

Supplements

Rationales of comorbidity selection

In this study, we initially choose all 17 categories of Charlson comorbidities in order to calculate the score. However, as the score only encompasses categories chosen to represent one's general health status and to predict mortality, many kinds of comorbidities that might be relevant to gout are missed. Therefore, we went on to select more categories of comorbidities to supplement Charlson comorbidities in order to give a broader picture of comorbidity burden in gout patients. We choose these comorbidities based on the prior knowledge of potential association either by published studies or by our clinical experiences. Sometimes, there is no direct evidence between gout and specific comorbidity but if a link with hyperuricaemia exists, we may also choose to include.

For anaemia, our clinical experience found many gout patients have anaemia due to gastrointestinal bleeding. Later, we found study suggesting potential links between gout and anaemia.[1] There are several studies linking cardiac arrhythmias with hyperuricaemia, but there is no direct evidence linking gout and arrhythmias.[2-4] We include neurological diseases[5] and multiple sclerosis[6] because evidence suggests hyperuricaemia may protect against these disease because antioxidant properties of uric acid. We included depression and psychosis because there is evidence linking uric acid levels to psychiatric disorders.[7-9] Hypothyroidism has been linked to hyperuricaemia because insufficient thyroid hormone may induce reversible renal insufficiency.[10] Direct evidence linking gout and hypothyroidism is lacking. Because of hyperuricaemia, urinary stone risk may be higher in gout but population-based evidence is lacking.[11] Finally we notice several case reports indicating valvular tophi and subsequent valvular disease.[12, 13]

Validation of recorded death in CPRD

In order to validate the recorded death and death date in CPRD, we requested data from the death registration from the Office of National Statistics for all patients registered between 2004 and 2006 who had consented to participate in the linkage scheme, which covered the period between 1st January 1998 and 10th January 2012. Overall, there were 3,522,601 participants from practices who had consented to the linkage scheme in this period. Data on cause of death were only available from these practices. Of these, 209,154 participants were identified as deceased in the CPRD but according to death registration, 197,139 participants had died. As shown in table S1, the sensitivity, specificity, positive predictive value and negative predictive value of a CPRD recorded death were 0.99, 0.99, 0.93 and 1.00, respectively. The CPRD recorded death dates were identical to that recorded in death registration in 89.0% of deceased patients identified by both CPRD and death registration. The difference between recorded dates of death was less than 3 months in 98.5% of deceased patients. Therefore the recording of death and death date in the CPRD is generally consistent with death registration.

Table S1. Performance of CPRD recorded death

CPRD	Death registration		Total	PPV	NPV
	recorded	Not recorded			
Recorded	195,047	14,107	209,154	93.3%	
Not recorded	2,092	3,311,355	3,313,447		99.9%
Total	197,139	3,325,462	3,522,601		
Sensitivity	98.94%				
Specificity		99.6%			

Footnote: PPV, positive predictive value; NPV, negative predictive value.

Table S2. Comorbidities present 10 years and 1 year before index date. Figures are number (percentage) of subjects with comorbidity and odds ratios (95% CI).

	10 year period before index date				1 year period before index date			
	Cases	Controls	Unadjusted OR	Adjusted OR ^a	Cases	Controls	Unadjusted OR	Adjusted OR ^a
Charlson index^b								
0	24,152 (61.75)	28,171 (72.03)	Reference	Reference	32,061 (81.97)	34,309 (87.72)	Reference	Reference
1-2	11,359 (29.04)	8,945 (22.87)	1.59 (1.53–1.64)*	1.39 (1.34–1.45)*	6,294 (16.09)	4,409 (11.27)	1.59 (1.52–1.66)*	1.36 (1.30–1.43)*
3-4	2,729 (6.98)	1,604 (4.10)	2.21 (2.07–2.37)*	1.89 (1.76–2.03)*	650 (1.66)	340 (0.87)	2.16 (1.89–2.46)*	1.77 (1.54–2.05)*
≥5	871 (2.23)	391 (1.00)	2.97 (2.63–3.37)*	2.51 (2.19–2.86)*	106 (0.27)	53 (0.14)	2.27 (1.63–3.16)*	1.78 (1.25–2.55)*
Neoplasms								
Solid malignancy, leukemia and lymphoma	2,092 (5.35)	1,758 (4.49)	1.21 (1.13–1.29)*	1.18 (1.10–1.26)*	604 (1.54)	532 (1.36)	1.14 (1.01–1.28)*	1.13 (1.00–1.28)
Metastatic solid tumors	54 (0.14)	64 (0.16)	0.84 (0.59–1.21)	0.88 (0.59–1.31)	25 (0.06)	30 (0.08)	0.83 (0.49–1.42)	0.89 (0.50–1.59)
Cardiovascular diseases								
Hypertension	13,615 (34.81)	7,313 (18.70)	2.64 (2.54–2.74)*	2.07 (1.99–2.16)*	5,178 (13.24)	2,652 (6.78)	2.26 (2.14–2.38)*	1.78 (1.69–1.89)*
Cardiac arrhythmias	3,442 (8.80)	1,455 (3.72)	2.65 (2.48–2.84)*	2.55 (2.38–2.74)*	998 (2.55)	384 (0.98)	2.69 (2.38–3.03)*	2.47 (2.17–2.80)*
Cerebrovascular disease	2,344 (5.99)	1,617 (4.13)	1.50 (1.41–1.61)*	1.44 (1.34–1.55)*	548 (1.40)	368 (0.94)	1.51 (1.32–1.72)*	1.38 (1.19–1.59)*
Congestive heart failure	3,339 (8.54)	919 (2.35)	4.49 (4.13–4.87)*	4.37 (4.01–4.76)*	1,043 (2.67)	259 (0.66)	4.31 (3.74–4.96)*	4.10 (3.53–4.76)*
Myocardial infarction	2,138 (5.47)	1,079 (2.76)	2.06 (1.91–2.23)*	1.88 (1.74–2.04)*	289 (0.74)	156 (0.40)	1.86 (1.53–2.26)*	1.78 (1.44–2.19)*
Peripheral vascular disease	1,506 (3.85)	922 (2.36)	1.69 (1.55–1.84)*	1.58 (1.44–1.73)*	361 (0.92)	185 (0.47)	1.97 (1.65–2.36)*	1.92 (1.58–2.33)*
Valvular heart disease	888 (2.27)	376 (0.96)	2.43 (2.15–2.75)*	2.47 (2.17–2.82)*	206 (0.53)	79 (0.20)	2.69 (2.07–3.51)*	2.58 (1.94–3.42)*
Genitourinary diseases								
Urolithiasis	368 (0.94)	256 (0.65)	1.44 (1.23–1.69)*	1.31 (1.11–1.56)*	72 (0.18)	26 (0.07)	2.77 (1.77–4.34)*	2.61 (1.61–4.25)*
Renal diseases	1,192 (3.05)	212 (0.54)	5.98 (5.14–6.95)*	5.96 (5.09–6.98)*	535 (1.37)	83 (0.21)	6.72 (5.31–8.51)*	6.63 (5.18–8.48)*
Metabolic and endocrine diseases								
Uncomplicated diabetes mellitus	2,769 (7.08)	2,279 (5.83)	1.24 (1.17–1.32)*	0.90 (0.85–0.96)*	1,813 (4.64)	1,370 (3.50)	1.36 (1.26–1.46)*	0.98 (0.90–1.06)
Diabetes mellitus with complications	507 (1.30)	442 (1.13)	1.15 (1.01–1.31)*	0.87 (0.76–1.00)	197 (0.50)	170 (0.43)	1.16 (0.94–1.43)	0.85 (0.68–1.07)
Hyperlipidaemia	3,955 (10.11)	2,100 (5.37)	2.10 (1.98–2.22)*	1.71 (1.61–1.82)*	996 (2.55)	451 (1.15)	2.30 (2.05–2.58)*	1.91 (1.69–2.16)*
Hypothyroidism	1,410 (3.61)	874 (2.23)	1.68 (1.54–1.83)*	1.50 (1.37–1.65)*	376 (0.96)	188 (0.48)	2.02 (1.69–2.41)*	1.82 (1.51–2.20)*
Gastrointestinal and hepatic diseases								
Peptic ulcer disease	790 (2.02)	695 (1.78)	1.14 (1.03–1.26)*	1.10 (0.98–1.23)	81 (0.21)	74 (0.19)	1.14 (1.03–1.26)	1.10 (0.98–1.23)
Mild liver disease	151 (0.39)	114 (0.29)	1.33 (1.04–1.70)*	1.13 (0.87–1.47)	36 (0.09)	23 (0.06)	1.33 (1.04–1.70)*	1.13 (0.87–1.47)
Moderate to severe liver disease	32 (0.08)	27 (0.07)	1.19 (0.71–1.98)	1.19 (0.68–2.06)	8 (0.02)	4 (0.01)	1.19 (0.71–1.98)	1.19 (0.68–2.06)
Chronic pulmonary diseases	5,316 (13.59)	3,844 (9.83)	1.46 (1.40–1.53)*	1.30 (1.23–1.36)*	2,393 (6.12)	1,637 (4.19)	1.46 (1.40–1.53)*	1.30 (1.23–1.36)*
Musculoskeletal and connective tissue diseases								
Osteoarthritis	4,268 (10.91)	3,049 (7.80)	1.51 (1.44–1.59)*	1.27 (1.20–1.34)*	1,002 (2.56)	656 (1.68)	1.55 (1.41–1.72)*	1.31 (1.17–1.46)*
Rheumatologic disease	2,786 (7.12)	2,392 (6.12)	1.18 (1.12–1.26)*	0.94 (0.88–0.99)	1,224 (3.13)	995 (2.54)	1.25 (1.15–1.36)*	0.94 (0.85–1.03)
Neurological and mental disorders								
Dementia	117 (0.30)	219 (0.56)	0.53 (0.42–0.66)*	0.54 (0.42–0.68)*	55 (0.14)	92 (0.24)	0.59 (0.42–0.83)*	0.60 (0.42–0.86)*
Hemiplegia	152 (0.39)	143 (0.37)	1.06 (0.85–1.34)	1.15 (0.90–1.47)	26 (0.07)	22 (0.06)	1.18 (0.67–2.09)	1.32 (0.72–2.42)
Multiple sclerosis	30 (0.08)	58 (0.15)	0.52 (0.33–0.80)*	0.61 (0.38–0.99)*	6 (0.02)	19 (0.05)	0.32 (0.13–0.79)*	0.27 (0.10–0.71)*
Other neurological diseases	692 (1.77)	850 (2.17)	0.81 (0.73–0.90)*	0.83 (0.75–0.93)*	175 (0.45)	236 (0.60)	0.84 (0.61–0.90)*	0.75 (0.60–0.91)*
Psychosis	158 (0.40)	210 (0.54)	0.75 (0.61–0.93)*	0.71 (0.57–0.89)*	38 (0.10)	51 (0.13)	0.75 (0.49–1.13)	0.63 (0.40–1.19)
Depression	4,732 (12.10)	4,064 (10.39)	1.20 (1.14–1.25)*	1.09 (1.04–1.15)*	1,200 (3.07)	992 (2.54)	1.22 (1.12–1.33)*	1.11 (1.01–1.22)*
Other comorbidities								
Anaemia	3,605 (9.22)	2,371 (6.06)	1.63 (1.54–1.72)*	1.40 (1.32–1.49)*	798 (2.04)	396 (1.01)	2.06 (1.82–2.33)*	1.84 (1.61–2.10)*
Psoriasis	1,253 (3.20)	878 (2.24)	1.44 (1.32–1.58)*	1.32 (1.20–1.45)*	355 (0.91)	206 (0.53)	1.72 (1.45–2.05)*	1.55 (1.29–1.87)*
HIV infection	12 (0.03)	3 (0.01)	4.00 (1.13–14.17)*	7.06 (1.69–29.51)*	3 (0.01)	0	-	-

Footnote: a. adjusted for age, gender, index year, BMI class, smoking status and alcohol consumption. b. Charlson index includes myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes mellitus [DM], DM with chronic complications, renal diseases, any malignancy [including leukaemia and lymphoma], metastatic solid tumour and human immunodeficiency virus [HIV] infection. * p<0.05

Table S3. Cumulative probability of all-cause mortality after diagnosis of gout. Figures are probability of death (percentage).

	Incident gout patients					Controls					P value
	At diagnosis	1 year	2 years	5 year	10 year	At diagnosis	1 year	2 years	5 year	10 year	
Overall	0	3.13	6.12	14.43	26.98	0	2.36	4.54	11.14	21.66	<0.001
Men	0	2.60	5.22	12.58	23.54	0	2.15	4.16	10.06	19.93	<0.001
Women	0	4.52	8.50	19.32	36.17	0	2.92	5.53	13.97	26.18	<0.001

Table S4 Predictors for all-cause mortality

Characteristics	Adjusted hazard ratios (95% confidence intervals)		
	All patients	Men	Women
Model 1: unadjusted	1.34 (1.29–1.39)	1.26 (1.21–1.32)	1.51 (1.42–1.60)
Model 2: adjusted for age, sex, index year, BMI class, smoking status and alcohol consumption	1.22 (1.17–1.27)	1.17 (1.11–1.23)	1.32 (1.23–1.41)
Model 3: adjusted for age, sex, index year, BMI class, smoking status and alcohol consumption and all comorbidities at index date	1.13 (1.08–1.18)	1.08 (1.02–1.15)	1.23 (1.14–1.33)

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