gout treated with intensive urate-lowering therapy. *Arthritis Care Res (Hoboken).* 2014;66:82-5.
13. Eason A, House ME, Vincent Z, et al. Factors associated with change in radiographic damage scores in gout: a prospective observational study. *Ann Rheum Dis* 2016;75: 2075-9.
14. Rapkin BD, Schwartz CE. Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. *Health Qual Life Outcomes.* 2004;2:14.
15. Roddy E, Zhang W, Doherty M. Are joints affected by gout also affected by osteoarthritis? *Ann Rheum Dis.* 2007;66:1374-7

Chapter 8

Risk of infections in patients with gout: a population-based cohort study

Bart Spaetgens, Frank de Vries, Annemariëk Driessen, Bert Leufkens, Patrick Souverein, Annelies Boonen, Jos van der Meer, Leo Joosten

Accepted for publication in Sci Rep 2017

Abstract

To investigate the risk of various types of infections (pneumonia and urinary tract infection (UTI)), and infection-related mortality in patients with gout compared with population-based controls. A retrospective cohort study was conducted using data from the UK Clinical Practice Research Datalink (CPRD). All patients with a first diagnosis of gout and aged >40 years between January 1987-July 2014, were included and matched with up to two controls. Time-varying Cox proportional hazards models were used to estimate the risk of infections and mortality. 131,565 patients and 252,763 controls (mean age: 64 years, 74% males, mean follow-up of 6.7 years) were included in the full cohort. After full statistical adjustment, the risk of pneumonia was increased (adj. HR 1.27, 95% CI 1.18 to 1.36), while the risk of UTI (adj. HR 0.99, 95% CI 0.97 to 1.01) was similar in patients compared to controls. No differences between patients and controls were observed for infection-related mortality due to pneumonia (adj. HR 1.03, 95% CI 0.93 to 1.14) or UTI (adj. HR 1.16, 95% CI 0.98 to 1.37). In conclusion, patients with gout did not have decreased risks of pneumonia, UTI or infection-related mortality compared to population-based controls.

Introduction

Gout is worldwide the most common type of inflammatory arthritis with estimates of prevalence ranging from 2.5% in Europe to 3.9% in the United States.¹⁻³ It is a chronic disease with different disease manifestations varying from acute self-limiting attacks to chronic tophaceous gout.⁴ Gout and the accompanying hyperuricaemia have also been associated with a large number of comorbidities, such as cardiovascular disease, hypertension, diabetes and chronic kidney disease, although it remains unclear whether there is a causal relation with these comorbidities.^{5,6}

The pathogenesis of gout is well understood, with a major role for monosodium urate (MSU) crystals which are formed during a state of hyperuricaemia.⁷ In the joints these MSU crystals elicit an inflammatory response by activation of the NLRP3 inflammasome, which eventually leads to production of the pro-inflammatory cytokine interleukin (IL)-1 β .⁸⁻¹⁰ Also, in patients with tophaceous gout, it has been shown that pro-inflammatory cytokines such as IL-1 β are expressed in the tophus, suggesting a state of chronic inflammation induced and/or stimulated by MSU crystals.¹¹ Isolated peripheral blood mononuclear cells (PBMCs) of patients with gout produce more IL-1 β when stimulated with MSU, when compared to blood cells of healthy controls.¹² Further, MSU seems to enhance the function of these PBMCs by epigenetic mechanisms resulting in increased cytokine production ('Trained Immunity').¹³ Recent evidence further revealed that the production of IL-1 β and IL-6 were higher in patients with gout, and serum concentrations correlated with serum uric acid (sUA).¹⁴ As such, the net result of aforementioned pathways suggest a pro-inflammatory state in patients with hyperuricaemia and/or gout.¹⁴

The presence of a pro-inflammatory state related to hyperuricaemia has led to the hypothesis that patients with gout may have an enhanced resistance to infections, because previous research indicated that IL-1 β augments the quality of host defence against bacteria and viruses.¹⁵ However, the clinical correlate of this concept has never been explored. Since gout is classically treated with colchicine for acute flares, and with allopurinol for long-term uric acid lowering treatment (ULT), it is important to consider a potential effect of these drugs on the relation between gout and infections. As such, we hypothesized that (I) patients with gout acquire fewer community-acquired infections (e.g., pneumonia, urinary tract infection (UTI)) and encounter a lower infection-related mortality rate, (II) treatment with colchicine enhances infections, because of its immunosuppressive effects, and (III) treatment with allopurinol neutralizes the protective role of high sUA levels of infections.

In view of the above, the objective of this study was to investigate the risk of various types of infections (pneumonia and UTI), and infection-related mortality in patients with gout compared with population-based controls without gout.

Patients and methods

Design and data source

A retrospective cohort study was conducted using data from the British Clinical Practice Research Datalink (CPRD) GOLD (January 1987 - July 2014). CPRD is formerly known as the General Practice Research Database (GPRD) and contains the computerized medical records of approximately 13 million patients under care of general practitioners in the United Kingdom (UK) who are representative for 6.9% of the total UK population. Practices contribute to CPRD, only when their data quality is up to research standards. Since 1987, data recorded in the CPRD include demographic information, prescription details, lifestyle parameters, clinical events, preventive care provided and specialist referrals. CPRD has been extensively validated,¹⁶ and used previously to study gout,¹⁷ and infections including pneumonia.¹⁸ About 75% of all practices in England (58% of all UK CPRD practices) were linked to data of the Office of National Statistics (ONS) (January 1998 - January 2012).¹⁹ The ONS provided data for the causes of death and the exact date as recorded on death certificates by a medical doctor. Linkage of death certificates to CPRD has a high level of validity.²⁰

Ethical approval

CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies with external data linkages, including ONS mortality data. The present study is based on anonymised and unidentifiable CPRD data and is also approved by the Independent Scientific Advisory Committee (ISAC) of the Medicine and Healthcare products Regulatory Agency (protocol number 14_123R), which is primarily responsible for reviewing the study protocols. In the case of this observational research no further ethical approval deemed necessary by ISAC.

Study population

All patients with a first diagnosis of gout during the period of valid data collection (from 1 January 1987 to 30 June 2014) and aged above 40 years during the period of valid CPRD data collection were included. Each patient with gout was matched by year of birth, sex, and practice to up to two patients without a diagnosis of gout using incidence density sampling. The date of the first recorded diagnosis of gout defined the index date and controls were assigned the same index date as their matched patient with gout. Patients or controls with a history of exposure to colchicine and ULT (allopurinol, febuxostat and/or uricosuric drugs) before index date were excluded.

When the outcome infection-related mortality was evaluated, data were restricted to the participants with linkage to ONS data. For this analysis, the period of valid data collection was restricted from 1 January 1998 to 31 December 2011.

Study outcome(s) and covariates

The primary outcomes of interest were a first event of pneumonia (specified by read codes) or UTI (specified by read codes or prescriptions for nitrofurantoin or trimethoprim, since in the UK nitrofurantoin is exclusively, and trimethoprim in 95% of all cases prescribed for the treatment of UTI). The secondary outcome of interest was infection-related mortality (death related to pneumonia [International Classification of Diseases, Tenth Revision (ICD-10) codes: J10.0-J18.9] or UTI [ICD-10 codes: N39.0]). Potential confounders assessed at baseline included sex, body mass index (BMI), smoking status and alcohol use. Age and an estimated glomerular filtration rate (eGFR) were included as time-dependent variables at the start of each (30-day) time interval. When pneumonia or infection-related mortality due to pneumonia was the outcome, potential confounders included a history of pneumonia (more than 3 months ago), a history of sinusitis, influenza infection, stroke, lung cancer, chronic obstructive pulmonary disease (COPD), acute bronchitis, asthma, diabetes, dementia, epilepsy/seizures, dysphagia, HIV/AIDS and the use of the following medications within the previous 6 months: antipsychotics, acid suppressants, bronchodilators/inhaled corticosteroids, anticonvulsants, immunosuppressants or systemic glucocorticoids and within 1 year prior: an influenza vaccination, and within 5 year prior: a pneumococcal vaccination. When UTI or infection-related mortality due to UTI were the outcome, potential confounders included a history of diabetes, malignancies excluding non-melanoma skin cancer, HIV/AIDS, recent use (within the previous 3 months) of urinary catheters, and the use of immunosuppressants or systemic glucocorticoids in the 6 months before. All confounders but age were treated as categorical variables.

Statistical analysis

Analyses were conducted using time-varying Cox proportional hazard models to estimate the risk of each outcome with exposure to gout. Patients were followed from the index date up to the end of data collection, the outcome of interest, the date of transfer out of the practice area or death, whichever came first. Follow-up was stratified into periods of 30 days. Potential confounders were included in the final model if they independently changed the β -coefficient of the univariate analysis by $\geq 5\%$, or when consensus (within the research team) about inclusion was reached, supported by scientific evidence. Analyses were repeated after stratification for treatment (current (<31 days), recent (31-91 days), past (>91 days) users) with allopurinol or colchicine. Data management and statistical analyses were conducted using SAS 9.3 (PHREG procedure).

Results

In total, 162,181 patients with gout and 323,988 controls aged 40+ years were identified. Next, 30,284 gout patients and 15,400 controls with a prescription of colchicine or ULT before index date were excluded, and a remaining 56,105 subjects who were no longer matched. As a result, 131,565 patients with gout were included along with 252,763 controls without gout (mean age: 64 years, 74% males) with a mean follow-up of 6.7 years for both patients and controls in our full cohort. When infection-related mortality was the outcome 69,987 patients and 134,549 controls for whom death-certificate data were available for analyses after linkage to the ONS (Figure 8.1) were included.

Baseline characteristics of patients with gout and controls in both cohorts are shown in Table 8.1. Patients with gout had, compared to controls, a higher BMI, more often an eGFR below 60 ml/min/1.73m², consumed more often alcohol, suffered more frequently of asthma and/or COPD, diabetes, ischemic heart disease and atrial fibrillation. Furthermore, patients with gout were more likely users of systemic glucocorticoids or bronchodilators. No differences were observed for a history of malignancies, HIV or use of urinary catheters or immunosuppressant drugs.

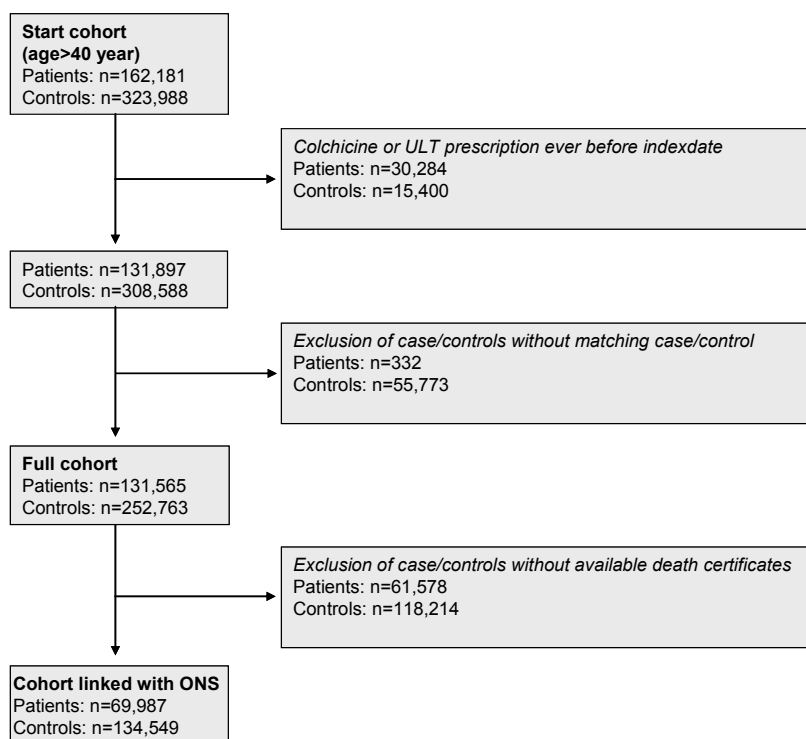


Figure 8.1 Flowchart of the study subjects.

Table 8.1 Baseline characteristics of patients with gout and controls, separately for the full sample and the sample that could be linked to death certificate data from the Office of National Statistics (ONS)^a

Characteristics	Full Cohort		Cohort linked with ONS	
	Gout patients n=131,565	Controls n=252,763	Gout patients n=69,987	Controls n=134,549
Mean follow-up time, years (SD)	6.7 (5.1)	6.7 (5.1)	7.3 (4.9)	7.2 (5.0)
Number of men	97,179 (73.9)	186,021 (73.6)	52,024 (74.3)	99,612 (74.0)
Age				
Mean age at index date, years (SD)	64 (13.5)	64 (13.5)	64 (13.5)	64 (13.5)
40-49 years	23,304 (17.7)	46,032 (18.2)	12,474 (17.8)	24,607 (18.3)
50-59 years	27,968 (21.3)	54,730 (21.7)	14,967 (21.4)	29,380 (21.8)
60-69 years	31,262 (23.8)	59,875 (23.7)	16,614 (23.7)	31,896 (23.7)
70+ years	49,031 (37.3)	92,126 (36.4)	25,932 (37.1)	48,666 (36.2)
BMI				
Mean BMI at index date, kg/m ² (SD)	29 (5.2)	27 (4.8)	29 (5.2)	27 (4.8)
<20.0 kg/m ²	1,756 (1.3)	7,461 (3.0)	954 (1.4)	4,030 (3.0)
20.0-24.9 kg/m ²	21,146 (16.1)	63,823 (25.3)	11,624 (16.6)	35,430 (26.3)
25.0-29.9 kg/m ²	46,675 (35.5)	80,677 (31.9)	25,449 (36.4)	43,679 (32.5)
30.0-34.9 kg/m ²	25,308 (19.2)	30,167 (11.9)	13,510 (19.3)	15,747 (11.7)
≥35.0 kg/m ²	12,107 (9.2)	10,909 (4.3)	6,143 (8.8)	5,609 (4.2)
Missing	24,573 (18.7)	59,726 (23.6)	12,307 (17.6)	30,054 (22.3)
Smoking status				
Never	62,964 (47.9)	118,635 (46.9)	33,274 (47.5)	63,441 (47.2)
Current	26,517 (20.2)	60,059 (23.8)	14,715 (21.0)	32,704 (24.3)
Ex	38,941 (29.6)	60,101 (23.8)	20,961 (29.9)	32,625 (24.2)
Missing	3,143 (2.4)	13,968 (5.5)	1,037 (1.5)	5,779 (4.3)
Alcohol use				
No	18,772 (14.3)	40,138 (15.9)	9,473 (13.5)	20,179 (15.0)
Yes	101,993 (77.5)	178,735 (70.7)	55,652 (79.5)	98,483 (73.2)
Missing	10,800 (8.2)	33,890 (13.4)	4,862 (6.9)	15,887 (11.8)
eGFR most recent within previous year				
eGFR, ml/min/1.73m ² (SD)	73 (22.7)	81 (22.0)	73 (22.7)	81 (22.0)
>90 ml/min/1.73m ²	14,769 (11.2)	34,509 (13.7)	7,456 (10.7)	17,412 (12.9)
60-89 ml/min/1.73m ²	38,052 (28.9)	63,485 (25.1)	21,267 (30.4)	35,780 (26.6)
30-59 ml/min/1.73m ²	19,251 (14.6)	16,428 (6.5)	10,771 (15.4)	9,306 (6.9)
15-29 ml/min/1.73m ²	1,609 (1.2)	878 (0.3)	889 (1.3)	499 (0.4)
<15 ml/min/1.73m ²	183 (0.1)	186 (0.1)	106 (0.2)	106 (0.1)
Missing	57,701 (43.9)	137,277 (54.3)	29,498 (42.1)	71,446 (53.1)
History of comorbidities				
Pneumonia	3,280 (2.5)	4,801 (1.9)	1,735 (2.5)	2,653 (2.0)
UTI	13,010 (9.9)	21,979 (8.7)	6,828 (9.8)	11,599 (8.6)
HIV	70 (0.1)	156 (0.1)	18 (0.0)	59 (0.0)
Lung cancer	207 (0.2)	460 (0.2)	103 (0.1)	224 (0.2)
Malignancies ^b	14,363 (10.9)	25,684 (10.2)	7,729 (11.0)	13,706 (10.2)
Asthma / COPD	18,829 (14.3)	29,940 (11.8)	9,903 (14.1)	15,852 (11.8)
Sinusitis	14,754 (11.2)	26,043 (10.3)	7,920 (11.3)	14,181 (10.5)
Diabetes	11,151 (8.5)	16,952 (6.7)	5,872 (8.4)	8,731 (6.5)
Dementia	985 (0.7)	3,071 (1.2)	448 (0.6)	1,472 (1.1)
Epilepsy	2,143 (1.6)	4,523 (1.8)	1,091 (1.6)	2,333 (1.7)
Dysphagia	2,371 (1.8)	4,169 (1.6)	1,248 (1.8)	2,259 (1.7)
Ischaemic heart disease	19,492 (14.8)	24,177 (9.6)	10,132 (14.5)	12,651 (9.4)
Atrial fibrillation/flutter	11,544 (8.8)	10,972 (4.3)	6,016 (8.6)	5,848 (4.3)
Stroke	7,681 (5.8)	11,457 (4.5)	3,888 (5.6)	5,908 (4.4)

Table 8.1 (continued)

Characteristics	Full Cohort		Cohort linked with ONS	
	Gout patients n=131,565	Controls n=252,763	Gout patients n=69,987	Controls n=134,549
Drug use within six months before				
Bronchodilators	14,423 (11.0)	21,495 (8.5)	7,426 (10.6)	11,128 (8.3)
Inhaled corticosteroids	7,052 (5.4)	10,902 (4.3)	3,811 (5.4)	5,989 (4.5)
Antipsychotics	1,252 (1.0)	3,602 (1.4)	630 (0.9)	1,878 (1.4)
Anticonvulsants	2,785 (2.1)	5,671 (2.2)	1,367 (2.0)	2,894 (2.2)
Systemic corticosteroids	5,538 (4.2)	7,915 (3.1)	2,908 (4.2)	4,177 (3.1)
Immunosuppressants	835 (0.6)	1,549 (0.6)	465 (0.7)	798 (0.6)
Influenza vaccination (1 year before)	48,379 (36.8)	80,038 (31.7)	28,345 (40.5)	48,188 (35.8)
Pneumococcal vaccination (5 years before)	23,174 (17.6)	38,350 (15.2)	12,846 (18.4)	21,805 (16.2)

SD, standard deviation; ^a ONS, the Office of National Statistics; BMI, Body mass index; eGFR, estimated Glomerular Filtration Rate; HIV, Human Immunodeficiency Virus; COPD, Chronic Obstructive Pulmonary Disease. Data represent the number (%) of patients, unless stated otherwise. ^b Excluding non-melanoma skin cancer.

Table 8.2 shows that gout was associated with a 34% increased risk of pneumonia, after adjustment for age and sex (HR 1.34, 95% CI 1.25 to 1.43). Full statistical adjustment led to a marginal reduction in the risk estimate (adjusted (adj.) HR 1.27, 95% CI 1.18 to 1.36). Further stratification by use of gout medication showed that there was no increased risk of pneumonia with current colchicine use (adj. HR 0.88, 95% CI 0.54 to 1.44), while recent and past use was associated with a doubled pneumonia risk. Current exposure to allopurinol was associated with an increased risk of pneumonia (adj. HR 1.41, 95% CI 1.23 to 1.61), which was similar compared to the risk of non-allopurinol use. Discontinuation of allopurinol barely altered the risk of pneumonia.

Table 8.2 Risk of pneumonia in patients with gout compared to matched controls, stratified by use of colchicine and allopurinol.

	No. of pneumonia events (n=3,586)	Age/sex adjusted HR (95% CI)	Adjusted HR ^a (95% CI)
No Gout	2,048	Reference	Reference
Gout	1,538	1.34 (1.25 to 1.43)	1.27 (1.18 to 1.36)
By colchicine exposure			
Never use	1,159	1.24 (1.15 to 1.33)	1.22 (1.13 to 1.31)
Current use (<31 days)	16	1.16 (0.71 to 1.90)	0.88 (0.54 to 1.44)
Recent use (31-91 days)	32	2.09 (1.48 to 2.97)	1.60 (1.13 to 2.27)
Past use (>91 days ago)	331	1.80 (1.60 to 2.02)	1.49 (1.32 to 1.68)
By allopurinol exposure			
Never use	954	1.22 (1.13 to 1.32)	1.18 (1.10 to 1.28)
Current use (<31 days)	262	1.65 (1.45 to 1.87)	1.41 (1.23 to 1.61)
Recent use (31-91 days)	119	1.76 (1.46 to 2.11)	1.58 (1.31 to 1.91)
Past use (>91 days ago)	203	1.43 (1.24 to 1.65)	1.39 (1.21 to 1.61)

HR: indicates hazards ratio; CI, confidence interval; PY, person years. ^a Adjusted for age, sex, body mass index, smoking status, alcohol use, the most recently recorded estimated glomerular filtration rate in the past year, a history of dementia, dysphagia, and the use of bronchodilators, inhalation corticosteroids, systemic corticosteroids, non-insulin anti-diabetic drugs, insulin within 6 months before, the use of influenza vaccinations 1 year before and the use of pneumococcal vaccinations 5 years before.

Table 8.3 shows that gout was associated with a 14% increased risk of UTI, after adjustment for age and sex (HR 1.14, 95% CI 1.12 to 1.17). After full statistical adjustment this increased risk disappeared (adj. HR 0.99, 95% CI 0.97 to 1.01). The following confounders were responsible for this shift: sex, a history of chronic kidney disease, cancer, stroke, recent use of a urinary catheter and the use of systemic corticosteroids or anti-diabetics 6 months prior. Further stratification by the use of medication showed an increased risk of UTI with current and recent colchicine use (adj. HR 1.42, 95% CI 1.24 to 1.64 and adj. HR 1.29, 95% CI 1.12 to 1.49), whereas past colchicine use was not associated with an increased risk (adj. HR 1.00, 95% CI 0.95 to 1.06) compared to controls. Current and recent use of allopurinol was associated with a similar risk of UTI compared to controls (adj. HR 1.05, 95% CI 0.99 to 1.12 and adj. HR 1.04, 95% CI 0.94 to 1.14, respectively). However, past use of allopurinol was associated with a 27% reduced risk of UTI (adj. HR 0.73, 95% CI 0.67 to 0.80).

Table 8.3 Risk of urinary tract infection (UTI) in patients with gout compared to matched controls, stratified by use of colchicine and allopurinol.

	No. of UTI Events (n=35,807)	Age/sex adjusted HR (95% CI)	Adjusted HR ^a (95% CI)
No Gout	22,719	Reference	Reference
Gout	13,088	1.14 (1.12 to 1.17)	0.99 (0.97 to 1.01)
By colchicine exposure			
Never use	10,596	1.11 (1.08 to 1.14)	0.97 (0.94 to 1.01)
Current use (<31 days)	225	1.83 (1.62 to 2.07)	1.42 (1.24 to 1.64)
Recent use (31-91 days)	235	1.71 (1.52 to 1.93)	1.29 (1.12 to 1.49)
Past use (>91 days ago)	2,032	1.27 (1.22 to 1.33)	1.00 (0.95 to 1.06)
By allopurinol exposure			
Never use	9,256	1.15 (1.12 to 1.18)	1.01 (0.98 to 1.05)
Current use (<31 days)	1,864	1.31 (1.26 to 1.37)	1.05 (0.99 to 1.12)
Recent use (31-91 days)	766	1.19 (1.11 to 1.27)	1.04 (0.94 to 1.14)
Past use (>91 days ago)	1,202	0.90 (0.85 to 0.95)	0.73 (0.67 to 0.80)

HR: indicates hazards ratio; CI, confidence interval; PY, person years. ^a Adjusted for age, sex, body mass index, smoking status, alcohol use, the most recently recorded estimated glomerular filtration rate in the past year, a history of cancer, stroke and the use of an urinary catheter, systemic corticosteroids, non-insulin antidiabetic drugs and insulin 6 months before.

Table 8.4 shows that there was no association between infection-related mortality due to pneumonia and exposure to gout versus controls (adj. HR 1.03, 95% CI 0.93 to 1.14). Stratification by use of gout medication also did not alter the risk estimates.

Table 8.5 shows that no association between infection-related mortality due to UTI and exposure to gout versus controls was observed (adj. HR 1.16, 95% CI 0.98 to 1.37). Stratification by use of gout medication revealed that never use of colchicine (adj. HR 1.25, 95% CI 1.04 to 1.49) and recent allopurinol use (adj. HR 1.56, 95% CI 1.00 to 2.43) were associated with an increased risk of mortality due to UTI.

Table 8.4 Risk of infection-related mortality due to pneumonia, in patients with gout compared to matched controls, stratified by use of colchicine and allopurinol.

	No. of events (death) (n=1,965)	Age/sex adjusted HR (95% CI)	Adjusted HR ^a (95% CI)
No Gout	1,390	Reference	Reference
Gout	575	0.97 (0.88 to 1.07)	1.03 (0.93 to 1.14)
By colchicine exposure			
Never use	475	0.99 (0.89 to 1.10)	1.07 (0.96 to 1.19)
Current use (<31 days)	<5 events ^b	0.67 (0.25 to 1.78)	0.65 (0.24 to 1.74)
Recent use (31-91 days)	<5 events ^b	0.61 (0.27 to 1.36)	0.61 (0.27 to 1.37)
Past use (>91 days ago)	92	0.92 (0.76 to 1.12)	0.92 (0.75 to 1.13)
By allopurinol exposure			
Never use	384	0.98 (0.87 to 1.10)	1.06 (0.94 to 1.19)
Current use (<31 days)	91	1.20 (0.97 to 1.48)	1.22 (0.98 to 1.52)
Recent use (31-91 days)	30	0.89 (0.63 to 1.25)	0.95 (0.67 to 1.33)
Past use (>91 days ago)	70	0.93 (0.73 to 1.18)	0.97 (0.76 to 1.23)

HR: indicates hazards ratio; CI, confidence interval; PY, person years. ^a Adjusted for age, sex, body mass index, smoking status, alcohol use, the most recently recorded estimated glomerular filtration rate in the past year, a history of dementia, dysphagia, stroke, epilepsy, ischaemic heart disease, sepsis and the use of bronchodilators, inhalation corticosteroids, systemic corticosteroids, non-insulin anti-diabetic drugs and insulin within 6 months before, the use of influenza vaccinations 1 year before and the use of pneumococcal vaccinations 5 years before. ^b According to Independent Scientific Advisory Committee (ISAC) guidance on the content of protocols for research using CPRD data no cell containing <5 events are reported.

Table 8.5 Risk of infection-related mortality due to UTI, in patients with gout compared to matched controls, stratified by use of colchicine and allopurinol.

	No. of events (death) (n= 697)	Age/sex adjusted HR (95% CI)	Adjusted HR ^a (95% CI)
No Gout	454	Reference	Reference
Gout	243	1.19 (1.01 to 1.40)	1.16 (0.98 to 1.37)
By colchicine exposure			
Never use	195	1.24 (1.04 to 1.48)	1.25 (1.04 to 1.49)
Current use (<31 days)	<5 events ^b	0.94 (0.23 to 3.76)	0.75 (0.19 to 3.02)
Recent use (31-91 days)	<5 events ^b	1.48 (0.62 to 3.60)	1.23 (0.51 to 2.99)
Past use (>91 days ago)	42	1.12 (0.82 to 1.52)	0.99 (0.72 to 1.36)
By allopurinol exposure			
Never use	158	1.14 (0.95 to 1.37)	1.14 (0.94 to 1.38)
Current use (<31 days)	31	1.15 (0.79 to 1.67)	1.03 (0.71 to 1.51)
Recent use (31-91 days)	20	1.62 (1.04 to 2.52)	1.56 (1.00 to 2.43)
Past use (>91 days ago)	34	1.27 (0.89 to 1.82)	1.22 (0.85 to 1.74)

HR: indicates hazards ratio; CI, confidence interval; PY, person years. ^a Adjusted for age, sex, body mass index, smoking status, alcohol use, the most recently recorded estimated glomerular filtration rate in the past year, a history of dementia, dysphagia, stroke, epilepsy, ischaemic heart disease, sepsis and the use of bronchodilators, inhalation corticosteroids, systemic corticosteroids, non-insulin anti-diabetic drugs and insulin within 6 months before. ^b According to Independent Scientific Advisory Committee (ISAC) guidance on the content of protocols for research using CPRD data no cell containing <5 events are reported.

Discussion

This study showed that the risk of pneumonia, UTI or infection-related mortality was not reduced in patients with gout compared to population-based controls. Moreover, stratification by treatment with colchicine did not identify subgroups with reduced risks for pneumonia, UTI or infection-related mortality either, while stratification by treatment with allopurinol only showed a decreased risk of UTI in past users. On the contrary, we found that patients with gout had an elevated risk of pneumonia. Therefore, the results of the present study were not in line with our main hypothesis that patients with gout would have a decreased risk of acquiring infections. In addition, our findings regarding our secondary hypotheses, i.e. that treatment with colchicine (because of its immunosuppressive effects) or allopurinol (because it reduces sUA and therefore neutralizes the protective role of sUA) might enhance infections were inconsistent.

To the best of our knowledge, this is the first study that evaluated the risk of community-acquired infections in patients with gout versus matched controls. A previous population-based study by Lim et al.,²¹ investigated the risk of septic arthritis in patients with gout, and revealed that gout patients had a 2.6-fold increased risk of developing septic arthritis when compared to non-gouty controls. However, the protective effect of a pro-inflammatory state is unlikely to play a major role in the pathophysiology of septic arthritis in these patients. Local joint damage due to gout, and possibly arthrocentesis and intra-articular injections, but also misdiagnosis of the disease, since gout and septic arthritis have similar disease features, might have contributed to this increased risk. Our study also showed increased risks of infection in certain subgroups, although only for pneumonia this risk persisted after adjusting for classic confounders. The risk of UTI disappeared after statistically adjustment for confounders (chronic kidney disease, systemic corticosteroids, use of anti-diabetics, sex and use of an urinary catheter). From a pathophysiological view, there is no good reason why gout itself should increase the risk of infections after adjusting for confounders. It is possible that a true inverse association may have not been detected due to a wide range of epidemiological limitations, such as misclassification bias, detection bias or residual confounding. Although we were able to adjust for many possible confounders, it is likely residual confounding still has occurred. First, our data show that gout patients have a higher BMI, suffer more often from chronic kidney disease, asthma and/or COPD and diabetes, and were also more likely to use systemic glucocorticoids. Despite the fact we have adjusted for these confounders in our analysis, we acknowledge we were unable to correct for all potential confounders such as under-ascertained comorbidities and for the severity of health impact of some confounders, which occur more often in gout patients. Second, another concern is that glucocorticoids, which are well-known to increase the risk of infections, were prescribed more to gout patients. Although this was adjusted for, it may have introduced information bias, while exposure to glucocorticoids was measured, as for all

drugs, from prescriptions. As such, we have no information whether these drugs were actually taken. Not taking these drugs (adherence is a well-known problem in gout patients) could have led to an underestimation of the true risk. Third, missing data with respect to smoking, BMI or eGFR might have introduced residual confounding as a result of imperfect adjustment of these variables.

Although our data do not support our hypothesis of a net pro-inflammatory state that enhances resistance to infections in patients with gout, it is too early to reject the hypothesis based on these data alone. Trained immunity (or innate immune memory) is mediated by epigenetic reprogramming of monocytes and/or macrophages.²² This reprogramming when induced by BCG is present for approximately 1 year.²³ However, it is possible that sUA-induced trained immunity is not so long lasting as was demonstrated for BCG or β -glucan.²⁴ It is also possible that the clinical protective effect of sUA is small or might be counteracted by other mechanisms (such as residual confounding, or the fact this is a population-based cohort in which sUA levels are not sharply increased).

The impact of treatment with allopurinol and colchicine was more difficult to explain due to inconsistent findings. It was interesting to see that especially past allopurinol use was associated with a decreased risk of UTI compared to controls. A possible explanation might be that the rise in sUA after discontinuation of allopurinol (non-compliance to allopurinol is well recognized²⁵) is protective in acquiring infections, while in current and recent users allopurinol might neutralize the protective effect of sUA. With regard to pneumonia, never using allopurinol was associated with the lowest infection risks. These patients might have been exposed more consistent to higher sUA levels over time, but still might have an increased risk when compared to controls due to residual confounding. For colchicine we hypothesized that it enhances infections because of its anti-inflammatory and immune-modulatory effects. Case-reports and case studies have shown that patients with colchicine overdose develop infectious complications,²⁶⁻²⁸ also in the absence of neutropenia, a well-established side effect.²⁹ Also, in patients using normal doses of colchicine and with normal cell counts, inhibitory effects of colchicine on leukocyte functions, such as degranulation,³⁰ chemotaxis and adherence,³¹ might be present. However, it is of note that the use of colchicine for acute gout in the UK is limited. Moreover, the effects were not consistent with the expected direction. Finally, it cannot be excluded that patients with current colchicine use actually had an infection that triggered an acute attack/flare and therefore a prescription of colchicine.

Our hypothesis that patients with gout have a reduced risk of infection-related mortality, could not be confirmed. This finding is in line with findings from a study on mortality in patients with gout that had specified causes of death, other than cardiovascular death.³² This retrospective cohort study that used the National Death Registry in Taiwan showed that women with gout had an excess mortality due to infectious diseases (standardized mortality ratio 2.25) compared to women without gout. However, this association disappeared after multivariate adjustment. Literature

on mortality in patients with gout has shown that patients with gout have an increased risk of cardiovascular mortality, as well as all-cause mortality.³³ As such, it would be interesting to investigate whether patients with gout, who had acquired an infection might die because of cardiovascular causes rather than due to infections. Not in the least, because it is known that infections might exacerbate underlying cardiovascular disease.³⁴ This was however beyond the scope of this study.

Our study has several strengths. It has a large sample size, used general population data and had a follow-up. The large amount clinical information routinely and longitudinally collected in clinical practice, allowed us to statistically adjust for many potential confounders such as, age, sex, smoking status, alcohol use, comorbidity and use of medication.

Our study has other limitations that need to be addressed. First, SUA levels, which play a key role in our hypothesis, are not routinely collected in CPRD. Patients with gout therefore acted as a surrogate representing the status of hyperuricaemia. Second, the use of diagnostic codes, mainly registered by general practitioners rather than rheumatologists, to define gout might have resulted in non-differential misclassification of the outcome and a bias towards null. Still, gout, but also the outcomes (pneumonia, UTI and mortality) are already extensively studied in CPRD and studies performed with CPRD have been extensively validated.^{16,35}

Third, diagnostic bias may have masked a protective effect of gout on infections, because patients with gout may more often visit their general practitioner compared to controls. This may have increased their likelihood to be diagnosed with a pneumonia or UTI.

In conclusion, this study did not support the hypothesis that patients with gout may acquire fewer community-acquired infections, such as pneumonia and UTI or have lower infection-related mortality. In contrast, this study showed that patients with gout had an increased risk of pneumonia and UTI, although for the latter these increased risks were attributable to classic risk factors. Therefore, the clinical relevance of these findings remain unclear and the effects seem small. Future research is needed to elucidate the exact mechanisms between uric acid, interleukins, infections and the role of colchicine and allopurinol.

References

1. Wijnands JM, Viechtbauer W, Thevissen K, et al. Determinants of the prevalence of gout in the general population: a systematic review and meta-regression. *Eur J Epidemiol*. 2015;30:19-33.
2. Kuo CF, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis*. 2015;74:661-7.
3. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum*. 2011;63:3136-41.
4. Richette P, Bardin T. Gout. *Lancet*. 2010;375:318-28.
5. Robinson PC, Merriman TR, Herbison P, et al. Hospital admissions associated with gout and their comorbidities in New Zealand and England 1999-2009. *Rheumatology (Oxford)*. 2013;52:118-26.
6. Stamp LK, Chapman PT. Gout and its comorbidities: implications for therapy. *Rheumatology (Oxford)*. 2013;52:34-44.
7. McCarthy DJ, Hollander JL. Identification of urate crystals in gouty synovial fluid. *Ann Intern Med*. 1961;54:52-60.
8. Martinon F, Petrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440:237-41.
9. Chen CJ, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J Clin Invest*. 2006;116:2262-71.
10. Liu-Bryan R. Intracellular innate immunity in gouty arthritis: role of NALP3 inflammasome. *Immunol Cell Biol*. 2010;88:20-3.
11. Dalbeth N, et al. Cellular characterization of the gouty tophus: a quantitative analysis. *Arthritis Rheum*. 2010;62:1549-56.
12. Mylona EE, Mouktaroudi M, Crisan TO, et al. Enhanced interleukin-1 β production of PBMCs from patients with gout after stimulation with Toll-like receptor-2 ligands and urate crystals. *Arthritis Res Ther*. 2012;14:R158.
13. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. *Cell Host Microbe*. 2011;9:355-61.
14. Crisan TO, Cleophas MC, Oosting M, et al. Soluble uric acid primes TLR-induced proinflammatory cytokine production by human primary cells via inhibition of IL-1Ra. *Ann Rheum Dis*. 2016;75:755-62.
15. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood*. 1996;87:2095-147.
16. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69:4-14.
17. Wijnands JM, van Durme CM, Driessen JH, et al. Individuals with type 2 diabetes mellitus are at an increased risk of gout but this is not due to diabetes: A population-based cohort study. *Medicine (Baltimore)*. 2015;94:e1358.
18. van der Zanden R, de Vries F, Lalmohamed A, et al. Use of dipeptidyl-peptidase-4 inhibitors and the risk of pneumonia: A population-based cohort study. *PLoS One*. 2015;10:e0139367.
19. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44:827-36.
20. Gallagher AM, Williams T, Leufkens HG, et al. The impact of the choice of data source in record linkage studies estimating mortality in venous thromboembolism. *PLoS One*. 2016;11:e0148349.
21. Lim SY, Lu N, Choi HK. Septic arthritis in gout patients: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54:2095-9.
22. Netea MG, Joosten LA, Latz E, et al. Trained immunity: A program of innate immune memory in health and disease. *Science*. 2016;352:aaf1098.
23. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A*. 2012;109:17537-42.
24. Crisan TO, Netea MG, Joosten LA. Innate immune memory: Implications for host responses to damage-associated molecular patterns. *Eur J Immunol*. 2016;46:817-28.
25. De Vera MA, Marcotte G, Rai S, et al. Medication adherence in gout: a systematic review. *Arthritis Care Res (Hoboken)*. 2014;66:1551-9.

26. Katz R, Chuang LC, Sutton JD. Use of granulocyte colony-stimulating factor in the treatment of pancytopenia secondary to colchicine overdose. *Ann Pharmacother*. 1992;26:1087-8.
27. Critchley JA, Critchley LA, Yeung EA, et al. Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol*. 1997;16:229-32.
28. Ben-Chetrit E, Navon P. Colchicine-induced leukopenia in a patient with familial Mediterranean fever: the cause and a possible approach. *Clin Exp Rheumatol*. 2003;21(4 Suppl 30):S38-40.
29. Kocak Z, Akay H, Guvenmez S, et al. Colchicine intoxication and infection risk: a case report. *J Clin Pharm Ther*. 2008;33:451-2.
30. Malawista SE, Bodel PT. The dissociation by colchicine of phagocytosis from increased oxygen consumption in human leukocytes. *J Clin Invest*. 1967;46:786-96.
31. Rinehart JJ, Boulware T. Microfilament and microtubule function in human monocytes. *J Lab Clin Med*. 1977;90:737-43.
32. Kuo CF, Yu KH, See LC, et al. Elevated risk of mortality among gout patients: a comparison with the national population in Taiwan. *Joint Bone Spine*. 2011;78:577-80.
33. Kuo CF, See LC, Luo SF, et al. Gout: an independent risk factor for all-cause and cardiovascular mortality. *Rheumatology (Oxford)*. 2010;49:141-6.
34. Smeeth L, Thomas SL, Hall AJ, et al. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351:2611-8.
35. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract*. 2010;60:e128-36.

Chapter 9

Knowledge, illness perceptions and stated clinical practice behaviour in management of gout: a mixed methods study in general practice

Bart Spaetgens, Tobias Pustjens, Lieke EJM Scheepers, Hein JEM Janssens, Sijf van der Linden, Annelies Boonen

Clin Rheumatol 2016;35:2053–2061

Abstract

The objective of the present study is to explore knowledge, illness perceptions and stated practice behaviour in relation to gout in primary care. This is a mixed methods study among 32 general practitioners (GPs). The quantitative assessment included the Gout Knowledge Questionnaire (GKQ; range 0–10; better) and Brief Illness Perceptions Questionnaire (BIPQ; nine items, range 0–10; stronger). Structured individual interviews obtained further qualitative insight into knowledge and perceptions, in the context of daily practice. Among 32 GPs, 18 (56.3%) were male, mean age 44.4 years (SD 9.6) and mean working experience 17.1 years (SD 9.7). Median score [interquartile ranges (IQR)] on the GKQ was 7.8 [6.7–8.9] and 9.0 [8.0–10.0], when presented as open or multiple-choice questions, respectively. The BIPQ (median; [IQR]) revealed that gout was seen as a chronic disease (8.0; [7.0–9.0]), affecting life and emotions moderately (6.5; [5.0–7.0]), having many severe symptoms (8.0; [7.0–9.0]) and in which treatment could be very helpful (8.0; [7.0–9.0]). Further interviews revealed large variation in specific aspects of knowledge and about gaps concerning indications for uric acid-lowering therapy (UALT), duration of UALT, target serum uric acid (sUA) level or duration of prophylactic treatment. Finally, patients' adherence was not checked systematically. Specific knowledge gaps and discrepancies between perceptions and stated practice behaviour were identified, which might hamper effective management of this welltreatable disease. Improving evidence on the rationale and effectiveness of treatment targets and adherence interventions, tailoring guidelines to general practice and intensification of implementation of guidelines in primary health care seem to be needed.

Introduction

Gout is a chronic rheumatic disease with a reported prevalence of 2.5% in the UK and 3.9% in the USA, making it the most common inflammatory joint disease.¹⁻³ Despite being a well-treatable disease, it is recognized that the management of gout is suboptimal in both primary⁴ and secondary care.⁵ In a primary care study among patients with gout, low levels of allopurinol prescribing (57%), serum uric acid (sUA) level testing (55%) and achievement of target sUA level (<0.36 mmol/l) (22.4%) during a 5-year study period were shown.⁶ In secondary care, adherence to American College of Rheumatology (ACR) guideline recommendations by rheumatologists could be highly improved, shown by a mean adherence score of 5.8 out of 8 ACR guideline recommendations. Low adherence on first-line uric acid-lowering therapy (UALT) dosage, acute prophylaxis dosage and length of prophylaxis was shown.⁵ Common barriers for effective management can be distinguished into patient and physician barriers. Important barriers among patients were not only misperception of the severity and chronicity of gout, but also inadequate patient education resources, resulting in poor adherence to treatment.⁷⁻⁹ Among physicians, underestimation of long-term complications and insufficient knowledge about the indications for UALT and about adequate dosing of UALT have already been suggested.^{10,11}

On the same line, some qualitative studies explored barriers to effective gout management among patients and physicians.¹²⁻¹⁶ Despite general practitioners (GPs) being the most relevant (in most countries) health care professionals when it comes to diagnosing and treating the disease, the studies in current literature included only a low number of GPs. Therefore, broad insight into how gout is managed by GPs is missing. Notwithstanding, linking knowledge, perceptions and stated practice behaviour is essential when planning to improve gout management for patients with gout.

The current study uses a quantitatively and qualitatively approach to understand knowledge, illness perceptions and stated clinical behaviour of GPs when managing gout with specific attention to the role of UALT, sUA level and prophylactic treatment.

Materials and methods

Study design and data collection

A mixed methods approach was used to investigate and understand specific knowledge gaps in pathophysiology and management of gout, illness perceptions about the disease and clinical stated practice behaviours in management. The Good Reporting of A Mixed Methods Study (GRAMMS) guidelines as provided by the Enhancing the QUALity and Transparency Of health Research (EQUATOR) network were followed.^{17,18}

The study was conducted in the southern part of the Netherlands. During a period of 2 weeks, GPs were asked to participate in the study. After agreeing, questionnaires on

demographics, gout knowledge and gout perceptions were administered, followed by a structured interview to explore indepth understanding and to relate both issues to practice behaviour. The structured interviews were audiotaped and transcribed verbatim. The GPs consented to quote part of the interviews in anonymized form.

Demographics

General questions about age, sex, years working experience as GP, hours involved in patient care, estimated number of patients with gout per year, practice type, recent education on gout (within the last year, yes/no) and familiarity with gout (on a 0-10 scale, 0 being not familiar and 10 being extremely familiar) were recorded.

Gout knowledge questionnaire

The Gout Knowledge Questionnaire (GKQ) aims to assess knowledge of patients or physicians and addresses ten multiple-choice questions related to the pathogenesis, treatment of acute attacks and also management of chronic gout.^{19,20} GPs were first asked to answer the questions while blind for the answer options. In case that they hesitated (or did not use one of the questionnaire answer options), the interviewer showed the original GKQ multiple-choice answers. The GKQ was previously translated into Dutch according to the International Society for Pharmacoeconomics and Outcome Research (ISPOR) principles of good practice,²¹ which is consistent with the approach proposed as best practice in rheumatology by Beaton.²² As each correct answer provides a score of one, the total score ranges from 0 to 10, with higher scores indicating better knowledge.

Brief illness perceptions questionnaire

When completing the validated Dutch version of the Brief Illness Perceptions Questionnaire (BIPQ),^{23,24} the GPs were asked to rate their personal perceptions, while imagining that they would suffer from gout with an "average" disease course. The BIPQ is a nine-item questionnaire that assesses cognitive and emotional perceptions of a disease, within nine domains (Q1: consequences, Q2: timeline, Q3: personal control, Q4: treatment control, Q5: identity, Q6: coherence, Q7: emotional representation, Q8: concern, Q9: cause). Q1 to Q8 are scored on an 11-point numeric rating scale (0 to 10), with higher scores representing a more threatening view per domain. Q9 additionally permits to list up to three items that play a causative role in the disease.

Structured interviews

After completing the questionnaires, the GPs were interviewed to gain more in-depth insight into knowledge and perceptions and link these to clinical practice behaviour,

specifically with regard to the role of sUA in diagnosis and follow-up, appropriate usage of UALT and the role of adherence in relation to management of the disease.

Data analysis

Descriptive statistics were used to present the demographics and results of questionnaires, and means with standard deviation (SD) or medians with interquartile ranges [IQR] were used depending on skewness of data.

For qualitative analysis, the verbatim transcripts were read repeatedly and independently by two readers. Using the grounded theory approach, a coding system with categories that were identified in the previous step was developed as well as a taxonomy of the data.²⁵ The two readers met regularly to discuss coding and interpretation of data. Wherever necessary, consensus was reached after discussing specific passages or a third reader acted as referee. Representative quotes were collected during data analysis and reported based on the frequency of the particular (and similar) quotes.

Results

Demographic characteristics

Thirty-two GPs were interviewed. Eighteen (56.3%) were male; the mean age was 44.4 years (S.D. 9.6 years); the mean number of years of working experience as GP is 17.1 years (S.D. 9.7 years). The GPs were 34.1 h (S.D. 11.0) per week involved in patient care, and only four (12.9%) had followed an educational event on gout in the past year. The estimated number (mean) of new patients with gout in their practice was 8.9 (S.D. 7.0) per year, and familiarity with the disease was scored as 7.0 out of 10.0 (S.D. 1.1) (Table 9.1).

Table 9.1 Baseline characteristics for general practitioners (GP) (n=32).

Age (years), mean $\pm$ S.D.	44.4 $\pm$ 9.6
Male sex; n (%)	18 (56.3)
Practice type, n (%)	
Group practice	15 (46.9)
Private practice	4 (12.5)
Self-employed substitute	10 (31.2)
Other	3 (9.4)
Years' experience as GP, mean $\pm$ S.D.	17.1 $\pm$ 9.7
Hours involved in patient care, mean $\pm$ S.D. [range]	34.1 $\pm$ 10.9 [8-55]
Estimated new patients with gout per year, mean, (median), [IQR]	8.9 (7.0) [4.3-11.5]
Recent (<1 year) education in gout, n (%)	5 (15.6)
Self-reported Gout familiarity (score 0-10), mean $\pm$ S.D. [range]	7.0 $\pm$ 1.1 [5-9]
Gout Knowledge Questionnaire (score 0-10), mean, (median), [IQR]	
Open answers	7.4 (7.8) [6.7-8.9]
Multiple choice answers	9.1 (9.0) [8.0-10.0]

Gout knowledge

The mean scores (number of correct answers) for the GKQ were 7.4 (median 7.8) [IQR 6.7-8.9] and 9.1 (9.0) [8.0-10.0] when answering an open or multiple-choice question with the original answer options, respectively. The numbers (%) of GPs with correct answers for each item are summarized in Table 9.2. Questions on the cause of gout (Q1, Q3), signs indicating an acute attack (Q2), treatment of an acute attack (Q4) and recognition of allopurinol being UALT (Q5) were correctly answered by 88 to 100% of the GPs in the open questioning part, respectively. Questions on flare prevention (Q9) and comorbidity (Q10) were answered correctly by 72 and 50%, respectively, but improved to 97 and 100% when presenting the original answer options. On the other hand, the question on the target value ("ideal value") (Q6) was answered correctly by 12%, in the open question, but it increased to 84% when presenting the original answer options. Finally, the questions about non-pharmacological interventions (Q7) and duration of UALT (Q8) improved to only 75 and 69% correct answers after seeing the answer options.

Illness perceptions about gout

The results of the perceptions of GPs about gout are summarized in Table 9.3. GPs considered gout to be a chronic disease (Q2: median 8.0), with (a considerable number of) severe symptoms (Q5: median 8.0), but with moderate impact on life and emotions (Q1 and Q8: median 6.5), and for which treatment is very helpful (Q4: median 8.0). They believed that gout is not strongly influenced by personal actions (Q3: median 4.0). A large variation was observed in perceptions of the amount of concerns gout can raise (Q6: median 5.0, IQR 3.3-6.8) and the level of understanding of the disease (median 6.0, IQR 3.3-7.0). Finally, 16 of 32 (50%) reported diet (alcohol, obesity) to be a major contributing cause of gout (Q9).

Qualitative analysis on knowledge, beliefs and practice behaviour

Table 9.4 shows the most frequent quotes per topic that were collected during the data analysis.

Assessment of serum uric acid and (use) of uric acid lowering therapy

First, divergent opinions about the usefulness of sUA to diagnose gout were observed. Ten GPs believe that sUA is necessary to diagnose gout, as gout cannot be diagnosed in the absence of hyperuricaemia. Twelve GPs indicated that sUA levels are required in some specific situations, namely the following: (1) "to differentiate gout from other diagnoses in atypical cases" (six GPs) and (2) "to strengthen the diagnosis of gout, which will lead to better treatment" (six GPs). The remaining ten GPs felt that sUA is not necessary and not even useful to diagnose gout. Reasons were (1) "gout is a clinical

diagnosis, preferably confirmed by joint aspiration" (four GPs) and 2) "a low sUA level does not exclude gout" (three GPs) and "sUA may be low, in particular when patients have an acute gouty arthritis" (three GPs).

Table 9.2 Gout knowledge level of general practitioners per question (n=32).

Question	Open question, correct answered, n(%)	Multiple choice, correct answered, n(%)
1) Q: What causes gout? Answer options: a) too little calcium, b) too much uric acid, c) an infection, d) diabetes	31 (96.9)	32 (100)
2) Q: How do you know if you have an acute attack of gout? Answer options: a) you have a painful swollen joint, b) you have a change in blood tests, c) your skin gets red and itchy, d) you have a lump on your ear	30 (93.8)	32 (100)
3) Q: What inside the joint causes attacks of gout? Answer options: a) bacteria, b) viruses, c) crystals, d) calcium	30 (93.8)	32 (100)
4) Q: Which of these is a good treatment during a sudden painful attack of gout in someone with no other medical condition? Answer options: a) exercise, b) allopurinol, c) NSAIDs like ibuprofen, naproxen or indomethacin, d) benzbromarone	32 (100)	32 (100)
5) Q: Lowering your blood uric acid can help prevent future attacks of gout. Which of these drugs can lower your blood uric acid? Answer options: a) allopurinol, b) prednisone, c) NSAIDs like ibuprofen, naproxen or indomethacin, d) colchicine	28 (87.5)	32 (100)
6) Q: What is the ideal blood uric acid level to aim for after treatment of gout? Answer options: a) lower than 0.59 mmol/l, b) lower than 0.48 mmol/l, c) lower than 0.36 mmol/l, d) lower than 0.12 mmol/l	4 (12.5)	27 (84.4)
7) Q: In order to reduce the serum uric acid, what can you do in addition to medications? Answer options: a) drink more beer, b) eat more seafood, c) eat more red meat, d) lose weight if you are overweight	Not applicable	24 (75.0)
8) Q: If you are taking a drug to lower your blood uric acid levels, how long do you need to take this drug? Answer options: a) one month, b) one year, c) two years, d) forever	20 (62.5)	22 (68.8)
9) Q: When taking a drug to lower your blood uric acid levels, there can be a temporary increase in gouty attacks. How can you prevent such attacks? Answer options: a) skip doses of the drug and restart, b) drink less water, c) drink alcohol every day, d) take daily colchicine	23 (71.9)	31 (96.9)
10) Q: Which is a medical condition that is common in patients with gout? Answer options: a) high blood pressure, b) cancer, c) AIDS, d) asthma	16 (50.0)	30 (93.8)
<i>Total correct score mean (median) [IQR]</i>	7.4 (7.8) [6.7-8.9]	9.1 (9) [8-10]

Table 9.3 Results of the BIPQ in general practitioners.

	Mean, (median) [IQR]	n (%)
Q1 Consequences (10 = severely affects life)	6.2 (6.5) [5.0-7.0]	
Q2 Timeline (10 = continues forever)	7.5 (8.0) [7.0-9.0]	
Q3 Personal control (10 = extreme amount)	4.3 (4.0) [3.0-5.0]	
Q4 Treatment control (10 = extremely helpful)	7.8 (8.0) [7.0-9.0]	
Q5 Identity score (10 = many severe symptoms)	7.7 (8.0) [7.0-9.0]	
Q6 Illness concern (10 = extremely concerned)	5.0 (5.0) [3.3-6.8]	
Q7 Coherence (10 = understands very clearly)	5.7 (6.0) [3.3-7.0]	
Q8 Emotional representation (10 = extremely affected emotionally)	6.2 (6.5) [5.0-8.0]	
Q9: Top listed causes:		
1. Diet (alcohol, obesity)		16(50.0)
2. Hereditary		13 (40.6)
3. Medication (i.e. diuretics)		12 (37.5)

Second, reasons to start treatment with UALT were very diverse. The most important reasons were the number of gout attacks per year: "The main reason to start with UALT is when patients have more than 3 gout attacks per year", severity of symptoms: "If patients have fewer attacks (e.g. <3), but the complaints during the attack are severe, then this is a reason to start UALT" and hyperuricaemia in case of a gout attack. Only six GPs mentioned tophi as reason to start with UALT, and three of these GPs determined the effectiveness of UALT, based on the resolution of (if present) tophi.

Third, with regard to duration of UALT, 12 GPs did not prescribe lifelong UALT, for one or more different reasons. Seven of these GPs tried to stop the UALT after 1 year: "If patients have no gout attacks for a longer period of time (e.g. 1 year), I try to reduce and eventually stop UALT"; five GPs suggested that UALT could be stopped after adjustment of lifestyle: "Allopurinol is prescribed lifelong, unless patients change their lives in such a way, you do not expect them to get gout attacks anymore (after weight reduction or stopping diuretics)"; six GPs terminated UALT in the occurrence of renal impairment. One GP thought that allopurinol could be used to treat an acute gouty arthritis.

Fourth, when initiating UALT, nine did not add prophylactic treatment to prevent flares. These GPs advised changing medication/lifestyle (three GPs), prescribed higher doses (or a combination) of UALT in case of flares during the drug start-up phase (three GPs) or waited until the patient was attack-free for a longer period before starting UALT (three GPs). Of the 23 GPs starting colchicine or a non-steroidal anti-inflammatory drug (NSAID) during UALT start-up, none prescribed prophylactic treatment for longer than 2 months: "I combine allopurinol and colchicine to prevent acute gout flares, for a period of 2–4 weeks". (14 GPs).

Finally, to determine effectiveness of UALT, 26 GPs determined sUA, of which six only in case patients continue to have attacks. Seventeen GPs explicitly stated that they did not strive for the target level of 0.36 mmol/l but based effectiveness of UALT on the absence of new gout attacks and stated that higher sUA levels were acceptable: "The target level of 0.36 mmol/l is not a strict treatment goal. I accept higher serum uric acid

levels if the number of acute attacks is decreased". Six GPs never determine sUA to monitor treatment.

Table 9.4 Themes from qualitative analysis with representative quotes.

Number / Themes	Quotes
1 Knowledge	"I don't know the target level of serum uric acid; I always look in the lab form for the reference values." (which are 0.20-0.42 mmol/l)
2 Illness perceptions	"Gout is a chronic devastating systemic disease, leading to functional disability." "The associated kidney disease or heart failure are very serious conditions, but the acute attacks are the worst for patients."
3 Necessity of uric acid	"Gout cannot be diagnosed without the presence of hyperuricemia." "Serum uric acid is not useful, because it will be low in patients with an acute attack"
4 Treatment with UALT	"The main reason to start with UALT is when patients have more than 3 gout attacks per year." "If patients have fewer attacks (e.g. <3), but the complaints are very severe, then this is a reason to start UALT."
5 Duration of treatment with UALT	"Allopurinol is prescribed lifelong, unless patients change their lives in such a way, you do not expect them to get gout attacks anymore (after weight reduction or stopping diuretics)." "If patients have no gout attacks for a longer period of time (e.g. 1 year), I try to reduce and thereafter stop the UALT."
6 Flare prophylaxis	"I combine allopurinol and colchicine to prevent acute gout flares, for a period of 2-4 weeks." "I never prescribe allopurinol after an acute flare, first I prescribe colchicine (or a NSAID) and after 4 weeks I stop it and start allopurinol." "I do not prescribe prophylactic treatment, I advise patients to drink more and sometimes stop diuretics."
7 Target level serum uric acid	"The target level of 0.36 mmol/l is not a strict treatment goal. I accept higher serum uric acid levels if the number of acute attacks is decreased." "If patients have gout, I try to reduce the serum uric acid level below 0.36 mmol/l in order to reduce the hyperuricemia-associated risk of cardiovascular events. Furthermore, I will check and if necessary adjust cholesterol, blood pressure and glucose."
8 Adherence	"Adherence to UALT is not a problem in patients with gout, since they are well aware of the fact they will get new gout attacks if they do not take their medication." "I think patients with gout take their medication (UALT) very well in the beginning, but in the course of time become less adherent. Then these patients will return with a gout flare." "I have too little time to check whether patients with gout are adherent."
9 Lifestyle advices	"I refer my patients to a website (www.thuisarts.nl)* where all truths and untruths about gout are presented. If I am correct, there is no evidence for all these dietary advices" "I give the same lifestyle advices as I give patients in cardiovascular risk management" "I warn patients for the possible danger of alcohol and organ meats. Also, I try to motivate them to lose some weight"

* a Dutch website with the most essential information in plain language, understandable by patients, about diseases treated by GPs, an initiative from the Dutch College of GPs.

Adherence to drug therapy

Nineteen GPs believed that patients with gout are adherent to their drug treatment. "Patients are well aware of the fact new gout attacks will occur if they don't take their medication". Of the 13 GPs that assumed that patients were not adherent to therapy, nine GPs believed that they were adherent in the beginning but stop UALT over time: "I think patients with gout take their medication (UALT) very well in the beginning, but in over the course of time become less adherent". All GPs assumed that these patients would restart therapy themselves in case of a new attack. Only eight GPs actively monitored patient adherence by planning appointments at a regular interval (varying from 1 month in the start-up phase to once a year), during which two determined sUA to assess adherence. Seven GPs check adherence when patients had an appointment for any reason. Furthermore, when specifically inquired, 12 confirmed that they checked regularly whether patients pickup their repeat prescriptions, but only electronically and no contact with the nonadherent patients would follow. If non-adherence was recognized (in any way), only 12 GPs would discuss the effects and complications of being non-adherent. Ten GPs admitted to spend insufficient effort in the follow-up of adherence. Main reasons are lack of time or beliefs that patients are adherent anyhow.

Lifestyle advice in patients with gout

Sixteen GPs believed that diet and drinking habits were main contributing causes of gout (BIPQ (Q9)), and all of these mentioned that adjustment of these factors (weight loss, less alcohol, no organ meats, drink more water) would lower sUA in addition to medication. It was therefore surprising to see that only four GPs gave any lifestyle advice(s) to patients with gout. Seven GPs explicitly mentioned that adjustment of diet was outdated.

Discussion

Our study adds fuel to the ongoing debate about why gout, a treatable disease, is often insufficiently controlled.^{8,26} The strength of this study is that it is the first to address, at the same time, knowledge, illness perceptions and stated clinical practice behaviour in GPs, the medical professionals that commonly diagnose and treat gout. Moreover, the use of a mixed quantitative and qualitative approach allowed to gain in-depth insight into the consequences of gout knowledge and (inadequate) perceptions on gout in general practice, while, at the same time, providing an overall quantification. In Figure 9.1, we summarized several potential barriers identified in our study and illustrated graphically how these barriers might eventually effect quality of care in patients with gout.

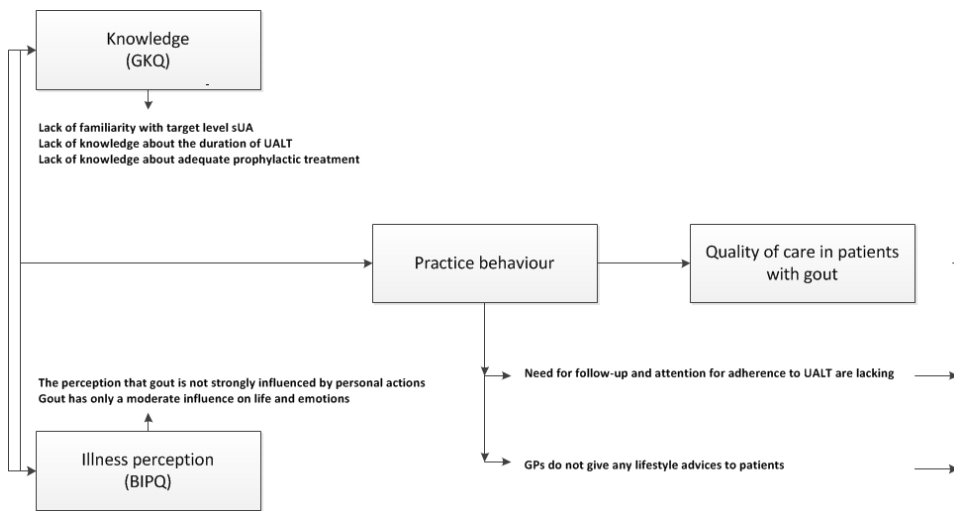


Figure 9.1 Identified barriers to optimal management in patients with gout treated by general practitioners.

The GPs' knowledge, as measured with the GKQ, on pathophysiology, signs and symptoms and treatment of an acute gout attack was mostly excellent, although only half of them indicated that dietary factors play a causative role in gout. However, GKQ-data combined with interviews on knowledge and practice behaviour learned that there is a large variation in the long-term management of gout, specifically in reasons to start UALT, the duration of UALT prescribing and prophylactic treatment at initiation of UALT. The latter finding is in line with one other study already showing inappropriate use of prophylactic colchicine among 74% of the patients under care of a primary care physician.²⁷ Furthermore, although GPs have a pragmatic and realistic view on the evaluation of effectiveness of UALT, it was interesting that most GPs were not aware of the sUA target level of 0.36 mmol/l as recommended by guidelines and stated to use (if any) the upper limit of laboratory normal ranges (0.42 mmol/l). Finally, half of the GPs indicated that dietary factors play a causative role in gout, but only few would give lifestyle advices to improve and eliminate causative factors, although it might be attributed partly due to lack of high-quality evidence for specific dietary interventions (avoidance of alcohol, weight loss).²⁸ Moreover, lifestyle interventions could have a role in management of gout-associated comorbidities (e.g. cardiovascular diseases, renal disease).

It is well known that also perception of the burden of disease influences the dedication of professionals to a disease and its management. It was therefore reassuring that the GPs perceived gout as a chronic disease with severe symptoms and important impact, in which treatment is very helpful. The GPs' illness perceptions are in accordance with those of 142 patients with gout, which showed that patients also viewed gout as a

chronic condition responsive to therapy, but not influenced by personal actions.²⁹ Nevertheless, there was a striking unawareness among GPs with respect to need for follow-up and/or attention for adherence, as most GPs sincerely believed that patients were adherent to treatment. Other reasons to not make follow-up appointments or check adherence regularly were lack of time or believe that patients who were non-adherent would present themselves automatically when having a new gout flare, actually referring to the patients' personal responsibility. So, even when adherence was checked by the GP, actions to improve inadequate adherence were rare.

We realize that the interpretation of the results of our study might be difficult, since we did not actually evaluated quality of care by auditing GPs' adherence to treatment guidelines or quality indicators (QI). Nevertheless, using the ACR and European League Against Rheumatism (EULAR) guidelines as external standard,³⁰⁻³² we implicitly took a large number of the formulated QI by Mikuls et al.³³ into account. A first example would be the QI about the role of follow-up of sUA level when prescribing UALT: "IF a gout patient is given a prescription for a xanthine oxidase inhibitor, THEN a serum urate level should be checked at least once during the first 6 months of continued use, BECAUSE periodic serum urate measurements are required for appropriate dose adjustments of xanthine oxidase inhibitors (escalations or reductions)". A second example would be the QI about behavioural modifications: "IF a patient is diagnosed with gout and has either (1) obesity (defined as a body mass index ≥ 28 kg/m²) or (2) frequent alcohol use (≥ 1 alcoholic beverage per day), THEN as part of their overall therapy, patients should be advised on the importance of weight loss and/or decreased alcohol use, BECAUSE weight loss and reduction of alcohol intake may be beneficial components of gout therapy". On this line, it is important to realize that the guideline on "arthritis", including recommendations how to diagnose and manage gout of the Dutch College of General Practitioners (NHG), currently does not mention a specific sUA level as a treatment target, does not recommend prophylactic treatment when initiating UALT and does not provide specific advises on behavioural modifications, follow-up or monitoring of adherence for patients with gout.³⁴ On the other hand, while the GPs' standard mentioned the presence of tophi as indication to initiate UALT, 26 GPs do not mention tophi as a reason to start UALT. Although guidelines are a good starting point to improve quality of care, it is well known that recommendations do not guarantee ubiquitous agreement or compliance with them. Harrold et al. reported among a random sample of US PCPs (including 444 GPs) that only 9.6% of the GPs were aware of the guidelines and adhered to recommended treatment for acute, intercritical and tophaceous gout in only 47, 3.4 and 12.5% of the cases, respectively.³⁵ In addition to (non)awareness, physicians (including GPs) are experts with strong opinions whom might not always agree with recommendations in guidelines and might question the evidence.

Although already a large amount of evidence is available and summarized in the 2006 EULAR and 2012 ACR guidelines, it should be recognized that the strength of evidence for several recommendations, such as the role and value using sUA as a target for

treatment, still needs improvement. As such, we believe that QI that are part of GP's audit might be more effective. Nevertheless, these QI still require strong evidence and a costly organization for monitoring and auditing.

Last, the differences in views between GP and international guidelines might be explained by the heterogeneity of the disease itself and important differences in disease spectra between primary and secondary care will be present. Undoubtedly, GPs treat the milder cases. Therefore, one of the outstanding issues is to collect high-quality registry data in primary care and identify factors that might predict poor prognosis.

This study has other limitations that need to be addressed. First, GPs were recruited from one region in the Netherlands. This might limit the generalizability of these results to all GPs in (and outside) the Netherlands. Nevertheless, we included a broad spectrum of GP that was also representative for the Dutch situation, with regard to years of working experience, sex distribution and age, as this is necessary for qualitative studies (in the Netherlands, 56% of the GPs are male with a mean age of 48.8 years and of which 46% have a fulltime employment). As such, the current study represents to date the largest qualitative study in gout. The number of 32 GPs is acceptable from a quantitative view, as for the qualitative part of the study, the theoretical saturation points of information were reached. Second, the GKQ was developed as a multiplechoice questionnaire with some of the multiple-choice answers being too obvious in our opinion. Therefore, the questionnaire was presented first with open-ended items (i.e. hiding the answer options), thereby eliciting quotes and thus supporting the qualitative analyses. Finally, in our study, as in any study with qualitative analyses, it might be possible that the interviewer, the questionnaires (that were completed before the interview) or the semi-structured character of the interview itself unintentionally influenced the GPs' answers.

In conclusion, among a sizable proportion of GPs, we have identified specific knowledge gaps and discrepancies between illness perceptions and stated clinical practice behaviour of GPs that might imply risks for shortcoming patient management in primary health care. Improvement of knowledge of evidence-based treatment targets, implementing adherence interventions and tailoring up-to-date guidelines to general practice are needed to ultimately improve the care of all patients with gout.

References

1. Kuo CF, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74:661-7.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricaemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 2011;63:3136-41.
3. Wijnands JM, Viechtbauer W, Thevissen K, et al. Determinants of the prevalence of gout in the general population: a systematic review and meta-regression. *Eur J Epidemiol* 2015;30:19-33.
4. Jeyaruban A, Larkins S, Soden M. Management of gout in general practice - a systematic review. *Clin Rheumatol* 2015;34:9-16.
5. Oderda GM, Shiozawa A, Walsh M, et al. Physician adherence to ACR gout treatment guidelines: perception versus practice. *Postgrad Med* 2014;126:257-67.
6. Robinson PC, TaylorWJ, Dalbeth N. An observational study of gout prevalence and quality of care in a national Australian general practice population. *J Rheumatol* 2015;42:1702-7.
7. De Vera MA, Marcotte G, Rai S, et al. Medication adherence in gout: a systematic review. *Arthritis Care Res (Hoboken)* 2014;66:1551-9.
8. Doherty M, Jansen TL, Nuki G, et al. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis* 2012;71:1765-70.
9. Johnston ME, Treharne GJ, Chapman PT, et al. Patient information about gout: an international review of existing educational resources. *J Rheumatol* 2015;42:975-8.
10. Stamp LK, Merriman TR, Barclay ML, et al. Impaired response or insufficient dosage? Examining the potential causes of "inadequate response" to allopurinol in the treatment of gout. *Semin Arthritis Rheum* 2014;44:170-4.
11. Ogdie AR, Hoch S, Dunham J, et al. A roadmap for education to improve the quality of care in gout. *Curr Opin Rheumatol* 2010;22:173-80.
12. Singh JA. Challenges faced by patients in gout treatment: a qualitative study. *J Clin Rheumatol* 2014;20:172-4.
13. van Onna M, Hinsenveld E, de Vries H, et al. Health literacy in patients dealing with gout: a qualitative study. *Clin Rheumatol* 2015;34:1599-603.
14. Harrold LR, Mazor KM, Velten S, et al. Patients and providers view gout differently: a qualitative study. *Chronic Illn* 2010;6:263-71.
15. Spencer K, Carr A, Doherty M. Patient and provider barriers to effective management of gout in general practice: a qualitative study. *Ann Rheum Dis* 2012;71:1490-5.
16. Chandratne P, Mallen CD, Roddy E, et al. "You want to get on with the rest of your life": a qualitative study of health-related quality of life in gout. *Clin Rheumatol*. 2016;35:1197-205.
17. O'Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. *J Health Serv Res Policy* 2008;13:92-8.
18. Equator Network. The Enhancing the QUALity and Transparency of health Research (EQUATOR) network website. Available from URL: <http://www.equator-network.org> [accessed on 20 March 2015]
19. Zhang LY, Schumacher HR, Su HH, et al. Development and evaluation of a survey of gout patients concerning their knowledge about gout. *J Clin Rheumatol* 2011;17:242-8.
20. Li QH, Dai L, Li ZX, et al. Questionnaire survey evaluating disease-related knowledge for 149 primary gout patients and 184 doctors in South China. *Clin Rheumatol* 2013;32:1633-40.
21. Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for Patient-Reported Outcomes (PRO) measures: report of the ISPOR Task Force for translation and cultural adaptation. *Value Health* 2005;8:94-104.
22. Beaton DE, Bombardier C, Guillemin F, et al. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine (Phila Pa 1976)* 2000;25:3186-91.
23. Broadbent E, Petrie KJ, Main J, et al. The brief illness perception questionnaire. *J Psychosom Res* 2006;60:631-7.
24. de Raaij EJ, Schroder C, Maissan FJ, et al. Cross-cultural adaptation and measurement properties of the Brief Illness Perception Questionnaire-Dutch Language Version. *Man Ther* 2012;17:330-5.
25. Pope C, Mays N. Qualitative research in health care, 3rd edn. Malden, Mass.: Blackwell Pub./BMJ Books 2006.

26. Rashid N, Coburn BW, Wu YL, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. *J Rheumatol* 2015;42:504-12.
27. George M, Pullman-Mooar S, Hussain F, et al. Evaluating appropriate use of prophylactic colchicine for gout flare prevention. *Arthritis Care Res (Hoboken)* 2012;66:1258-62.
28. Moi JH, SriranganathanMK, Falzon L, et al. Lifestyle interventions for the treatment of gout: a summary of 2 Cochrane systematic reviews. *J Rheumatol* 2014;Suppl 92:26-32.
29. Dalbeth N, Petrie KJ, House M, et al. Illness perceptions in patients with gout and the relationship with progression of musculoskeletal disability. *Arthritis Care Res (Hoboken)* 2011;63:1605-12.
30. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65:1312-24.
31. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricaemia. *Arthritis Care Res (Hoboken)* 2012;64:1431-46.
32. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1447-61.
33. Mikuls TR, MacLean CH, Olivieri J, et al. Quality of care indicators for gout management. *Arthritis Rheum* 2004;50:937-43.
34. Janssens HJLH, Van Peet PG, Gorter KJ, et al. NHG Standaard Artritis. *Huisarts Wet* 2009;52:439-53.
35. Harrold LR, MazorKM, Negron A, Ogarek J, Firreno C, Yood RA. Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire. *Rheumatology (Oxford)* 2013;52:1623-9.

Chapter 10

Summary and general discussion

Summary and discussion of main findings

This thesis contains several studies that focus on outcomes in patients with gout. As described in **Chapter 1**, outcome research in medicine is a challenging and dynamic process. A key aim is to identify outcome *domains* (e.g. *joint damage*) that have to be assessed in research or clinical practice, and to propose valid *instruments* (e.g. *conventional radiography*) to measure these domains. Within rheumatology, Outcome Measures in Rheumatology Clinical Trials (OMERACT) is an initiative that seeks consensus on domains and instruments, that should be minimally assessed in clinical trials in the various diseases.^{1,2} While ‘minimal’ or ‘core’ sets of domains and instruments present a major advantage to harmonize outcome assessment in clinical trials, they do not fill in broader needs of outcome research when it comes to understand the full impact of the disease on functioning and health. This thesis addressed some knowledge gaps that are important when it comes to outcome research in observational studies, trials and perhaps clinical practice in gout. The specific areas and domains that have been studied are presented in Figure 10.1, that visualizes the OMERACT framework.

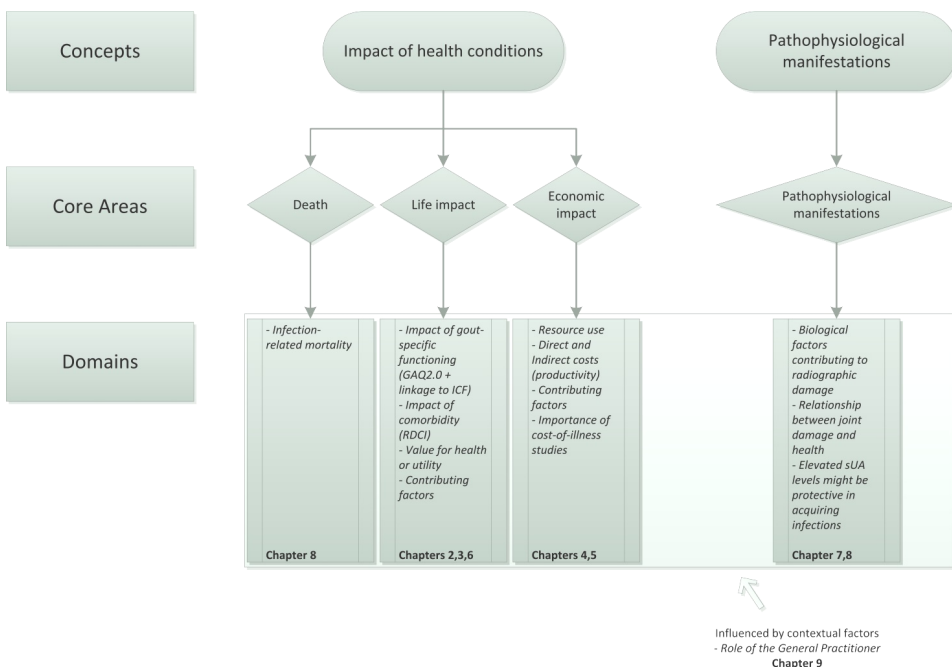


Figure 10.1 Adapted Framework of Concepts, Core Areas, & Domains for Outcome Measurement in patients with gout.

Adapted from: Developing core outcome measurement sets for clinical trials: OMERACT Filter 2.0 by Boers et al. *Journal of Clinical Epidemiology* 2014. Adapted with permission

Some of our studies focussed on the validity and clinimetric properties of specific instruments (the Gout Assessment Questionnaire 2.0 (GAQ2.0), the Rheumatic Diseases Comorbidity Index (RDCI) and the gout-modified Sharp van der Heijde score for radiographic damage) representing domains or subdomains in two outcome areas, life impact and pathophysiological manifestations. In other studies, the impact of gout itself on these outcomes, as well as the mutual relationships between outcomes were investigated. Finally, the role and influence of the setting in which the disease is managed has been explored, since this might be a relevant contextual factor, influencing outcome in gout.

In this chapter we first summarize the main results of each chapter and then discuss the findings while integrating information from the different chapters.

Life impact of gout

Validating patient reported outcomes

To further enable insight into the impact of gout and its associated cardiovascular, metabolic, renal and other³⁻¹⁰ comorbidities on patients, we studied measurement properties of instruments that will be helpful to understand patient-experienced functioning and health. These studies were conducted among 126 patients who were included in a recently started gout cohort at the Maastricht University Medical Centre (MUMC).

The Gout Assessment Questionnaire (GAQ) 2.0 is the only disease-specific patient-reported outcome (PRO) that aims to assess the impact of gout on a broad range of areas relevant for patients' health.^{11,12} Previously, limited evidence prevented its endorsement as PRO by OMERACT in the clinical and research setting. To improve applicability in research, further refinement of the instrument was recommended.¹³ Therefore, **Chapter 2** presents the cross-cultural translation and validation of the Dutch version of the GAQ 2.0, and generated new evidence on validity. Our study showed the GAQ2.0 had acceptable clinimetric properties with low floor/ceiling effects (floor effects ranged from 0.9 to 5.3% and ceiling effects ranged from 0.0 to 2.9%), sufficient to excellent internal consistency (Cronbach's α =0.83-0.94 for 4 of the 5 subscales) and test-retest reliability (ICC 0.73-0.86 for 4 of the 5 subscales). We also showed, by linking the GAQ2.0 to the International Classification of Functioning, Disability and Health (ICF), that it measures different aspects of health than generic instruments.¹⁴ The GAQ2.0 seems to have a stronger emphasis on emotional functions and less on limitations or physical activities. As such, the GAQ2.0 might be less suitable to measure physical function as its scope is broader. However, with PROs becoming increasingly important in outcome research, after all patient experience cannot be captured by objective biomedical findings, we believe the GAQ2.0 is a promising instrument to assess and

understand the impact of gout on functioning and health. The availability of additional language versions enhances its application in more cohorts and trials, and creates additional value for future research.

Gout has been associated with a large number of (lifestyle related) comorbidities. Therefore, in addition to gout itself, comorbidity might contribute to impaired functioning and health.⁷ To measure and adjust for comorbidity in studies on gout, the Rheumatic Diseases Comorbidity Index (RDCI) is considered an interesting instrument because it can be calculated based on self-report as well as on database-retrieved data.^{15,16} In **Chapter 3**, we investigated the content and construct validity of the Rheumatic Diseases Comorbidity Index (RDCI). Concerning its content, we explored the added value of adding obesity and kidney disease, as these comorbidities occur more often in gout and potentially would impact functioning and health. However, this modification resulted only in a minor improvement of construct validity for health outcome. In terms of feasibility, we therefore recommend the use of the original RDCI avoiding inconsistent use and incomparability of data. Strong correlations of the RDCI with other commonly used comorbidity indices, the Charlson Comorbidity Index¹⁷ and Functional Comorbidity Index¹⁸ ($r=0.78$ and $r=0.75$, respectively) were shown, confirming construct validity. Next, multivariable regression analyses showed that comorbidity measured with the RDCI had substantial additional influence on generic measures of physical function and physical health (the explained variance was 5.4% and 11.0% for HAQ and SF-36-physical component subscale, respectively) and direct costs (explained variance 4.0%). As such, we found evidence supporting the construct validity of the RDCI to measure comorbidity in patients with gout and proved the relevance of comorbidity in relation to health impact. Future research should focus on longitudinal data and whether the RDCI might also predict deterioration in long-term health outcome, resource utilisation, social role participation and mortality in the future. Another outstanding issue focuses on the external validation of this instrument in other populations, at least in a population-based sample.

Economic burden of gout and health utility

In **Chapter 4-6**, we assessed the burden of disease in patients with gout under care of a rheumatologist in the same baseline data of the gout cohort of the MUMC. Disease burden is the impact of a health problem measured by different indicators. It is often quantified as costs and/or in terms of quality or disability adjusted life years (QALYs/DALYs).¹⁹ In **Chapter 4**, we comprehensively investigated direct and indirect costs, including non-medical direct costs and presenteeism (compromised productivity while working) and investigated which factors drive the costs in patients with gout. We showed that the costs-of-illness of patients with gout are considerable, with direct costs being €5647 per patient per year. We found that 56.3% of the direct costs were constituted by non-medical resource use, representing professional household care and informal care by family and friends. When adding the costs of productivity loss (from the 30 patients (24%) with a paid job) to the direct costs-of-illness, costs further raised

to €6914 per patient per year when considering costs of sick leave and to €10,894 per patient per year when considering costs of sick leave and presenteeism. We noted these figures were comparable to costs-of-illness in ankylosing spondylitis and rheumatoid arthritis. Factors driving the costs were presence of cardiovascular disease, limitations in physical function (measured with the HAQ-DI) and female sex. We also found that the GAQ2.0 had an independent value in explaining direct costs. With regard to presenteeism, it should be noted presenteeism is a relevant concept but has mainly been validated as a PRO.²⁰ Therefore, caution is needed as not all presenteeism measures accurately reflect actual loss of productivity at the workplace.²¹ As such, future research into the true relation between self-reported productivity loss and actual loss of productivity is needed. In **Chapter 5** we comment on a systematic review about the economic burden of gout (published around the same time as our study).²² One of the main conclusions of this review was that the economic impact of the disease is important, but likely still underestimated. Two important reasons were mentioned. First, cost calculations on direct costs do not provide the complete picture as they are limited to direct medical costs and do not include direct non-medical costs. Second, cost calculations on indirect costs are scarce and incomplete, since only costs of sick leave (and not presenteeism) were included. As such, we were able to emphasize our findings of high societal costs which are the result of non-medical resource use and sick leave and presenteeism (which both enormously drive the costs) and to highlight the importance of comprehensively investigating all costs-of-illness in patients with gout. In addition to costs, in **Chapter 6** we investigated, in the same sample of patients with gout under care of a rheumatologist, health utility measured by the most commonly used approaches (e.g. EQ-5D,²³ SF-6D,²⁴ EQ-5D VAS). As such, we found that compared to the general population, a substantially higher proportion of patients with gout experienced moderate or severe limitations in the EQ-5D domains: mobility (65.6 vs. 12.4%), self-care (23.8 vs. 7.7%), daily activity (49.2 vs. 24.1%) and pain (75.6 vs. 44.8%), but not in anxiety/depression (17.9 vs. 19.1%). Furthermore, they also indicated a significantly worse overall health assessed by EQ-5D VAS score (66.1 vs. 79.5). In addition, we showed that the different approaches to assess value for health provide different utility values. This is important to keep in mind when incorporating utility values as QALYs in economic modelling. It was interesting to find that functional limitations (measured by HAQ-DI), cardiovascular disease, and also gout-specific features assessed by the GAQ2.0 were independent contributors to health utility, regardless of which method was used. In contrast to the widespread belief that only comorbidity and not gout per se has an adverse impact on functioning and health, we have now clearly shown that both gout-related comorbidities, but also the disease itself contribute to worse utility. This has important implications for clinical practice, since gout is a well-treatable and (at least partly) avoidable disease.

The finding that the disease-specific GAQ2.0 had additional value in explaining costs and utility scores is interesting and contributes to the further refinement of this

instrument. In further detail, the GAQ2.0-subscales about gout concerns ('gout concern overall' and 'gout concern during attack') were associated with costs and utility scores, while the subscale 'unmet treatment needs' was only associated with costs. An unexpected finding was to see that the influence of tophi and gout flares on costs and utility, was almost negligible. Possibly, the GAQ2.0 already captured the negative influence of flares or tophi. Of course, it can simply be that flares and presence or the number of tophi do not affect patient perceived outcome.²⁵

At the start of this thesis, the GAQ2.0 was the only disease-specific PRO applicable for gout and its final impact on long-term outcomes still needs further exploration. As a next step, meaningful thresholds, such as what cut-off of the GAQ2.0 or its subscales would be considered as problematic should be defined. For its use in clinical trials, a better insight in sensitivity to change needs further exploration. A randomized controlled trial assessed the minimal clinically important difference (MCID) which is between 5 and 8 points (on a 0-100 scale) for the different subscales.²⁶ Finally, it would be of interest to assess whether the GAQ2.0 has a role in clinical practice. For example, the GAQ2.0 could function as an instrument that reveals the patient's perception of gout impact on functioning and health, which in turn could help doctors to have a better understanding of their patient's disease and might even be helpful in shared decision making.²⁷ As such, PROs have potential to enhance patient involvement in disease management and to improve quality of care, eventually reducing unnecessary health care utilization, costs and loss of functioning and health.²⁸

Pathophysiologic manifestations in gout

Validating conventional radiography to assess joint damage

Within the OMERACT framework of outcome, joint damage is a domain within the area 'pathophysiological manifestations'. Joint damage had already been selected as a core outcome domain for clinical trials in gout, and imaging was proposed as an instrument.²⁹ However, data on validity of different imaging methods was lacking. In **Chapter 7**, we evaluated the construct validity of radiographic damage by conventional radiography (XR) in the same sample of patients with gout under care of a rheumatologist, as an approach to measure joint damage, as it is the most feasible imaging technique currently available. Doing so, we explored which biological factors contributed to radiographic damage and investigated the relationship between radiographic damage and health outcomes. We found that higher serum uric acid levels, presence of tophi and disease duration were significantly associated with erosions on XR, while patients with tophi also had more joint space narrowing. Furthermore, radiographic damage was associated with physical function assessed by HAQ, but not with overall physical health measured by the physical component subscale of the SF-36. We concluded that these findings support the construct validity

of conventional radiography to assess joint damage in the feet. Further research should (I) focus on the external validation of XR to assess joint damage in another population, (II) focus on the role of joint damage in both hand and feet and (III) explore whether there is a role for XR in clinical practice and whether XR-guided monitoring of joint damage would influence outcome (e.g. better physical functioning).

Pro-inflammatory state and infections

In **Chapter 8**, we investigated less frequently occurring outcomes: infections and infection-related mortality. Starting point for this study was recent evidence that showed that uric acid (by high serum levels, but also in the presence of monosodium urate crystals) leads to a pro-inflammatory state in patients with hyperuricaemia/gout, which in turn might lead to enhanced resistance to infections.³⁰⁻³² Data from a large general population-based cohort from the United Kingdom (Clinical Practice Research Datalink (CPRD)),^{33,34} were used to investigate the risks of various types of infections (pneumonia and urinary tract infection (UTI)), and infection-related mortality in patients with gout compared with population-based controls without gout. We did not find a decreased risk of infections, or lower infection-related mortality in patients with gout. In contrast, our study showed that patients with gout had an increased risk of pneumonia (HR 1.34; 95% CI 1.25-1.43) and UTI (HR 1.14; 95% CI 1.12-1.17), although these increased risks were (only partly for pneumonia) attributable to classic risk factors, including comorbidity (HR 1.27; 95% CI 1.18-1.36 for pneumonia and HR 0.99; 95% CI 0.97-1.01 for UTI). However, accounting for the observational nature in a real life setting, the effects should be considered small. It is possible that the clinical protective effect of serum uric acid (sUA) is small due to the fact this is a population-based cohort, or might be counteracted by other mechanisms, such as residual confounding. Furthermore, misclassification also might have occurred, since sUA was not measured directly, but by a general practitioner's (GP's) diagnosis of gout. In the light of the aforementioned reasons we believe it is too early to reject the hypothesis of a net pro-inflammatory state that enhances resistance to infections. Therefore, future research is needed to elucidate the mechanisms between uric acid, interleukins and infections.

Management of gout

The role of the general practitioner in relation to outcome

Despite being a well-treatable disease, it is recognized that gout management is suboptimal in both primary and secondary care.^{35,36} With GPs being the most relevant healthcare professionals when it comes to managing the disease, we investigated in **Chapter 9** among a group of 32 GPs specific knowledge gaps, illness perceptions and stated clinical practice that might affect quality of care in patients with gout. Using a mixed methods (quantitative and qualitative) approach we were able to investigate

knowledge and illness perceptions on gout of 32 GPs and to quantify them to some extent. As such, we showed that the GPs' overall knowledge on signs, symptoms and treatment of gout was mostly excellent, while also their illness perceptions that gout is a chronic disease with severe symptoms and important impact, in which treatment is very helpful, were reassuring. An interesting finding was that most GPs were not aware of the sUA target level of 0.36 mmol/l and the recommendation to start prophylactic treatment when initiating uric-acid lowering therapy. However, it is important to realize that the current Dutch national guideline for GPs (NHG standaard) does not mention a specific sUA target level or prophylactic treatment which is in contrast to treatment recommendations for rheumatologists. On the other hand, tophi are mentioned as a reason to initiate uric-acid lowering therapy, but only 6 of the 32 GPs mentioned this during the interviews. Although guidelines are a good starting point to improve quality of care, it is well known that recommendations in guidelines do not guarantee compliance with them.³⁷ Furthermore, it should be recognized that the strength of evidence for several recommendations in current ACR and EULAR guidelines, such as the sUA target level, ('treat to target') needs more support from clinical data.³⁸⁻⁴⁰ In conclusion, when measuring health outcome, factors that might not be directly related to the disease itself, called contextual factors, might influence the outcome of interest. An important contextual factor in disease management is the environment/setting in which the patient is treated. Differences in views between GPs and rheumatologists, who both treat patients with gout, and their guidelines might be explained by the heterogeneity of clinical presentations of the disease. In general, the GPs will treat the milder cases.

Generalizability of the results

The main strengths and limitations of the different studies included in this thesis have been described in the respective chapters itself. However, before the overall conclusions on the work in this thesis can be formulated, a general reflection on the patient population that was used is required.

In Chapters 2 to 7 we used data from a cohort of patients with gout under care of a rheumatologist at the University Hospital of Maastricht, the Netherlands. First, one can question whether these patients are representative for all patients with gout. On this line, it can be mentioned that the hospital serves mainly as a regional hospital for Maastricht and its surroundings. Further, patients included in the cohort represented the full spectrum of disease, varying from one episode of gouty arthritis to severe tophaceous gout. Notwithstanding, the sample will likely have an overrepresentation of patients with a more severe disease compared to patients in primary care. Likely, patients referred by a GP suffer from more severe gout with for example recurrent attacks or tophaceous gout. Furthermore, a substantial proportion of patients in the cohort were referred by other medical specialists (cardiologists, nephrologists,

pulmonologists) within the hospital, and likely also represent the more severe spectrum of the disease with more comorbidities. Consequently, the data on impact of the studied outcomes, such as costs, utility values and radiographic damage are only representative for patients in a second (partially third line) line referral cohort. Nevertheless, since our cohort represented the full spectrum of disease, the possible slight overrepresentation of severe disease will probably have no important influence on the validity of the instruments.

Second, the Dutch healthcare and social security system, is not necessarily comparable to that in other countries. Differences in healthcare and social security systems across countries are likely to affect referral to secondary care but also resource use, unit prices of resources, occurrence of sick leave, and valuation of experienced health impact (and thus utility values).

While the current data on the burden of gout cannot be generalized to the general population, it is important to realize that, it is for this (sub-)group under care of a rheumatologist, that the majority of innovative pharmacologic treatments are being developed. As many of these new drugs are expensive the current data are useful to understand the burden of the disease in this group, and will be valuable when developing models to assess cost-effectiveness.

Our studies do not contribute to the discussion on the heterogeneity of gout and the existence of different clinical phenotypes of the disease, varying from patients with isolated gout and only few comorbidities, patients with obesity, metabolic syndrome and diabetes, to a group of patients with (end-stage) cardiovascular disease, renal failure and diuretic use.⁴¹ Future research should focus on the exploration and further identification of different phenotypes in patients, since these might reflect different pathophysiological processes which eventually might influence the impact of gout on health outcome.

Conclusion and future perspectives

This thesis contributes to the assessment and understanding of previously unexplored aspects of outcome research in patients with gout. Outcome research itself is a challenging and dynamic process. Capturing the impact on functioning and health of a disease that has such heterogeneous manifestations as gout is difficult. However, we believe we made a valiant attempt by (I) validating instruments that measure both gout-specific characteristics (GAQ2.0, joint damage imaging) as well as comorbidity (RDCI), (II) understanding the independent influence of gout-specific characteristics and comorbidity on functioning and health from a patient's perspective, but also on costs-of-illness and health loss from a societal perspective, and (III) exploring the role and influence of the setting in which the disease is managed. At the same time, it stimulated us to formulate further needs in outcome research. Future work should focus on collecting high-quality registry data in primary care, the setting in which the largest burden of disease is found and on the usability of patient-reported outcome measures in the clinical setting. Furthermore, the heterogeneity of the disease makes it necessary to identify factors that might predict poor prognosis and to explore the different clinical phenotypes of the disease.

References

1. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. *J Clin Epidemiol*. 2014;67:745-53.
2. Boers M, Brooks P, Strand CV, et al. The OMERACT filter for Outcome Measures in Rheumatology. *J Rheumatol*. 1998;25:198-9.
3. Puig JG, Martinez MA. Hyperuricemia, gout and the metabolic syndrome. *Curr Opin Rheumatol*. 2008;20:187-91.
4. Kuo CF, Grainge MJ, Mallen C, et al. Comorbidities in patients with gout prior to and following diagnosis: case-control study. *Ann Rheum Dis*. 2016;75:210-7.
5. Krishnan E, Svendsen K, Neaton JD, et al. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med*. 2008;168:1104-10.
6. Seminog OO, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. *Rheumatology (Oxford)*. 2013;52:2251-9.
7. Stamp LK, Chapman PT. Gout and its comorbidities: implications for therapy. *Rheumatology (Oxford)*. 2013;52:34-44.
8. Kuo CF, Yu KH, Luo SF, et al. Gout and risk of non-alcoholic fatty liver disease. *Scand J Rheumatol*. 2010;39:466-71.
9. Kuo CF, Luo SF, See LC, et al. Increased risk of cancer among gout patients: a nationwide population study. *Joint Bone Spine*. 2012;79:375-8.
10. McAdams-DeMarco MA, Maynard JW, Coresh J, et al. Anemia and the onset of gout in a population-based cohort of adults: Atherosclerosis Risk in Communities study. *Arthritis Res Ther*. 2012;14:R193.
11. Hirsch JD, Lee SJ, Terkeltaub R, et al. Evaluation of an instrument assessing influence of Gout on health-related quality of life. *J Rheumatol*. 2008;35:2406-14.
12. Colwell HH, Hunt BJ, Pasta DJ, et al. Gout Assessment Questionnaire: Initial results of reliability, validity and responsiveness. *Int J Clin Pract*. 2006;60:1210-7.
13. Singh JA, Taylor WJ, Simon LS, et al. Patient-reported outcomes in chronic gout: a report from OMERACT 10. *J Rheumatol*. 2011;38:1452-7.
14. Cieza A, Geyh S, Chatterji S, et al. ICF linking rules: an update based on lessons learned. *J Rehabil Med*. 2005;37:212-8.
15. England BR, Sayles H, Mikuls TR, et al. Validation of the rheumatic disease comorbidity index. *Arthritis Care Res (Hoboken)*. 2015;67:865-72.
16. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2007;21:885-906.
17. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-83.
18. Groll DL, To T, Bombardier C, et al. The development of a comorbidity index with physical function as the outcome. *J Clin Epidemiol*. 2005;58:595-602.
19. Gold MR, Stevenson D, Fryback DG. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. *Annu Rev Public Health*. 2002;23:115-34.
20. Tang K, Boonen A, Verstappen SM, et al. Worker productivity outcome measures: OMERACT filter evidence and agenda for future research. *J Rheumatol*. 2014;41:165-76.
21. Kessler RC, Maclean JR, Petukhova M, et al. The effects of rheumatoid arthritis on labor force participation, work performance, and healthcare costs in two workplace samples. *J Occup Environ Med*. 2008;50:88-98.
22. Rai SK, Burns LC, De Vera MA, et al. The economic burden of gout: A systematic review. *Semin Arthritis Rheum*. 2015;45:75-80.
23. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208.
24. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21:271-92.
25. Chandratne P, Roddy E, Clarson L, et al. Health-related quality of life in gout: a systematic review. *Rheumatology (Oxford)*. 2013;52:2031-40.

26. Khanna D, Sarkin AJ, Khanna PP, et al. Minimally important differences of the gout impact scale in a randomized controlled trial. *Rheumatology (Oxford)*. 2011;50:1331-6.
27. Sarkin AJ, Levack AE, Shieh MM, et al. Predictors of doctor-rated and patient-rated gout severity: gout impact scales improve assessment. *J Eval Clin Pract*. 2010;16:1244-7.
28. Higginson IJ, Carr AJ. Measuring quality of life: Using quality of life measures in the clinical setting. *Bmj*. 2001;322:1297-300.
29. Grainger R, Dalbeth N, Keen H, et al. Imaging as an Outcome Measure in Gout Studies: Report from the OMERACT Gout Working Group. *J Rheumatol*. 2015;42:2460-4.
30. Mylona EE, Mouktaroudi M, Crisan TO, et al. Enhanced interleukin-1 β production of PBMCs from patients with gout after stimulation with Toll-like receptor-2 ligands and urate crystals. *Arthritis Res Ther*. 2012;14:R158.
31. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. *Cell Host Microbe*. 2011;9:355-61.
32. Crisan TO, Cleophas MC, Oosting M, et al. Soluble uric acid primes TLR-induced proinflammatory cytokine production by human primary cells via inhibition of IL-1Ra. *Ann Rheum Dis*. 2016;75:755-62.
33. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69:4-14.
34. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract*. 2010;60:e128-36.
35. Oderda GM, Shiozawa A, Walsh M, et al. Physician adherence to ACR gout treatment guidelines: perception versus practice. *Postgrad Med*. 2014;126:257-67.
36. Robinson PC, Taylor WJ, Dalbeth N. An Observational Study of Gout Prevalence and Quality of Care in a National Australian General Practice Population. *J Rheumatol*. 2015;42:1702-7.
37. Harrold LR, Mazor KM, Negron A, et al. Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire. *Rheumatology (Oxford)*. 2013;52:1623-9.
38. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2016.
39. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012;64:1431-46.
40. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64:1447-61.
41. Richette P, Clerson P, Perissin L, et al. Revisiting comorbidities in gout: a cluster analysis. *Ann Rheum Dis*. 2015;74:142-7.

Samenvatting

Samenvatting

Jicht is een gewrichtsontsteking, ook wel artritis genoemd, en is wereldwijd de meest voorkomende reumatische aandoening. Jicht komt vaker voor bij mannen en begint meestal na het 40^e levensjaar. Het ontstaat doordat urinezuurkristallen na een periode van verhoogd urinezuur in het bloed, neerslaan in de gewrichten en een ontstekingsreactie veroorzaken. Klassiek wordt de ziekte gekenmerkt door plotse en voorbijgaande aanvallen van heftige pijn, roodheid en zwelling in één of meerdere gewrichten. Een subgroep van patiënten ontwikkelt echter frequente, recidiverende aanvallen of zelfs chronische artritis. Dit kan samengaan met het ontstaan van tophi (neergeslagen urinezuurkristallen in de huid, kraakbeen of bot), die uiteindelijk tot chronische gewrichtsschade kunnen leiden. Bij patiënten met jicht blijken een aantal andere aandoeningen, ook wel comorbiditeiten genoemd, vaker voor te komen. Vooral hoge bloeddruk, hart- en vaatziekten en verminderde nierfunctie worden vaker vastgesteld bij patiënten met jicht.

Logischerwijs heeft jicht met zijn onvoorspelbare aanvallen of chronische schade, maar ook als gevolg van aanwezige comorbiditeiten, een belangrijke invloed op de gezondheid van patiënten die deze ziekte hebben. Het onderzoek naar de invloed van jicht op gezondheid is momenteel echter beperkt. Mogelijk komt dit doordat jicht in feite een goed behandelbare ziekte is, waardoor men niet onmiddellijk een belangrijke invloed op gezondheid verwacht. Daarom werd er in dit proefschrift aandacht besteed aan:

- (I) het in kaart brengen van de ziektelast en zorgconsumptie (inclusief ziektekosten) van patiënten met jicht die onder behandeling zijn van een reumatoloog;
- (II) de rol van zowel comorbiditeiten, alsook ziekte-specifieke kenmerken daarin; en
- (III) de rol van de huisarts (in termen van kennis en ziekteperceptie) in de behandeling van patiënten met jicht.

Om bovenstaande doelen te verwezenlijken, besteedden we in dit proefschrift verder specifieke aandacht aan de betrouwbaarheid van de verschillende instrumenten die in klinische studies de bovengenoemde ziektelast moeten meten.

Ten eerste, hebben wij daarom een drietal meetinstrumenten onderzocht op hun geldigheid en geschiktheid om te bepalen wanneer deze instrumenten gebruikt kunnen worden in studies met patiënten. De Gout Assessment Questionnaire 2.0 (GAQ2.0), een Engelse vragenlijst die de ziekte-specifieke invloed van jicht tracht te meten, werd door ons in het Nederlands vertaald en getest op zijn test-kenmerken bij Nederlandse jicht patiënten. De Nederlandse versie bleek consistent, betrouwbaar en goed in staat de invloed van ziekte-specifieke kenmerken op gezondheid te meten. Belangrijk is dat de GAQ2.0 ook andere aspecten van gezondheid lijkt te meten vergeleken met de bestaande generieke meetinstrumenten en dus aanvullende waarde heeft.

De geldigheid van de jicht-gemodificeerde Sharp-van der Heijde score (SvdH-mG) om gewrichtsschade op röntgenfoto's te scoren werd nagegaan door de relatie tussen bekende biologische factoren (zoals urinezuur en tophi) en de schade op röntgenfoto's van de voeten te onderzoeken. Wij toonden aan dat patiënten die ouder waren, meer tophi hadden, hun urinezuur-streefwaarde niet behaalden, en een langere ziekteduur hadden, meer schade op röntgenfoto's hadden. Verder bleek dat hoe meer schade deze patiënten op de röntgenfoto's hadden, hoe meer beperkingen zij ervoeren.

Ten slotte werd de toepasbaarheid van de Rheumatic Diseases Comorbidity Index (RDCI), een instrument dat de invloed van comorbiditeiten op ziektelast poogt te kwantificeren, onderzocht. De RDCI is een instrument dat zowel als patiënt-gerapporteerde vragenlijst, alsook door dossierstudie ingevuld kan worden. Comorbiditeiten, gemeten met de RDCI, bleken een onafhankelijke, negatieve invloed op het fysiek functioneren en kwaliteit van leven van patiënten met jicht te hebben.

Ten tweede, hebben wij de maatschappelijke ziektelast van jicht in kaart gebracht bij patiënten die onder behandeling zijn van een reumatoloog. Enerzijds deden wij dit door het in kaart brengen van de ziektekosten (die onder andere het gevolg zijn van zorgconsumptie en verlies van werk-productiviteit). Anderzijds hebben wij de gezondheid en utiliteit van deze patiënten vergeleken met die van de algemene populatie in Nederland en hebben wij utiliteiten met verschillende methoden en vanuit verschillende perspectieven gemeten. Een utiliteit-score vat de maatschappelijke waardering van gezondheidstoestanden, samen in één getal dat varieert tussen 0 ('dood') en 1 ('perfect gezond'). Vervolgens onderzochten wij welke factoren van invloed waren op zowel de ziektekosten, alsook de verschillende utiliteitsmaten.

Wij vonden een opvallend grote ziektelast in termen van maatschappelijke ziektekosten. De gemiddelde kosten, opgebouwd uit zorgconsumptie en verlies van werk-productiviteit, van een gemiddelde jichtpatiënt onder behandeling van een reumatoloog, bedragen €6.914,- per jaar. Deze kosten lopen op tot €10.894,- per patiënt per jaar, wanneer de kosten van verminderde werk-productiviteit worden meegenomen. De ziektekosten van patiënten met jicht zijn daarmee aanzienlijk en zelfs vergelijkbaar met andere reumatische aandoeningen, zoals reumatoïde artritis en ankyloserende spondylitis, ook wel ziekte van Bechterew genoemd. Het was interessant om te zien dat beperkingen in het fysiek functioneren, geslacht, maar ook comorbiditeit en jicht-specifieke kenmerken van invloed waren op de ziektekosten.

In vergelijking met de algemene Nederlandse populatie ervaren patiënten met jicht aanzienlijk vaker beperkingen in de domeinen mobiliteit (66% vs. 12%), zelfzorg (24% vs. 8%), dagelijkse activiteiten (49% vs. 24%), pijn (76% vs. 45%), maar niet angst/depressie (18 vs. 19%). Bovendien scoren ze ook subjectief hun algemene gezondheid lager (66.1 vs. 79.5 uit een maximale score van 100). Vervolgens toonden wij aan dat het gebruik van verschillende meetinstrumenten of andere perspectieven

leidden tot verschillende utiliteitwaarderingen van de gezondheidstoestand van jichtpatiënten. Dit is een belangrijke bevinding omdat utiliteit gebruikt wordt om economische evaluaties te verrichten. De beoordeling of een behandeling kosteneffectief is, zal dus afhankelijk zijn van welk instrument gebruikt wordt om dit te meten. Het was wel geruststellend dat de factoren die tot een lagere utiliteit leidden, voor de verschillende instrumenten grotendeels hetzelfde waren. Zo vonden wij dat hart- en vaatziekten, fysiek functioneren gemeten met de HAQ-DI en jicht-specifieke kenmerken gemeten met de GAQ2.0, allen van invloed waren op de gemeten utiliteit.

Ten slotte, hebben wij de rol van de huisarts omtrent het behandelen van patiënten met jicht in kaart gebracht. Hoewel jicht beschouwd wordt als een redelijk eenvoudig behandelbare aandoening, worden toch nog veel patiënten verwezen naar de tweede lijn omdat ze herhaalde aanvallen hebben of tophi ontwikkelen. Daarom hebben we bij huisartsen de kennis, ziektepercepties en het behandelen en begeleiden van patiënten met jicht onderzocht. Voor wat betreft de kennis, bleek de kennis omtrent de symptomen en de behandeling van een acute jichtaanval uitstekend. Huisartsen bleken niet op de hoogte van de serum urinezuur streefwaarde van 0.36 mmol/l en ze starten ook niet met profylactische colchicine behandeling, wanneer ze urinezuur verlagende therapie voorschrijven. Dit is niet vreemd, want de Nederlandse Huisartsen Standaard vermeldt hier niets over. Wel werd jicht beschouwd als chronische ziekte, die gepaard gaat met ernstige symptomen en een belangrijke invloed op de kwaliteit van leven heeft. Er bestaat een opvallende discrepantie tussen de percepties en behandeling en begeleiding van patiënten. Zo geven huisartsen aan dat jicht zeer goed te behandelen is, vinden ze het een chronische ziekte, maar vervolgens hebben ze weinig aandacht (mogelijk als gevolg van tijdgebrek) voor medicatie-trouw. Wij denken dat verder onderzoek in de huisartsenpraktijk, kan bijdragen aan een betere behandeling voor patiënten met jicht.

Samenvattend hebben wij in dit proefschrift bijgedragen aan het meten en beter begrijpen van uitkomsten bij patiënten met jicht, de ziektelast van patiënten met jicht gekwantificeerd en de rol van de huisarts in de behandeling van patiënten met jicht onderzocht. Zodanig draagt dit proefschrift bij aan uitkomsten-onderzoek bij patiënten met jicht. Desalniettemin blijven er veel vragen onbeantwoord, zoals de heterogeniteit waarmee de ziekte zich presenteert en welke gevolgen dit heeft voor de ziektelast en/of behandeling van patiënten in de eerste dan wel tweede lijn.

Valorisation

Valorisation

In this thesis, we aimed to contribute to the assessment and understanding of as yet underexplored aspects of outcome research in patients with gout. We already reflected on the process of valorisation, which is defined as “transferring academic wisdom to societal benefit” in the discussion of the individual chapters.

In this addendum we describe how the research performed in this thesis could provide relevant benefit for the general public and discuss some overarching societal, economical and clinical implications.

First, we contributed to the validation of several instruments to measure gout-specific outcomes, and comorbidity in patients with gout. As such, we are now able to better assess and understand the impact of the disease on functioning and health. The availability of instruments that assess relevant outcome measures in a standardized and scientifically sound manner contributes to meaningful and sustainable care when the effects of innovative medications or care interventions are being studied.

Second, we applied the validated instruments to investigate the independent influence of gout-specific characteristics and comorbidity on functioning and health from a patient’s perspective, but also on costs-of-illness and health loss from a societal perspective.

Finally, our research emphasizes the fact that gout should be seen as a chronic rheumatic, inflammatory disease and not only as an acute transient arthritis.

Societal implications

As a part of the Global Burden on Disease initiative in 2010, it was reported that the burden of gout (expressed as disability-adjusted life years, DALYs) significantly increased between 1990 and 2010¹. Parallel with this rising burden of disease, a broad range of initiatives emerged to improve outcomes in patients with gout. A key element in the evaluation of such initiatives is the extent to which they improve health and reduce DALYs (or improve quality-adjusted life years, QALYs). Health utility (summarized in a single value between 0 and 1, representing death and perfect health respectively) is considered to be the most appropriate approach to do so. Assessing overall health is not only important from the patient perspective, those who experience the disease, but also from the societal perspective, the general population that is not prejudiced and able to judge objectively.

However, to date, data on utility values and explanatory variables contributing to utility in patients with gout were very scarce. Therefore, in this thesis we have contributed to the understanding of utility values in patients with gout by completing the most commonly used and feasible health utility instruments (EuroQol-5-dimensions, EuroQol-Visual Analog Scale and Short Form-6-dimensions)^{2,3}. For example, our data show that, although there are only minor differences in the variables that contribute to lower utility values, substantial differences up to +/- 0.20 between the different instruments are certainly not exceptional. This is an important finding when utility

values are used to calculate QALYs and used in economic evaluations, as these rather large differences may lead to different interpretations of health status. It is of utter most importance for policy makers and healthcare insurers to be aware of these issues.

Economic implications

Considering the growing global economic burden of healthcare on the one hand, and the large economic burden of gout⁴, with an estimation of costs exceeding \$6 billion in the United States per year⁵ on the other hand, it becomes increasingly important to further gain insight into costs-of-illness (COI). As such, the cost analyses in this thesis provide data that can be used in economic evaluations of new (but often expensive) pharmacological treatment options or care interventions that are currently being developed and tested. Also, our comprehensive data including direct and indirect costs with non-medical resource use and productivity loss while at work taken into account, provide valuable information for policy makers and rational healthcare resource allocation in times when budgets are increasingly restricted.

Clinical implications

In addition to the above-mentioned societal and economic implications that cannot be generalized to the general population, it is important to acknowledge that this thesis also contributed to gout research in general practice. Since the management of the disease is known to be suboptimal in both primary and secondary care, we have investigated knowledge, illness perceptions and clinical practice behaviour among a group of general practitioners. Although general practitioners have excellent knowledge on the pathophysiology and signs and symptoms of acute gout and although they perceive gout as a chronic disease there were some remarkable discrepancies between their knowledge and perceptions and clinical behaviour. In particular, there was surprisingly little attention to adherence and even when adherence was checked, actions to improve inadequate adherence were rare. The findings in this thesis could be seen as a wake-up call to general practitioners to improve treatment on the one hand, but to researchers and guideline developers to improve knowledge of evidence-based treatment targets, implementing adherence interventions and tailoring up-to-date guidelines on the other hand. Moreover, it would be interesting to investigate whether better adherence will eventually reduce the economic and societal burden of the disease and improves the health of individual patients with gout.

References

1. Smith E, Hoy D, Cross M, et al. The global burden of gout: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014;73:1470–6.
2. Centre for Health Economics. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
3. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271–92.
4. Rai SK, Burns LC, DeVera MA, et al. The economic burden of gout: a systematic review. *Semin Arthritis Rheum* 2015;45:75–80.
5. Wertheimer A, Morlock R, Becker MA. A revised estimate of the burden of illness of gout. *Curr Ther Res Clin Exp* 2013;75:1–4.

Dankwoord

Dankwoord

Mijn dank gaat in eerste instantie uit naar alle patiënten en huisartsen, die bereid waren mee te werken met ons onderzoek.

Verder wil ik graag bedanken:

Mijn promotores en copromotor, prof. dr. A.E.R.C.H. Boonen, prof. dr. J. M.J.P. van der Linden, en dr. F. de Vries.

Beste Annelies, je nieuwsgierigheid en bijzonder onuitputtelijke enthousiasme werkten uitdagend en inspirerend. Afspraken om 6.15 uur op de stafgang Interne Geneeskunde of e-mails om 4.14 uur 's nachts (moest je nog naar bed of was je alweer wakker?), niets was te gek en je had (lees: maakte) altijd alle tijd. Ik heb veel van je geleerd de afgelopen jaren en hoop dat we onze samenwerking in de toekomst voortzetten!

Beste Sjef, ik heb geluk gehad. Geluk dat jij er nog was, omdat je emeritaat telkens “nog heel eventjes” werd uitgesteld. Op een gegeven moment werd er maar besloten om de afdeling te verbouwen, om je zodoende uit “je hok” weg te krijgen. Ik heb bijzonder veel geleerd van je (geschreven, maar heel goed leesbare) commentaren op alle hoofdstukken en ben dan ook erg vereerd dat ik “een van je laatste kunstjes” mag zijn.

Beste Frank, dank dat je mijn copromotor wil zijn. Jouw balans tussen wetenschappelijk integer en enorm kritisch aan de ene kant, maar ook pragmatisch en vlot werkend aan de andere kant is fenomenaal. Jouw input en tips ‘hoe efficiënt een artikel te schrijven’, hebben er dan ook voor gezorgd dat ‘de vaart erin bleef’, ook op moeilijke momenten.

De leden van de beoordelingscommissie, prof. dr. R.P. Koopmans, prof. dr. C.P. van Schayck, prof. dr. M.A.F.J. van de Laar, dr. M. Hilgsmann en dr. T. Jansen. Ik wil jullie graag bedanken voor de tijd en moeite die jullie genomen hebben om mijn proefschrift te lezen en te beoordelen.

Alle coauteurs. In willekeurige volgorde; José Wijnands, Caroline van Durme, Tobias Pustjens, Lieke Scheepers, Thea Schoonbrood, An Tran-Duy, Casper Webers, Hein Janssens, Annemarië Driessen, Bert Leufkens, Patrick Souverein, Leo Joosten en Jos van der Meer, bedankt voor de prettige samenwerking en jullie belangrijke bijdrage aan één of meerdere hoofdstukken in dit proefschrift.

Mijn mede-promovendi bij de reumatologie. Carmen, Ivette, Joost, Michiel, Andrea, Antje, Mayke en Simon, wat was het gezellig dat ene jaar dat ik bij jullie heb mogen doorbrengen. Ik had nog nooit zoveel koffie gedronken, maar volgens jullie hoorde dat er gewoon bij. Lieke, Lianne en Ellis, jullie behoorden op 1 juni 2014 plotseling tot de leukste kamer van de afdeling. Wat een gezelligheid (lees: lawaai!). Nog een geluk dat

jullie af en toe gingen meten bij de Maastricht Studie of in Venlo vertoefden. Jullie zijn nu ook (bijna) klaar! Zo zie je maar dat gezelligheid niet ten koste van productiviteit hoeft te gaan!

Mijn collega's bij de reumatologie: Ontzettend bedankt voor jullie interesse en hulp bij mijn onderzoek. Een speciaal woord van dank aan de collega's van het secretariaat. Peggy, Yvonne en Marian, bedankt voor jullie ondersteuning bij mijn onderzoek, het oplossen van 'DBC-gedoe' en/of het regelen van afspraken in de drukke agenda van Annelies. Marian, leuk dat we nu weer samenwerken bij de ouderengeneeskunde.

Mijn collega's bij de interne geneeskunde. Het combineren van onderzoek naast klinische taken en opleiding was niet altijd even makkelijk. Ik wil de Maastrichtse AIOS en internisten dan ook bedanken voor hun begrip, interesse en hulp waar nodig. Verder bedankt voor de gezelligheid die varieert van diverse cabaretvoorstellingen tot 'gewone' gezelligheid in een overvolle assistentenkamer.

In het bijzonder wil ik dr. Bas Havekes en prof. dr. Coen Stehouwer bedanken, zij weten wel waarom. Die fles wijn komt eraan.

Mijn collega's bij Team Ouderengeneeskunde, mede dankzij jullie kom ik iedere dag met veel plezier naar m'n werk. Jullie hebben mij de tijd en ruimte gegeven om naast de huisbezoeken, spreekuren en besprekingen af en toe ook 'samen met Tiny te zitten (Tiny bedankt!)' en mijn proefschrift af te ronden. In het bijzonder wil ik dr. Wubbo Mulder en dr. Fabienne Magdelijns bedanken. Wubbo, onze eerste ontmoeting is inmiddels 10 jaar geleden. Je maakte me als tutor van blok 2.5 meteen enthousiast voor het vak. Bedankt voor alle adviezen die jij me gegeven hebt en nog steeds geeft. Fabienne, bedankt voor al je hulp, overlegmomentjes over het proefschrift (en andere dingen) en voor het beantwoorden van al mijn praktische vragen, jij hebt het immers kortgeleden nog allemaal meegemaakt. Ik hoop dat we in de toekomst nog lang mogen samenwerken.

Nicole en Nordin. Bedankt dat jullie me willen ondersteunen als paranimf. Ik denk oprecht dat dit het eerste echt zinnige is dat we met z'n drieën doen, de vreselijke klaag-app, 'all you can eat'-spareribs, IC-stage, discipline overstijgend onderwijs en de FCCS-cursus met borrelavond en binge eating bij McDonalds uitgezonderd.

Mijn vrienden wil ik bedanken voor de vele gezellige momenten die me afgeleid hebben van werken aan dit proefschrift. Verder wil ik ze bedanken voor hun enorme betrokkenheid bij mijn proefschrift: "Wanneer is dat feest nu eindelijk? Schiet eens op!"

Een speciaal woord van dank, ik reken jullie immers ook tot mijn vrienden, gericht aan mijn schoonfamilie: Carl, Marion, Rob, Eveline, Fred, Regja en Nicole (op volgorde van binnenkomst), bedankt dat jullie mij in jullie familie hebben opgenomen. Het voelt als, maar is ook feitelijk een 2^e thuis (geweest).

Tot slot, pap en mam, bedankt voor jullie steun en het feit dat ik altijd heb kunnen doen wat ik wil. Mam, jij staat altijd klaar voor iedereen (al dan niet met koffie, fris, koekjes, muffins, cake, vlaai, taart of zondags eten). Pap, het allermooiste compliment dat ik kan krijgen, is als mensen zeggen dat ik op je lijk. Ik hoop maar dat ze hiermee niet verwijzen naar mijn (beginnend) grijze haren. Mark en Martijn, jullie hebben mij al op zoveel manieren en tijdens zoveel gelegenheden geholpen dat ik zonder twijfel kan zeggen dat jullie mijn twee favoriete broers zijn.

Lieve Ryanne, inmiddels zijn we al bijna 12 jaar samen en zijn we getrouwd. Iedere dag dat we langer samen zijn wordt het nog steeds een beetje leuker en eerlijker is eerlijker, dat komt niet alleen door mij. Bedankt voor alles, ik hou van je.

Curriculum vitae

Curriculum vitae

Bart Spaetgens werd geboren op 9 oktober 1987 te Brunssum. In 2006 behaalde hij zijn VWO diploma (Gymnasium) aan de Trevianum Scholengroep te Sittard. Aansluitend begon hij aan de studie geneeskunde aan de Universiteit Maastricht, alwaar hij in zijn laatste jaar een wetenschapsstage volgde op de afdeling Reumatologie van het Maastricht Universitair Medisch Centrum (MUMC+). Nadat hij in 2012 zijn artsexamen behaalde, startte hij in het MUMC+ met de opleiding Interne Geneeskunde (opleiders prof. dr. C.D.A. Stehouwer en prof. dr. R.P. Koopmans). Tijdens deze opleiding werd ook het wetenschappelijk onderzoek onder begeleiding van prof. dr. A.E.R.C.H. Boonen, prof. dr. J.M.J.P. van der Linden en dr. F. de Vries weer opgepakt, hetgeen uiteindelijk resulteerde in dit proefschrift. Hij zal zijn opleiding Interne Geneeskunde en differentiatie Ouderengeneeskunde (opleider dr. W.J. Mulder) in 2018 afronden.

