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Secular trend of gout incidence in the UK: an age-period-cohort analysis

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ABSTRACT

Objectives The incidence of gout in the UK appears to have declined since 2013; however, whether such a trend occurred across participants born in different years (ie, birth cohort) is unknown. We aimed to examine the effects of the birth cohort on gout incidence using an age-period-cohort (APC) model.

Design Cross-sectional study.

Setting Nationwide data from the UK primary care database.

Participants Individuals between 30 and 89 years of age were included. We excluded individuals who had gout history when entering the database and individuals with less than 1 year of continuous follow-up between 1 January 1999 and 31 December 2019.

Primary and secondary outcome measures Gout was identified using READ codes assigned by general practitioners. The incidence of gout between 1999–2013 and 2011–2019 was analysed with APC model.

Results The incidence of gout between 1999 and 2013 increased with birth cohorts. Compared with those born in 1949–1953 (reference), the age-adjusted and period-adjusted rate ratios (RRs) of incident gout increased from 0.39 (95% CI 0.34 to 0.46) in participants born in 1910–1914 to 2.36 (95% CI 2.09 to 2.66) in participants born in 1979–1983 (p for trend <0.001). In contrast, the incidence of gout between 2011 and 2019 decreased with birth cohorts. Compared with those born in 1949–1953 (reference), the age-adjusted and period-adjusted RRs of incident gout declined from 2.75 (95% CI 2.30 to 3.28) in participants born in 1922–1926 to 0.75 (95% CI 0.65 to 0.87) in participants born in 1976–1980 but then increased slightly to 0.95 (95% CI 0.77 to 1.17) in participants born in 1985–1989.

Conclusions The gout incidence between 1999 and 2013 in the UK increased with the birth cohorts and then decreased between 2011 and 2019 except for those born after 1980. Future monitoring is needed to help identify aetiological factors and guide preventive and treatment strategies for gout.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Data were collected from a large population-based representative sample over 20 years and provided a comprehensive and contemporary pattern of gout incidence in the UK.
⇒ The age-period-cohort model helps quantify the effects of age, period and birth cohort on the secular trend of the incidence of gout.
⇒ The rate ratios and corresponding 95% CIs were calculated to quantify the effects of age, period and birth cohort on gout incidence.
⇒ Gout diagnosis misclassification is inevitable in general practice healthcare databases.

INTRODUCTION

Gout is the most common form of inflammatory arthritis worldwide.[1] Recurrent flares are the hallmark of the clinical manifestation of gout and cause excruciating pain and functional limitation.[2] Studies have reported that recurrent gout flares and joint damage affect the quality of life, reduce economic productivity and increase healthcare costs.[3–6] In addition, people with gout have a high prevalence of comorbidities and an increased risk of mortality.[7]

Over the past three decades, the incidence rate of gout has risen by 5.5% worldwide.[8] Such a trend is expected to continue as the prevalence of established risk factors for gout, such as overweight/obesity and the ageing population, increase.[8 9] Recently, a study in the UK reported that the age-adjusted and sex-adjusted annual incidence of gout has been decreasing since 2013.[10] However, the study did not evaluate the effect of birth cohort on the risk of incident gout. Thus, it is unclear if such a trend is consistent across the different birth cohorts.

When assessing the secular trend of the risk of a disease, it is important to consider the year of birth (birth cohort). The effect of the birth cohort represents the totality of environmental influences for a particular group of individuals born within specific years. The unique experience among the individuals of a particular birth cohort may make the risk of disease differ from those of other birth cohorts genetically and/or environmentally. Many studies have shown that the birth cohort effect plays an important role in the risk of various diseases, including cancer,[11–13] cardiovascular disease,[14 15] diabetes,[16] liver disease[17] and overweight/obesity.[18] The

findings of the effect of the birth cohort on the secular trend of the disease may help identify the specific factors and develop appropriate preventive strategies to reduce disease risk for future generations. To our knowledge, few, if any, studies have assessed the effect of birth cohort on the risk of incident gout.

To address this knowledge gap, we applied an age-period-cohort (APC) model to examine the effect of the birth cohort on the risk of incident gout in the UK from 1999 to 2019.

METHODS

Data source

We used data from the IQVIA Medical Research Data (IMRD, incorporating data from The Health Improvement Network, a Cegedim database) UK primary care database, an electronic primary care database containing approximately 790 general practices and 17 million participants in the UK. Healthcare information on socio-demographics, anthropometrics, lifestyle factors, visits to general practitioners (GPs), diagnoses from specialists and hospital admissions, and laboratory test results are recorded at each practice. The READ classification system is used to code specific diagnoses.[19] Previous studies have demonstrated that participants within the IMRD database are representative of the UK general population regarding demographic and medical conditions and that the contained data collected are valid for both epidemiological and clinical studies.[20 21]

Study population

Eligible participants were individuals between 30 and 89 years of age who had no gout history when entering the IMRD database. All participants had at least 1 year of continuous enrolment with the general practice between 1 January 1999 and 31 December 2019.

Outcome

The outcome was the incident gout that developed during the study period (ie, from 1 January 1999 to 31 December 2019). Gout was identified using READ codes assigned by GPs to their patients.[19] The date of incident gout was defined as the date of the first READ code for gout.

Statistical analysis

Each subject was followed from the index date to the date of the first of the following events: (1) gout diagnosis, (2) transfer out of the IMRD GP practice, (3) study closing date of 31 December 2019, (4) death or (5) the date when the subject turned age 90 years. The incidence rate of gout was calculated by dividing the number of incident cases of gout by the person-years of follow-up accumulated over the calendar years (ie, period). To prevent an unstable incidence rate in specific APC strata, we grouped both age and calendar year using a 3-year interval (ie, age categories: 30–32, 33–35, … 87–89; categories of the calendar year: 1999–2001, 2002–2004, …. 2017–2019).[22] To appropriately fit the APC model,[22] we grouped birth cohorts using a 5-year partially overlapping interval, using the mid-year of birth to indicate the birth cohort: 1910–1914 (the 1912 cohort), 1913–1917 (the 1915 cohort), … 1985–1989 (the 1987 cohort). Detailed information is shown in online supplemental table S1.

To examine whether the secular trend of the risk of incident gout varied before 2013 and after 2013, we divided the study into two periods: 1999–2013 and 2011–2019. We calculated the overall and sex-specific age-standardised rates (ASRs) of incident gout according to calendar year, using age distribution in 2011–2013 as the standard. We applied an APC model to evaluate the effect of birth cohort on the risk of incident gout.[23 24] The APC model provides a visual depiction of the birth cohort effect on the risk of incident gout and estimates the rate

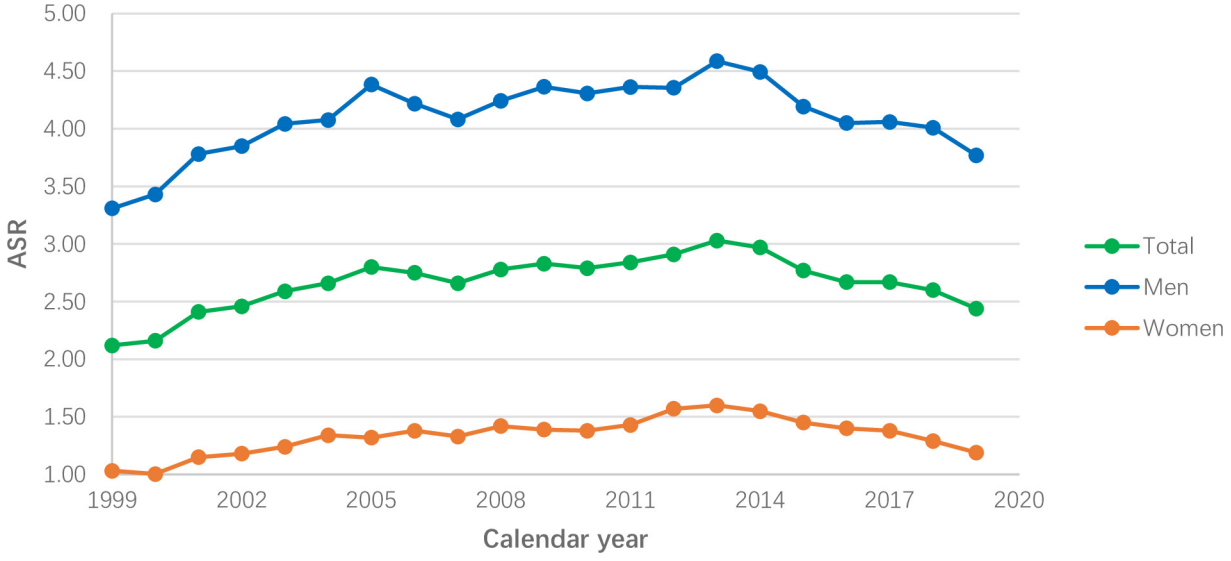

Figure 1 Age-standardised incidence rate of gout between 1999 and 2019, with age distribution in 2011–2013 as the standard. (green: total; blue: men; orange: women). ASR, age-standardised rate.

Table 1 Crude and age-standardised incidence rate of gout by calendar year

Calendar year	Cases	Follow years	Crude incidence*	ASR
1999	3716	1742751	2.13	2.12
2000	4353	2009215	2.17	2.16
2001	5974	2475794	2.41	2.41
2002	6774	2738357	2.47	2.46
2003	7632	2931754	2.60	2.59
2004	8174	3055156	2.68	2.66
2005	9112	3222389	2.83	2.80
2006	9294	3326976	2.79	2.75
2007	9153	3377872	2.71	2.66
2008	9874	3465972	2.85	2.78
2009	10142	3500231	2.90	2.83
2010	9837	3434139	2.86	2.79
2011	9971	3408436	2.93	2.84
2012	10175	3391289	3.00	2.91
2013	10314	3278565	3.15	3.03
2014	9505	3075061	3.09	2.97
2015	7867	2730034	2.88	2.77
2016	6598	2373088	2.78	2.67
2017	5924	2140325	2.77	2.67
2018	5369	1998808	2.69	2.60
2019	4743	1869569	2.54	2.44

*Incidence rate is presented as crude incidence per 1000 person-years, with age distribution in 2011–2013 as the standard.
ASR, age-standardised rate.

ratios (RRs) of incident gout for each birth cohort vs the birth cohort of 1949–1953 (reference), adjusting for age and period. We performed the same analyses in men and women separately.

To evaluate the robustness of the study findings, we performed a sensitivity analysis using a more restrictive definition of gout diagnosis.[25] Specifically, we defined incident gout using both READ code and prescriptions of either urate-lowering treatment and antigout medication (ie, allopurinol, colchicine, probenecid and sulfinpyrazone) within 90 days after the first-ever diagnosis of gout or non-steroidal anti-inflammatory drugs (NSAIDs) on the same day of the first-ever diagnosis of gout to make the gout diagnosis. This definition has a validity of 90% of gout diagnosis in the UK General Practice Research Database, now named the Clinical Practice Research Datalink,[26 27] in which 60% of participants overlap with IMRD.

All statistical tests were two sided, and a $p<0.05$ was considered statistically significant. The APC model was implemented using R tools.[28] All other analyses were performed using SAS software, V.9.4.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

The overall trend in gout incidence

Of 6551455 participants included in the analyses, 51.0% were women. During 21 years of follow-up, 164588 participants developed incident gout. The incidence rate of gout in men (4.5/1000 person-years) was higher than in women (1.6/1000 person-years). As shown in figure 1 and table 1, the ASRs of incident gout increased from 1999 to 2013 and then declined afterwards in the total population as well as in men and women, respectively.

Effect of birth cohort on gout incidence between 1999 and 2013

Between 1999 and 2013, the risk of incident gout increased monotonically from the early to the late birth cohorts (figure 2A). Compared with those born in 1949–1953, the RRs of incident gout increased from 0.39 (95% CI 0.34 to 0.46) in participants born in 1910–1914 to 2.36 (95% CI 2.09 to 2.66) in participants born in 1979–1983 (p for trend <0.001) (table 2). Similar associations were observed in both men and women (figure 2B,C) though

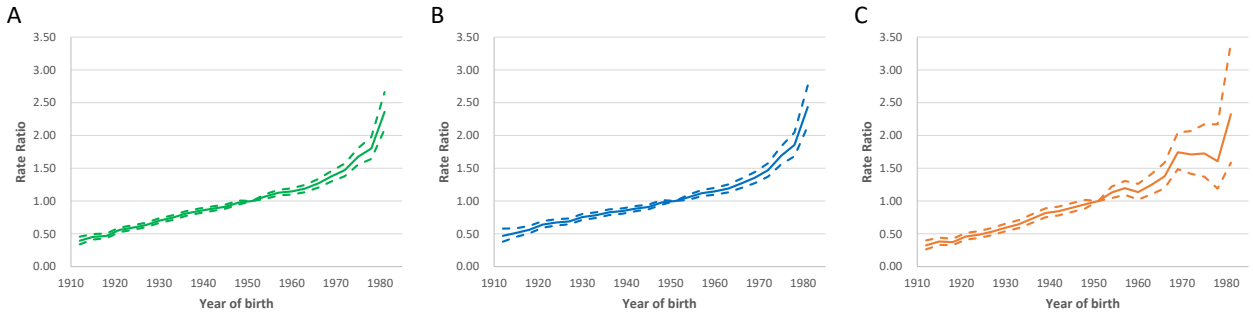

Figure 2 Effects of birth cohort on gout incidence between 1999 and 2013. The rate ratio of each birth cohort (1910–1983) compared with the reference birth cohort (1949–1953) was adjusted for age and period. (A) Total, (B) men and (C) women.

Table 2 Association between the birth cohort and incident gout adjusting for age and period

	Rate ratio	
	Period	
Birth cohort	1999–2013	2011–2019
1910–1914 (1912)	0.39 (0.34, 0.46)	NA
1913–1917 (1915)	0.45 (0.41, 0.50)	NA
1916–1920 (1918)	0.47 (0.43, 0.50)	NA
1919–1923 (1921)	0.56 (0.52, 0.60)	NA
1922–1926 (1924)	0.59 (0.56, 0.63)	2.75 (2.30, 3.28)
1925–1929 (1927)	0.63 (0.60, 0.67)	2.59 (2.25, 2.99)
1928–1932 (1930)	0.70 (0.67, 0.74)	2.36 (2.09, 2.67)
1931–1935 (1933)	0.75 (0.71, 0.78)	2.12 (1.90, 2.37)
1934–1938 (1936)	0.81 (0.77, 0.85)	1.91 (1.73, 2.10)
1937–1941 (1939)	0.85 (0.81, 0.88)	1.66 (1.52, 1.81)
1940–1944 (1942)	0.88 (0.85, 0.92)	1.44 (1.34, 1.56)
1943–1947 (1945)	0.91 (0.88, 0.95)	1.27 (1.19, 1.35)
1946–1950 (1948)	0.98 (0.95, 1.01)	1.12 (1.06, 1.18)
1949–1953 (1951)	1.00 (reference)	1.00 (reference)
1952–1956 (1954)	1.07 (1.03, 1.11)	0.95 (0.90, 1.00)
1955–1959 (1957)	1.13 (1.09, 1.17)	0.90 (0.84, 0.96)
1958–1962 (1960)	1.15 (1.10, 1.20)	0.84 (0.78, 0.91)
1961–1965 (1963)	1.19 (1.14, 1.25)	0.84 (0.77, 0.92)
1964–1968 (1966)	1.27 (1.20, 1.34)	0.80 (0.73, 0.89)
1967–1971 (1969)	1.38 (1.30, 1.46)	0.77 (0.69, 0.86)
1970–1974 (1972)	1.47 (1.38, 1.57)	0.74 (0.66, 0.84)
1973–1977 (1975)	1.68 (1.55, 1.81)	0.74 (0.65, 0.85)
1976–1980 (1978)	1.80 (1.64, 1.98)	0.75 (0.65, 0.87)
1979–1983 (1981)	2.36 (2.09, 2.66)	0.83 (0.70, 0.97)
1982–1986 (1984)	NA	0.88 (0.74, 1.06)
1985–1989 (1987)	NA	0.95 (0.77, 1.17)

NA, not applicable.

men showed overall higher RRs across all birth cohorts than women (online supplemental table S3). Sensitivity analysis using the more restrictive definition to diagnose gout showed similar results (online supplemental table S4). The incidence rate of gout increased with age and calendar year independently (p for trend <0.001) (online supplemental tables S5 and S6).

Effect of birth cohort on gout incidence between 2011 and 2019

In contrast, an inverse association of the birth cohort with the incidence rate of gout was observed between 2011 and 2019. In general, the risk of incident gout was higher among the participants born earlier than those born later (figure 3A). Compared with those born in 1949–1953, the RRs of incident gout decreased gradually from 2.75 (95% CI 2.30 to 3.28) among participants born in 1922–1926 to 0.75 (95% CI 0.65 to 0.87) among those born in 1976–1980 (table 2). However, the RRs of incident gout gradually rose again slightly among younger birth cohorts (ie, those born more recently) (figure 3A). Compared with those born between 1949—1953, the RRs of incident gout were 0.83, 0.88 and 0.95 among participants born between 1979–1983, 1982–1986 and 1985–1989, respectively (table 2). A similar pattern was observed in men and women (figure 3B,C and online supplemental table S3). Results from the sensitivity analysis also confirmed the study findings (online supplemental table S4). The risk of incident gout increased with age until 70th, then declined (online supplemental table S5). It decreased gradually between 2011 and 2019 (p for trend<0.001) (online supplemental table S6).

DISCUSSION

Using a nationally representative general population sample in the UK, we found that the effect of the birth cohort on the risk of incident gout between 1999 and 2013 differed from that between 2011 and 2019. The risk of incident gout increased monotonically from the early to the late birth cohorts between 1999 and 2013. However,

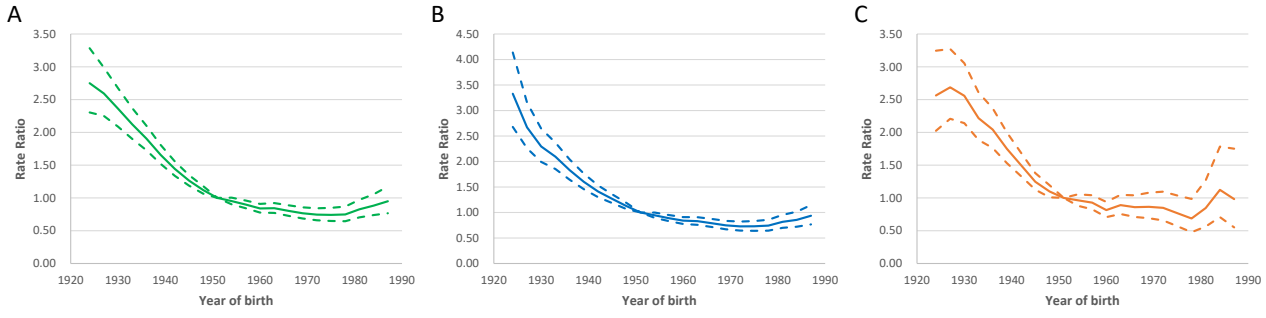

Figure 3 Effects of birth cohort on gout incidence between 2011 and 2019. The rate ratio of each birth cohort (1922–1989) compared with the reference birth cohort (1949–1953) was adjusted for age and period. (A) Total, (B) men and (C) women.

an inverse association was observed between 2011 and 2019. In general, the risk of incident gout after 2013 was higher among participants born earlier than those born later, except those born after 1980 whose risk of incident gout slightly bounced back up. Similar patterns were observed in men and women, respectively. The results from the sensitivity analysis that used a more restrictive criterion to diagnose incident gout also confirmed these findings.

Two previous studies have examined the relation of age, period and birth cohort to the prevalence of gout.[29 30] The results of these studies provided useful information on the burden of gout on society. Our study focused on the incidence of gout. The prevalence of gout is determined by both incidence and disease duration, and disease duration could be affected by gout management. To better understand the potential risk factors for gout, we focused on the incidence. The findings from the incident gout study can shed light on the potential risk factor for gout occurrence[31] and guide the development of appropriate preventive strategies to mitigate the risk of incident gout in the future.

A positive association between birth cohort and risk of incident gout between 1999 and 2013 in our study implies that the confluence of risk factors exposure results in more incident gout among late than early birth cohorts. Increased alcohol consumption and overweight/obesity over time may be the potential explanations for the birth cohort effect on the risk of gout during that period.[32 33]

We confirmed the previous report that the incidence of gout has been decreasing since 2013. Such a pattern was observed in both men and women and across different birth cohorts. The reasons for such a decline are not fully understood. Temporal changes in several key risk factors for gout do not correspond to the changes in the incidence of gout. For example, the Health Survey for England 2021 showed that the proportion of overweight or obese rose from 52.9% in 1993 to 64.3% in 2021,[34] and people born after the 1980s in the UK had much higher age-specific and sex-specific risk of overweight and obesity than those born before 1980s.[35] Chronic kidney disease (CKD) is another important risk factor for gout. The prevalence of CKD (stages 1–5) in the UK fell significantly from 2003 to 2010, but such a trend did not continue to 2016.[36] The per capita consumption of fructose-containing drinks, another risk factor for gout has been stable from the middle of the 2000s–2019 in the UK.[37] Thus, the temporal patterns of these three risk factors (ie, overweight/obesity, CKD and soft drink consumption) cannot explain the recent decline in the risk of gout.

On the other hand, alcohol consumed per capita in the UK has fallen steadily since the mid-2000s, especially among young people.[38] Also, the prevalence of hypertension and mean systolic and diastolic blood pressure has been steadily declining from 1994 to 2018.[39] Although these two factors may partially explain the decline in the risk of incident gout in recent years, the changes in alcohol consumption and prevalence of hypertension occurred much earlier than the change in the risk of incident gout. Thus, these two factors lack a close temporal association with a change in the risk of incident gout.

Previous studies reported that the risk of gout varies between racial and ethnic populations.[40] Over the past two decades, the ethnic distribution in the UK population has changed significantly. In 2001, 13.5% of people in the UK were non-white British, but this percentage has increased to 19.5% in 2011 and 25.6% in 2021,[41] mainly due to international migration. One study reported that Asian Americans had a slightly lower prevalence of gout than American White, but their prevalence of gout was doubled over 6 years and became even higher than that of American White, indicating that both genetic and environmental factors play roles in the development of gout.[42] Future studies examining the incidence rate of gout according to racial/ethnic origin in the UK could help to identify risk factors and their interaction on the secular trend of gout.

Moreover, the decline in the risk of incident gout in recent years may be partially explained by changes in healthcare-seeking behaviour, as it may affect the identification of incident gout cases. However, the incidence rate of gout decreased more rapidly than the healthcare-seeking behaviour during this period (ie, 19.4% vs 5.6% in 2019 compared with 2013). Thus, a change in healthcare-seeking behaviour seems unlikely to account for the decline in the rate of incident gout during this period. This phenomenon may also be influenced by factors like the reduction of red meat consumption.[43] Additionally, knowledge gaps and discrepancies between GPs' perceptions of the illness and their clinical practices may play a role in explaining changes in the risk of incident gout.[44–47]

To our knowledge, this is the first study to disentangle the effects of age, calendar year and birth cohort on the risk of incident gout over the past 21 years. The APC model estimated birth cohort effect adjusted for interrelated age and period effect, which may change the incidence of gout, enable us to observe the shift in the incidence rate of gout and capture significant trends in particular populations to provide targeted suggestions of causation. Although the APC model has an inherent issue of collinearity to separate the effects of age, period and birth cohort on the risk of gout, the conclusion generated from the APC model is backed up by a clear pattern of the age-specific incidence rate of gout across the period and birth cohort. In addition, the findings were consistent in men and women, indicating the robustness of our study findings. Also, the IMRD database is a large population-based representative sample of the UK general population, allowing us to report the most comprehensive and contemporary pattern of gout incidence in the UK.

Our study has several limitations. First, the reduction in the incidence of gout after 2013 was mainly observed among participants born before 1980 but not among those born afterwards. Therefore, we cannot be sure

whether the burden of gout in the UK will be reduced in the coming years owing to the lack of a clear picture of the secular trend of gout incidence among the younger population. Continuously monitoring the risk of incident gout among the younger population and racial minority groups shall help identify the potential risk factors for the secular trend of incident gout and assess the burden of this disease on the UK population. Second, the misclassification of gout diagnoses is unavoidable when using the GP's healthcare database. However, when we used more restrictive criteria to diagnose gout, that is, combining GPs' diagnoses and the use of medication, we reached the same conclusion, supporting the robustness of the study findings. Third, in the current study, the incident gout was based on the GP's diagnoses. It is quite possible that some gout patients may not seek care for their disease; thus, the incidence rate of gout may be underestimated. Finally, we did not directly investigate the underlying causes for the temporal trend of the incidence of gout, especially why the incidence rate has been declining since 2013. Future studies are required to identify the main risk factors attributable to the decline.

In conclusion, the risk of incident gout between 1999 and 2013 increased with birth cohorts, while the risk of incident gout between 2011 and 2019 decreased with birth cohorts, slightly bounced back more recently (ie, after 1980). The findings suggest that future monitoring of gout incidence, especially for those born after 1980, is needed to help identify aetiological facors related to this change and to guide appropriate preventive and treatment strategies for gout.

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Contributors All authors have read and approved the final manuscript. XD acts as an guarantor for the overall content of the study. JY, JW, GL and XD had full access to all the data in the study and take responsibility for its integrity and the accuracy of the data analysis. XD, JW, GL, YZ, CZ and JY designed the study. JY, YZ, WZ, MD, NL, CZ, GL, JW and XD supported data acquisition, analysis and interpretation for this work. JY, JW and YZ drafted the manuscript. JY, YZ, WZ, MD, NL, CZ, GL, JW and XD provided critical revisions of the manuscript for important intellectual content. JY, NL and YZ contributed to statistical analysis of data. JW, GL, YZ and CZ supported administrative, technical and material aspects. JW, WZ, MD, GL, YZ and CZ supervised the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the scientific review committee for the IMRD database (22SRC040) and the institutional review board at Xiangya Hospital (2018091077) approved this study with a waiver of informed consent. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. While we are unable to share the data sets, code lists are available on request.

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