Title: Has the gout epidemic peaked in the UK? A nationwide cohort study using data from the Clinical Practice Research Datalink, from 1997 to across the COVID-19 pandemic in 2021.

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The burden of gout increased globally across the 20th and 21st centuries[1]. However, a study using cross-sectional datasets demonstrated stable prevalence of hyperuricaemia and gout in the USA between 2007 and 2016[2]. Additionally, given poor persistence with urate lowering treatment (ULT), the impact of COVID-19 pandemic on ULT prescription in a nationwide cohort merits assessment to ascertain any detrimental impact[3]. The objectives of this study were to examine temporal trends in incidence and prevalence of gout, and ULT prescription between 1997 and 2021.

Anonymized data from Clinical Practice Research Datalink (CPRD), one of the largest databases of electronic health records originating during routine clinical care were used. The study, approved by the ISAC of MHRA (Ref:20_000233), spanned from 01/01/1997 to 31/08/2021. Gout status and ULT prescriptions were ascertained using Read and product codes (Supplementary material).

Point prevalence (95% confidence intervals (CI)) of gout on 1st July of each year was calculated with CPRD population registered on that date as denominator. Incidence (95%CI) of gout per 1,000 person-years in each calendar year was calculated using number of incident cases and total follow-up period in that year. The incidence and prevalence were directly standardised to the study population for age, sex, and length of registration in CPRD[3] (Supplementary material). Proportion (95%CI) of prevalent gout cases prescribed ULT within 90-days prior to 1st July in each year, and incident gout cases prescribed ULT within one-year of diagnosis were calculated and directly standardised to the relevant study populations. Standardised rates were used to examine temporal trend using Joinpoints analysis. Crude rates for 1999 and 2021 were stratified by age and sex to compare age-sex distribution of gout before and during the COVID-19 pandemic.

Data for 373,371 gout patients were included. The standardised prevalence (95%CI) of gout increased from 0.98(0.97-0.96)% in 1997 to 2.33(2.31-2.35)% in 2021, with annual average percentage change (AAPC) (95%CI) 3.9(3.3-4.4)% (Figure 1). The standardised incidence (95%CI) of gout increased from 1.31(1.26-1.37)/1,000 person-years in 1997 to 1.97(1.94-2.01)/1,000 person-years in 2013, and reduced to 0.98(0.94-1.03)/1,000 person-years in 2021. The standardised prevalence of ULT prescription increased from 25.92% in 1997 to 39.53% in 2021 (AAPC (95%CI) 1.3(1.0-1.5)%), whereas the proportion of incident gout cases prescribed ULT within 1-year reduced. Fewer women than men were prescribed ULT ever, and within 1-year of diagnosis, despite older age at onset and higher comorbidity burden as reported previously[4].

The standardised prevalence of gout remained stable across the pandemic while the standardised incidence (95%CI) reduced from 1.54(1.50-1.58)/1,000 person-years in 2019, to 1.07(1.00-1.07) and 0.98 (0.94-1.03)/1,000 person-years in 2020 and 2021 respectively. The age-sex distribution of prevalent gout was similar in 2019 and 2021 (Figure S1). However, gout incidence was significantly lower in 2021 than in 2019 across all ages and in both sexes (Figure S1). The prevalence (95%CI) of ULT prescription in gout improved from 36.72(36.41-37.02)% in 2019 to 39.53(39.19-39.91)% in 2021.

The gout epidemic appears to have peaked in the UK in 2013, with a significant reduction in incidence between 2013 and 2019 i.e. before the COVID-19 pandemic potentially due to reduction in alcohol and red-meat consumption[5,6]. The sharp decline in its incidence during the COVID-19 pandemic likely represents under-diagnosis, potentially due to inability to seek healthcare due to restrictions imposed on the population and COVID-19 related workload on the health-service, rather than due to

improved lifestyle, as alcohol consumption increased during COVID-19 pandemic[7]. However, this may cause a surge in gout cases presenting to health services in the near future.

Overall, ULT prescriptions increased steadily since 2010, without any detrimental impact of the COVID-19 pandemic, as observed for other rheumatic diseases[8]. While encouraging, additional steps e.g. partnership with primary-care, guideline implementation are needed for continued improvement. The modest increase in ULT among prevalent gout cases during the pandemic may be driven by worsening gout control potentially due to increased alcohol consumption[7], as prevalence of first ULT prescription within 1-year of diagnosis continued to decline in this period.

Competing interests: AA has received departmental research grants from AstraZeneca and Oxford Immunotec, speaker bureau fees from Menarini, scientific meeting support from Pfizer, consulting fees from Inflazome and author royalties from UpToDate and Springer, unrelated to this work. The other authors have no conflict of interest to declare.

Contributorship: AA conceived the idea for the study, contributed to the study design, performed the analysis, interpreted the results and critically reviewed the paper. AJA contributed to the study design, interpretation of the results and critically reviewed the paper. LT contributed to the study design, advised on the analysis and interpretation of the results and critically reviewed the paper. MM contributed to the study design and critically reviewed the paper.

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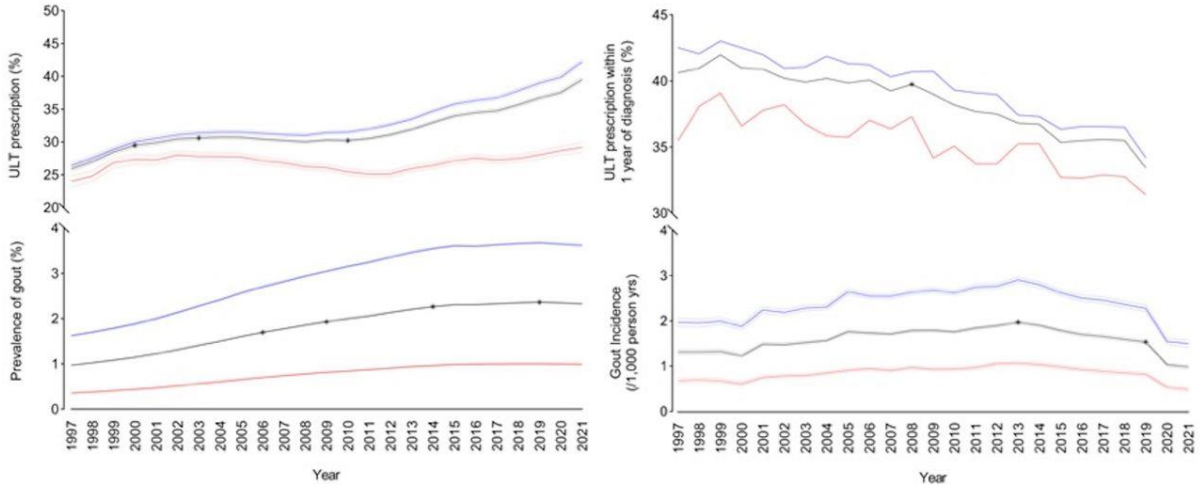
Ethical approval information: The study was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Regulatory Authority (MHRA) (Ref: 20_000233).

Data access: Data included in this study are available from the CPRD. The statistical codes may be obtained from the corresponding author on reasonable request.

Patient and public involvement: Not applicable.

Figure legend:

Figure 1: *Temporal trend 1997-2021*. (A) Gout prevalence (lower left panel). The APC (95%CI) was 6.6(6.4 to 6.8)%, 4.4(2.7 to 6.0)%, 3.3(2.8 to 3.8)%, 0.8(0.2 to 1.3)%, and -0.8(-2.9 to 1.3)% in 1997-2006, 2006-2009, 2009-2014, 2014-2019, 2019-2021 respectively. (B) Gout incidence (lower right panel). The APC (95%CI) during 1997-2013, 2013-2019, and 2019-2021 was 2.6(2.0 to 3.2)%, -4.5(-7.2 to -1.8)%, and -23.2(-39.0 to -3.3)% respectively. (C) ULT prevalence (upper left panel). The APC (95%CI) between 1997-2000, 2000-2003, 2003-2010, 2010-2021 was 4.5(2.4 to 6.6)%, 1.4(-1.9 to 4.8)%, -0.4(-0.9 to 0.1) and 2.3(2.1-2.5)% respectively. (D) ULT prescription within 1 year of diagnosis (upper right panel). The APC (95%CI) between 1997-2008, 2008-2019 was -0.4 (-0.7- to -0.2)%, -1.3 (-1.5 to -1.1)% respectively. *significant joinpoints. Blue line male, red line female, black line overall. Dotted lines 95% CI.



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Supplementary material

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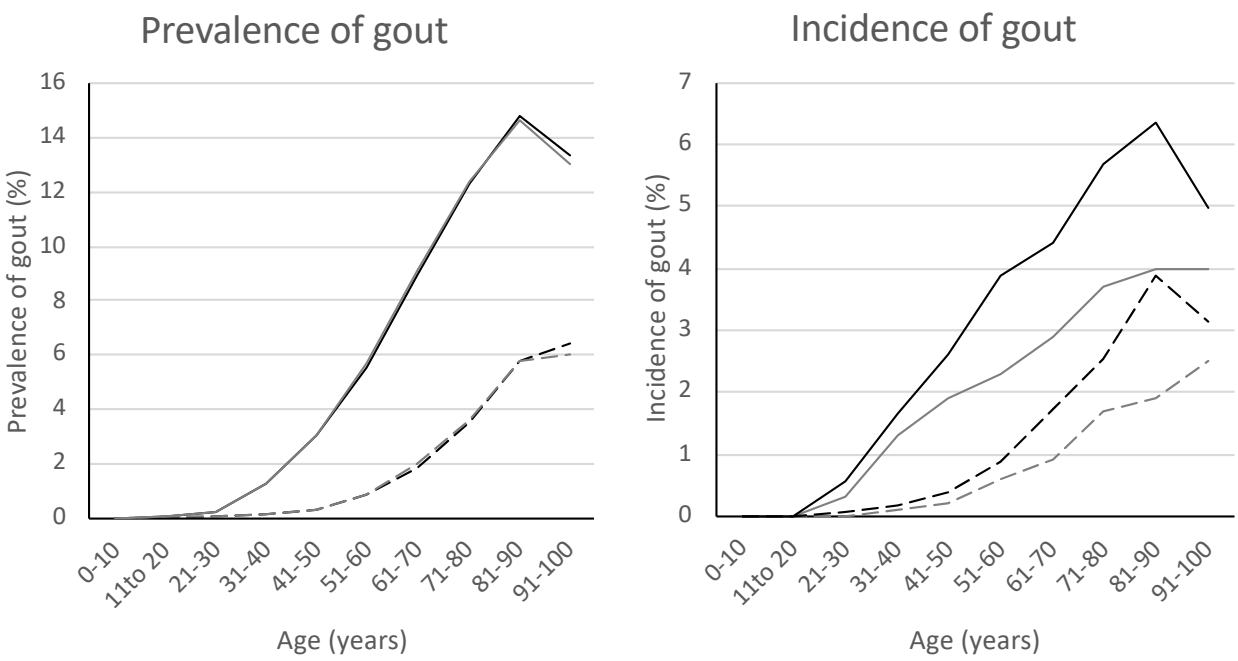
1. *Case definition:* Gout was defined using published Read code list expanded with additional codes[3]. Prevalent gout cases had either prior primary-care consultation for gout or had specific Read codes indicating long-term gout only. Incident gout cases consulted for gout for the first time with at-least one-year prior disease-free registration in the CPRD. The requirement to have one-year disease free registration minimises the risk of classifying prevalent cases as incident[3]. For ascertaining incident gout cases, separate at-risk cohorts comprising of all individuals registered with up-to-standard practices who had no diagnostic codes for gout before the latest of their current registration date plus 365 days or January 1st of the calendar year were constructed. Follow-up started from the latest of these two dates to the earliest of first gout diagnosis, transfer out of GP surgery, death, December 31st of the year; or, for the year 2021, the study end date.

Definition of urate lowering treatment (ULT) prescription: ULT prescription was defined as a prescription of allopurinol, febuxostat, benzbromarone, probenecid or sulfinpyrazone. Product codes were used to ascertain ULT prescription.

2. *Variables for direct standardization:* The incidence and prevalence were directly standardised to the entire study population across the study period for age (10-year age-band), sex, and length of registration in CPRD (=<1, >1-5, >5-10, >10-15, >15-20, >20-25, >25 years). The latter was included because increasing length of registration in CPRD increases incidence and prevalence estimates of gout in CPRD[3].
3. *Joinpoint analysis:* Joinpoint analysis was done using the Joinpoint Trend Analysis Software version 4.9.0.0 obtained from https://surveillance.cancer.gov/joinpoint/ and developed by the National Cancer Institute (NCI) of the National Institute for Health (NIH). It uses Bayesian Information Criterion to generate different numbers of joinpoints indicating points in time where trends in the prevalence and incidence change significantly and to fit separate linear trends in each time segment. Initially a model is fitted without joinpoints (i.e., a straight line fitted to the data) with joinpoints added whenever a change in trend over time is statistically significant. Annual percentage changes (APC) for each segment and average APC (AAPC) for the entire study period are calculated.



4. Figure S1: (A) Crude prevalence of gout 2019 and 2021, stratified by age and sex. (B) Crude incidence of gout 2019 and 2021, stratified by age and sex. Solid black line male 2019, long dash line black female 2019. Grey solid line male 2021, grey long dash line female 2021.

1 ***5.*** **Read codes used to ascertain gout status.**

Gout				
Medcode	**Readcode**	**Readterm**	**Incident gout**	**Prevalent gout**
709	C34..00	Gout	1	1
2857	N023.00	Gouty arthritis	1	1
3759	1443.00	H/O: gout		1
4440	C34y200	Gouty tophi of other sites	1	1
9874	C34y500	Gouty tophi of hand	1	1
10080	C340.00	Gouty arthropathy	1	1
11462	C342.00	Idiopathic gout	1	1
12594	N023z00	Gouty arthritis NOS	1	1
14996	6691.00	Initial gout assessment	1	1
16475	669..00	Gout monitoring		1
17284	2D52.00	O/E - auricle of ear - tophi	1	1
21687	C345.00	Gout due to impairment of renal function	1	1
24153	C34z.00	Gout NOS	1	1
27521	C34yz00	Other specified gouty manifestation NOS	1	1
28999	C34y.00	Other specified gouty manifestation	1	1
29658	6693.00	Joints gout affected		1
34006	6695.00	Date gout treatment started		1
34105	6699.00	Gout treatment changed		1
35660	6692.00	Follow-up gout assessment		1
35664	N023700	Gouty arthritis of the ankle and foot	1	1
36481	C34y000	Gouty tophi of ear	1	1
43646	669A.00	Date gout treatment stopped		1
44566	C344.00	Drug-induced gout	1	1
45465	N023300	Gouty arthritis of the forearm	1	1
49775	N023600	Gouty arthritis of the lower leg	1	1
50067	C34y300	Gouty iritis	1	1
52101	N023400	Gouty arthritis of the hand	1	1
52103	6698.00	Gout drug side effects		1
52117	669Z.00	Gout monitoring NOS		1
52969	C341.00	Gouty nephropathy	1	1
57334	G557300	Gouty tophi of heart	1	1
58064	N023x00	Gouty arthritis of multiple sites	1	1
58746	6697.00	Gout associated problems		1
59344	C34y400	Gouty neuritis	1	1
60541	N023y00	Gouty arthritis of other specified site	1	1
61145	C341z00	Gouty nephropathy NOS	1	1
68209	6696.00	Date of last gout attack		1
72471	N023100	Gouty arthritis of the shoulder region	1	1
93677	N023800	Gouty arthritis of toe	1	1
93689	C34y100	Gouty tophi of heart	1	1

94539	Nyu1700	[X]Other secondary gout	1	1
97539	N023200	Gouty arthritis of the upper arm	1	1
108901	C346.00	Acute exacerbation of gout	1	1
111834	C343.00	Lead-induced gout	1	1
113314	N023000	Gouty arthritis of unspecified site	1	1
114211	C341000	Gout nephropathy unspecified	1	1

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2 ***6.*** **Product codes to ascertain urate lowering treatment prescription**

Product code	Drug substance name	Product code	Drug substance name
11975	Allopurinol	42859	Febuxostat
34005	Allopurinol	43336	Febuxostat
41612	Allopurinol	42536	Febuxostat
23368	Allopurinol	43161	Febuxostat
46941	Allopurinol	77342	Benzbromarone
44239	Allopurinol	47263	Benzbromarone
368	Allopurinol	31662	Probenecid
19037	Allopurinol	68886	Probenecid
78470	Allopurinol	8944	Probenecid
64906	Allopurinol	1302	Probenecid
41520	Allopurinol	5204	Sulfinpyrazone
34566	Allopurinol	20133	Sulfinpyrazone
67256	Allopurinol	18519	Sulfinpyrazone
72223	Allopurinol	9951	Sulfinpyrazone
34711	Allopurinol	13419	Sulfinpyrazone
44240	Allopurinol	10554	Sulfinpyrazone
24215	Allopurinol		
67748	Allopurinol		
34930	Allopurinol		
30768	Allopurinol		
19201	Allopurinol		
33484	Allopurinol		
34947	Allopurinol		
71008	Allopurinol		
74645	Allopurinol		
41541	Allopurinol		
76	Allopurinol		
34278	Allopurinol		
77467	Allopurinol		
34573	Allopurinol		
68025	Allopurinol		
13467	Allopurinol		
76324	Allopurinol		
7805	Allopurinol		
413	Allopurinol		

41664	Allopurinol		
71717	Allopurinol		
78521	Allopurinol		
5182	Allopurinol		
17255	Allopurinol		
76616	Allopurinol		
72153	Allopurinol		
45352	Allopurinol		
83504	Allopurinol		