Incident Gout: Risk of Death and Cause-specific Mortality in Western Sweden – a Nested Case Control Study

Mats Dehlin (mats.dehlin@gu.se)

Dept of Rheumatology and Inflammation, Sahlgrenska Academy, University of Gothenburg, Sweden
https://orcid.org/0000-0001-5165-0968

Tatiana Zverkova Sandström

University of Gothenburg Institute of Medicine: Goteborgs universitet Institutionen for medicin

Lennart TH Jacobsson

University of Gothenburg Institute of Medicine: Goteborgs universitet Institutionen for medicin

Research article

Keywords: Gout, Mortality, Dementia, Population based Registry study, western Sweden, risk of death

Posted Date: June 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-586033/v1

Abstract

Background

Excess mortality in gout has mainly been attributed to cardiovascular disease (CVD). In the light of decreased CVD-mortality in general we wanted to evaluate the risk of overall mortality in gout and cause-specific contributions to mortality beyond CVD as well as temporal trends of it.

Methods

All incident cases of gout between 2006-2015 in western Sweden were identified in the healthcare database VEGA. Up to 5 population controls per case matched on age, sex and county were identified. Relevant comorbidities were identified for 5 years preceding index date in VEGA. Follow-up until the first of death, migration or study end 31 of December 2017. Cause of death was identified and cause-specific mortality grouped as: cardiovascular disease (CVD), renal disease (RD), dementia (DEM), infections, diabetes, diseases of the digestive system (DDS), lung diseases, cancer (CA) and other. Effect of gout on risk of death was calculated using COX regression on whole population and stratified by sex, adjusted for demographics and comorbidities. Death incidence rate were compared between the two time periods, 2006-2010 and 2011-2015.

Results

We identified 22055 cases of incident gout and 98 946 controls, mean age (SD) 67.3-66.3 (15.3-15.4) years and 67.6-66.5% males. All comorbidities were more common at baseline among gout cases except for dementia which was more common in controls. Overall risk for death in incident gout was increased with 3%. Gout cases had a significantly increased risk for death by CVD, RD and DDS and a significantly decreased risk for death by DEM and CA. Similar results were found when stratifying for sex. There were no significant differences in incident death rate ratios in total, and subdivided into CVD and non CVD cause of death, between cases and controls in the two time periods examined.

Conclusions

A 3% increase in all-cause death in patients with gout highlights the importance in addressing not only CVD risk factors in the management of gout patients. Furthermore, gout was associated with reduced mortality from dementia and these findings calls for further study, not least because of possible effects of urate lowering therapy on risk of dementia.

Background

Gout is the most common inflammatory joint disease in the world [1]. It is caused by oversaturation of urate, hyperuricemia, leading to deposition and crystallization of urate in joints and tendons which triggers a pronounced immunological reaction in susceptible individuals resulting in severe pain and excessive inflammation [2]. Acute treatment of gout is available and effective, examples hereof are Non

Steroidal Anti Inflammatory Drugs (NSAID), corticosteroids and colchicine. Prophylactic treatment with urate lowering therapy (ULT) is cheap, available and offers a “cure” for the disease but in spite of this it is suboptimally used in Sweden and the world [3, 4]. Gout is closely associated to a number of comorbidities; some with unclear causality such as cardiovascular disease (CVD) and cancer [5, 6] while some lead to hyperuricemia thus increasing the risk of gout, examples hereof are renal disease and obesity [7]. Neurodegenerative diseases, dementia and Parkinson, have been associated with a decreased risk in patients with gout or hyperuricemia [8, 9] although there are conflicting results [10–12]. To further complicate matters, CVD is a risk factor for dementia [13].

Gout has been associated with an increased mortality from CVD [14, 15], death overall [16] and cause specifically for in particular kidney disease, endocrine and metabolic disease [17, 18]. Comorbidities are probably the most important risk factor for death but others have been investigated. Low level of education has been shown to be related to premature mortality in the general population [19] but also in patients with gout [20]. Presence of tophi and high urate, markers of more severe gout disease, have also been shown to increase the risk for cardiovascular death [21, 22]. However, treatment with ULT has not so far been shown to have a protective effect on mortality [23]. Females represent a minority of gout patient and have to a lesser extent been studied but the mortality risk has been shown to be increased in both sex although the risk increment was higher in females [17, 18, 24]. Studies of the effects of gout disease duration on mortality risk have shown contradictory result [18, 25].

A recent registry study from Sweden including all inhabitants aged ≥ 18 years in the southern county Skåne showed a 17% increased risk of all-cause mortality. For cause-specific mortality the study showed an increased risk for death from renal disease, diseases of the digestive system, CVD and infections, whereas the risk was decreased for death from dementia [26].

Life expectancy is increasing worldwide as well as in Sweden. This is to a large extent explained by a decrease in CVD mortality due to improved cardiovascular health care [27]. Decreased mortality in rheumatoid arthritis over the last decades have been shown and this may also be explained by decrease in CVD mortality [28], whereas a similar trend have not been observed in patients with gout over the same time period [29]. One explanation for this may be an increasing impact of non-CVD comorbidities on mortality in patients with gout. Following this, it is important to increase the knowledge and provide contemporary results regarding both all-cause and cause-specific mortality in gout. This may also have implications for future treatment recommendations.

In the present study, our aims were to determine the relative risks in incident gout patients in comparison to the general population 1) for overall death 2) for cause-specific mortality and 3) to examine possible temporal trends.

Methods

Data sources

The Western Swedish Health Care Register (VEGA)

The register contains information about all healthcare contacts in in- and outpatient secondary care clinics and in primary care in the WSHCR. Date of contact and primary and secondary diagnoses given by the treating physician according to the Swedish version of the International Statistical Classification of Diseases (ICD-10) are registered. VEGA was used to identify gout cases and to retrieve information about relevant comorbidities for cases and controls. For gout cases, the date of the first gout diagnosis was used as the index date/date of identification.

The Swedish Census Register

The census register holds demographic information about all registered inhabitants of Sweden including date of death and emigration. The census register was used to identify up to 5 controls for each case, matched for age, sex and place of residence on municipality level at the year of identification. Controls were assigned the same index date/date of identification as their corresponding case.

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

The LISA register is administered by Statistics Sweden and holds annual registers on all individuals 16 years of age and older. From here data on education level, income, marital status, birthplace outside Sweden and migration was retrieved.

The Swedish Prescribed Drug register

All prescribed drugs and date for dispensation by Swedish pharmacies are recorded in the Swedish Prescribed Drug register. Prescription of ULT (ATC-code M04AA and M04AB) was retrieved from here. The register has been available since 1 July 2005.

The Cause of Death register

The Swedish Cause of Death Register contains information from death certificates recorded according to the ICD- 10 system [30]. The Swedish Cause of Death Register follows recommendations from the World Health Organization for identifying the underlying cause of death [30]. It has been shown to have high validity with respect to main diagnostic categories [31, 32]. We identified the underlying cause of death for all study subjects who died between Jan 1st 2006 and Dec 31st 2017.

The cancer register

The Swedish Cancer Register, maintained by the National Board of Health and Welfare, was founded in 1958 and covers the whole population of Sweden. All data on cancer comorbidity was retrieved from here.

Study population

The Swedish healthcare system is tax-funded and offers universal access. Gout is typically diagnosed and treated in a primary care setting. All inhabitants, aged ≥ 18 years, in the Western Swedish Health Care Region (WSHCR) from January 1 2006 to December 31 2015 constituted the study population. The population of WSHCR is approximately 1.6 million (20% of the total population of Sweden)[33], and the region is considered to be representative for Sweden with regard to health status, healthcare seeking and socioeconomics.[33, 34]

To select individuals most likely to have new-onset gout, we included individuals, aged ≥ 18 years, with a diagnosis of gout in the VEGA-register during 2006–2015. The VEGA database was then searched for gout diagnoses back to January 1, 2000, and individuals with a prior diagnosis of gout were excluded. All included cases thus have a period free from gout diagnosis of at least 5 years before their index date. Gout diagnosis was defined by the presence of an ICD-10 code for gout (M10), registered at a visit to a physician in the VEGA-database. We excluded individuals with dispensation of ULT (ATC-code M04AA and M04AB) prior to first gout diagnosis. Up to 5 controls per case matched by age, year and municipality at the year of gout diagnosis was identified in the Swedish Census Registry. Controls with a prescription of ULT were excluded. The case definition has been previously validated by means of record review which showed a high validity of ICD-10 codes for gout in the VEGA-database [35]. Follow-up started from index date and ended at date of death, relocation outside of WSHCR or the end of the study (December 31, 2017), whichever occurred first.

Outcome

The outcomes were all-cause mortality and cause-specific mortality defined as: cardiovascular disease, renal disease, dementia, infections, diabetes, diseases of the digestive system, lung diseases, neoplasms and other. For definitions based on ICD-10 codes see supplementary Table 1. We identified the underlying cause of death for all study subjects who died between start of follow-up and Dec 31st 2017. To examine temporal trends of death in incident gout, we divided the study period in two, 2006–2010 and 2011–2015. Thereafter, we calculated incident death rate ratios in total, and subdivided into CVD and non CVD cause of death, between cases and controls in the two time periods.

Confounders

The following confounders were recorded in the year of the index date for cases and controls: sex, marital status, income, education, and whether the person was born outside of Sweden. The following comorbidities were considered as possible confounders and they were identified in the VEGA database for at least 5 years prior to the year of the index date: alcohol related disorders, hypertension, ischemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, dementia and lung diseases, Data on neoplasms was retrieved from the Swedish Cancer Registry. For definitions based on ICD-10 codes see supplementary Table 1.

Statistics

All data management and analyses were performed in SAS 9.4 and R 4.0.3. Baseline features were described as count (percent) of categorical data and as mean (standard deviation (SD)) along with median (25th and 75th percentiles) of continuous data. Incidence rate of total mortality and cause-specific mortality were calculated per 1000 person-year under assumption of Poisson distribution. Cause-specific mortality was treated through-out the study as follows: the cause of death in question was considered as event and the other causes of death were censured. 95% confidence intervals of incidence rate ratios were calculated under assumption of normal distribution for the natural logarithm of IRR. Hazard ratios were computed with Cox proportion hazard model. Impact of death of other causes on a specific cause was computed with Fine-Gray method with the death of other causes as a competing risk [36].

Results

From the total adult population of WSHCR between 2006 and 2015, with a yearly average population of 1 264 150 individuals, we identified 22055 cases of incident gout and 98 946 controls, for details see Table 1. After certain exclusions (Table 1) the mean age (SD) was 67.1 (15.3) years in the gout cohort compared with 66.3 (15.4) in the controls and 67.6% were males in the gout cases compared with 66.5 in the controls, Table 2. Mean annual income, level of education and being born in Sweden was lower in the gout subjects, Table 2. The identified comorbidities were more common among the gout cases with the exception of dementia that was overrepresented in the non-gout control subjects, Table 2. When stratified for sex, the overall picture was similar but the incident female gout cases were older, mean (SD) age, 71.6 (15.1) years compared to males, 65.3 (15.0), supplementary Table 2.

Table 1
Flowchart of the study population,

	Cases	Controls
Identified in VEGA	56 771	
Identified in The Swedish Census Register		110081
Re-used / missing personal identification number	-78	0
=	56693	110 081
No diagnosis of gout	-6199	N/A
=	50494	110 081
Not VGR resident	-117	0
=	50377	110 081
Gout diagnosis before 2006	-11249	-69
=	39128	110 012
Gout diagnosis after 2015	-9932	N/A
=	29196	110 012
First emigration date before diagnosis	-216	-28
=	28980	109 984
First immigration date 30 days after diagnosis	-43	-176
=	28937	109 808
ULT (M04AA, M04AB) within 5 years before diagnosis	-6860	-1432
=	22077	108 376
Age at diagnosis < 18 years	-22	
=	22055	108 376
Died before Index date	0	-291
	22055	108 085
Control more than once	N/A	-9139
Study population	**22055**	**98 946**

VEGA = The Western Swedish Health Care Register, VGR = Western Sweden Health Care Region,

Table 2
Baseline characteristics in gout cases and general population controls

	Gout cases, n = 22 055	Controls, n = 98 946
Age, years, mean (SD)	67.1 (15.3)	66.3 (15.4)
Male sex, n (%)	14 926 (67.6)	65 914 (66.5)
Annual income, EURO, mean (SD)	20 663 (36 930)	21 647 (29 636)
Education, n (%)		
≤ 9 years	8 716 (39.6)	36 480 (36.9)
10–12 years	8 938 (40.6)	38 459 (39.0)
≥ 13 years	4 013 (18.2)	22 391 (22.7)
Married, n (%)	11 718 (53.3)	52 694 (53.4)
Born outside Sweden, n (%)	3 216 (14.6)	13 611 (13.8)
Comorbidities, n (%)		
Alcohol related disorders	932 (4.2)	2 337 (2.4)
Hypertension	12 590 (57.1)	35 276 (35.7)
Ischemic heart disease	5 217 (23.7)	13 265 (13.3)
Heart failure	4 180 (19.0)	6 603 (6.7)
Cerebrovascular disease	2 269 (10.3)	7 568 (7.7)
Diabetes mellitus	3 965 (18.0)	10 550 (10.7)
Dyslipidemia	5 756 (26.1)	15 859 (16.0)
Obesity	1 033 (4.7)	1 642 (1.7)
Chronic kidney disease	964 (4.4)	822 (0.8)
Dementia	545 (2.5)	3 909 (4.0)
Lung diseases	3 181 (14.4)	9 242 (9.3)
Neoplasm	2 608 (11.8)	10 760 (10.9)
Follow-up time:		
Mean (SD)	5.5 (3.0)	5.6 (3.0)
Median (Q1; Q3)	5.2 (3.2; 7.7)	5.3 (3.2; 7.7)

After a mean (SD) follow-up time of 5.5 (3.0) years for gout cases and 5.6 (3.0) years for controls, we identified 5 817 (26.4%) deaths among the gout cases, resulting in an incidence rate (IR) of 47.7per 1000 person years, which was significantly higher compared to the 20 753 (21.0%) deaths, IR 37.6 per 1000 person years, among controls, with an incidence rate ratio (IRR) (95% CI) of 1.27 (1.23–1.31), Table 3. Overall, CVD was the major cause of death in both groups, although significantly more common in gout individuals with an IRR (95% CL) of 1.56 (1.50–1.63), Table 3. Death by renal disease, infections, diabetes, diseases of the digestive system, lung diseases and other were all significantly more common in gout subjects compared to controls, Table 3. The opposite was found for death caused by dementia, IR (95% CL) 2.01 (0.50–8.01)in gout subjects compared to 3.96 (1.48–10.60) in controls, IRR 0.51 (0.45–0.58), Table 3. We have also performed a sensitivity analysis on IRRs for total deaths comparing gout cases with controls stratified by age groups, in all subjects and by sex, which showed significantly higher IRRs in gout cases in all age groups in total and divided by sex with the exception of females aged 18–40 where no significant difference was seen, see suppl table 3.

Table 3
Number of deaths and incidence rates in cases and controls by causes of death

Cause of death, n (%)	Gout cases, n = 22 055	Incidence rate per 1000 person-years (95% CI)	Controls, n = 98 946	Incidence rate per 1000 person-years (95% CI)	Incidence rate ratio (95% CI)
Total deaths	5 817 (26.4)	47.74 (35.95–63.40)	20 753 (21.0)	37.60 (27.32–51.76)	1.27 (1.23–1.31)
Cardiovascular disease	2 905 (49.9)	23.84 (15.96–35.62)	8 406 (40.5)	15.23 (9.22–25.17)	1.56 (1.50–1.63)
Renal diseases	102 (1.8)	0.84 (0.10–7.13)	171 (0.8)	0.31 (0.01–10.48)	2.70 (2.11–3.45)
Dementia	245 (4.2)	2.01 (0.50–8.01)	2 185 (10.5)	3.96 (1.48–10.60)	0.51 (0.45–0.58)
Infections	362 (6.2)	2.97 (0.95–9.26)	1 193 (5.8)	2.16 (0.57–8.20)	1.37 (1.2–1.55)
Diabetes	202 (3.5)	1.66 (0.36–7.60)	500 (2.4)	0.91 (0.12–7.10)	1.83 (1.55–2.15)
Diseases of the digestive system	183 (3.2)	1.50 (0.30–7.43)	534 (2.6)	0.97 (0.13–7.10)	1.55 (1.31–1.84)
Lung diseases	254 (4.4)	2.08 (0.54–8.10)	912 (4.4)	1.65 (0.36–7.59)	1.26 (1.10–1.45)
Neoplasms	1 006 (17.3)	8.26 (4.17–16.33)	4 650 (22.4)	8.43 (4.29–16.55)	0.98 (0.9–1.05)
Other	558 (9.6)	4.58 (1.83–11.44)	2 202 (10.6)	3.99 (1.50-10.64)	1.15 (1.05–1.26)

CI = confidence intervals

All-cause mortality was significantly increased in the gout group with a hazard ratio (HR) of 1.24 (95% CI 1.21–1.28) when adjusting for age and sex but decreased to 1.03 (95% CI 1.00-1.06) in the fully adjusted model, Table 4. Stratifying by sex, the relative impact of gout on all-cause mortality was higher and significantly increased only in females compared to males in the fully adjusted model, HR 1.10 (95% CI 1.05–1.15) versus 0.99 (95% CI 0.95–1.03) respectively, Table 4. Death attributed to CVD was significantly higher in gout cases overall, HR 1.13 (95% CI 1.08–1.18), a finding seen for both male and females, Table 4. Death due to renal disease and diseases of the digestive system were significantly higher in gout overall, HR 1.53 (95% CI 1.16–2.01) and 1.27 (95% CI 1.07–1.52) respectively, but when stratifying for sex renal disease was only significantly increased in males with gout, HR 1.59 (95% CI 1.15–2.20) while death due to digestive diseases only was significantly increased in females, HR 1.43

(95% CI 1.08–1.89) respectively, Table 4. Death attributed to dementia was on the other hand significantly lower in gout cases overall 0.65 (95% CI 0.57–0.75), both for males 0.64 (95% CI 0.53–0.78) and for females 0.67 (95% CI 0.56–0.82), Table 4. Furthermore, this reduced risk in gout cases was seen for all of the four most common specific causes of death categorized under dementia: unspecified dementia, Alzheimer disease, vascular dementia and Parkinson disease, suppl table 4. On the other hand, dementia as a comorbidity at baseline was relatively more common in the control subjects in two of the three largest death cause groups, CVD and infections, but not in cancer compared to cases; this held true both in total and stratified by sex, suppl table 5. A lower risk in gout patients was also seen for death caused by lung diseases and neoplasms overall, HR 0.85 (95% CI 0.73–0.98) and 0.90 (95% CI 0.83–0.96) respectively, but only significantly in males when stratifying for sex, HR 0.80 (95% CI 0.66–0.98) and 0.86 (95% CI 0.79–0.94) respectively, Table 4. For information on specific diagnosis of death in each category, see suppl table 4.

Table 4
Cause-specific mortality overall and stratified by sex, gout cases compared to controls

Causes of death	Cause-specific mortality				Cause-specific mortality, Fine-Gray method			
	Overall		Male	Female	Overall		Male	Female
	Model 1	Model 2	Model 2	Model 2	Model 1	Model 2	Model 2	Model 2
Cardiovascular disease	1.54 (1.47–1.60)	1.13 (1.08–1.18)	1.07 (1.01–1.13)	1.23 (1.14–1.32)	1.54 (1.48–1.61)	1.17 (1.12–1.23)	1.13 (1.06–1.20)	1.25 (1.16–1.34)
Renal diseases	2.62 (2.05–3.35)	1.53 (1.16–2.01)	1.59 (1.15–2.20)	1.32 (0.79–2.20)	2.47 (1.93–3.15)	1.55 (1.15–2.08)	1.64 (1.16–2.31)	1.30 (0.72–2.36)
Dementia	0.51 (0.45–0.58)	0.65 (0.57–0.75)	0.64 (0.53–0.78)	0.67 (0.56–0.82)	0.45 (0.40–0.52)	0.68 (0.59–0.78)	0.70 (0.57–0.84)	0.67 (0.55–0.82)
Infections	1.34 (1.19–1.51)	1.11 (0.98–1.26)	1.05 (0.90–1.23)	1.21 (0.98–1.48)	1.25 (1.11–1.40)	1.13 (1.00-1.28)	1.10 (0.94–1.28)	1.19 (0.97–1.46)
Diabetes	1.79 (1.52–2.11)	0.94 (0.79–1.12)	0.89 (0.71–1.11)	1.03 (0.78–1.36)	1.69 (1.43–1.99)	0.98 (0.82–1.17)	0.96 (0.76–1.20)	1.02 (0.77–1.35)
Diseases of the digestive system	1.52 (1.29–1.80)	1.27 (1.07–1.52)	1.18 (0.94–1.49)	1.43 (1.08–1.89)	1.44 (1.22–1.71)	1.30 (1.09–1.56)	1.24 (0.98–1.55)	1.41 (1.06–1.87)
Lung diseases	1.24 (1.08–1.42)	0.85 (0.73–0.98)	0.80 (0.66–0.98)	0.90 (0.71–1.12)	1.17 (1.02–1.34)	0.86 (0.75-1.00)	0.83 (0.68–1.01)	0.89 (0.71–1.11)
Neoplasms	0.95 (0.89–1.02)	0.90 (0.83–0.96)	0.86 (0.79–0.94)	0.97 (0.86–1.11)	0.90 (0.84–0.96)	0.91 (0.84–0.97)	0.88 (0.80–0.96)	0.98 (0.86–1.11)
Other	1.12 (1.02–1.23)	1.03 (0.93–1.14)	1.02 (0.91–1.15)	1.04 (0.88–1.23)	1.06 (0.96–1.16)	1.05 (0.95–1.16)	1.06 (0.94–1.19)	1.03 (0.87–1.22)
All-cause mortality	1.24 (1.21–1.28)	1.03 (1.00-1.06)	0.99 (0.95–1.03)	1.10 (1.05–1.15)				

Causes of death	Cause-specific mortality				Cause-specific mortality, Fine-Gray method			
	Overall		Male	Female	Overall		Male	Female
	Model 1	Model 2	Model 2	Model 2	Model 1	Model 2	Model 2	Model 2

adjusted hazard ratios, 95% confidence intervals, and with competing risk Cox proportional hazard model with the method proposed by Fine and Gray,

CI = confidence intervals

Model 1: adjusted for sex and age at baseline

Model 2: adjusted for sex and age at baseline, marital status, income, education, born outside of Sweden, alcohol related disorders, hypertension, ischemic heart disease, heart failure, cerebrovascular disease, diabetes mellitus, dyslipidemia, obesity, chronic kidney disease, dementia, lung diseases, any neoplasm

In the sensitivity analysis, where possible impact of competing causes of death on our results was evaluated with the method proposed by Fine and Gray [36], all point estimates were in the same direction and of similar magnitude, see Table 4.

There were no significant differences in incident death rate ratios in total, and subdivided into CVD and non CVD cause of death, between cases and controls in the two time periods examined, 2006–2010 versus 2011–2015, see supplementary table 4.

Discussion

In this study, we found significantly increased total number of deaths in the gout cases. After adjusting for age, sex, birthplace outside Sweden and relevant comorbidities we found a 3% increased risk in all-cause mortality among the gout cases. Furthermore, the gout patients had a significantly increased risk for death caused by CVD, renal disease, and diseases of the digestive system and a significantly decreased risk for death caused by dementia, lung diseases and neoplasms. Similar results were found in men and women when stratifying for sex. We found no significant temporal trends of death rate between the first and the last part of the study period.

CVD

As expected CVD was the main cause of death for patients with gout in our study in line with previous studies [14, 15, 18, 22, 37]. Not only do the patients have an extensive CVD morbidity at time of first gout diagnosis, but in addition gout is treated with acute medication with potentially cardiotoxic medicines such as NSAIDs or corticosteroids over time. This emphasizes the need for CVD screening in gout patients but also an increased use of ULT to diminish the need for acute treatment. Furthermore, gout comes with episodes of severe inflammation which may have negative impact on CVD. This is supported

by results from the CARES trial in 2017 where treatment with the anti-inflammatory, anti-gout, interleukin-1 inhibitor canakinumab decreased the risk of recurrent cardiovascular events [38].

Renal disease

Death caused by renal disease was significantly increased in the gout patients in line with previous studies [18, 39]. Decreased renal secretion of urate by genetic predisposition and / or kidney disease is a major cause of hyperuricemia, which in a proportion will lead to gout [40]. At time of diagnosis, the gout patients in this study had an increased occurrence of multiple risk factors for kidney damage such as hypertension, diabetes and obesity. In addition, they also have an increased use of acute medication with potentially nephrotoxic NSAIDs for gout attacks. With appropriate and increased use of ULT, such need for acute treatment could be diminished. The possible negative effect of gout upon kidney disease is still an unresolved matter where further research effort is needed [41].

Infections

In the present study, death due to infections was not increased in gout patients. The risk was found increased in the recent population based registry study from the southern county Skåne, Sweden [26] and in a in a cohort study from Taiwan comparing 6000 (1400 female) gout patients with the general population [37]. A population based cohort study using data from the UK Clinical Practice Research Datalink that included 130 000 gout patients and 250 000 controls from 1987 to 2014 showed that patients with gout did not have an increased risk of infection-related mortality [42] while a Dutch prospective cohort study with crystal proven gout showed an increased risk for death due to infectious disease as well as cancer and CVD [22]. Frequency of gout increases with age and so do comorbidities. A recent study from the US by Singh et al have shown an increase in serious infections leading to hospitalization over the last two decades in gout patients. The most common infections seen were pneumonia and sepsis, with age and comorbidities as the major identified contributing factors [43]. In the present study, pneumonia and sepsis were the major infectious causes of death in both cases and controls. These findings emphasize the EULAR guidelines regarding vaccination from 2019 where it is advised to consider pneumococcal vaccination for the majority of patients with inflammatory rheumatic diseases [44].

Dementia

In our study, gout protected against death by dementia which was also showed in the aforementioned population based registry study from the southern county Skåne, Sweden [26]. Register studies have shown a decreased risk for dementia in gout individuals [45], metaanalysis of cross-sectional studies have shown protective effect of (increasing) urate on risk for Alzheimers dementia [9] while longitudinal studies show conflicting results [10–12]. In the present study, we lack data on urate levels. Obesity is strongly associated to both gout and hyperuricemia and was more common in the gout subjects in our study. The obesity paradox refers to the dual, age-dependent, effects on dementia, where overweight and obesity in middle age are associated with an increased future dementia risk in old age but when

examined later in life higher BMI is linked to better cognition and decreased mortality [46] which may influenced the results in our study. It should be noted that our capture of obesity at baseline likely lacked sensitivity and we did not have data on BMI. Our findings are however supported by the observation that diagnosed dementia was less common in gout cases vs controls already at start of follow-up. The possible protective effect of hyperuricemia on dementia development needs to be further examined and related to the treatment target for urate suggested by current ACR and EULAR treatment guidelines [47, 48].

Lung disease

Gout has not been found to be associated to smoking [49, 50] although exposure to air pollution or inorganic dust may have a role in gout pathogenesis [51, 52]. Nevertheless, lung diseases were a more common comorbidity in the gout population of our study and in spite of this we saw a significant protective effect of gout on death by lung diseases in males which haven't been shown in earlier studies [17, 26]. In the current study we have no data on smoking, however in 2017 we performed a questionnaire study on 800 gout patients in the same region of western Sweden as this study was performed and there we found no differences in frequency of current smoking compared to non-gout controls but a significantly higher degree of former smokers among gout patients in both males and females [53]. The two most common lung related causes of death in the current study in both cases and controls were chronic obstructive pulmonary disease and interstitial pulmonary disease but small numbers limit further analysis.

Cancer

Prevalence of neoplasms were higher at time of first gout diagnosis compared to non-gout controls in our study. In spite of this, we saw a a protective effect of gout on death attributed to cancer which haven't been shown in earlier population based studies [17, 26]. Gout is characterized by hyperuricemia which has potent antioxidant properties possibly protecting against cancer. However, gout is also closely associated to insulin resistance, obesity and increased alcohol intake which are all well known carcinogenic risk factors. An increased risk for some cancers have been shown in gout patients, particularly urological cancers, cancers of the digestive system and lung cancer [54]. In the current study, the four major causes of death by cancer were cancer of the prostate, lung, pancreas and large intestine / colon in both cases and controls. This mirrors the incidence and mortality of cancer in Sweden [55].

Digestive system

The increased risk of death from diseases of the digestive system in our study is supported by previous studies[17, 26]. Diagnosed alcohol related disorders were significantly higher at time of first gout diagnosis compared to the controls in our study. This was reflected in alcoholic liver disease being the only significantly increased cause-specific death related to diseases of the digestive system in the gout cases in the study.

Diabetes

Diabetes was one of the more common comorbidities at baseline in the gout patients of our study but in spite of this we could not find an elevated risk of death by diabetes which has been shown in earlier studies [17, 56].

General risk factors

Higher income is associated with decreased mortality in the Nordic countries [57] and lower level of education is a risk factor for increased mortality in the general population as well as in gout patients [19, 20]. The gout patients in our study had lower income and educational level compared to controls and they were also more often born outside Sweden. Increased mortality risk due to CVD and cancer has been shown in Swedish immigrants [58, 59]. The mortality risk increment in women compared to men with gout must be interpreted in the context of factors such as a lower overall mortality in women, higher age of gout onset and consequently more comorbidities at start and during follow-up [60].

There are some limitations to this study. First, as in all register studies there is a risk for misclassification of diagnosis. However, we have in a previous study found the gout diagnosis valid to a high degree [61]. Secondly, obesity and alcohol abuse was in the study only defined with ICD-10 codes at baseline and we lack data specifically on BMI and alcohol intake, at baseline and during follow-up, which will lead to an underestimation of these risk factors. Third, we lack data on smoking. Fourth, urate may have a role in many of the mortality causes in the study, not least dementia, but we lack data on urate levels.

There are also some strengths to this study. The study is population based and the sample size is quite large minimizing the risk for selection bias. Data on cause of death, comorbidities and cancer were collected from three different registers which all have almost complete coverage of the population. The study was performed on incident cases of gout minimizing the risk for survival bias. Furthermore, sensitivity analysis was performed and showed no impact of competing causes of death on our results.

Conclusions

To conclude, in this study we have shown a 3% increase in all-cause death in patients with gout highlighting the importance in addressing not only CVD risk factors but also infections, diseases of the digestive system and renal diseases in the management of patients with gout. Furthermore, gout was associated with reduced mortality from dementia and these findings calls for further study, not least because of possible effects of urate lowering therapy on risk of dementia

List Of Abbreviations

cardiovascular disease (CVD)

hazard ratio (HR)

incidence rate (IR)

incidence rate ratio (IRR)

International Statistical Classification of Diseases 10 (ICD-10)

Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

Non Steroidal Anti Inflammatory Drugs (NSAID)

Standard deviation (SD)

The Western Swedish Health Care Register (VEGA)

urate lowering therapy (ULT)

Western Swedish Health Care Region (WSHCR)

Declarations

Ethics approval and consent to participate

Ethical approval for the study was granted from the Ethical Review Board of Gothenburg, Sweden. Patient consent was waived, as data were derived from administrative registers that do not require such consent

Consent for publication

Not applicable

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Funding for the study was received from the following sources, which did not influence either the design of the study, the collection and analysis of the data, or the preparation of the manuscript: Reumatikerfonden and Gothenburg University. All researchers assigned as authors state their complete independence from the funders with regard to this study.

Authors' contributions

All authors have contributed substantially in the process of completing this study and had full access to the data, specified as follows: MD contributed to the conception and design of the study, as well as managing and interpretation of data, and drafting and revising the manuscript. TZS contributed to interpretation of data, was responsible for statistical work and participated in drafting and revising the manuscript. LTHJ contributed to the conception and design of the study, as well as interpretation of data, and drafting and revising the manuscript. All authors have approved the manuscript and agree to be accountable.

Acknowledgements

Not applicable

References

1. Dehlin M, Jacobsson L, Roddy EJAC: **Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors**. *Nature Reviews Rheumatology* 2020:1-11.
2. So AK, Martinon F: **Inflammation in gout: mechanisms and therapeutic targets**. *Nature Reviews Rheumatology* 2017, **13**(11):639-647.
3. Dehlin M, Ekström EH, Petzold M, Strömberg U, Telg G, Jacobsson LT: **Factors associated with initiation and persistence of urate-lowering therapy**. *Arthritis research therapy* 2017, **19**(1):6.
4. Kuo C-F, Grainge MJ, Mallen C, Zhang W, Doherty M: **Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England**. *JAMA* 2014, **312**(24):2684-2686.
5. Wang W, Xu D, Wang B, Yan S, Wang X, Yin Y, Wang X, Sun B, Sun X: **Increased risk of cancer in relation to gout: a review of three prospective cohort studies with 50,358 subjects**. *Mediators of inflammation* 2015, **2015**.
6. van Durme C, van Echteld IA, Falzon L, Aletaha D, van der Heijde DM, Landewé RB: **Cardiovascular risk factors and comorbidities in patients with hyperuricemia and/or gout: a systematic review of the literature**. *The Journal of Rheumatology Supplement* 2014, **92**:9-14.
7. Drivelegka P, Sigurdardottir V, Svärd A, Jacobsson LT, Dehlin M: **Comorbidity in gout at the time of first diagnosis: sex differences that may have implications for dosing of urate lowering therapy**. *Arthritis research therapy* 2018, **20**(1):108.
8. Yu Z, Zhang S, Wang D, Fan M, Gao F, Sun W, Li Z, Li S: **The significance of uric acid in the diagnosis and treatment of Parkinson disease: An updated systemic review**. *Medicine* 2017, **96**(45).
9. Khan AA, Quinn TJ, Hewitt J, Fan Y, Dawson J: **Serum uric acid level and association with cognitive impairment and dementia: systematic review and meta-analysis**. *Age* 2016, **38**(1):16.
10. Euser S, Hofman A, Westendorp R, Breteler MM: **Serum uric acid and cognitive function and dementia**. *Brain* 2009, **132**(2):377-382.
11. Latourte A, Soumaré A, Bardin T, Perez-Ruiz F, Debette S, Richette P: **Uric acid and incident dementia over 12 years of follow-up: a population-based cohort study**. *Annals of the Rheumatic Diseases* 2018,

77(3):328-335.

12. Scheepers LE, Jacobsson LT, Kern S, Johansson L, Dehlin M, Skoog I: **Urate and risk of Alzheimer's disease and vascular dementia: A population-based study**. *Alzheimer's Dementia* 2019, **15**(6):754-763.
13. Fillit H, Nash DT, Rundek T, Zuckerman A: **Cardiovascular risk factors and dementia**. *The American journal of geriatric pharmacotherapy* 2008, **6**(2):100-118.
14. Clarson L, Chandratre P, Hider S, Belcher J, Heneghan C, Roddy E, Mallen C: **Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis**. *European journal of preventive cardiology* 2015, **22**(3):335-343.
15. Kok VC, Horng J-T, Lin H-L, Chen Y-C, Chen Y-J, Cheng KF: **Gout and subsequent increased risk of cardiovascular mortality in non-diabetics aged 50 and above: a population-based cohort study in Taiwan**. *BMC cardiovascular disorders* 2012, **12**(1):1-9.
16. Lottmann K, Chen X, Schädlich PK: **Association between gout and all-cause as well as cardiovascular mortality: a systematic review**. *Current rheumatology reports* 2012, **14**(2):195-203.
17. Kuo C-F, Yu K-H, See L-C, Chou I-J, Tseng W-Y, Chang H-C, Shen Y-M, Luo S-F: **Elevated risk of mortality among gout patients: a comparison with the national population in Taiwan**. *Joint Bone Spine* 2011, **78**(6):577-580.
18. Teng GG, Ang L-W, Saag KG, Mimi CY, Yuan J-M, Koh W-P: **Mortality due to coronary heart disease and kidney disease among middle-aged and elderly men and women with gout in the Singapore Chinese Health Study**. *Annals of the rheumatic diseases* 2012, **71**(6):924-928.
19. Kunst AE, Mackenbach JP: **The size of mortality differences associated with educational level in nine industrialized countries**. 1994, **84**(6):932-937.
20. Kiadaliri A, Moreno-Betancur M, Turkiewicz A, Englund M: **Educational inequalities in all-cause and cause-specific mortality among people with gout: a register-based matched cohort study in southern Sweden**. *International journal for equity in health* 2019, **18**(1):164.
21. Perez-Ruiz F, Martínez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan EJAotrd: **Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout**. 2014, **73**(1):177-182.
22. Disveld IJ, Zoakman S, Tim LTA, Rongen GA, Kienhorst LB, Janssens HJ, Fransen J, Janssen M: **Crystal-proven gout patients have an increased mortality due to cardiovascular diseases, cancer, and infectious diseases especially when having tophi and/or high serum uric acid levels: a prospective cohort study**. *Clinical rheumatology* 2019, **38**(5):1385-1391.
23. Hay CA, Prior JA, Belcher J, Mallen CD, Roddy E: **Mortality in patients with gout treated with allopurinol: a systematic review and meta-analysis**. *Arthritis Care Research* 2020.
24. Stack A, Hanley A, Casserly L, Cronin C, Abdalla A, Kiernan T, Murthy B, Hegarty A, Hannigan A, Nguyen H: **Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality**. *QJM: An International Journal of Medicine* 2013, **106**(7):647-658.

25. Choi HK, Curhan G: **Independent impact of gout on mortality and risk for coronary heart disease**. *Circulation* 2007, **116**(8):894-900.
26. Vargas-Santos AB, Neogi T, da Rocha Castelar-Pinheiro G, Kapetanovic MC, Turkiewicz A: **Cause-Specific Mortality in Gout: Novel Findings of Elevated Risk of Non–Cardiovascular-Related Deaths**. *Arthritis Rheumatology* 2019, **71**(11):1935-1942.
27. O'Flaherty M, Buchan I, Capewell S: **Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s?** 2013, **99**(3):159-162.
28. Myasoedova E, Gabriel SE, Matteson EL, Davis JM, Therneau TM, Crowson CS: **Decreased Cardiovascular Mortality in Patients with Incident Rheumatoid Arthritis (RA) in Recent Years: Dawn of a New Era in Cardiovascular Disease in RA?** 2017, **44**(6):732-739.
29. Fisher MC, Rai SK, Lu N, Zhang Y, Choi HK: **The unclosing premature mortality gap in gout: a general population-based study**. *Annals of the rheumatic diseases* 2017, **76**(7):1289-1294.
30. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, Feychting M, Ljung RJEjoe: **The Swedish cause of death register**. 2017, **32**(9):765-773.
31. Johansson LA, Westerling R: **Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics**. *International journal of epidemiology* 2000, **29**(3):495-502.
32. Socialstyrelsen NBoHaW: **Dödsorsaksstatistik: historik, produktionsmetod-er och tillförlitlighet. Komplement till rapporten Dödsorsaker** 2010.
33. Statistiska Centralbyrån: **Folkmängden efter region, civilstånd, ålder och kön. År 1968 - 2014 www.scb.se**. 2012.
34. Ministry of Health and Social Affairs SGO: **Updated high-cost protection – outpatient care and medication**.
35. Dehlin M, Stasinopoulou K, Jacobsson L: **Validity of gout diagnosis in Swedish primary and secondary care-a validation study**. *BMC musculoskeletal disorders* 2015, **16**(1):149.
36. Austin PC, Lee DS, Fine JP: **Introduction to the Analysis of Survival Data in the Presence of Competing Risks**. 2016, **133**(6):601-609.
37. Kuo CF, Yu KH, See LC, Chou IJ, Tseng WY, Chang HC, Shen YM, Luo SF: **Elevated risk of mortality among gout patients: a comparison with the national population in Taiwan**. *Joint Bone Spine* 2011, **78**(6):577-580.
38. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD: **Antiinflammatory therapy with canakinumab for atherosclerotic disease**. *New England journal of medicine* 2017, **377**(12):1119-1131.
39. Kuo C-F, Yu K-H, See L-C, Chou I-J, Tseng W-Y, Chang H-C, Shen Y-M, Luo S-FJJBS: **Elevated risk of mortality among gout patients: a comparison with the national population in Taiwan**. 2011, **78**(6):577-580.
40. Kapetanovic MC, Nilsson P, Turesson C, Englund M, Dalbeth N, Jacobsson L: **The risk of clinically diagnosed gout by serum urate levels: results from 30 years follow-up of the Malmö Preventive**

Project cohort in southern Sweden. *Arthritis Research Therapy* 2018, **20**(1):190.

41. Roughley M, Sultan AA, Clarson L, Muller S, Whittle R, Belcher J, Mallen CD, Roddy E: **Risk of chronic kidney disease in patients with gout and the impact of urate lowering therapy: a population-based cohort study**. *Arthritis research therapy* 2018, **20**(1):243.
42. Spaetgens B, de Vries F, Driessen JHM, Leufkens HG, Souverein PC, Boonen A, van der Meer JWM, Joosten LAB: **Risk of infections in patients with gout: a population-based cohort study**. *Scientific Reports* 2017, **7**(1):1429.
43. Singh JA, Cleveland JD: **Serious Infections in People with Gout in the United States: A National Study of Incidence, Time-trends and Outcomes**. *Arthritis Care Research* 2020.
44. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, Breedveld FC, D'Amelio R, Dougados M, Kapetanovic MC *et al*: **2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases**. 2020, **79**(1):39-52.
45. Hong J-Y, Lan T-Y, Tang G-J, Tang C-H, Chen T-J, Lin H-Y: **Gout and the risk of dementia: a nationwide population-based cohort study**. *Arthritis Research Therapy* 2015, **17**(1):139.
46. García-Ptacek S, Faxén-Irving G, Čermáková P, Eriksdotter M, Religa D: **Body mass index in dementia**. *European journal of clinical nutrition* 2014, **68**(11):1204-1209.
47. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, Gelber AC, Harrold LR, Khanna D, King C: **2020 American College of Rheumatology guideline for the management of gout**. *Arthritis care & research* 2020, **72**(6):744-760.
48. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, Coyfish M, Guillo S, Jansen T, Janssens H: **2016 updated EULAR evidence-based recommendations for the management of gout**. *Annals of the rheumatic diseases* 2017, **76**(1):29-42.
49. Fanning N, Merriman TR, Dalbeth N, Stamp LK: **An association of smoking with serum urate and gout: a health paradox**. In: *Seminars in Arthritis and Rheumatism: 2018*: Elsevier; 2018: 825-842.
50. Lee YH: **Assessing the causal association between smoking behavior and risk of gout using a Mendelian randomization study**. *Clinical rheumatology* 2018, **37**(11):3099-3105.
51. Ryu H, Seo M, Choi H, Cho J, Baek H: **THU0427 Ambient air pollution and risk of acute gout flares; a time-series study**. In.: BMJ Publishing Group Ltd; 2017.
52. Sigurdardottir V, Jacobsson L, Schiöler L, Svärd A, Dehlin M, Toren K: **Occupational exposure to inorganic dust and risk of gout: a population-based study**. *RMD open* 2020, **6**(2):e001178.
53. Dehlin M, Scheepers L, Landgren A, Jacobsson L, Lindström U, Klingberg E, Bergsten U: **FRI0244 Life style factors and comorbidities in gout patients compared to the general population**. In.: BMJ Publishing Group Ltd; 2018.
54. Wang W, Xu D, Wang B, Yan S, Wang X, Yin Y, Wang X, Sun B, Sun XJMoi: **Increased risk of cancer in relation to gout: a review of three prospective cohort studies with 50,358 subjects**. 2015, **2015**.
55. Cancercentrum: **Cancer i Sverige Registerdata över förekomst och dödlighet 1970 - 2017**. 2020.

56. Schlesinger N, Elsaid M, Rustgi V: **AB0885 THE RELATIONSHIP BETWEEN METABOLIC SYNDROME SEVERITY AND THE RISK OF MORTALITY IN GOUT PATIENTS: A POPULATION-BASED STUDY**. 2019, **78**(Suppl 2):1910-1910.
57. Mortensen LH, Rehnberg J, Dahl E, Diderichsen F, Elstad JI, Martikainen P, Rehkopf D, Tarkiainen L, Fritzell J: **Shape of the association between income and mortality: a cohort study of Denmark, Finland, Norway and Sweden in 1995 and 2003**. 2016, **6**(12):e010974.
58. Gadd M, Johansson SE, Sundquist J, Wändell P: **Morbidity in cardiovascular diseases in immigrants in Sweden**. *Journal of internal medicine* 2003, **254**(3):236-243.
59. Abdoli G, Bottai M, Sandelin K, Moradi TJTB: **Breast cancer diagnosis and mortality by tumor stage and migration background in a nationwide cohort study in Sweden**. 2017, **31**:57-65.
60. Drivelegka P, Sigurdardottir V, Svärd A, Jacobsson LT, Dehlin MJAr, therapy: **Comorbidity in gout at the time of first diagnosis: sex differences that may have implications for dosing of urate lowering therapy**. 2018, **20**(1):108.
61. Dehlin M, Stasinopoulou K, Jacobsson LJBmd: **Validity of gout diagnosis in Swedish primary and secondary care-a validation study**. 2015, **16**(1):149.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytables.docx