Cost of Illness and Determinants of Costs Among Patients with Gout

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ABSTRACT. ***Objective.*** 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. (First Release Nov 15 2014; J Rheumatol 2015;42:335–44; doi:10.3899/jrheum.140679)

Key Indexing Terms:

GOUT	COST OF ILLNESS	ABSENTEEISM
PRESENTEEISM	COMORBIDITIES	ECONOMIC EVALUATION

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[6,7,8,9,10].

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)[12,13,14,15,16,17,18,19,20]. 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

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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 1 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 the University of Maastricht, the Netherlands. The hospital serves as a university center, 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 Center. 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/1.73 m^2), 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 center; (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 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 × 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 proba-

bility 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 1 shows that 106 (84%) were male, mean age was 66.6 ± 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 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.

Table 1. Demographic and disease characteristics of the study sample.

Characteristics	n = 126
Age, yrs, mean ± SD (range)	66.6 ± 10.4 (42–89)
Male sex, n (%)	106 (84.1)
Education, n (%)	
Low, high school or lower	89 (70.6)
High, college or higher	37 (29.4)
Disease duration, yrs, mean ± SD (range)	11.2 ± 10.6 (0.5–52)
Tophaceous gout, n (%)	60 (47.6)
No. gout flares last yr, mean ± SD (range)	3.1 ± 7.4 (0–25)
Uric acid-lowering therapy, n (%)	83 (67.5)
BMI, kg/m^2, mean ± SD (range)	29.6 ± 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 ± SD	0.63 ± 0.58
GAQ2.0, gout impact scales: 0–100, mean ± SD	
Gout concern overall	53.9 ± 22.4
Gout medication side effects	45.3 ± 21.3
Unmet gout treatment need	48.1 ± 13.8
Well-being during attack	45.0 ± 11.3
Gout concern during attack	44.7 ± 22.1
GAQ2.0: physical health past 4 weeks (1–6)	3.5 ± 3.9
GAQ2.0: mental health past 4 weeks	2.8 ± 1.0
GAQ2.0: quality of life past 4 weeks	3.1 ± 1.0
GAQ2.0: pain past 4 weeks	3.2 ± 1.2
GAQ2.0: disease activity because of gout (1–10)	4.2 ± 2.6
GAQ2.0: pain because of gout (1–10)	3.7 ± 2.6

BMI: body mass index; COPD: chronic obstructive pulmonary disease; HAQ-DI: Health Assessment Questionnaire–Disability Index; GAQ2.0: Gout Assessment Questionnaire version 2.0.

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).

Productivity loss and indirect costs. Table 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 3. Multivariable regression for direct costs showed that female sex (OR 5.13, 95% CI 0.87–29.41), CVD (OR 7.50, CI 2.30–24.40), functional disability (OR 3.20, CI 1.05–9.31), unmet gout treatment needs (OR 1.04, CI 0.99–1.09), and pain (OR 1.19, CI 0.97–1.41) were independently related to higher costs.

Table 2. Resource use, productivity loss (WPAI), and annual costs across the different cost-categories of patients with gout (n = 126). Values are mean (median, interquartile range) unless otherwise specified.

Characteristic	Patients with Resource Use, n (%)	Resource Use per 6 Mos	Annual Costs, €/Patient	Total Direct Costs, %
Consultation, no. 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, no. visits*	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
Nonmedical resource use, hours of help/week				
Household care, professional	16 (12.7)	0.8 (0, 0–0)	1442 (0, 0–0)	25.6
Informal care by family and friends	26 (20.6)	2.7 (0, 0–0)	1735 (0, 0–0)	30.7
Total direct costs			5647 (1148, 258–5239)	100
	Time, %	Total Costs/Week, €/Patient	Annual Costs, €/Patient	Indirect Cost of Total, %
Paid productivity loss, n = 30				
Absenteeism	9.6 (0, 0–25)	96 (0, 0–34)	4982 (0, 0–1791)	
Presenteeism	26.9 (0, 0–55)	301 (155, 0–436)	15,657 (8067, 0–22,683)#	
Total indirect costs for total group, n = 126				
Absenteeism			1267 (0, 0–0)	
Presenteeism			3980 (0, 0–0)	
Total costs				
Total direct and indirect costs, absenteeism only, n = 126			6914 (1279, 258–7543)	18.3
Total direct and indirect costs, absenteeism and presenteeism, n = 126			10,894 (1840, 314–14,467)	48.1

* Physiotherapy, occupational therapy, or exercise therapy. # Presenteeism is not calculated in total costs (friction cost approach). WPAI: Work Productivity and Activity Impairment Questionnaire.

For total costs (excluding presenteeism), multivariable regression analysis revealed that again female sex (OR 4.67, CI 0.85–25.64), CVD (OR 5.67, CI 1.91–16.81), functional disability (OR 3.70, CI 1.34–10.17), and also unmet gout treatment needs (OR 1.04, 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, CI 1.05–29.41), CVD (OR 5.09, CI 1.81–14.34), and functional disability (OR 3.38, CI 1.31–8.70). The Nagelkerke R^2 of these multivariable models were 0.48, 0.42, and 0.38, respectively.

Figure 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%.

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

Table 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	
	Direct Costs				Total Costs, Absenteeism				Total Costs, Absenteeism and Presenteeism			
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age, per yr	1.041 (1.003–1.080)	**0.032**		—**	1.032 (0.955–1.070)	**0.090**		—**	1.007 (0.973–1.042)	0.864		—*
Female sex	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 (0.451–2.218)	1.000		—*	1.000 (0.451–2.218)	1.000		—*	0.718 (0.322–1.599)	0.417		—*
BMI	1.029 (0.956–1.108)	0.443		—*	1.039 (0.965–1.119)	0.306		—*	1.090 (1.006–1.181)	**0.036**		—**
Gout-specific												
Disease duration, per yr	0.958 (0.921–0.996)	**0.031**		—**	0.966 (0.931–1.003)	**0.070**		—**	0.972 (0.938–1.008)	0.130		—*
No. 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		—*
Comorbidities, y/n												
Diabetes	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	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	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	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**
Functional disability												
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**
Gout Impact Scales												
Gout concern overall	1.024 (1.005–1.043)	**0.011**		—**	1.021 (1.003–1.040)	**0.021**		—**	1.012 (0.995–1.029)	0.178		—*
Gout medication side effects	1.017 (0.998–1.036)	**0.073**		—**	1.015 (0.997–1.034)	0.107		—*	1.009 (0.991–1.027)	0.332		—*
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		—*
Well-being during attack	1.003 (0.970–1.038)	0.843		—*	1.010 (0.976–1.045)	0.579		—*	1.024 (0.990–1.061)	0.164		—*
Gout concern during attack	1.013 (0.996–1.031)	0.142			1.010 (0.993–1.027)	0.255		—*	1.001 (0.984–1.018)	0.914		—*
GAQ2.0 part 2												
GAQ2.0 physical health	1.540 (1.011–2.346)	**0.044**		—**	1.461 (0.968–2.204)	**0.071**		—**	1.279 (0.865–1.892)	0.217		—*
GAQ2.0 mental health	1.415 (0.962–2.081)	**0.078**		—**	1.332 (0.906–1.929)	0.148		—*	1.076 (0.747–1.549)	0.695		—*
GAQ2.0 quality of life	1.518 (1.004–2.296)	**0.048**		—**	1.512 (1.001–2.284)	**0.049**		—**	1.328 (0.896–1.969)	0.158		—*
GAQ2.0 pain	1.570 (1.107–2.227)	**0.011**		—***	1.464 (1.044–2.051)	**0.027**		—***	1.264 (0.920–1.737)	0.149		—***
GAQ2.0 disease activity	1.287 (1.100–1.506)	**0.002**		—**	1.245 (1.068–1.452)	**0.005**		—**	1.109 (0.959–1.282)	0.162		—*
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**		—**	1.206 (1.039–1.401)	**0.014**		—**

Values in bold face are significant at p ≤ 0.10 and are included in the multivariable analysis. * The variable was not tested in a multivariable regression because of a p value > 0.10 in univariable analysis. ** The variable was not selected during multivariable regression analysis (backward selection). *** The variable was not tested because of collinearity. BMI: body mass index; UALT: uric acid-lowering therapy; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; HAQ-DI: Health Assessment Questionnaire–Disability Index; GAQ2.0: Gout Assessment Questionnaire version 2.0.

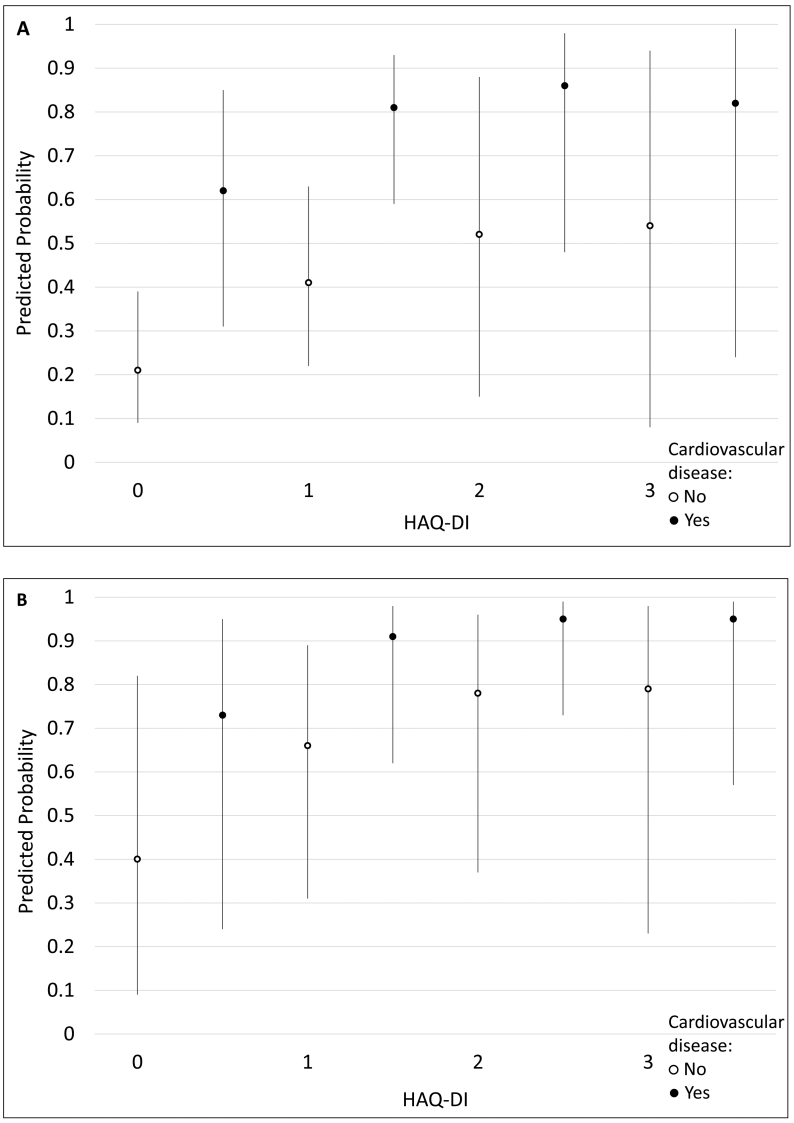

Figure 1. (A) Predicted probability (95% CI) of higher-than-median total costs for men with gout. (B) Predicted probability (95% CI) of higher-than-median total costs for women with gout. HAQ-DI: Health Assessment Questionnaire-Disability Index.

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)[12,13,14,15,16,17,18,19,20]. 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 health-care practices and social security systems between different countries, affecting not only resource use, but also the unit

Table 4. Available literature on cost of illness in gout.

Literature	Source and Population	Design and Perspective	Cost-categories and Method of Assessment	Costing Method	Direct Costs per Patient per Yr	Indirect Costs per Patient per Yr
Wu, *et al* 2008[12]	Patients with gout > 65 yr: n = 11,935 Age (SD): 71.4 (4.5) Male: 73.5% USA	Retrospective analyses of 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). Yr of costing: 2005.	Direct gout-related costs: US$876 Direct all-cause healthcare costs: US$14,734 Direct all-cause healthcare costs in controls: US$9219 (adjusted for comorbidities: US$11,696)	Not calculated
Brook, *et al* 2006[13]	Employed patients with gout: n = 1171 Age: 45.9 (0.5) Male: 85.0% USA	Retrospective analyses of 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). Yrs of costing: 2001–2004.	Direct gout-related costs: US$124 Direct all-cause healthcare costs: US$3957 Direct all-cause healthcare costs in controls: US$1721	Indirect all-cause costs: US$2885 Indirect all-cause costs in controls: US$1548
Sicras-Mainar, *et al* 2013[14]	Patients with gout > 18 yr: n = 3130 Age (SD): 55.8 (12.2) Male: 81.1% Spain	Retrospective health insurance database (serving 6 primary care centers and 2 hospitals). Mixed payer and societal perspective.	Direct healthcare resources: primary care visits, specialist visits, laboratory tests, imaging, drug prescriptions, days in hospital, and emergency department visits; assessed through medical records. Indirect costs: sick leave (days disability and job loss); unclear how assessed.	Direct healthcare costs using insurance payments (tariffs) 2007. Indirect costs using minimum wage.	Direct all-cause healthcare costs: €2228	Indirect all-cause costs: €68
Park, *et al* 2012[15]	Patients with gout > 18 yr with at least 2 serum uric acid levels: n = 352 Age: 61.0 (15) Male: 72.4% USA 3 cohorts based on sUA level < 6, 6–9, > 9 mg/dl are presented.	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 no. unique drug prescriptions were obtained from an integrated health delivery system.	Direct healthcare costs were estimated using medical and pharmacy claims. Yr of costing: 2010.	Direct gout-related costs: sUA < 6: US$332 sUA 6–9: US$352 sUA 9: US$663 Direct all-cause healthcare costs: sUA < 6: US$11,365 sUA 6–9: US$11,551 sUA 9: US$14,474	Not calculated
Saseen, *et al* 2012[16]	Patients with gouty arthritis: n = 15,669 Age: 58 yrs (14.1) Male: 77.3% USA 2 groups based on infrequent vs frequent gout (< 3 or > 3 attacks).	Retrospective medical and pharmacy service claims database.	Direct healthcare resources: no. 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. Yrs of costing: 2005–2010.	Direct gout-related costs: < 3 attacks: US$210 > 3 attacks: US$889 Direct all-cause healthcare costs: < 3 attacks: US$10,685 > 3 attacks: US$10,913	Not calculated

Table 4. Continued.

Literature	Source and Population	Design and Perspective	Cost-categories and Method of Assessment	Costing Method	Direct Costs per Patient per Yr	Indirect Costs per Patient per Yr
Halpern, *et al* 2009[17,18]	Patients with gout flares: n = 18,243 Age: 53.9 yrs (13.5) Male: 84.2% USA 3 cohorts based on sUA level < 6, 6–9, > 9 mg/dl are presented.	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. Additional claims for laboratory tests and drug prescriptions.	Direct healthcare costs were estimated using medical, laboratory, and pharmacy claims. Yrs of costing: 2002–2004.	Direct gout-related costs: sUA < 6: US$259/505 sUA 6-9: US$477/696 sUA 9: US$562/677 Direct all-cause healthcare costs: not calculated	Not calculated
Lynch, *et al* 2013[19]	Employed patients with gout: 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	Retrospective analyses insurance cohort.	Direct healthcare resources: no. outpatient visits, emergency department visits, hospitalizations (and days hospitalized), and drug prescriptions assessed from insurance claims. Indirect costs: sick leave, short and longterm disability, and compensation assessed from payment roll.	Direct healthcare costs were estimated using medical and pharmacy claims. Indirect costs were calculated from employment payroll and system (compensation).	Direct all-cause healthcare costs: < 3 attacks: US$9009 > 3 attacks: US$9748	Indirect all-cause costs: < 3 attacks: US$915 > 3 attacks: US$2021 It is important to mention that the difference between < 3 and > 3 attacks is mainly the result of the short-term disability (US$1663 in the last category).
Wu, *et al* 2012[20]	Patients with refractory gout, defined as ≥ 3 attacks: n = 679 Age: 50.4 (9.2) Male: 91.5% USA They also presented a subgroup: patients with refractory gout ≥ 6 attacks: n = 195 Age: 49.9 (9.0) Male 90.3%	Retrospective analyses insurance cohort.	No. 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 attack: US$5924 ≥ 6 attack: US$12,620 Direct all-cause healthcare costs: ≥ 3 attack: US$17,603 ≥ 6 attack: US$25,778 Direct all-cause healthcare costs in controls: US$4312–6891 (2 figures are given because of matched cohorts.)	Not calculated

sUA: serum uric acid.

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[32,33,34]. 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.

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 1 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.

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APPENDIX 1. Costs per unit for contacts with health professionals, admissions in healthcare facilities, nonmedical resource use, and paid productivity loss.

Consultation, No. Visits	Cost per Visit, €
Rheumatologist	
University hospital	129
General hospital	64
General practitioner	28
Other medical specialist	
University hospital	129
General hospital	64
Psychologist	80
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 center	340
Nonmedical 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