**Factors associated with change in health-related quality of life in people with gout: a three-year prospective cohort study in primary care**

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**Abstract**

**Objective.** To describe factors associated with change in health-related quality of life (HRQOL) in people living with gout in primary care.

**Methods.** In a UK prospective cohort study, adults with a diagnosis of gout registered with 20 general practices completed the Gout Impact Scale (GIS) (scale 0-100), Short-Form-36 Physical Function subscale (PF10) (0-100) and Health Assessment Questionnaire Disability Index (HAQ-DI) (0-3) via postal questionnaires at baseline and 6, 12, 24 and 36 months. Linear mixed modelling was used to investigate factors associated with change in HRQOL over three years.

**Results.** 1184 participants responded at baseline (adjusted response 65.6%); 990 (83.6%) were male, mean (SD) age 65.6 (12.5) years. 818, 721, 696, and 605 responded at 6, 12, 24 and 36 months, respectively. Factors associated with worse disease-specific and generic HRQOL over three years were flare frequency (≥5 flares GIS subscales, PF10), oligo/polyarticular flares (GIS subscales, PF10, HAQ-DI), worse pain (GIS subscales, PF10, HAQ-DI), body pain (GIS subscales, PF10, HAQ-DI), and more severe depression (GIS subscales, PF10, HAQ-DI) (p-value ≤ 0.05). More severe anxiety was associated with worse disease-specific HRQOL only (GIS subscales). Older age (PF10), being female (PF10, HAQ-DI) and BMI (HAQ-DI) were associated with worse generic HRQOL (p-value ≤ 0.05).

**Conclusion.** Gout-specific, comorbid and socio-demographic factors were associated with change in HRQOL over a three-year period highlighting people at risk of worse outcomes who could be targeted for interventions.

**Key words** Gout, Health-related quality of life, primary care, prospective cohort study

**Introduction**

Gout is a common inflammatory arthritis affecting 2.5% of the UK population [1] but is often sub-optimally managed [2-3], despite the availability of effective urate-lowering therapy. Health-related quality of life (HRQOL) and activity limitation have been highlighted as essential outcome domains for chronic gout by Outcome Measures in Rheumatology Clinical Trials (OMERACT).[4] HRQOL is impaired in people living with gout in comparison to population normative values [5-9] and age and sex-matched controls.[10-11]

Various factors have been shown to be associated with HRQOL in people with gout. Gout-related characteristics associated with HRQOL or activity limitation in either cross-sectional or prospective studies include gout flare frequency, experiencing a current or recent flare, the number of joints affected by gout, gout ‘severity’ or ‘activity’, living with gout for longer, tophi, elevated serum urate levels and allopurinol use [6-7, 9, 12-23]. Comorbidities (including anxiety and depression), pain, BMI, older age, sex, deprivation, marital status, ethnicity, educational attainment and alcohol consumption have also been associated with HRQOL or activity limitation [6-7, 9-11, 12, 17-18, 21-22, 24-26].

A systematic review highlighted that most studies of HRQOL in gout are cross-sectional and/or based in hospital populations.[27] There is a paucity of studies to have prospectively investigated HRQOL in primary care, where most people with gout are managed, and few studies have followed-up participants beyond 1 year or considered both disease-specific and general HRQOL.[27]

The objective of this prospective cohort study was to describe the gout-specific, comorbid and socio-demographic factors associated with change in disease-specific and generic HRQOL over three years in people with gout in primary care.

**Methods**

**Study design and participants**

This was a three-year prospective cohort study based in primary care in the West Midlands, UK.[28] Ethical approval was granted by North West-Liverpool East Research Ethics Committee (REC) reference 12/NW/0297.

Adults aged >18 years who had consulted with gout or received a prescription for allopurinol or colchicine in the preceding two years were recruited from 20 participating general practices. Read codes, which are a coded hierarchy of clinical codes based on ICD-9 codes used for diagnostic coding in primary care in the UK, were used to identify gout consultations. Eligible participants were mailed a baseline questionnaire (October/November 2012) and then follow-up questionnaires after 6, 12, 24 and 36 months. Participants provided written informed consent to participate, and participants were asked to provide additional consent for the general practice to provide the research team with information about comorbidities, medication, and investigations from their medical record. [28]

**Health-related quality of life measures**

The Short-Form-36 Health Survey (SF-36) and health assessment questionnaire disability index (HAQ-DI) have been endorsed by OMERACT as generic outcome measures for HRQOL and activity limitation respectively in gout.[4, 29] The Gout Impact Scale (GIS) is a gout-specific HRQOL measure and consists of five subscales covering different domains of disease-specific HRQOL; gout concern overall (CO), medication side effects (MSE), unmet treatment need (UTN), wellbeing during an attack (WBDA), and concern during an attack (CDA).[13] The Gout Impact Scale (GIS) subscales [13], Short-Form-36 Physical Function subscale (SF-36 PF10) [30] and Health Assessment Questionnaire Disability Index (HAQ-DI) [31] were included in the postal questionnaire survey at all five time-points. Each of the five GIS subscales are scored from 0 to 100, with higher scores indicating worse disease-specific HRQOL.[32] The SF-36 PF10 is scored from 0 to 100, with a low score indicating that an individual is limited a lot in performing physical activities.[30,33] The HAQ-DI is scored from 0 to 3, with higher scores indicating greater activity limitation and a score of 3 indicating complete disability.[31] Items within these outcome measures refer to the current situation (GIS CO, MSE, UTN, CDA and SF-36 PF10), during the last gout flare (GIS WBDA), or during the previous week (HAQ-DI).

**Gout-specific, comorbid, socio-demographic and anthropometric variables**

Gout-specific characteristics (gout flare frequency, age of gout onset, current flare (yes/no), history of oligo- or polyarticular flares (ever)) were self-reported in the questionnaires. Participants were asked if they had ever been diagnosed with diabetes, hypertension, hyperlipidaemia, myocardial infarction, angina, cerebrovascular accident, transient ischaemic attack, renal failure or renal calculi and asked to self-report their height and weight. Depression and anxiety were assessed using the patient health questionnaire-9 (PHQ-9) [34] and the generalised anxiety questionnaire (GAQ-7)[35] respectively. Participants were asked about the presence (pain, aching or stiffness for one day or longer in the 4 weeks prior to baseline) and severity (0-10 numeric rating score (NRS) in past one week) of pain anywhere in the body. Socio-demographic characteristics comprised age, sex, ethnicity, marital status, attendance at further education and alcohol consumption. Gout duration was calculated by subtracting age at gout diagnosis from current age. The total number of comorbidities was the count of the number of self-reported comorbidities. BMI was calculated using self-reported weight and height. Neighbourhood deprivation was determined from the rank of the Indices of Multiple Deprivation (IMD) using participant postal codes.[36] Presence of tophi, serum urate level (highest recorded), and estimated glomerular filtration rate (eGFR) during the two-year period prior to baseline were obtained from the medical record, where available. Chronic kidney disease (CKD) stage ≥3 was defined as eGFR<60 mL/min/1.73m2.

**Statistical analysis**

Participant characteristics and HRQOL outcomes were described using descriptive statistics (numbers and percentages for categorical data; means and standard deviations for continuous data). Factors associated with change in the five GIS subscales, SF-36 PF10 and HAQ-DI over three years were explored using multivariable linear mixed models (LMMs). A full modelling strategy is given in supplementary figure S1. Briefly, it was made up of three stages: (1) identifying the optimal model without covariates i.e. the need for inclusion of a random intercept and slope, (2) identifying an appropriate covariance structure and (3) using backward deletion techniques to remove covariate interactions with time from the model. Restricted maximum likelihood (REML) was used to estimate the LMMs parameters, but for skewed outcomes maximum likelihood estimation (MLE) with robust standard errors was used.[37-38] Missing data in outcome measures were incorporated into the LMMs [38-39] hence imputation of missing data prior to analysis was deemed unnecessary.[40] Longitudinal mixed-model analysis operates under the assumption that missing data are missing at random.[39-40]

Baseline and time-varying gout-specific, comorbid and socio-demographic variables were included in the LLMs. Baseline variables were disease duration, number of comorbidities, eGFR <60mL/min/1.73m2, body pain, PHQ-9 score, GAD-7 score, age, sex, ethnicity, IMD decile, marital status, attendance at further education, and alcohol consumption. Time-varying variables were number of gout flares, experiencing a current flare, history of oligo/polyarticular flares, allopurinol use, pain NRS, and BMI. Continuous variables were added to the LMMs in their continuous form, aiming to maximise the predictive information provided by that variable [41] (disease duration, number of comorbidities, pain NRS, PHQ-9 score, GAD-7 score, age, IMD decile, and BMI). All of the gout-specific, comorbid, socio-demographic and anthropometric variables were included in each LMM to adjust for potential confounding. Participants were included in the final linear mixed model for each quality of life outcome if they had at least one value for that quality of life outcome, as well as data for other variables in the model. The shape of the relationship between the outcomes and the continuous variables was checked using squared terms for continuous variables.

Interactions between each variable and time were included in the model to test whether the impact of any of the variables on the outcomes changed over time [42], but were only retained in the model if the p-value for the beta (β) coefficient was <0.05 and the AIC for the model with the interaction was lower than the model excluding it.[38,43-44]

To investigate the model fit, marginal and conditional pseudo-R-squared were calculated for each LMM. Histograms and Q-Q plots of LMM residuals, and scatterplots of LMM residuals verses fitted outcome values, were used to investigate whether residuals were normally distributed and displayed constant variance respectively.

Descriptive statistics at baseline were analysed using SPSS version 24, LMMs were undertaken using Stata version 14 and pseudo-R-squared using R version 4.1.2.

**Interpretation of linear mixed method beta coefficients**

The β coefficients of LMMs indicate the difference in the HRQOL outcome measure for participants at a time-point with a variable compared to those without the variable (categorical variable) or with a 1-unit increase in a variable (continuous variable) (when adjusted for all other variables in the model). For example, for the time-varying variable gout flares, the β coefficient for one flare represents the difference in the HRQOL outcome at each time-point associated with experiencing one flare, compared with not experiencing a flare. Whereas for a time invariant variable such as body pain, the β coefficient represents the difference in the HRQOL outcome at baseline for participants reporting body pain, compared with participants not experiencing any body pain.

 When the interaction term was included in the final model, the difference in HRQOL associated with that particular variable was not assumed to be the same at each time-point.

Worse HRQOL outcomes were indicated by positive β coefficient on the GIS subscales and HAQ-DI, and a negative β coefficient on the SF-36 PF10.

**Results**

**Cohort characteristics**

1184 participants responded to the baseline questionnaire (adjusted response 65.6%; questionnaire responders as a proportion of the eligible participants at that time-point), of whom 818 (79.7%), 721 (73.0%), 696 (75.4%), and 605 (68.4%) responded at 6, 12, 24 and 36 months, respectively (supplementary figure S2). Participants’ mean (SD) age was 65.6 (12.5) years at baseline, 990 (83.6%) were male, and 1126 (95.1%) were White-European (table 1). The most common self-reported comorbidity was hypertension (731 (61.7 %)). Mean (SD) gout duration was 11.91(12.13) years. Having two or more gout flares in the 12 months prior to baseline was reported by 494 (41.7%) and 624 (53.2%) self-reported using allopurinol (table 1). Participants’ mean (SD) HRQOL scores at baseline were: GIS Concern Overall (CO) 48.65 (28.33), GIS Medication Side Effects (MSE) 40.45 (26.33), GIS Unmet Treatment Need (UTN) 33.46 (20.57), GIS Wellbeing During an Attack (WBDA) 45.19 (26.41), GIS Concern During an Attack (CDA) 40.13 (24.35), SF-36 PF10 63.58 (33.08), and HAQ-DI 0.51 (0.71). Responders to follow-up questionnaires had lower GIS UTN (less unmet treatment need) and HAQ-DI scores (less activity limitation) and higher SF-36 PF10 (better generic HRQOL) scores at baseline in comparison with non-participants at later follow-up time-points (supplementary table S1). The mean (SD) scores for each HRQOL measure indicated slightly better HRQOL at 36 months compared with baseline (supplementary table S2).

 Most variables included in the LMM had less than 10% missing values at each time-point, except for serum urate (missing 61.1%), body pain (18.2%), eGFR (21.4%), and PHQ-9 (12.0%) (supplementary table S3). Due to the high percentage of missing data for serum urate and the low prevalence of tophi, they were not included in the analysis. As the SF-36 PF10 and HAQ-DI outcomes were skewed maximum likelihood estimation (MLE) with robust standard errors was used for the LMM analysis of these variables.

 All models included a random intercept, allowing the level of the outcome at baseline to vary across participants. The models for the GIS subscales and HAQ-DI also included a random slope, allowing the change in the outcome over time to vary across participants, and had an unstructured covariance structure. The likelihood ratio test (LRT) and slope variance results for the SF-36 PF10 LMM did not support the inclusion of a random slope.[35-36]

**Gout-specific factors associated with HRQOL**

Gout-specific factors associated with worse outcomes over three years were: gout flares (≥5 flares GIS CO β=19.36(15.70, 23.03), MSE β=10.14(6.29, 14.00), UTN β=12.27(8.99, 15.54), CDA β=8.15(4.82, 11.48), SF-36 PF10 β=-8.33(-12.5, -4.15)), experiencing a current flare (GIS CO β=4.22(1.11, 7.34), UTN β=6.88(3.96, 9.80)), oligo-/polyarticular flares (ever) (GIS CO β=4.89(2.78, 7.00), MSE β=2.85(0.62, 5.09), WBDA β=3.45(1.51, 5.39), CDA β=3.30(1.38, 5.23), SF-36 PF10 β=-2.70(-4.61, -0.80), HAQ-DI β=0.04(0.01, 0.08)), and allopurinol use (SF-36 PF10 β=-3.74(-6.41, -1.06)) (table 2). Worse HRQOL was observed as the number of flares experienced increased. Gout-specific factors associated with better outcomes over three years:, allopurinol use (GIS UTN β=-7.22(-9.36, -5.09)), and a longer disease duration (GIS CO β=-0.27(-0.41, -0.13), MSE β=-0.17(-0.32, -0.01), UTN β=-0.12(-0.22, -0.02), CDA β=-0.15(-0.29, -0.02)) (table 2). The statistically significant beta coefficient for experiencing a current flare and GIS WBDA does not have interpretability as the association between experiencing a current flare and GIS WBDA varied by time (see ‘Interactions with time’ section).

**Comorbid factors associated with HRQOL**

Comorbid factors associated with worse outcomes over three years were the total number of comorbidities (SF-36 PF10 β=-1.34(-2.63, -0.05)), CKD stage≥3 (SF-36 PF10 β=-4.28(-8.09, -0.46), HAQ-DI β=0.10(0.01, 0.20), worse pain (pain NRS) (GIS CO β=1.24(0.82, 1.66), UTN β=0.63(0.26, 1.00), WBDA β=1.57(1.18, 1.95), CDA β=0.51(0.12, 0.89), SF-36 PF10 β=-2.03(-2.56, -1.50) and HAQ-DI β=0.05(0.04, 0.06)), the presence of body pain (GIS CO β=5.21(1.71, 8.70), GIS MSE β=7.69(3.91, 11.47), SF-36 PF10 β=-3.59(-7.07, -0.11), HAQ-DI β=0.09(0.01, 0.17)), more severe depression (PHQ-9 score) (GIS MSE β=0.61(0.06, 1.17), WBDA β=1.11(0.57, 1.65) , CDA β=0.84(0.35, 1.32), SF-36 PF10 β=-2.19(-2.78, -1.60) and HAQ-DI β=0.05(0.03, 0.06)) and more severe anxiety (GAD-7) (GIS CO β=0.61(0.03, 1.18), MSE β=0.72(0.10, 1.34), CDA β=1.06(0.52, 1.61)) (table 2).

**Socio-demographic and anthropometric factors associated with HRQOL**

Older age (SF-36 PF10 β=-0.74(-0.90, -0.58)), being female (SF-36 PF10 β=-12.84(-17.89, -7.80), HAQ-DI β=0.17(0.03, 0.30)), and higher BMI (HAQ-DI β=0.01(0.00, 0.01)) were associated with worse outcome over three years (table 3). Socio-demographic factors associated with better outcomes were: older age (GIS CO β=-0.53(-0.69, 0.37), MSE β=-0.27(-0.45, -0.10), WBDA β=-0.43(-0.60, -0.26), CDA β=-0.25(-0.40, -0.10)), attendance at further education (GIS UTN β=-2.53(-5.05, -0.02), WBDA β=-3.98(-7.88, -0.08)), living in a less socioeconomically deprived area (IMD score) (SF-36 PF10 β=0.60(0.04, 1.16)), and consuming alcohol (Daily or almost daily GIS WBDA β=-7.84(-14.62, -1.06), SF-36 PF10 β=14.23(7.11, 21.35), HAQ-DI β=-0.30(-0.49, -0.12)) (table 3).

The statistically significant beta coefficients for both older age and deprivation and HAQ-DI do not have interpretability as the associations between both older age and deprivation and HAQ-DI varied with time (see ‘Interactions with time’ section).

**Interactions with time**

The interactions for the following variables and time were retained in the following LMM models; experiencing a current flare (GIS WBDA, GIS CDA models) (table 2), non-White European (GIS CDA), age (HAQ-DI) and indices of multiple deprivation (HAQ-DI) (table 3). These interactions indicate that the change in HRQOL associated with these particular variables was not the same at each time-point. For example, the interaction between non-White European and time indicates that the relationship between GIS WBDA and time is different depending on whether or not someone is non-White European.

**Linear Mixed Model**

The linear mixed model is a reasonable approximation to the data as evidence by the pseudo r-squared values (table S4), the residuals showed no evidence of heteroskedasticity or heterogeneity, and were normally distributed (figure S3). Overall a reasonable fit to the data was observed.

**Discussion**

This large study is the first to investigate the factors associated with change in both disease-specific (GIS subscales) and generic (SF-36 PF10, HAQ-DI) HRQOL over time in a prospective cohort of people living with gout in primary care. Whilst gout flares were the major factor associated with worse HRQOL over three years and exhibited a dose-response relationship, history of oligo/polyarticular flares, the presence of body pain, worse pain severity, and worse depression score were also associated with both worse disease-specific and generic HRQOL. Longer disease duration, older age, and attendance at further education were associated with better disease-specific HRQOL, and living in a less socio-economically deprived area and alcohol consumption with better generic HRQOL.

The findings of this prospective study are consistent with previous cross-sectional studies, where frequent gout flares were associated with worse GIS subscale and SF-36 PF10 scores [12-13] and the number of joints affected by gout with worse GIS subscale, SF-36 PF10 and HAQ-DI scores.[10, 12, 18] Our finding that allopurinol use was associated with better HRQOL, measured by GIS unmet treatment need (UTN), is in keeping with a recent RCT that reported better GIS UTN scores over two years in participants with greater adherence to ULT.[23] However, allopurinol use was associated with worse SF-36 PF10 scores, which is in contrast with the lack of association between both generic HRQOL or disability and allopurinol use in several previous cross-sectional analyses.[10-11 ,15] The association between allopurinol use and worse HRQOL (PF10) could be explained by participants with worse physical function or more severe comorbidities or gout symptoms being more likely to be prescribed allopurinol. Longer gout duration was associated with better disease-specific HRQOL in most GIS subscales, which could in part be attributable to the process of adaption to a chronic illness over time which can influence how a person reflects on their HRQOL.[45]

As observed in previous cross-sectional studies [12], gout-related factors tended to be associated with the disease-specific GIS subscales, whereas comorbid, anthropometric and socio-demographic factors were associated with the generic measures of HRQOL (SF-36 PF10, HAQ-DI).

This study uniquely investigates change in HRQOL over three years in a large primary care cohort of people with gout. It is the longest study investigating the factors associated with both disease-specific and generic HRQOL in people living with gout. Using different measures of HRQOL allows its multidimensional aspects to be explored.[43-44] The inclusion of a range of variables relevant to disease-specific and generic HRQOL aimed to reduce the potential for unmeasured confounding. Limitations of this study require acknowledgement. Tophi and serum urate were not included as variables owing to the low prevalence of tophi coded in the medical record and the high proportion of participants without a serum urate level recorded. The diagnosis of gout was based on a GP diagnosis rather than the gold standard of monosodium urate crystal identification, however joint aspiration is performed infrequently in primary care and a sensitivity and specificity of over 90% has been reported for a Read-coded diagnosis of gout.[47] Whilst the SF-36 has been endorsed as a HRQOL measure for gout studies by OMERACT [29], only the physical function subscale was included as previous studies had shown that impaired HRQOL in people with gout is predominantly in the physical domain [27] and to reduce the burden of questionnaire completion to participants. As responders to follow-up questionnaires had lower unmet treatment need, less activity limitation and better generic HRQOL at baseline in comparison with non-participants at later follow-up time-points, it is possible that the findings, such as the strength of the associations observed, may have been different if no attrition bias had been identified. Finally, participants were recruited from a single geographical region in England so findings may not be generalizable to other regions or countries.

The strong association observed between gout flares and deterioration in disease-specific HRQOL supports recommendations in national and international gout management guidelines that the option of ULT should be explained to all people with a diagnosis of gout but particularly recommended to people experiencing two or more gout flares in the previous year.[48-50] We identified people at risk of worse outcomes over time, for example people with more frequent flares, oligo/polyarticular flares, worse pain and more severe depression, who could be targeted for specific interventions. Interventions which optimise ULT and target modifiable risk factors such as pain and depression have the potential to attenuate deterioration in HRQOL in people living with gout. Living in a less deprived area and attendance at further education were associated with better generic and disease-specific HRQOL respectively, suggesting that outcomes in gout are linked to health inequality. Interventions, education, and resources for gout may therefore need to be tailored for use in areas of deprivation and lower educational attainment. Owing to the paucity of previous studies prospectively investigating HRQOL in primary care, this study was intentionally exploratory in nature.

In conclusion, this study identified gout-specific, comorbid and socio-demographic factors associated with change in disease-specific and generic HRQOL in people living with gout in primary care, highlighting people at risk of worse outcomes over three years and at greatest need for targeted interventions.

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| Rheumatology key messages |
| * Gout-specific, comorbid and socio-demographic factors associated with health-related quality of life (HRQOL) were identified.
* Gout flare frequency, oligo/polyarticular flares, pain, and depression were associated with worse HRQOL (disease-specific, generic).
* Interventions, education and resources could be targeted at risk of a worse gout outcome.
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**Disclosures/ conflict of interest:**

None

**Data availability statement:**

Data are available upon reasonable request via open or restricted access through a strict controlled access procedure. In the first instance data requests and enquiries should be directed to medicine.datasharing@keele.ac.uk

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| **Table 1** Baseline characteristic |
|  | Characteristics all responders at baseline(n=1184) |
| Male  | 990(83.6) |
| Age mean (SD) | 65.61(12.49) |
| Neighbour deprivation status† : |  |
|  Most deprived | 369(31.2) |
|  Middle | 405(34.2) |
|  Least deprived | 410(34.6) |
| White European | 1126(95.1) |
| Married or cohabiting | 882(74.5) |
| Attendance at further education  | 249(21.0) |
| BMI kg/m2 mean (SD) | 29.13(5.11) |
| Alcohol frequency:  |  |
|  Never | 113(9.5) |
|  Special occasions | 155(13.1) |
|  1 to 3 times per month | 109(9.2) |
|  Once or twice per week | 254(21.5) |
|  3 to 4 times per week | 263(22.2) |
|  Daily or almost daily | 273(23.1) |
| Self-reported comorbidities: |  |
|  Diabetes  | 205(17.3) |
|  Cerebrovascular Accident (CVA)  | 37(3.1) |
|  Hypertension (HT) | 731(61.7) |
|  Transient ischaemic attack (TIA) | 62(5.2) |
|  Hyperlipidaemia (HL) | 508(42.9) |
|  Myocardial Infarction (MI)  | 119(10.1) |
|  Renal failure (RF) | 56(4.7) |
|  Renal calculi | 81(6.8) |
|  Angina | 147(12.4) |
| Number of comorbidities, mean (SD)\* | 1.6 (1.4) |
| eGFR <60 mL/min/1.73m2 | 318(26.9) |
| Depression PHQ-9 score mean (SD) | 3.64(5.22) |
| Anxiety GAD-7 score mean (SD) | 2.79(4.49) |
| Body pain | 651(54.9) |
| Pain NRS in last week mean (SD) | 2.32(2.85) |
| Number of gout flares in 12 months preceding baseline: |  |
|  0  | 398(33.6) |
|  1  | 231(19.5) |
|  2  | 187 (15.8) |
|  3 | 103(8.7) |
|  4 | 67(5.7) |
|  ≥5  | 137(11.6) |
| Disease Duration years mean (SD) | 11.91(12.13) |
| Occurrence of current flare | 132(11.1) |
| Occurrence of oligo/ polyarticular flares | 436(36.8) |
| Record of tophi  | 25(2.1) |
| Maximum serum urate level mean (SD) µmol/L\* | 441.36(115.51) |
| Using allopurinol  | 630(53.2) |
| Figures are numbers (percentages) unless otherwise stated**.†** calculated using tertiles of indices of multiple deprivation (IMD). **\*total number of comorbidities** self-reported in baseline questionnaire (diabetes, hypertension, hyperlipidaemia, myocardial infarction, angina, cerebrovascular accident, transient ischaemic attack, renal failure, renal calculi). **eGFR <60** mL/min/1.73m2 indicative of chronic kidney disease.  **PHQ-9 score** ranges from 0 to 27 Minimal depression 0-4, Mild 5-9, Moderate 10-14, Moderately Severe 15-19, Severe 20-27; **GAD-7 score** ranges from 0 to 21 Minimal anxiety 0-4, Mild 5-9, Moderate 10-14, Severe 15-21; **Body pain** (including ache or discomfort or stiffness) for one day or longer in the 4 weeks prior to baseline**; NRS pain** **in last week** ranges from 0 (no pain ) to 10 (pain as bad as it can be).**In medical record** in the 2 years pre-baseline; \***highest serum urate** recorded in the 2 years pre-baseline. |

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| **Table 2** Gout-specific and comorbid factors associated with change in gout impact scales over three years |
|  | **GIS CO**n=595(β (95% CI)) | **GIS MSE**n=595(β (95% CI)) | **GIS UTN**n=591(β (95% CI)) | **GIS WBDA**n=593(β (95% CI)) | **GIS CDA**n=595(β (95% CI)) | **SF-36 PF10**n=554 (β (95% CI)) | **HAQ-DI**n= 594(β (95% CI)) |
| Intercept | **68.26(53.92, 82.60)** | **43.24(27.84,56.64)** | **34.20(23.85,44.55)** | **65.91(51.09,80.73)** | **40.15(26.69,53.60)** | **128.77(112.69,144.85)** | **-0.84(-1.18, -0.45)** |
| Time | **-0.12(-0.18, -0.07)** | -0.06(-0.11, 0.00) | **-0.6(-0.11, -0.02)** | **-0.20(-0.26, -0.14)** | -0.03(-0.08, 0.03) | -0.04(-0.09, 0.01) | **-0.01(-0.01, -0.00)** |
| **Gout-specific** |  |  |  |  |  |  |  |
| 0 gout flares□ | reference | reference | reference | reference | reference | reference | Reference |
| 1 gout flare□ | **6.20(3.95, 8.45)** | **3.36(0.98, 5.74)** | **4.45(2.35, 6.54)** | -1.73(-3.74, 0.29) | **2.52(0.48, 4.56)** | -1.07 (-3.25, 1.10) | -0.00(-0.04, 0.04) |
| 2 gout flares□ | **11.72(8.97, 14.47)** | **4.94(2.01, 7.86)** | **7.87(5.35, 10.39)** | -1.51(-3.98, 0.96) | **4.64(2.14, 7.13)** | **-4.10(-6.39, -1.80)** | 0.02(-0.03, 0.07) |
| 3 gout flares□ | **12.03(8.61, 15.44)** | **7.26(3.68, 10.84)** | **8.39(5.27, 11.52)** | 0.66(-2.42, 3.74) | **3.29(0.19, 6.38)** | **-3.56(-6.72, -0.40)** | 0.04(-0.04, 0.11) |
| 4 gout flares□ | **16.22(11.94, 20.51)** | **7.85(3.36, 12.34)** | **11.76(7.84, 15.68)** | 1.63(-2.21, 5.47) | **4.98(1.10, 8.86)** | **-7.96(-12.14, -3.78)** | 0.02(-0.07, 0.11) |
| ≥5 gout flares□ | **19.36(15.70, 23.03)** | **10.14(6.29, 14.00)** | **12.27(8.99, 15.54)** | 1.41(-1.94, 4.76) | **8.15(4.82, 11.48)** | **-8.33(-12.5, -4.15)** | 0.02(-0.06, 0.10) |
| Current flare | **4.22(1.11, 7.34)** | -0.34(-3.64, 2.95) | **6.88(3.96, 9.80)** | **-6.76(-10.26, -3.26)** | -3.33(-6.87, 0.22) | 1.28(-2.04, 4.61) | 0.01(-0.06, 0.07) |
| Current flare x Time | **-** | - | **-** | **0.30(0.11, 0.49)** | **0.25(0.06, 0.44)** | - | - |
| Oligo/polyarticular flares | **4.89(2.78, 7.00)** | **2.85(0.62, 5.09)** | -0.18(-2.02, 1.65) | **3.45(1.51, 5.39)** | **3.30(1.38, 5.23)** | **-2.70(-4.61, -0.80)** | **0.04(0.01, 0.08)** |
| Allopurinol use | -0.87(-3.56, 1.81) | 1.34(-1.51, 4.20) | -**7.22(-9.36, -5.09)** | 2.51(-0.09, 5.11) | 2.15(-0.34, 4.63) | **-3.74(-6.41, -1.06)** | 0.04(-0.01, 0.09) |
| Disease duration | **-0.27(-0.41, -0.13)** | **-0.17(-0.32, -0.01)** | **-0.12(-0.22, -0.02)** | -0.11( -0.26, 0.04) | **-0.15(-0.29, -0.02)** | 0.06(-0.07, 0.19) | -0.00(-0.01, 0.00) |
| **Comorbid** |  |  |  |  |  |  |  |
| Total number of Comorbidities | -0.07(-1.32, 1.18) | -0.11(-1.45, 1.24) | 0.61(-0.27, 1.49) | -0.14(-1.46, 1.18) | 0.41(-0.77, 1.59) | **-1.34(-2.63, -0.05)** | 0.03(-0.01, 0.06) |
| eGFR <60mL/min/1.73m2 | 1.36(-2.60, 5.33) | 0.51(-3.77, 4.80) | -2.05(-4.79, 0.69) | 1.51(-2.70, 5.72) | 2.15(-1.60, 5.89) | **-4.28(-8.09, -0.46)** | **0.10(0.01, 0.20)** |
| Pain NRS score | **1.24(0.82, 1.66)** | 0.43( -0.02, 0.87) | **0.63(0.26, 1.00)** | **1.57(1.18, 1.95)** | **0.51(0.12, 0.89)** | **-2.03(-2.56, -1.50)** | **0.05(0.04, 0.06)** |
| Body pain | **5.21(1.71, 8.70)** | **7.69(3.91, 11.47)** | 1.90(-0.52, 4.33) | 2.72(-0.98, 6.42) | 2.07(-1.23, 5.38) | **-3.59(-7.07, -0.11)** | **0.09(0.01, 0.17)** |
| PHQ-9 score | 0.50(-0.01,1.01) | **0.61(0.06, 1.17)** | 0.32(-0.04, 0.68) | **1.11(0.57, 1.65)** | **0.84(0.35, 1.32)** | **-2.19(-2.78, -1.60)** | **0.05(0.03, 0.06)** |
| GAD-7 score | **0.61(0.03, 1.18)** | **0.72(0.10, 1.34)** | -0.05(-0.45, 0.35) | 0.40(-0.21, 1.01) | **1.06(0.52, 1.61)** | -0.11(-0.73, 0.50) | 0.01(-0.01, 0.02) |
| **All of the gout-specific, comorbid, socio-demographic and anthropometric variables listed in this table and table 3 were included in the linear mixed model for each quality of life outcome. β** linear mixed model coefficient **□** in previous 12 months at baseline, 12 months and 36 months, in previous 6 months at 6 and 12 months  **Time-varying** variable in questionnaire at baseline, 6, 12, 24 and 36 months  **Number of comorbidities** total number of self-reported comorbidities in questionnaire; **eGFR** <60 mL/min/1.73m2 indicative of chronic kidney disease  **NRS pain** **in last week** ranges from 0 (no pain) to 10 (pain as bad as it can be)**; Body pain** (including ache or discomfort or stiffness) for one day or longer in the 4 weeks prior to baseline; **PHQ-9 depression score** ranges from 0 (minimal) to 27 (severe); **GAD-7 anxiety score** ranges from 0 (minimal) to 21 (severe).Each **GIS subscale** scored from **0 to 100;** higher scores on each scale indicating a greater impact of gout on HRQOL/worse HRQOL, positive **β** coefficient = worse, and negative **β** coefficient = better. **SF-36 PF10** scored from **0 to 100**; higher score indicating performs all types of physical activities including the most vigorous without limitations due to health, positive **β** coefficient = better, and negative **β** coefficient = worse. **HAQ-DI** scored from **0 to 3**; higher score indicating greater activity limitation, positive **β** coefficient = worse, and negative **β** coefficient = better.  |

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| **Table 3** Socio-demographic and anthropometric factors associated with change in gout impact scale (GIS) subscales over three years |
|  | **GIS CO** n=595(β (95% CI)) | **GIS MSE** n=595(β (95% CI)) | **GIS UTN**n=591(β (95% CI)) | **GIS WBDA**n=593(β (95% CI)) | **GIS CDA** n=595(β (95% CI)) | **SF-36 PF10**n=554 (β (95% CI)) | **HAQ-DI**n= 594(β (95% CI)) |
| Age | **-0.53(-0.69, 0.37)** | **-0.27(-0.45, -0.10)** | -0.03(-0.15, 0.08) | **-0.43(-0.60, -0.26)** | **-0.25(-0.40, -0.10)** | **-0.74(-0.90, -0.58)** | **0.01(0.01, 0.02)** |
| Age x Time |  |  |  |  |  | - | **0.00(0.00,0.00)** |
| Female | 2.71(-2.32, 7.74) | -1.03(-6.46, 4.40) | 2.50(-1.03, 6.03) | 1.04(-4.30, 6.38) | 2.04(-2.70, 6.78) | **-12.84(-17.89, -7.80)** | **0.17(0.03, 0.30)** |
| Non-White European | 1.43(-10.34, 13.20) | 4.37(-8.23, 16.97) | 4.73(-3.58, 13.04) | 0.80(-11.56, 13.15) | 1.05(-10.63, 12.72) | -4.25(-13.32, 4.81) | 0.02(-0.34, 0.37) |
| Non-White European x Time | - | - | - | - | **0.74(0.26, 1.22)** | - | - |
| IMD | 0.25(-0.31, 0.81) **a** | 0.37(-0.23, 0.98) **a** | 0.28(-0.11, 0.67) **a** | 0.35(-0.25, 0.94) **a** | 0.18(-0.35, 0.71) **a** | **0.60(0.04, 1.16**) **a** | **-0.01(-0.03, -0.00) a** |
| IMD x Time |  |  |  |  |  | - | **0.00(0.00, 0.00)** |
| Married or cohabiting | 2.44(1.44, 6.32) | - 0.01(-4.20, 4.18) | 1.02(-1.69, 3.73) | -0.07(-4.18, 4.04) | -1.61(-2.05, 5.28) | 0.30(-3.63, 4.23) | 0.00(-0.90, 0.10) |
| Further education | -1.15(-4.80, 2.51) | -1.56(-5.53, 2.40) | **-2.53(-5.05, -0.02)** | **-3.98(-7.88, -0.08)** | -3.43(-6.89, 0.31) | 2.23(-1.12, 5.58) | -0.05(-0.12, 0.03) |
| BMI | -0.03(-0.26, 0.19) | -0.02(-0.26, 0.21) | -0.12(-0.30, 0.06) | 0.03(-0.18, 0.24) | 0.19(-0.02, 0.39) | -0.17(-0.44, 0.10) | **0.01(0.00, 0.01)** |
| Alcohol consumption- Never | reference | reference | reference | reference | reference | reference | reference |
| Special occasions | -3.17(-10.19, 3.85) | -3.85(-11.43, 3.74) | 0.89(-4.04, 5.81) | -7.20(-14.61, 0.22) | -5.64(-12.26, 0.98) | **9.62 (1.86, 17.38)** | -0.14(-0.35, 0.07) |
| 1-3 times/month | -5.11(-12.37, 2.15) | 1.32( -6.52, 9.17) | -0.08(-5.14, 4.97) | **-7.78(-15.49, -0.62)** | -6.58(-13.44, 0.28) | **10.84(3.01, 18.68)** | **-0.25( -0.45, -0.05)** |
| 1-2 times/week | -0.97( -7.58, 5.64) | 0.57( -6.57, 7.71) | -1.40(-6.03, 3.23) | -2.61(-9.61, 4.38) | -2.68(-8.92, 3.56) | **11.69(4.64, 18.73)** | **-0.30( -0.47, -0.12)** |
| 3-4 times/week | -1.18( -7.76, 5.40) | 1.96(-5.15, 9.07) | -3.63(--823, 0.97) | -6.24(-13.20, 0.72) | -3.62(-9.82, 2.59) | **14.19(6.94, 21.45)** | **-0.31(-0.49, -0.13)** |
| Daily or almost daily | -4.67( -11.07, 1.72) | -3.30(-10.22, 3.62) | -3.21(-7.68, 1.27) | **-7.84(-14.62, -1.06)** | -5.37(-11.41, 0.68) | **14.23(7.11, 21.35)** | **-0.30(-0.49, -0.12)** |
| **All of the gout-specific, comorbid, socio-demographic and anthropometric variables listed in this table and table 2 were included in the linear mixed model for each quality of life outcome. β** linear mixed model coefficient  **Time-varying variable** in questionnaire at baseline, 6, 12, 24 and 36 months. **BMI** body mass index kg/m2 ; **IMD** Indices of multiple deprivation, highest score indicates least deprived, **a**per increase in IMD rank by one decile).Each **GIS subscale** scored from **0 to 100;** higher scores on each scale indicating a greater impact of gout on HRQOL/ worse HRQOL, positive **β** coefficient = deterioration, and negative **β** coefficient = improvement. **SF-36 PF10** scored from **0 to 100**; higher score indicating performs all types of physical activities including the most vigorous without limitations due to health, positive **β** coefficient = better, and negative **β** coefficient = worse.**HAQ-DI** scored from **0 to 3**; higher score indicating greater activity limitation, positive **β** coefficient = worse, and negative **β** coefficient = better. . |