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Is Gout Requiring Allopurinol Use Associated with an Excess Risk of Osteoporotic Fracture? Findings from a Danish Registry

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Abstract

Purpose—Gout, an acute inflammatory arthritis, is common and associated with elevated serum urate, obesity and high alcohol consumption. The mainstay of therapy is the urate-lowering agent allopurinol. Here we report the relationship between allopurinol prescription and fracture in a large registry population.

Methods—We established a Danish Register cohort of 86,039 adult cases (new allopurinol users) and 86,039 age, sex and propensity score matched controls (not exposed to allopurinol or with a gout diagnosis), with no diagnosis of malignancy in the year prior.

Results—We found a modest adjusted effect of allopurinol prescription on major osteoporotic fractures (HR 1.09; 95% CI 1.05, 1.14, p=0.04); and on hip fractures (HR 1.07; 95% CI 1.11, 1.14, p<0.001), robust to adjustment for confounding factors (age, sex, comorbidity, medication use). Associations were stronger in men than women, and among incident allopurinol users whose gout diagnosis had been confirmed by at least one hospital contact. Prespecified subanalyses by filled dose of allopurinol (mg/day in first year of prescription) showed increased hip and major fracture risk in women in the highest allopurinol dose grouping only, while a less strong dose effect was evident for fracture rates in men.

Conclusion—Gouty arthritis requiring allopurinol is associated with an excess risk of major or hip fracture, with an allopurinol dose effect evident in women such that women taking the highest doses of allopurinol – suggestive of more severe disease - were at increased risk relative to women taking lower doses.

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Keywords

osteoporosis; gout; fracture; cohort; allopurinol

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Introduction

Gout is the most prevalent form of inflammatory arthritis worldwide causing substantial morbidity and impaired quality of life [1–3]. The prevalence of gout increases with age in association with its primary risk factor, sustained hyperuricaemia. In the prevention of acute gout attacks, allopurinol, is the mainstay of therapy. The association of gout with poor bone health and fracture risk is hence of great public health importance, given both the high prevalence of this condition, and widespread use of allopurinol therapy, particularly at older ages.

Risk of osteoporotic fracture is greater among individuals with low bone density, and frequent fallers. Lifestyle and anthropometric characteristics of gout patients may contribute to fracture risk in a number of ways. Although one might speculate that bone mineral density (BMD) might be raised in gout patients because the metabolic syndrome and its constituent elements are common in gout patients [4,5], and obesity is generally considered protective against osteoporosis [6], recent reports have suggested that morbid obesity might be associated with an excess fracture risk, particularly at the ankle [7,8]. Furthermore, conditions associated with high levels of inflammation, with stimulation of the inflammatory cascade and production of pro-inflammatory cytokines (Il-1, IL-10, IL-6, TNF-α) are well-recognised to cause both localised and generalised osteoporosis [8,9]. In addition, gout patients may be inactive because of recurrent gouty flares, or may have an increased alcohol intake [10]. A recent meta-analysis found a relative risk for a diagnosis of gout of 2.64 (95% CI 2.26-3.09) for heavy drinking, classified as 3 or more alcoholic drinks per day, when compared with subjects who consumed minimal amounts of alcohol [11]. Finally, falls may be more common in gout sufferers with lower limb arthritis.

Gouty attacks are triggered when a raised serum urate provokes urate crystal deposition in the joints, leading to a fall in serum urate levels. Serum urate levels will be reduced by allopurinol treatment, if compliance is good. While previous studies, have examined the association of serum urate with fracture, and observed conflicting results [the MrOS study found a reduced risk of non-spine fracture and higher BMD among men with higher serum urate concentrations [12], while a study that used the Cardiovascular Health Study found a U shaped relationship between hip fracture and serum uric acid in men but not women] [13]In spite of in vitro models suggesting that allopurinol can reduce bone resorption [14] and promote bone formation [15], to our knowledge no previous research has addressed the relationship between *allopurinol use* and bone health.

The aim of this study was therefore to extend and inform this area of research by utilising a very large Danish registry to study fracture rates among a population of men and women filling one or more allopurinol prescriptions, a subset of whom had a hospital diagnosis of gout, to assess direction of association between allopurinol prescription and fracture risk in a very large population of both sexes.

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Materials and Methods

As already discussed, gout patients who suffer recurrent attacks are typically prescribed allopurinol, a xanthine oxidase inhibitor that lowers urate concentrations. Use of this medication is widespread in Denmark with 1.5% of women and 4.5% of men aged 65+ being allopurinol users (Data from Danish National Board of Health for 2012, www.medstat.dk accessed July 2014). However, as in many other countries, adherence and compliance with this medication is low, with many gout suffers filling only one prescription.

This study is an observational study from Denmark using data from several Danish registers. The study-population are selected by identifying all individuals who had at least one allopurinol prescription in the period from 1995 to 2011 in the Danish National Prescription Registry (DNPR). DNPR covers the entire nation´s population and contains all prescriptions issued by prescribers, general practitioners or specialists since 1994 [16].

In this study, the index date was defined as the date of the first prescription for allopurinol or matching date for background control subjects. We used 1995 as a run-in year to identify prevalent users of allopurinol and to identify the date of first allopurinol prescription for the years 1996-2011 to find all new users of allopurinol. Each incident user was first assigned up to ten age- and gender matched control subjects from the Danish civil registration system (comprising all Danish citizens) who were not allopurinol users. This was used for basic descriptive analysis of the allopurinol cohort (table available from the authors on request). Patients were then further matched on quintiles of propensity score to identify a more highly matched 1:1 control population for assessment of outcomes by conditional Cox proportional hazards models in an open cohort design. A caliper of 0.2 was applied. The design of the study is shown in Figure 1.

Variables used as baseline descriptors and as candidates for inclusion in the propensity score model included ICD-10 hospital diagnoses (inpatient and outpatient) from 1995 to 2012, Charlson index components derived from hospital contacts, any prior major osteoporotic fractures. These variables were extracted from the Danish National Patient Registry, which contains discharge diagnoses of hospitalised patients indicating the main medical reason for diagnostic procedures or treatment [17] Number of other medications in the past year, prednisolone use in the past year, use of HRT, use of osteoporosis drugs, use of antihypertensives, statins, NSAIDs, insulin, oral antidiabetics and anticoagulants (all: any use in the past year) were extracted from the DNPR. In addition to these variables, we also adjusted for ICD-10 diagnoses indicative of chronic kidney disease or diabetes in our final models. Analyses were restricted to adults over the age of 18 years. The Danish Civil Persons register was used to access dates of death in order to censor Cox regressions on the date of death or the date of end of study (31.12.2012), whichever was the earlier date.

Because allopurinol may be used as an adjunct to chemotherapy in malignant disease, patients with a recent cancer diagnosis (in the past twelve months before the first allopurinol prescription) were excluded from both the gout cohort and the potential control population prior to matching.

The project was approved by Statistics Denmark (project 704127) and by the National Board of Health for data access. The study was not a clinical trial and ethics committee approval was not required.

Results

Baseline characteristics and matching

The initial study population consisted of 1,043,861 individuals over the age of 18 years, 104,026 allopurinol users and 939,835 controls (Figure 1) selected from a population of 113,131 incident allopurinol users and 1,396,640 potential population controls.

The propensity score matching identified a highly matched (1:1) population with 172,078 individuals (86,039 in each group, table 1). The mean age was 63 years and ranged from 18 to 103 years, one third were women and two thirds were men. The distribution of comorbidity among allopurinol users and controls was more balanced than before propensity score matching though modest residual imbalances that were nominally statistically significant remained and had to be controlled for in the Cox regressions. Hence, prior fractures were slightly more prevalent in allopurinol users (15% vs 14%, $p<0.001$) and this was also true for major osteoporotic fractures (6.5% vs 5.7%, $p<0.001$). Use of osteoporosis drugs was very low in both groups, 1.6% in allopurinol users and 1.2% in control subjects ($p<0.001$).

Incident fractures

A total of 13,071 (15%) allopurinol users and 12,170 (14%) controls sustained fractures; the number of major osteoporotic fractures was 5,565 (6.5%) and 4,885 (5.7%), respectively. Incidence rates stratified by age and sex for the two groups are shown in table 2. Table 3 shows the association of allopurinol prescription with fracture before and after adjustment for relevant potential confounders (prior fracture, renal disease, comorbidities, Charlson index, drug history). We found a modest adjusted effect of allopurinol prescription on major osteoporotic fractures (HR 1.09; 95% CI 1.05, 1.14, $p=0.04$); and on hip fractures (HR 1.07; 95% CI 1.11, 1.14, $p<0.001$). Effects were stronger in men than women.

Disease severity

Among patients who were incident allopurinol users and who also had at least one hospital contact with a gout diagnosis, suggestive of more severe gout compared with patients who were exclusively managed in private practice, (about 20% of allopurinol users, median number of allopurinol prescriptions 12 versus 6 in non-hospital group), we found stronger associations (Table 4). After adjustment for relevant potential confounders (prior fracture, renal disease, comorbidities, Charlson index, drug history), we found an increased adjusted effect of allopurinol prescription on major osteoporotic fractures (HR 1.26; 95% CI 1.15, 1.39, $p<0.001$); and on hip fractures (HR 1.21; 95% CI 1.04, 1.41, $p=0.02$). Again, results were stronger in men than women. In a sensitivity analysis to address any potential confounding effect of renal disease, we included chronic kidney disease in our confounder panel; we also identified patients on particularly low doses of allopurinol (100mg daily) as this may reflect impaired renal function. These extra analyses made little difference to our

findings; no significant interactions were found, and stratification confirmed the same effect size and direction.

Dose response analysis

Finally, we performed prespecified subanalyses to consider the filled dose of allopurinol as mg/ day over the first year of therapy, including pauses in treatment. We took this approach rather than basing our calculations on the total cumulative dose up to the time of fracture to remove the possibility that our results would be biased by differences in cumulated time, because individuals who fracture early would on average fill fewer allopurinol prescriptions in the time period between the index date and the date of fracture even if allopurinol had no true relation to fracture risk. Including allopurinol used after the fracture event as a predictor would have been flawed of course. Table 5 shows the risk of fracture according to tertile of allopurinol exposure. It shows that fracture risk was elevated in the women who received the highest allopurinol dose [hip 1.22 (95% CI 1.06-1.410 p=0.007; major fracture 1.13 (95% CI 1.03-1.24) p=0.01) but a dose effect was less apparent in men.

Discussion

We have observed increased rates of fracture among patients in receipt of allopurinol for a presumed diagnosis of gout, with elevated fracture rates among women in the highest tertile of drug prescription relative to their peers but less of a dose effect evident among men. This relationship between allopurinol and fracture risk remains after adjustment for other medications, including steroids and osteoporosis treatments, and for co-morbidities such as cardiovascular disease. When we confined our analysis to individuals who also had a hospital diagnosis of gout (no doubt the severe end of the spectrum) our observations were strengthened. Our findings suggest that gout requiring allopurinol may be a risk factor for fracture.

There are, of course, a number of limitations to our study. Perhaps the most significant is the lack of serum urate levels available to us. We used propensity score matching to achieve balancing of potential confounders as much as possible, but the potential of residual confounding remains. We have no information on body habitus, lifestyle factors such as alcohol consumption, nor falls information. In any study such as this, there will be a trade-off between the size of the population and the exact matching between cases and controls. The choice we made was based on retaining a large sample population which were comparatively well (though not perfectly) matched. However, this analysis of a very large, representative, well characterised data set has allowed us to report a clear excess of fracture among patients receiving allopurinol for gouty arthritis, and further studies of relationships with bone mineral density as an outcome are now planned.

Although uncontrolled inflammation, coexisting metabolic syndrome, lifestyle, body habitus and falls risk may all partially explain the results we have presented, a direct effect of urate lowering agents on bone has also been suggested by other researchers. In recent work, Orriss and colleagues demonstrated that inhibition of xanthine oxidase activity by allopurinol promotes osteoblast differentiation leading to increased bone formation [15] and a beneficial lowering of bone resorption has also been demonstrated in studies in mouse calvarial

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cultures [14]. Furthermore since uric acid inhibits 1-alpha hydroxylase protein expression and activity in vivo, it has been suggested that higher uric acid levels are associated with higher parathyroid hormone levels [18], which may be detrimental to bone health, and highlights the need to maintain uric acid levels in the normal range.

Our results suggest that gout requiring allopurinol use is a risk factor for osteoporotic fractures in both men and women, but the association is dose dependent with no signal suggesting that high adherence to allopurinol reduces fracture risk, despite observations in vitro that allopurinol is likely to be beneficial to skeletal health. Therefore the most likely explanation may be that greater severity of gout, with consequent higher and more rigorous use of allopurinol is more strongly associated with increased risk of fracture than milder disease. The observation of a more pronounced impact on fracture risk in hospital treated patients is suggestive of the same thing. To test the importance of lifestyle factors, and medication use, a randomised controlled trial would probably be required to remove the possibility of residual confounding.

The previous literature regarding relationships between uric acid and fracture risk has shown conflicting results. While fracture rates were lower in participants with higher uric acid levels in MrOS [12], the opposite was observed in a study by Mehta et al [13]. In MrOS, the relative hazard of hip and non-spine fracture was assessed in 1680 men 65 years of age or older in a model adjusted for age, race, body mass index, vitamin D, PTH, walking speed, PASE score, frailty and total hip bone density. In this cohort, hip bone mineral density measures were highest in those with the highest serum urate results; while non-spine fractures were less common at higher serum urate levels, no significant difference was observed in the rate of hip fractures. Given the efficacy of allopurinol as a urate lowering agent, one might speculate that these results are consistent with an association of lowering urate with higher fracture rates. By contrast, Mehta et al report higher hip fracture rates among men with the highest urate levels i.e. a level above 7mg/dL [13]. These findings mirror the stronger relationships we observed in men compared with women in our own study, and may reflect potential confounding by co-morbidity or a thresholding effect. It is possible that a U shaped relationship exists, with low or high urate levels both associated with adverse outcomes, through differing mechanisms. A recent study of heel ultrasound bone measures in men [19] found a positive association with serum urate levels – but omitted men with a diagnosis of gout or drug therapy that included urate lowering agents from the study, supporting our hypothesis that within the normal range of serum urate a positive association with bone density may exist, but at higher levels, and in the context of uncontrolled inflammatory arthritis of lower limb joints, fracture risk is elevated.

We found stronger relationships in men than women despite the much higher incidence rates of fractures in the female study subjects. Other investigators have investigated the relationship between uric acid levels and bone health in women as well as men [20]; a recent study reported that, after adjusting for multiple confounders, serum uric acid levels were positively associated with bone density at all sites in women. Recent work has also reported a longitudinal relationship between serum urate and bone health; it has been suggested that serum uric acid may be protective against the development of incident fractures in Korean men [21]. In their discussion however, the authors of this research concluded that it may be

higher uric acid levels *within the physiological range* that are beneficial; as discussed above, our own findings suggest that very high urate levels, associated with an acute, intense inflammatory arthritis and propensity to fall, may not be.

In conclusion, we report an association of allopurinol use with higher fracture rates that was particularly pronounced among men and in patients who also had a hospital diagnosis of gout, suggesting that severe gout itself rather than allopurinol is the reason for this increased risk. We saw increased fracture rates in women receiving the highest allopurinol dosages. Thus more severe disease – as evidenced by treatment in hospital clinics rather than in GP practice, or higher levels of medication use – was associated with high risk of fractures. While we are unable to adjust for all possible confounding factors, the available literature would suggest that modest elevations of serum urate in the absence of significant renal disease is often positively associated with bone density, and lower fracture rates. Our results add to the available evidence highlighting a possible link between allopurinol use and fracture risk; further work is now indicated.

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Mini-abstract

Using a Danish Register cohort of 86,039 adult new allopurinol users and propensity score matched controls we found that gout requiring allopurinol prescription was associated with an increased fracture risk.

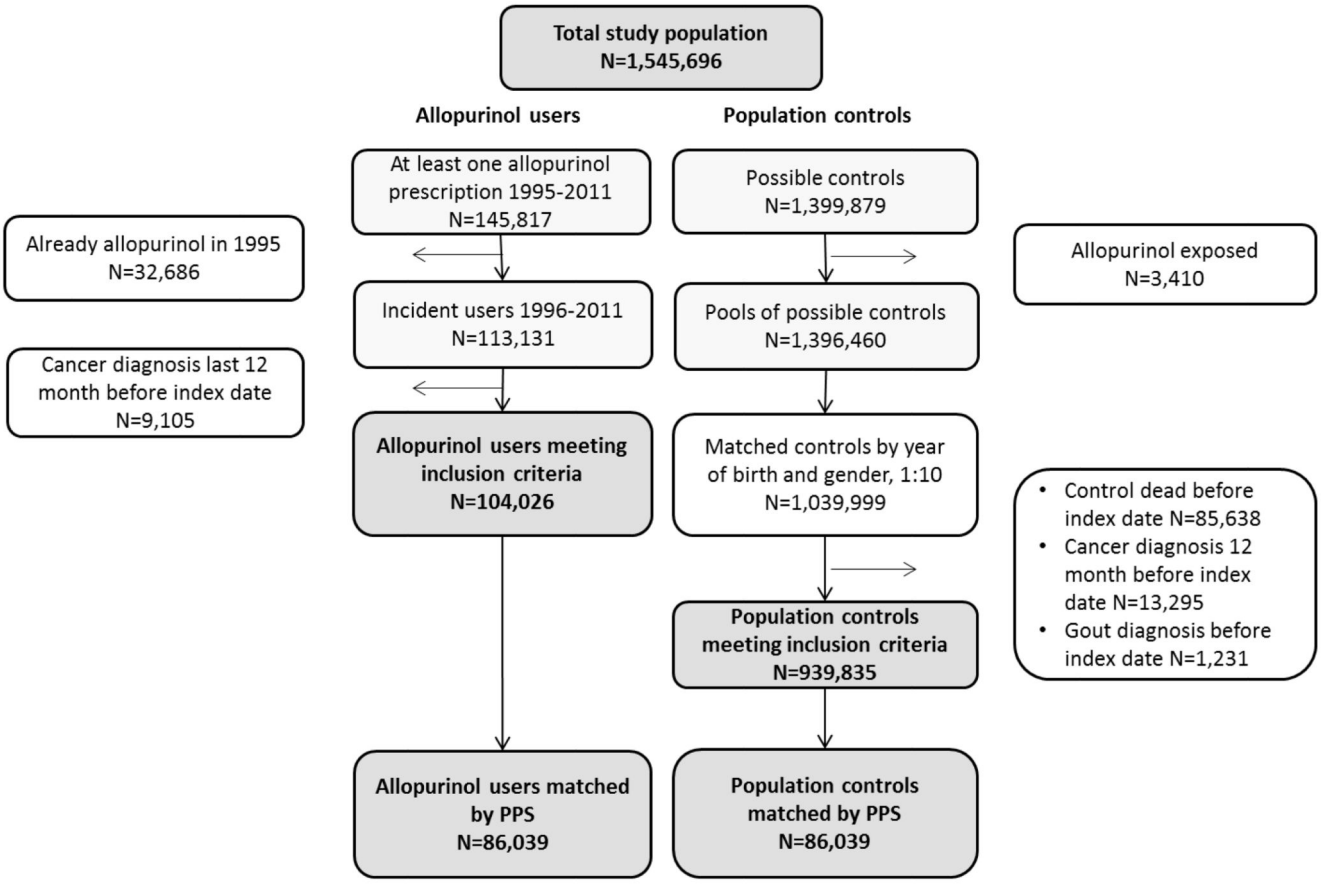

Figure 1.
Flow chart summarising the study

Table 1
Characteristics of allopurinol user and controls, propensity score matched 1:1

Comorbidity	All, N=172,078				
	Allopurinol user N= 86,039		Control (matched 1:1) N= 86,039		
	N	%	N	%	P (fishers exact)
Age Mean (SD)	63(15.1)		63(15.1)		0.985
Range (Min, Max)	18-103		18-103		
Sex Men	58,072	67	58,072	67	1.0
Women	27,967	33	27,967	33	
PPS (mean)	191		161		<0.001
PPS difference (mean)	44.3		44.3		1.0
Distance (mean)	222		222		1.0
Charlson index (mean)	0.93		0.74		<0.001
Charlson comorbidity components					
Myocardial infarction	5,504	6.4	4,289	5.0	<0.001
Heart failure	15,457	18	11,745	14	<0.001
Peripheral vascular disease	3,510	4.1	2,744	3.2	<0.001
Cerebrovascular disease	5,508	6.4	4,925	5.7	<0.001
Dementia	584	0.7	779	0.9	<0.001
Pulmonary disease	6,003	7.0	4,861	5.7	<0.001
Rheum/Collagen disorders	1,748	2,0	1,399	1.6	<0.001
Ulcer disease	2,806	3.3	2,288	2.7	<0.001
Mild liver disease	900	1.1	818	1.0	0.049
Diabetes without complications	5,134	6.0	4,038	4.7	<0.001
Diabetes with complications	1,929	2.2	1,342	1.6	<0.001
Paralysis	190	0.2	187	0.2	0.918
Renal failure	1,187	1.4	663	0.8	<0.001
Malignancy	2,599	3.0	2,221	2.6	<0.001
Severe liver dis	195	0.2	142	0.2	0.004
Metastatic cancer	86	0.1	114	0.1	0.056
AIDS or HIV	26	0.03	24	0.03	0.888
Fracture history					
Spine	446	0.5	416	0.5	0.322
Humerus	1,313	1.5	1,088	1.3	<0.001
Forearm	3,119	3.6	2,657	3.1	<0.001
Hip	1,281	1.5	1,362	1.6	0.117
Major osteoporotic	5,565	6.5	4,885	5.7	<0.001
Any fracture	13,071	15	12,170	14	<0.001
Medications					
Osteoporosis	1,358	1.6	1,058	1.2	<0.001

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Comorbidity	All, N=172,078				
	Allopurinol user N= 86,039		Control (matched 1:1) N= 86,039		
	N	%	N	%	P (fishers exact)
HRT	5,009	5.8	4,612	5.4	<0.001
Oral diabetes	5,331	6.2	4,197	4.9	<0.001
Insulin	2,025	2.4	1,711	2.0	<0.001
NSAID	50,765	59	46,020	54	<0.001
Prednisolone	5,137	6.0	4,120	4.8	<0.001
Lipid lowering	13,526	16	10,140	12	<0.001
Antihypertensive	31,147	36	25,403	30	<0.001

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Table 2

Rates of osteoporotic fracture among Danish subjects taking allopurinol, using 1:1 matching

HIP FRACTURE	**Untreated Incidence rate and 95% CI (per 1,000 patient years)**	**Allopurinol Incidence rate and 95% CI (per 1,000 patient years)**
Men 18-50	0.44 (0.34-0.56)	0.48 (0.37-0.6)
Men 50-75	2.25 (2.07-2.45)	2.49 (2.29-2.7)
Men 75+	14.31 (13.26-15.42)	14.34 (13.21-15.55)
Women 18-50	0.16 (0.04-0.4)	0.85 (0.52-1.3)
Women 50-75	4.32 (3.95-4.71)	5.11 (4.69-5.56)
Women 75+	24.88 (23.66-26.15)	23.45 (22.12-24.84)
MAJOR OSTEOPOROTIC FRACTURE	Untreated Incidence rate and 95% CI (per 1,000 patient years)	Allopurinol Incidence rate and 95% CI (per 1,000 patient years)
Men 18-50	3.48 (3.18-3.8)	4.93 (4.57-5.31)
Men 50-75	6.17 (5.86-6.48)	7.26 (6.92-7.62)
Men 75+	22.21 (20.9-23.59)	21.96 (20.55-23.44)
Women 18-50	4.58 (3.79-5.48)	6.62 (5.65-7.72)
Women 50-75	16.4 (15.68-17.15)	17.14 (16.36-17.94)
Women 75+	42.36 (40.76-44)	41.33 (39.56-43.16)

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Table 3

Risk of osteoporotic fracture among Danish subjects taking allopurinol, using 1:1 matching

	Hip fracture			*Major fracture*		
	Men	**Women**	**All**	**Men**	**Women**	**All**
Model 1	**1.13 (1.03, 1.24)**	1.07 (0.99, 1.16)	**1.10 (1.03, 1.16)**	**1.22 (1.16, 1.29)**	1.04 (0.99, 1.09)	**1.12 (1.08, 1.16)**
Model 2	1.09 (0.99, 1.20)	1.03 (0.95, 1.12)	1.05 (0.99, 1.12)	**1.20 (1.14, 1.27)**	1.00 (0.95, 1.05)	**1.08 (1.04, 1.13)**
Model 3	**1.11(1.01, 1.23)**	1.05 (0.96, 1.14)	**1.10 (1.00, 1.14)**	**1.21 (1.14, 1.29)**	1.00 (0.95, 1.06)	**1.09 (1.05, 1.14)**

Figures given are HRs, with 95% CIs
Model 1: allopurinol use
Model 2: allopurinol use, prior fracture, known comorbidity
Model 3: allopurinol use, prior fracture, known comorbidity, drug history

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Table 4

Risk of osteoporotic fracture among Danish subjects with a hospital diagnosis of gout, taking allopurinol, using 1:1 matching

	Hip fracture			*Major fracture*		
	Men	**Women**	**All**	**Men**	**Women**	**All**
Model 1	**1.36 (1.12, 1.66)**	1.14 (0.94, 1.39)	**1.25 (1.08, 1.44)**	**1.41 (1.25, 1.58)**	1.13 (0.99, 1.29)	**1.28 (1.17, 1.39)**
Model 2	**1.36 (1.1, 1.67)**	1.04 (0.85, 1.29)	**1.17 (1.01, 1.36)**	**1.38 (1.22, 1.56)**	1.07 (0.93, 1.23)	**1.23 (1.13, 1.35)**
Model 3	**1.44 (1.16, 1.79)**	1.04 (0.84, 1.30)	**1.21 (1.04, 1.41)**	**1.43 (1.26, 1.62)**	1.08 (0.93, 1.25)	**1.26 (1.15, 1.39)**

Figures given are HRs, with 95% CIs
Model 1: allopurinol use
Model 2: allopurinol use, prior fracture, known comorbidity
Model3: allopurinol use, prior fracture, known comorbidity, drug history

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Table 5
Risk of fracture according to allopurinol exposure

	Hip fracture	*P value*	*Major fracture*	*P value*
Women				
Lowest tertile, <82 mg/d	0.99(0.85-1.15)	0.87	0.95(0.86-1.04)	0.24
Mid tertile	0.95(0.83-1.08)	0.42	0.95(0.87-1.04)	0.24
Highest tertile, >164 mg/d	**1.22(1.06-1.41)**	**0.007**	**1.13(1.03-1.24)**	**0.01**
Men				
Lowest tertile, <82 mg/d	0.99(0.81-1.21)	0.92	**1.20(1.08-1.34)**	**0.001**
Mid tertile	1.18(0.99-1.40)	0.06	**1.16(1.05-1.29)**	**0.003**
Highest tertile, >164 mg/d	1.15(0.98-1.35)	0.09	**1.27(1.15-1.40)**	**0**

Figures given are HRs, with 95% CIs, adjusted for prior fracture, known comorbidity, drug history.
Cumulative allopurinol dose filled in the first treatment year divided by number of days, censored at death or fracture.