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Title: Latent class growth analysis of gout flare trajectories: a three-year prospective cohort study in primary care

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Abstract

Objective To investigate the existence of distinct classes of gout flare trajectories and compare their gout-specific, comorbid and sociodemographic characteristics.

Method In a prospective cohort study, adults with gout registered with 20 general practices self-reported the number of gout flares experienced at baseline and after 6, 12, 24, and 36 months via postal questionnaires. Latent class growth analysis (LCGA) was used to identify distinct gout flare trajectory classes. Statistical criteria and clinical interpretability were used to decide the optimal number of classes. Baseline comorbidities, medications, sociodemographic and gout-specific characteristics of members of each class were described.

Results 1164 participants (mean age 65.6 years (SD 12.5), 972 (84%) male) were included. Six latent gout flare trajectory classes were identified: 'frequent and persistent' (n=95), 'gradually worsening' (n=276), 'frequent then improving' (n=14), 'moderately frequent' (n=287), 'moderately frequent then improving' (n=143), and 'infrequent' (n=349). The 'frequent and persistent' trajectory had the most class members classified as obese and, along with the 'gradually worsening' class, the highest proportion who were socio-economically deprived. The 'frequent and persistent', 'gradually worsening' and 'frequent then improving' classes had the highest proportions of class members with an eGFR<60 mL/min/1.73m^2. The 'Infrequent' gout flare class was associated with more frequent allopurinol use and lower urate levels.

Conclusions Six distinct gout flare trajectories were identified. Infrequent flares were associated with allopurinol use and lower serum urate levels supporting the use of urate-lowering therapy to reduce flare frequency. The characteristics of flare trajectory classes could help to target interventions and improve patient care.

Introduction

Gout is the most common inflammatory arthritis affecting 3.8 % of the US population.[1] Despite its high prevalence and the availability of effective urate-lowering therapy, gout is often sub-optimally managed.[2-4] The clinical hallmark of gout is extremely painful acute inflammatory flares, which are typically sudden in onset and characterised by swelling, erythema, heat and tenderness of the affected joint.[5-7] Frequent flares are associated with poorer health-related quality of life [8], functional disability [9-10], higher use of healthcare resources [11-13], and lower work productivity.[12] Whilst it is well recognised that gout flares are recurrent, there is a paucity of literature quantifying flare frequency over time and risk factors for frequent flares are not well described. Existing studies have mostly investigated the risk of a recurrent flare in a follow-up time-period.[14-18] A different approach is to describe symptom trajectories over time, using follow-up data from multiple time-points, and allocating individual participants to specific trajectory classes. This approach has been used to investigate pain, activity limitation, psychological factors, and comorbidities in various musculoskeletal and rheumatological conditions.[19-24] However, to our knowledge, trajectories of gout flares have not been described. Thus, the objective of this study was to investigate the existence of distinct classes of gout flare trajectories in a prospective cohort of people living with gout in primary care and compare the gout-specific, comorbid and sociodemographic characteristics of members of different classes.

Patients and methods

Study design & population

This study was a three-year prospective cohort study based in primary care in the West Midlands, UK. [25]

Adults aged ≥18 years registered with one of twenty participating general practices and who had consulted with gout or received a prescription for allopurinol or colchicine in the preceding two years were mailed a baseline questionnaire. Gout consultations were identified by Read codes, a coded hierarchy of clinical codes based on ICD-9 codes, which is widely used for diagnostic coding in primary care in the UK. Participants provided written informed consent to participate and were also asked to provide consent for the practice to provide the research team with information about comorbidities, medication, and investigations from their medical record. Ethical approval for this cohort study was granted by North West-Liverpool East Research and Ethics Committee (REC) reference 12/NW/0297.

Data collection

Questionnaires were mailed at baseline (October/November 2012), and then at 6, 12, 24 and 36 months. Participants were asked to self-report the number of self-defined gout flares (0, 1, 2, 3, 4 or ≥5) they had experienced in the last 12 months (in the baseline, 24- and 36-month questionnaires) or 6 months (in the 6- and 12-month questionnaires) using the question "How many attacks of gout have you had in the last 12 months/6 months?". Baseline characteristics of participants were obtained from both questionnaire responses and medical record review. Gout-specific (age of gout onset, history of oligo- or polyarticular flares (ever)), comorbidities, sociodemographic (age, gender, attendance at further education), and anthropometric (height, weight) characteristics were self-reported in the baseline questionnaire. Gout

duration was calculated by subtracting age at gout diagnosis from current age. The total number of comorbidities was the sum of comorbidities self-reported in the baseline questionnaire (diabetes, hypertension, hyperlipidaemia, myocardial infarction, angina, cerebrovascular accident, transient ischaemic attack, renal failure, renal calculi). 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.[26] IMD ranks (neighbour deprivation) were categorised into tertiles. Extraction of data concerning presence of tophi (Read code or clinician free-text entry), serum urate level (highest recorded), estimated glomerular filtration rate (eGFR) and prescription of allopurinol, colchicine and diuretics were obtained from the medical record over the period two years prior to baseline.

Statistical analyses

Attrition bias was investigated by comparing comorbidities, medication, socio-demographic and gout-specific characteristics at baseline between responders and non-participants at each of the five time-points. Latent class growth analysis (LCGA) was used to identify distinct trajectories of gout flares, enabling classes of people with similar trajectories to be identified.[27-28] LCGA was undertaken using Mplus version 8.1 using full information maximum likelihood (FIML). FIML deals with missing data by using maximum likelihood estimation and all available outcome data for each participant, in order to derive parameter estimates for the model, to increase precision and reduce bias [29-30]. Consequently, all available data were used, including all participants who self-reported the number of gout flares experienced on at least one time-point. Following preliminary analysis involving latent growth curve modelling where the gout flares were modelled using different approaches

(linear, quadratic, ordinal, zero-inflated Poisson, negative binominal models), a quadratic ordinal model was selected as the most appropriate model for the LCGA. After fitting a one-class quadratic ordinal LCGA model, the number of trajectory classes was increased sequentially. The statistical fit of each model was assessed by comparing Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), Bootstrapped Likelihood Ratio Test (BLRT), Lo-Mendell–Rubin Likelihood Ratio Test (LMR-LRT), Entropy, and the number of members per class (%) based on the most likely class membership. Lower values for BIC and AIC indicate a better fitting model.[28, 31-32] A significance level of $p<0.05$ for BLRT and LMR-BLT indicates a better fit compared with a model with one fewer class. [32-34] Cut-offs of 1.0 (perfect), 0.8 (high), 0.6 (medium), and 0.4 (low) have been proposed for entropy [35], and class sizes smaller than 1% of the total cohort are considered to be insufficient.[27, 34] Trajectory classes were plotted with the probability of experiencing two or more gout flares because experiencing two or more gout flares in 12 months indicates recurrent flares where urate-lowering therapy would be particularly indicated.[36-38] After determining the optimal number of trajectory classes the baseline gout-specific, comorbid, sociodemographic and gout-specific characteristics of each trajectory class were compared descriptively using SPSS version 24. Sensitivity analyses were undertaken to compare the optimal number of trajectory classes selected in different data-sets with varying degrees of missing data (participants who reported gout flare frequency at (i) three or more time-points and (ii) all five time-points). Multiple imputation (MI) was undertaken on the descriptive characteristics of the latent classes using Stata 14, to ascertain whether the characteristics of the classes were influenced by missing data.

Results

1184 participants responded to the baseline questionnaire (adjusted response 65.9%; questionnaire responders as a proportion of those eligible for mailing); mean age was 65.6 (12.5) years and 990 (83.6%) were male.[39] Follow-up questionnaires were returned by 818, 721, 696 and 605 participants at 6, 12, 24 and 36 months respectively (supplementary figure S1). Continued responders tended to be younger, male, have longer gout duration, more commonly live in less deprived areas, have attended further education, and have a prescription of allopurinol, but report fewer gout flares at baseline than non-participants (table 1). 1164 participants self-reported the number of gout flares experienced on at least one time-point and were included in the LCGA. Their baseline characteristics did not appear to differ from the full cohort. 1079 participants (91%) consented to information about comorbidities, medication, and investigations being made available from their medical record review (supplementary figure S2)

Trajectories

On LCGA, the six-class solution was considered the best fit as this returned the lowest BIC, a statistically significant BLRT, and medium to high entropy. All class sizes were larger than 1% of the total number of participants included in the analysis (table 2). The trajectories of the six-class solution also had a plausible clinical interpretation. One gout flare trajectory class had a high probability of two or more flares at each time-point and was termed 'frequent and persistent' (n=95) (figure 1). The smallest class (n=14) displayed a sharp decrease in the probability of two or more gout flares after six months ('frequent then improving'). Further classes showed an increasing probability of two or more gout flares over time ('gradually worsening', n=276), a moderate probability of two or more gout flares over time ('moderately

frequent', n=287), and a decrease in the probability of two or more gout flares after baseline ('moderately frequent then improving', n=143). The largest class (n=349) had a very low probability of two or more gout flares at each time-point ('infrequent'). The sensitivity analyses in participants who reported gout flare frequency on (i) at least three time-points and (ii) all five time-points confirmed the six-class solution as the optimal model (supplementary tables S1 and S2) and revealed similar trajectory shapes for the six-class model in each data set.

Baseline characteristics of trajectory class members

The 'frequent and persistent', and 'gradually worsening' classes had the highest proportion of class members classified as most socioeconomically deprived (41.1%, 40.6% respectively) (table 3). Fewer participants in the 'frequent and persistent', 'frequent then improving' and 'gradually worsening' reported attending further education (11.6%, 7.1%, 15.2%) compared with other classes. Obesity was most common in the 'frequent and persistent' class (43.2%). The 'frequent and persistent', 'frequent then improving' and 'gradually worsening' classes had higher proportions of class members with an eGFR<60 mL/min/1.73m^2 (30.5%, 42.9%, 30.1% respectively) compared with other classes (table 3). The 'frequent then improving' class had the highest proportion of class members with a prescription for diuretics in the two years prior to baseline (42.9%). The 'frequent and persistent' and 'frequent then improving' classes had more members reporting oligo/polyarticular flares (68.4 and 78.6% respectively) and with a prescription for colchicine in the 2 years prior to baseline (46.3% and 50% respectively). The 'gradually worsening' class had the highest mean maximum serum urate level (480.5 µmol/L). Although tophi were infrequently recorded, they were most frequent in the 'frequent then improving' and 'frequent and persistent' classes (7.1% and 4.2%). The 'infrequent' class had

the highest proportion of class members with a prescription for allopurinol (73.4%) (table 3) and reporting allopurinol use at baseline (73.0%) (supplementary table S3), the lowest mean maximum serum urate level (377.1 µmol/L) and the longest mean disease duration (15.6 years). The 'infrequent' class had a greater proportion of class members with a serum urate <360 µmol/L (46.5%) and <300 µmol/L (24.2%) compared with other classes (table 3).

The proportion of missing data for these baseline characteristics is shown in supplementary table S4. The baseline characteristics of participants in separate trajectory classes did not change following multiple imputation (supplementary table S5).

Allopurinol use over-time

The proportion of participants taking allopurinol in the 'frequent then improving' class increased from 29% at baseline to 73% at 36 months (supplementary table S3) but there was little change in the median self-reported allopurinol dose either overall or in any class.

Discussion

To our knowledge, this is the first study to use LCGA to explore the existence of gout flare trajectories over time. We identified six distinct trajectory classes which displayed a range of patterns in gout flares over time including classes with a high probability of flares at all time-points, an increasing probability of flares over time, a moderate probability of flares, a consistently low probability of flares, and two classes which displayed a decreasing probability of flares over time.

Whereas previous studies have examined the risk of having recurrent flares over a follow-up period [14-18], this is the first study to use LCGA to describe gout flare trajectories using data from multiple follow up time-points and allocating individuals to specific trajectory classes.

Our findings are consistent with trajectories of disease activity [20] and joint pain [21,24] reported in other musculoskeletal conditions which have also displayed persistent, worsening, moderate, infrequent, and improving patterns of change. The distinct characteristics of different gout flare classes identified in this study are also consistent with factors associated with gout flares reported in previous studies. We found that participants in more frequent flare trajectories were commonly characterised by socioeconomic deprivation, non-attendance at further education, obesity, and chronic kidney disease. We have previously shown in a cross-sectional analysis using baseline data from this cohort that both deprivation and non-attendance at further education are associated with more frequent flares.[41] Both obesity and chronic kidney disease were found to be independent risk factors for first post-diagnosis recurrent flare in a large prospective study in UK general practice.[14] More frequent flares were also associated with obesity in a cross-sectional community study [15] and increase in BMI in the prospective Multiple Risk Factor for Intervention trial (MRFIT) dataset.[16] We also found that the 'frequent then improving' class had the highest proportion prescribed a diuretic although this finding should be interpreted with caution in view of the small class size. Diuretic use has been associated with increased risk of gout flares in an internet case-crossover study [17] and a cohort study using medical service data from Kaiser Permanente.[18] The higher proportion of class members in the frequent classes who reported oligo/polyarticular flares provides face validity that classes with frequent flares had more severe gout.

The finding that over a third of participants had self-reported gout flares which followed a persistently frequent or worsening trajectory is consistent with other studies reporting suboptimal management of gout in primary care.[42, 2] The 'gradually worsening' class had the highest mean serum urate level, consistent with previous studies which have shown that

a serum urate level above 360µmol/L (6mg/dL) is a risk factor for gout flares.[43-44, 11, 45-47] Furthermore, the 'infrequent flare' class had the lowest mean serum urate level, more participants with a serum urate at target (<300 µmol/L and <360 µmol/L) and the highest proportion prescribed allopurinol, supporting the beneficial effects of urate-lowering therapy on gout flare frequency.

Strengths of this study include the study size and primary care setting, ensuring generalisability of our findings. The selection of the optimal number of trajectory classes was based on both statistical and clinical considerations. The BIC and BLRT have been identified as the better performing information criteria and likelihood ratio test respectively in comparison to other indices [32] and the six-class model yielded the lowest BIC and a statistically significant BLRT. Growth mixture modelling (GMM) was trialled as an alternative to LCGA, however both the linear and quadratic slopes of the GMM had to be fixed to zero in order for the model to run, GMM took a prolonged period of time to run, and bootstraps for the BLRT did not converge for models beyond two classes. Hence, LCGA was used for this analysis.

The limitations of the study include the small size of the 'frequent then improving' class, representing 1.2% of the cohort (14 participants). This only just exceeds the minimum recommended class size of 1%. [27, 34] However, in view of the very distinctive and clinically relevant trajectory with a high probability of gout flares initially which then reduced after six months, the six-class solution was retained. Since participants were identified either by a Read code for gout or a prescription for allopurinol or colchicine, it is possible that we included people who were prescribed allopurinol or colchicine for other indications. However, no participants identified by a prescription only had a Read code for other indications for allopurinol (i.e. haematological malignancy or uric acid renal stones) (supplementary figure

S2). Whilst 400 participants identified by a prescription only did not consult for gout during the study period, it is plausible that patients treated with allopurinol would not have a flare severe enough to lead to consultation over a lengthy period. A further caveat is that 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 Read-coded diagnosis has been shown to have a sensitivity and specificity of over 90%.[48] Flares were self-reported rather than using a validated flares definition such as that by Gaffo et al [49], risking over-ascertainment, although self-reported flares have been widely used in clinical studies of this nature. [15-17,50] Finally, we did not collect data about the joint sites affected by flares.

The observations concerning the characteristics of members of the trajectory classes could provide an opportunity to target interventions and subsequently improve patient care. For example, education and resources could be tailored and prioritised to participants with characteristics associated with membership of the worst trajectories, such as socioeconomic deprivation, obesity or chronic kidney disease.

This analysis was intentionally exploratory in nature, due to the paucity of previous research investigating gout flare trajectories. As this is the first investigation of latent gout flare trajectories, it would be prudent to investigate gout flare trajectories in other cohorts.

In conclusion, this is the first time LCGA has been used to identify gout flare trajectories prospectively over time. We identified six distinct gout flare trajectory classes, which differed by sociodemographic, gout-specific, and comorbid characteristics. These gout flare trajectory classes and their characteristics could provide an opportunity to target interventions and subsequently improve patient care.

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Author contributions:

ER, CM and JB conceived the idea for and designed the study. ER SM and JB contributed to the acquisition of data. LW, JB, CM, SM and ER contributed to the design of the study. All authors analysed or interpreted the data. All authors contributed to manuscript preparation, and read and approved the final submitted manuscript.

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Figure labels and legends

Figure 1 Gout flares trajectories (six-class solution)

Figure legend

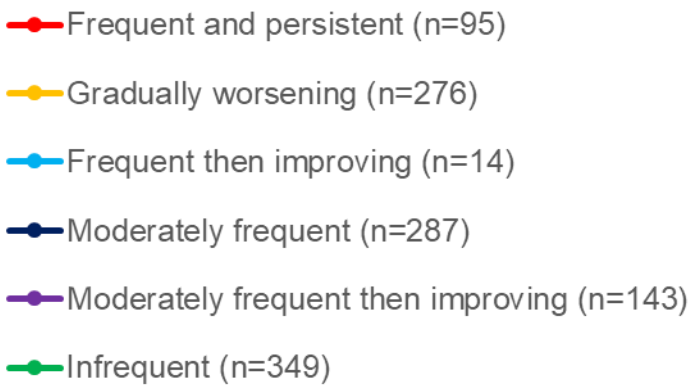


Table 1: Comparison of baseline characteristics of responders and non-participants

	Baseline	Response 12 Months		Response 24 Months		Response 36 Months	
	(n=1184)	Yes (n=721)	No (n=463)	Yes (n=696)	No (n=488)	Yes (n=605)	No (n=579)
Age mean (SD)	65.6 (12.5)	65.3 (11.7)	66.0 (13.7)	65.1 (11.5)	66.4 (13.8)	64.6 (11.5)	66.7 (13.4)
Male	990 (83.6)	629 (87.2)	361 (78.0)	609 (87.5)	381 (78.1)	541 (89.4)	449 (77.5)
Most deprived IMD tertile	369 (31.2)	200 (27.7)	169 (36.5)	193 (27.7)	176 (36.1)	164 (27.1)	205 (35.4)
Attendance at further education	249 (21.0)	175 (24.3)	74 (16.0)	170 (24.4)	79 (16.2)	157 (26.0)	92 (15.9)
Obesity	387 (32.7)	233 (32.3)	154 (33.3)	231 (33.2)	156 (32.0)	214 (35.4)	173 (29.9)
eGFR <60 mL/ min/1.73m^2 *	318 (26.9)	198 (27.5)	120 (25.9)	187 (26.9)	131 (26.8)	148 (24.5)	170 (29.4)
Comorbidities mean (SD)	1.6 (1.4)	1.6 (1.4)	1.7 (1.4)	1.6 (1.4)	1.7 (1.4)	1.6 (1.4)	1.7 (1.4)
Diuretic prescription*	286 (24.2)	183 (25.4)	103 (22.2)	169 (24.3)	117 (24.0)	136 (22.5)	150 (25.9)
Gout duration mean years (SD)	11.9 (12.1)	12.3 (11.8)	11.3 (12.7)	12.4 (11.5)	11.3 (13.0)	12.8 (11.7)	11.0 (12.5)
≥2 gout flares in previous 12 months	494 (41.7)	294 (40.8)	200 (43.2)	279 (40.1)	215 (44.1)	242 (40.0)	252 (43.5)
Allopurinol prescription*	646 (54.6)	440 (61.0)	206 (44.5)	419 (60.2)	227 (46.5)	371 (61.3)	275 (47.5)
Colchicine prescription*	345 (29.1)	222 (30.8)	123 (26.6)	203 (29.2)	142 (29.1)	176 (29.1)	169 (29.2)
History of oligo/ polyarticular flares (ever)	436 (36.8)	271 (37.6)	165 (35.6)	260 (37.4)	176 (36.1)	224 (37.0)	212 (36.6)
Tophi*	25(2.1)	17(2.4)	8(1.7)	13(1.9)	12(2.5)	12(2.0)	13(2.2)
Serum urate* µmol/L mean (SD)	441.4 (115.5)	439.2 (111.4)	445.6 (123.4)	437.4 (110.3)	448.1 (124.0)	437.5 (111.2)	446.0 (120.4)
Serum urate <360 µmol/L*†	108 (23.4)	67 (22.0)	41 (26.1)	68 (23.4)	40 (23.4)	58 (23.3)	50 (23.6)
Serum urate <300 µmol/L*†	54 (11.7)	36 (11.8)	18 (11.5)	34 (11.7)	20 (11.7)	31 (12.4)	23 (10.8)

n(%) unless stated otherwise, * from medical record review in the two years prior to baseline, **IMD** indices of multiple deprivation, **obesity** = BMI ≥30 kg/m^2, **eGFR** (estimated glomerular filtration rate) eGFR <60 indicates chronic kidney disease, **serum urate** was highest serum urate level recorded in the two years prior to baseline. †as a percentage of those with a serum urate in their medical record.

Table 2: Model fit results for LCGA of gout flare trajectories

Number of classes	AIC	BIC	BLRT	LMR-LRT	Entropy	Number per class (%) based on most likely class membership
1	11200.30	11235.72	-	-	-	1164 (100)
2	10096.37	10152.03	P value <0.001	P value <0.001	0.703	460/704 (39.5/60.5)
3	9900.38	9967.27	P value <0.001	P value <0.01	0.649	369/603/192 (31.7/51.8/16.5)
4[a]	9843.37	9939.50	P value <0.001	P value <0.01	0.623	360/299/409/96 (30.9/25.7/35.1/8.3)
5	9799.75	9916.12	P value <0.001	P value <0.05	0.616	354/140/330/251/ 89 (30.4/12.0/28.4/21.6/ 7.6)
6	9765.56	**9902.17**	**P value <0.001**	P value 0.1110	0.648	349/276/95/287/14/ 143 (29.9/23.7/8.2/24.7/1.2/ 12.3)
7[a,b]	9757.13	9913.97	P value <0.001	P value 0.0967	0.635	95/37/280/12/125/ 350/265 (8.2/3.1/24.1/1.0/10.7/ 30.1/22.8)
8[a,b,c]	9746.74	9923.83	P value <0.001	P value 0.1121	0.602	37/118/344/125/226/ 223/13/78 (3.2/10.1/29.6/10.7/19.4/ 19.1/1.1/6.7)

AIC, Akaike Information Criteria; **BIC**, Bayesian information criteria; **BLRT**, Bootstrap likelihood ratio test; **LMR-LRT**, Lo Mendell Rubin likelihood ratio test.

The **lowest BIC** and **statistically significant BLRT** for the six class solution indicated the optimal number of classes.

[a] model fixed to avoid singularity, warning given that model may not be identified, [b] Warning that not all of bootstraps converged, [C] Warning that some draws had smaller LRT than observed LRT

Table formatted as per Guidelines for Reporting on Latent Trajectory Studies (GRoLTs) [40]

Table 3: Baseline characteristics of gout flare trajectory classes

	All n= 1164	**frequent and persistent** n=95	**gradually worsening** n=276	**frequent then improving** n=14	**moderately frequent** n=287	**moderately frequent then improving** n=143	**infrequent** n=349
Age mean (SD)	65.6 (12.5)	64.2(12.5)	64.5(13.1)	68.7(9.5)	65.3(12.7)	65.5(12.5)	67.0(11.7)
Male	972 (83.5)	79(83.2)	226(81.9)	11(78.6)	248(86.4)	115(80.4)	293(84.0)
Most deprived IMD tertile	360 (30.9)	39(41.1)	112(40.6)	1(7.1)	82(28.6)	44(30.8)	82(23.5)
Attendance further education	245 (21.0)	11(11.6)	42(15.2)	1(7.1)	78(27.2)	27(18.9)	86(24.6)
Obesity	380 (32.6)	41(43.2)	97(35.1)	5(35.7)	85(29.6)	47(32.9)	105(30.1)
eGFR <60* mL /min/1.73m^2	311 (26.7)	29(30.5)	83(30.1)	6(42.9)	71(24.7)	34(23.8)	88(25.2)
Comorbidities mean (SD)	1.6 (1.4)	1.9(1.6)	1.7(1.5)	1.4(0.9)	1.5(1.3)	1.5(1.3)	1.7(1.3)
Diuretic Prescription*	280 (24.1)	28(29.5)	74(26.8)	6(42.9)	67(23.3)	41(28.7)	64(18.3)
Gout duration mean years (SD)	11.9 (12.0)	11.6(12.3)	11.0(11.6)	7.5(5.9)	9.6(11.2)	9.8(12.3)	15.6(12.3)
≥2 Gout flares in previous 12 months	494 (42.4)	91(95.8)	238(86.2)	13 (92.9)	76(26.5)	76(53.2)	0(0)
Allopurinol prescription*	635 (54.6)	47(49.5)	133(48.2)	7(50.0)	118(41.1)	74(51.7)	256(73.4)
Colchicine prescription*	340 (29.2)	44(46.3)	97(35.1)	7(50.0)	103(35.9)	48(33.6)	41(11.7)
History of oligo /polyarticular flares (ever)	432 (37.1)	65(68.4)	132(47.8)	11(78.6)	87(30.3)	44(30.8)	93(26.6)
Tophi*	25 (2.1)	4(4.2)	8(2.9)	1(7.1)	4(1.4)	4(2.8)	4(1.1)
Serum urate µmol/L * mean (SD)	441.0 (115.2)	469.1 (116.6)	480.5 (113.3)	461.4 (185.5)	450.7 (102.8)	434.5 (105.7)	377.2 (107.7)
Serum urate <360 µmol/L†	107 (23.4)	9 (17.6)	15 (14.7)	1 (14.3)	20 (16.3)	16 (21.3)	46 (46.5)
Serum urate† <300 µmol/	54 (11.8)	3 (5.9)	6 (5.9)	1 (14.3)	9 (7.3)	11 (14.7)	24 (24.2)

n(%) unless stated otherwise, * from medical record review in the two years prior to baseline, **IMD** indices of multiple deprivation, **obesity** = BMI ≥30 kg/m^2, **eGFR** (estimated glomerular filtration rate) eGFR <60 indicates chronic kidney disease, **serum urate** was highest serum urate level recorded in the two years prior to baseline. †as a percentage of those with a serum urate in their medical record.

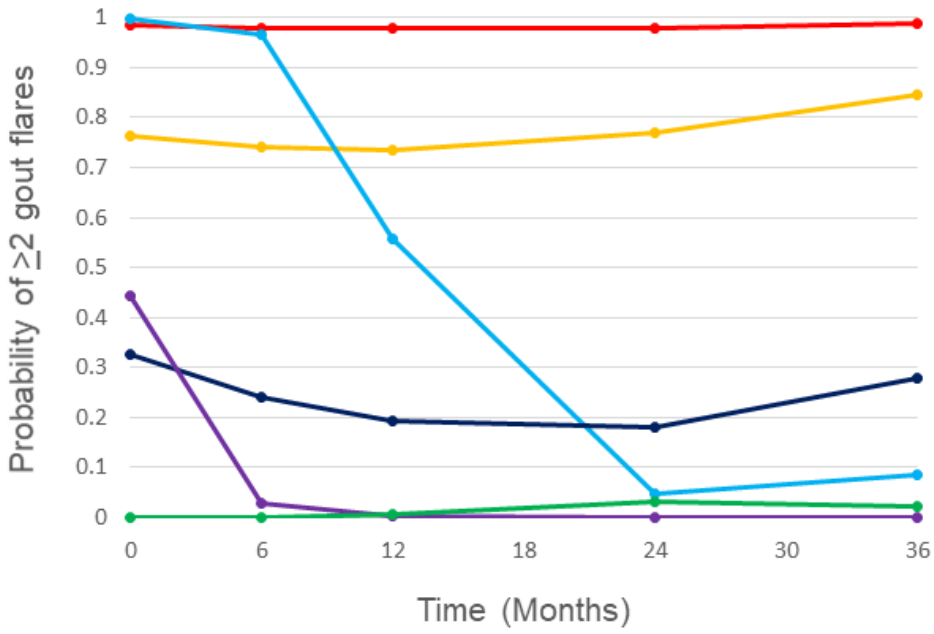
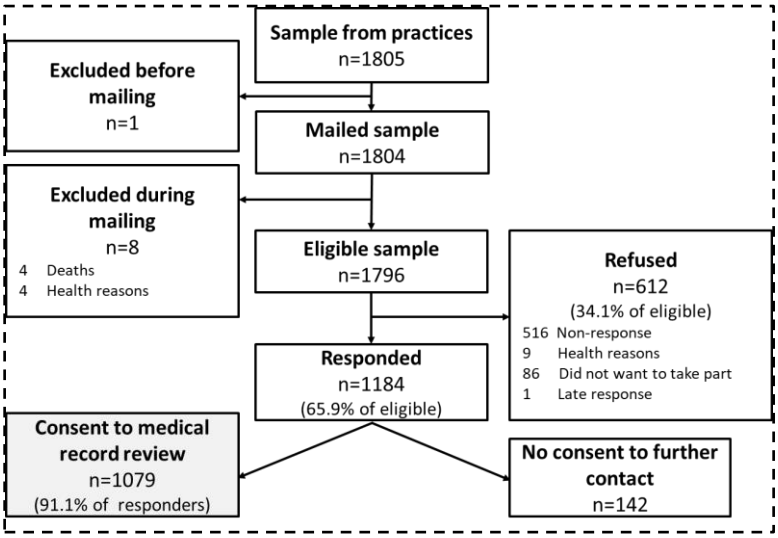
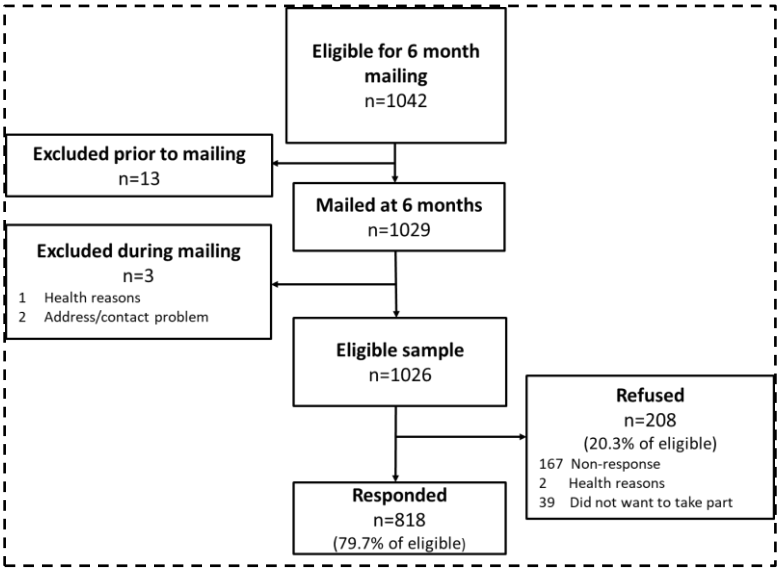

Probability of ≥2 gout flares
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
6
12
18
24
30
36
Time (Months)

Figure S1: *Eligible participants, responders, refusals and non-response at each questionnaire time-point*

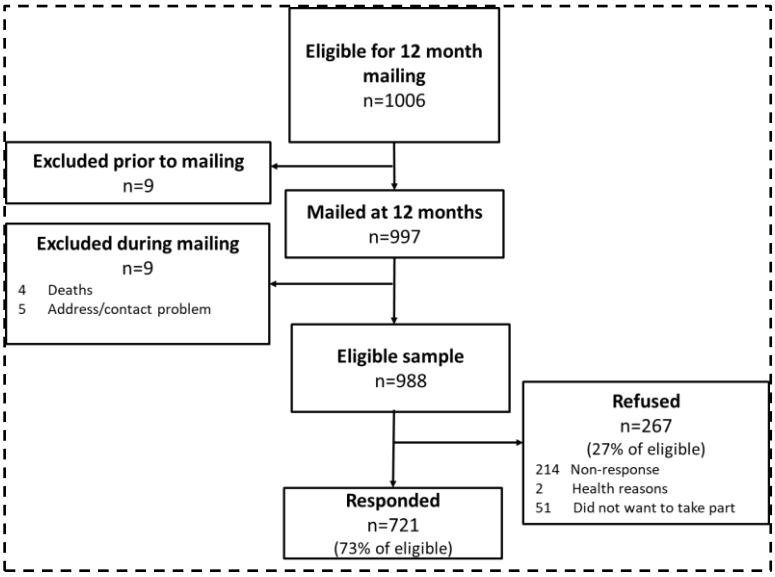
Baseline



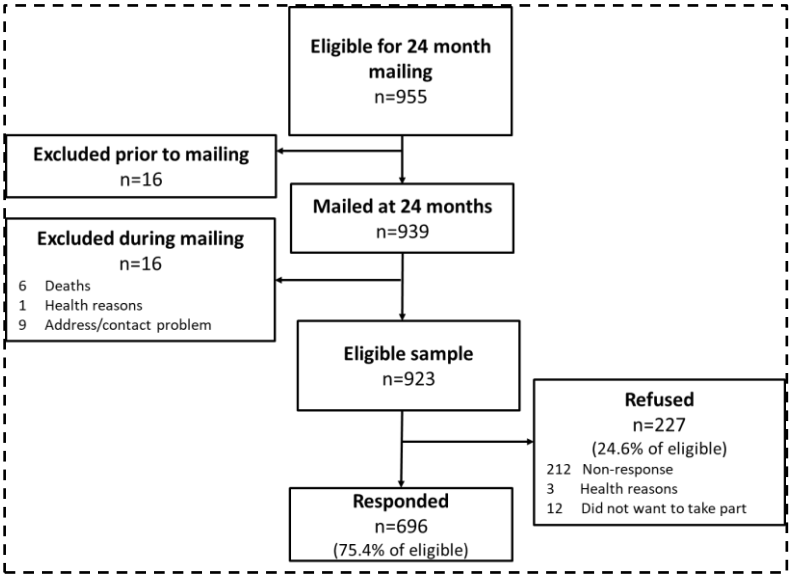
6 months



12 months



24 months



36 months

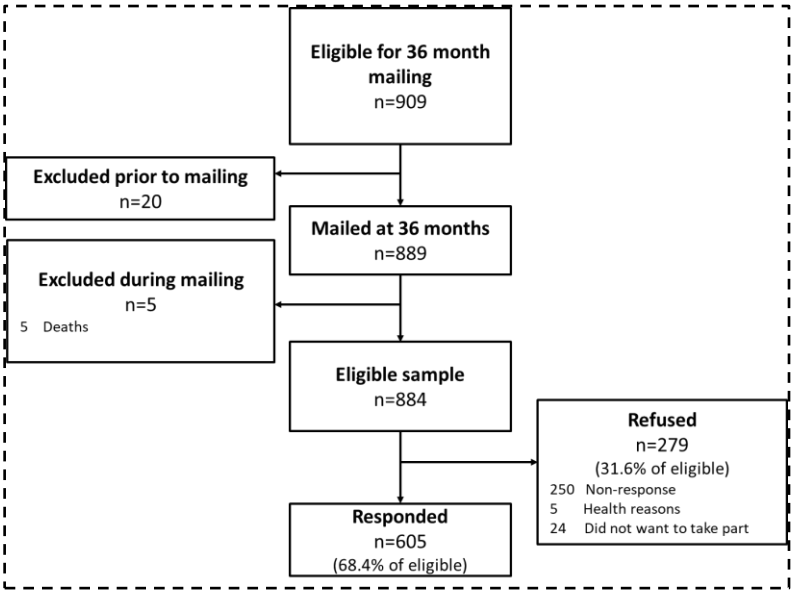

Eligible for 36 month mailing
n=909
Excluded prior to mailing
n=20
Mailed at 36 months
n=889
Excluded during mailing
n=5
5 Deaths
Eligible sample
n=884
Refused
n=279
(31.6% of eligible)
250 Non-response
5 Health reasons
24 Did not want to take part
Responded
n=605
(68.4% of eligible)

Figure S2: *Proportion of responders with Read code for gout or solely prescription of allopurinol or colchicine.*

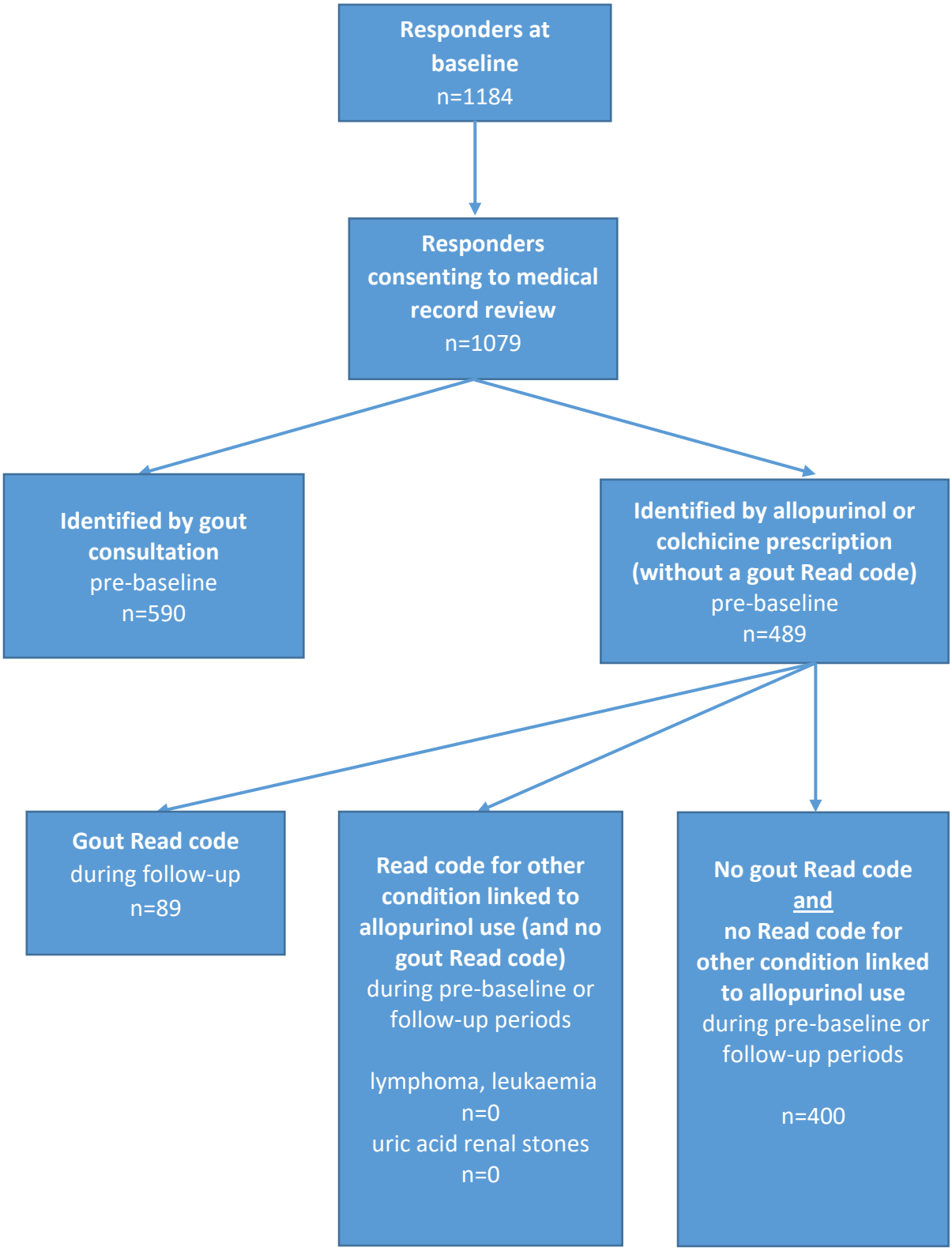


Table S1: Model fit results for LCGA of gout flare trajectories in participants who reported gout flare frequency on at least three time-points

Number of classes	AIC	BIC	BLRT	LMR-LRT	Entropy	Number per class (%) based on most likely class membership
1	9202.20	9234.11	-	-	-	729 (100)
2	8155.79	8206.30	P value <0.001	P value <0.001	0.850	457/272 (62.7/37.3)
3	7971.35	8040.22	P value <0.001	P value <0.05	0.783	239/114/376 (32.8/15.6/51.6)
4[a]	7919.65	8006.89	P value <0.001	P value <0.05	0.763	46/174/255/254 (6.3/23.8/35/34.9)
5	7877.64	7983.25	P value <0.001	P value 1 .000	0.749	112/32/164/215/ 206 (15.4/4.4/22.5/29.5/ 28.2)
6	7843.89	**7967.86**	**P value <0.001**	P value 0.0940	0.777	34/213/11/208/ 153/110 (4.7/29.2/1.5/28.5/ 21/15.1)
7[b,c]	7834.25	7976.59	P value <0.001	P value 0.3076	0.726	115/32/105/80/ 178/206/13 (15.8/4.4/14.4/10.9/ 24.4/28.3/1.8)
8[b,c]	7821.81	7982.52	P value <0.001	P value 0.0338	0.737	22/105/3/168/205/ 59/14/125 (3/14.4/4.3/23.1/28.1/ 8.1/1.9/17.1)

AIC, Akaike Information Criteria; **BIC**, Bayesian information criteria; **BLRT**, Bootstrap likelihood ratio test; **LMR-LRT**, Lo Mendell Rubin.
The **lowest BIC** and **statistically significant BLRT** for the six class solution indicated the optimal number of classes
[a] model fixed to avoid singularity, warning given that model may not be identified, [b] Warning that not all of bootstraps converged, [C] Warning that some draws had smaller LRT than observed LRT
Table formatted as per Guidelines for Reporting on Latent Trajectory Studies (GRoLTs) [40]

Table S2: Model fit for LCGA of gout flare trajectories in participants who reported gout flare frequency on all five time-points

Number of classes	AIC	BIC	BLRT	LMR-LRT	Entropy	Number per class (%) based on most likely class membership
1	6017.52	6046.07	-	-	-	437 (100)
2	5262.49	5307.37	P value <0.001	P value <0.001	0.876	284/153 (65/35)
3	5140.59	5201.79	P value <0.001	P value <0.01	0.823	61/238/138 (14/54.5/31.5)
4	5102.78	5180.30	P value <0.001	P value 0.0509	0.872	129/238/59/11 (29.5/54.5/13.5/2.5)
5[a]	5067.56	5161.40	P value <0.001	P value 0.2814	0.821	141/10/29/95/162 (32.3/2.3/6.6/21.7/37.1)
6	5036.77	**5146.93**	**P value <0.001**	**P value <0.001**	0.799	139/113/10/24/ 84/67 (31.8/25.9/2.3/5.5/ 19.2/15.3)
7[b,c]	5025.45	5151.93	P value <0.001	P value 0.3300	0.799	74/10/67/21/ 111/15/139 (16.9/2.3/15.3/4.8/ 25.4/3.4/31.8)
8[a,b,c]	5024.71	5167.50	P value <0.001	P value 0.1533	0.776	105/10/26/21/52/ 74/135/14 (24.0/2.3/6.0/4.8/11.9/ 16.9/30.9/3.2)

AIC, Akaike Information Criteria; **BIC**, Bayesian information criteria; **BLRT**, Bootstrap likelihood ratio test; **LMR-LRT**, Lo Mendell Rubin.
The **lowest BIC** and **statistically significant BLRT and LMR-LRT** for the six class solution indicated the optimal number of classes
[a] model fixed to avoid singularity, warning given that model may not be identified, [b] Warning that not all of bootstraps converged, [C] Warning that some draws had smaller LRT than observed LRT.
Table formatted as per Guidelines for Reporting on Latent Trajectory Studies (GRoLTs) [40]

Table S3: Self-reported allopurinol use and allopurinol dose over time

	Baseline	6 months	12 months	24 month	36 months
Self-reported allopurinol use†					
All participants	624 (53.6)	466(59.7)	435(60.3)	425(61.2)	377(62.3)
'frequent and persistent'	46(48.4)	21(46.7)	21(50.0)	19(48.7)	17(58.6)
'gradually worsening'	129(46.7)	81(51.9)	82(53.9)	81(54.0)	70(53.0)
'frequent then improving'	4(28.6)	7(53.8)	8(61.5)	7(53.8)	8 (72.7)
'moderately frequent''	115(40.1)	96(45.9)	94(46.5)	90(46.4)	78(46.7)
'moderately frequent then improving'	75(52.4)	67(53.6)	60(56.6)	57(59.4)	49(60.5)
'infrequent'	255(73.1)	194 (83.6)	170(82.5)	171(84.2)	155(83.8)
Median (IQR) self-reported allopurinol dose*					
All participants	300 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)
'frequent and persistent'	100 (100, 300)	300 (100, 300)	200 (100, 300)	300 (100, 300)	300 (100, 300)
'gradually worsening'	300 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)
'frequent then improving'	300 (300, 300)	300 (100, 300)	300 (100, 300)	300 (300, 300)	300 (100, 300)
'moderately frequent''	250 (100, 300)	300 (100, 300)	200 (100, 200)	200 (100, 300)	200 (100, 300)
'moderately frequent then improving'	250 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)
'infrequent'	300 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)	300 (100, 300)

†n(%) percentage of those who returned a questionnaire at each time-point in that class

Table S4: Missing data rates for the baseline variables used to describe the gout flare trajectory classes

	All n= 1164	**frequent and persistent** n=95	**gradually worsening** n=276	**frequent then improving** n=14	**moderately frequent** n=287	**moderately frequent then improving** n=143	**infrequent** n=349
Age	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Male	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Most deprived IMD tertile	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Attendance further education	60 (5.2)	5 (5.3)	18 (6.5)	0 (0)	18 (6.3)	4 (2.8)	15 (4.3)
Obesity	63 (5.4)	6 (6.3)	18 (6.5)	0 (0)	15 (5.2)	7 (4.9)	17 (4.9)
eGFR * mL /min/1.73m^2	247 (21.2)	19 (20.0)	68 (24.6)	3 (21.4)	64 (22.30	24 (16.8)	69 (19.8)
Comorbidities	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Diuretic Prescription*	99 (8.51)	7 (7.4)	25 (9.1)	1 (7.1)	28 (9.8)	4 (2.8)	34 (9.7)
Gout duration years	74 (6.1)	5 (5.3)	13 (4.7)	1 (7.1)	21 (7.3)	4 (2.8)	30 (8.6)
≥2 Gout flares in previous 12 months	41 (3.5)	3 (3.2)	10 (3.6)	1 (7.1)	11 (3.8)	0 (0)	16 (4.6)
Allopurinol prescription	99 (8.5)	7 (7.4)	25 (9.1)	1 (7.1)	28 (9.8)	4 (2.8)	34 (9.7)
Colchicine prescription	99 (8.5)	7 (7.4)	25 (9.1)	1 (7.1)	28 (9.8)	4 (2.8)	34 (9.7)
History of oligo /polyarticular flares (ever)	40 (3.4)	3 (3.2)	10 (3.6)	1 (7.1)	11 (3.8)	0 (0)	15 (4.3)
Tophi*	99 (8.5)	7 (7.4)	25 (9.1)	1 (7.1)	28 (9.8)	4 (2.8)	34 (9.7)
Serum urate µmol/L *	707 (60.7)	44 (46.3)	174 (63.0)	7 (50.0)	164 (57.1)	68 (47.6)	250 (71.6)

n(%) missing items per characteristic, ***** from medical record review in the two years prior to baseline, **IMD** indices of multiple deprivation, **obesity** = BMI >30 kg/m^2, **eGFR** (estimated glomerular filtration rate) eGFR <60 indicates chronic kidney disease, **comorbidities** = number of comorbidities self-reported in baseline questionnaire, **serum urate** was highest serum urate level recorded in the two years prior to baseline.

Multiple imputation method

Multiple imputation (MI) using chained equations was undertaken using Stata 14. The following variables were included in the MI model, auxiliary variables (with no missing data) were age, sex, index of multiple deprivation tertile, number of self-reported comorbidities and imputed variables were attendance at further education, BMI, eGFR <60 mL /min/1.73m^2, diuretic prescription, gout duration, ≥2 Gout flares in previous 12 months, allopurinol prescription, colchicine prescription, history of oligo /polyarticular flares (ever), tophi, serum urate. Continuous variables were imputed using predictive mean matching (pmm) and dichotomous variables were imputed using logistic regression (logit). 61 imputations were undertaken for each imputed variable, as serum urate was missing at 61% in this cohort. [1] Results were pooled using mi estimate to calculate proportions and misum to calculate means, estimates were pooled using Rubin's rule for pooling. [2]

The results of the MI can be found in supplementary table S5.

[1] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Tutorial in Biostatistics* 2011; 30: 377–399.

[2] Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Wiley: New York, 1987

Table S5: Baseline characteristics of gout flare trajectory classes results from multiple imputation (MI)

	All n= 1164	**frequent and persistent** n=95	**gradually worsening** n=276	**frequent then improving** n=14	**moderately frequent** n=287	**moderately frequent then improving** n=143	**infrequent** n=349
Age mean (SD)	65.6 (12.5)	64.2(12.5)	64.5(13.1)	68.7(9.5)	65.3(12.7)	65.5(12.5)	67.0(11.7)
Male	972 (83.5)	79(83.2)	226(81.9)	11(78.6)	248(86.4)	115(80.4)	293(84.0)
Most deprived IMD tertile	360 (30.9)	39(41.1)	112(40.6)	1(7.1)	82(28.6)	44(30.8)	82(23.5)
Attendance further education	**21.8**	**11.9**	**15.8**	**7.1**	**28.5**	**18.9**	**25.5**
Obesity	**34.5**	**44.9**	**37.7**	**35.7**	**31.6**	**34.3**	**31.6**
eGFR <60* mL /min/1.73m^2	**31.6**	**35.4**	**35.8**	**49.9**	**29.3**	**27.3**	**30.0**
Comorbidities mean (SD)	1.6 (1.4)	1.9(1.6)	1.7(1.5)	1.4(0.9)	1.5(1.4)	1.5(1.3)	1.7(1.3)
Diuretic Prescription*	**26.5**	**32.6**	**29.8**	**42.9**	**26.1**	**29.1**	**20.7**
Gout duration mean years (SD)	**11.8 (12.0)**	**11.5 (12.3)**	**11.1 (11.6)**	**7.6 (6.3)**	**9.7 (11.3)**	**9.7 (12.1)**	**15.3 (12.2)**
≥2 Gout flares in previous 12 months	**44.0**	**97.5**	**88.2**	**100.0**	**28.3**	**53.1**	**1.3**
Allopurinol prescription*	**59.1**	**52.6**	**51.7**	**50.0**	**46.0**	**53.8**	**79.8**
Colchicine prescription*	**31.9**	**51.2**	**39.9**	**52.3**	**38.1**	**33.8**	**13.7**
History of oligo /polyarticular flares (ever)	**38.5**	**68.8**	**49.8**	**83.4**	**31.9**	**30.8**	**28.6**
Tophi*	**2.4**	**4.2**	**3.4**	**7.1**	**1.6**	**3.0**	**1.2**
Serum urate µmol/L * mean (SD)	**430.9 (114.2)**	**470.3 (108.3)**	**465.0 (110.3)**	**489.5 (153.6)**	**438.0 (109.5)**	**434.6 (105.3)**	**383.4 (106.9)**
Serum urate <360 µmol/L	**25.7**	**16.8**	**17.3**	**9.6**	**20.2**	**23.1**	**41.2**
Serum urate <300 µmol/	**13.9**	**4.9**	**7.9**	**9.6**	**12.2**	**13.2**	**25.8**

% unless stated otherwise, **imputed variable results in bold**, * from medical record review in the two years prior to baseline, **IMD** indices of multiple deprivation, **obesity** = BMI ≥30 kg/m^2, **eGFR** (estimated glomerular filtration rate) eGFR <60 indicates chronic kidney disease , **comorbidities** = number of comorbidities self-reported in baseline questionnaire, **serum urate** was highest serum urate level recorded in the two years prior to baseline.