

Title: The risk of gout among patients with sleep apnea: a matched cohort study

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ABSTRACT

Objective Obstructive sleep apnea (OSA) is associated with a range of serious comorbidities. This study investigates whether people with OSA are more likely to develop gout than those without OSA in both short and long term.

Methods A matched retrospective cohort study was undertaken in the UK Clinical Practice Research Datalink. Individuals aged ≥ 18 years with an incident diagnosis of OSA between 1990 and 2010 were identified and matched on age, gender and practice to up to four individuals without OSA; follow-up was until end of 2015. Hazard ratios (HR) were estimated using Cox regression adjusted for general health, lifestyle and comorbid characteristics. Risk of incident gout was assessed at different time points and BMI category specific results presented.

Results Study sample included 15,879 patients with OSA and 63,296 without; median follow-up was 5.8 years. 4.9% OSA and 2.6% non-OSA patients developed gout. Incidence rate per 1000 person-years was 7.83 (95%CI 7.29, 8.40) and 4.03 (3.84, 4.23) among those with and without OSA respectively; adjusted HR 1.42 (1.29, 1.56). The risk of incident gout among OSA patients compared to those without was highest one to two years after index date (1.64 (1.30, 2.06)). This finding persisted among those overweight and obese. For those with normal BMI the highest significant HR 2.02 (1.13, 3.62) was observed at two to five years post index date.

Conclusions People with OSA continued to be at higher risk of developing gout beyond the first year after OSA diagnosis. Peak incidence of gout varies according to BMI.

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Gout is the most prevalent inflammatory arthropathy, affecting approximately 2.5% of adults in the UK in 2012 (1). In addition to being the most painful form of acute arthritis it is associated with considerable co-morbidity including the metabolic syndrome, hypertension, obesity, insulin resistance, and cardiovascular disease (2-4). Obstructive sleep apnea (OSA) is also a common problem in primary care settings, having a similar prevalence to gout of between 4 and 10% (5), although there is evidence that it is under-diagnosed in this setting (6). As with gout, OSA is associated with a similar range of serious comorbidities (7-9).

Evidence suggests that elevated serum uric acid levels, the cause of gout, are also frequently identified in patients with OSA (10). However, despite prevalent hyperuricaemia in patients with OSA, shared risk factors with gout of obesity and alcohol consumption, and research identifying the associations between gout and other co-morbidities, few studies have considered the possibility of an association between OSA and gout.

The intermittent hypoxia present in OSA enhances nucleotide turnover generating purines which are metabolised to uric acid (11), providing a biologically plausible mechanism by which OSA predisposes to hyperuricaemia and gout. In a small cross-sectional observational study undertaken in a local primary care database, we found an association between gout and sleep disorders but had insufficient power to demonstrate an independent association between gout and OSA (12). A single cohort study, undertaken in a UK primary care database, The Health Improvement Network (THIN), found that people with OSA had 50% higher risk of developing incident gout over a one-year follow-up period than those without OSA, regardless of gender or obesity status (13). However, it is unclear whether such findings would persist beyond the relatively short follow-up period of one year and whether the risk of gout is perhaps at its highest beyond the first year after diagnosis of

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OSA. This study aimed to address these shortfalls of previous studies, by re-examining the association between OSA and subsequent development of gout over a longer follow-up period, assessing the risk at different time points following OSA diagnosis, and subgrouping on BMI, using a matched retrospective cohort study in a sample from UK general practice.

Patients and Methods

Clinical Practice Research Datalink

Primary care is the most common first point of entry into the health system in the UK for those suffering with a new symptom or illness, such as OSA or gout, therefore the Clinical Practice Research Datalink (CPRD) was chosen as the appropriate data source for this study. CPRD is a large, validated and extensively used on-going UK database of routinely collected primary care information, such as consultations and prescriptions, on some 5.5 million registered patients (approximately 9% of the UK population), shown to be representative of the general UK population (14,15). GPs enter the data using coding schemes such as Read codes and British National Formulary (BNF) codes and practices that contribute data to CPRD undergo regular cycle of training and audit; the data from a particular practice is eligible for use only once it has been deemed “up-to-standard” (UTS). The systematic review of studies investigating validation of diagnoses in CPRD found that high proportion of cases were confirmed for over 180 different diagnoses, with a median of 89% Read Code diagnoses confirmed via different validation methods (16).

Obstructive sleep apnea exposure

Exposed patients were those aged 18 years and over with a first-ever diagnosis of OSA recorded between 01/01/1990 and 31/12/2010; the date of diagnosis was defined as index

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date. The unexposed comparison group was drawn by assigning each patient with OSA to up to four individuals without a diagnosis of OSA at any point (unexposed patients). In order to ensure that adequate number of unexposed patients remained, twenty were initially matched to each exposed patient. Matching was performed on the basis of general practice, gender and year of birth (within 3 years). The index date for unexposed patients was the date of OSA diagnosis of their matched OSA patient. Patients with a gout diagnosis or prescription of allopurinol or colchicine in the period before index date were removed from analysis. All patients were required to have two years of up-to-standard data prior to index date.

Furthermore, unexposed patients were required to have consulted with the practice within a year of the index date. This ensured that those without OSA were active members of the practice and removed the possibility of artificially inflating any association between OSA and gout by comparing OSA patients to “non-consulters”.

Outcome

The outcome of interest was time from index date to first diagnosis of gout, defined using relevant Read codes, up to the end of March 2015. For those patients that had no record of gout, end of study was defined as the earliest of date of death, date of transfer from practice, date of last collection of records from the practice, or 31st March 2015.

Covariates

Covariates believed to potentially confound the relationship between OSA and gout were selected based on their previously established association with incidence of gout and/or OSA (17-19). These included age and gender (largely accounted for through the matched study design), type II diabetes mellitus, ischemic heart disease, hypertension,

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hyperlipidaemia, use of diuretic drugs, obesity and alcohol consumption. Information on presence of comorbidities, weight (used to calculate body mass index (BMI)) and alcohol consumption was identified in the period prior to the index date, and denoted in terms of binary presence/absence indicators (assuming that no record implies absence of diagnosis) for comorbidities; valid height measurements were taken at any time point. Alcohol consumption was categorized as never/ever and BMI was categorized as normal (BMI<25)/overweight (BMI 25-30)/obese (BMI \geq 30); weight entries of <30kg or >250kg and height entries of <1.2m or >2.2m were ignored in calculation of BMI. Categories for missing data were defined for alcohol consumption and BMI in order to preserve sample size.

The list of Read codes (used for identification of OSA, gout, diabetes, ischemic heart disease, hypertension and hyperlipidaemia) and product codes (used for identification of allopurinol, colchicine and diuretic drugs) were compiled by a GP (CM), a rheumatologist (ER) and, for OSA, a respiratory medicine consultant and another GP (SW, RH). Any disagreements were resolved by consensus. Lists of all such codes used may be found in the morbidity section of the medical record data research repository at www.keele.ac.uk/mrr.

Statistical analysis

Characteristics of the sample at index date were summarized using descriptive statistics. Incidence rates, and corresponding 95% Confidence intervals (CIs), of gout were calculated per 1000 person years. Cox proportional hazard regression models were used to obtain associations between OSA status and time to diagnosis of gout, in terms of hazard ratios (HRs). Corresponding 95% CIs were based on robust standard errors to

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account for any possible clustering due to matching. Initially crude HRs were obtained, followed by adjustment for age, gender, diabetes mellitus, ischemic heart disease, hypertension, hyperlipidaemia, use of diuretic drugs, BMI and alcohol consumption.

It has previously been shown that increased risk of gout due to OSA persists across obesity status (13). Therefore, models were re-fit adjusting further for sleep apnea*BMI interaction and stratified effect sizes were obtained, via *lincom* command in Stata which calculates appropriate linear combinations of coefficients and associated confidence intervals. The association between OSA and gout was explored over the whole follow-up, and also at 1, 2, 5 and 10 years post index date, again using the *lincom* command.

Assumption of proportionality of hazards was assessed using graphical methods and Schoenfeld residuals; if unsatisfied, interactions of corresponding covariates with appropriate functions of time were included in the model. Right censoring was assumed non-informative and was taken as the earliest of date of death, date of transfer from practice, date of last collection of records from the practice, or 31st March 2015.

All analyses were performed using Stata software (version 13.1) (20).

The study was approved by the CPRD Independent Scientific Advisory Committee (ISAC) (project 14-047).

Sensitivity analyses

The first sensitivity analysis assessed whether our main findings were influenced by potential presence of unmeasured confounding, using a method proposed by Lin and colleagues (21). We assumed a binary unmeasured confounder with an associated HR of 2.5 among both exposed and unexposed patients (guided by the strongest association

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between observed covariates and gout as observed in our data) and varied its prevalence among the exposed and unexposed patients. The second sensitivity analysis concerned assessment of results arising from complete case analyses which ignore missing data. Multiple imputation was not considered as it was suspected that missing data for BMI and alcohol was not missing at random. Finally, we assessed whether our main findings were altered by using available alcohol and weight data recorded at any point (rather than prior to index only), a common approach, though erroneous in studies of exposure effect, used in CPRD analyses involving lifestyle characteristics to minimize extent of missing data.

Results

Analysis sample

The study identified 17,198 patients with incident OSA between 1990 and 2010, who were matched on approximate 1:20 ratio to 341,257 patients that had no record of OSA. Following exclusion of those with inadequate period of UTS data, those with a record of allopurinol or colchicine prescription prior to index date, the unexposed patients that did not consult their practice within a year of their OSA patient's index date, and the patients left without a match following these exclusions, 15,879 OSA patients remained and 185,049 unexposed patients. Up to four available unexposed patients per OSA patient were then chosen at random, resulting in 63,296 unexposed patients. Figure 1 depicts the derivation of the sample group for the analyses.

Patients' characteristics at index date are summarised in Table 1. The mean age and gender of the two exposure groups were similar (mean age 52.2 years and 76% male, in both) as expected due to the matched study design. Those with OSA had higher prevalence of *all* comorbidities, were more likely to have been prescribed diuretic

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medications and were more likely to be obese and current drinkers. Furthermore, they were less likely to have missing information regarding BMI and alcohol use.

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782 (4.9%) OSA and 1,651 (2.6%) non-OSA patients developed gout during follow-up with median time to gout diagnosis being 5.66 years (interquartile range 3.58-8.28) and 5.83 years (3.93-8.55) in the two groups respectively. Incidence rate per 1000 person-years was 7.83 among those with OSA and 4.03 among those without OSA (crude HR 1.94 (95% CI 1.78, 2.12)). On adjustment for covariates considered in this study, this effect diminished but remained statistically significant HR 1.42 (95% CI 1.29, 1.56) (Table 2).

The interaction between sleep apnea and BMI was statistically significant (p-value<0.001), therefore results are also presented by BMI group (Table 2). The increased risk of gout for sleep apnea patients compared to those free of sleep apnea was noted in all BMI categories, mostly so in the normal BMI group, adjusted HR 1.76 (95%CI 1.22, 2.53), with corresponding estimates for overweight and obese groups given as 1.27 (1.06, 1.54) and 1.40 (1.21, 1.61)

There was also a significant interaction between sleep apnea and time. The association between sleep apnea and gout was significant across all time periods following the index date (Table 3), except for 0 to 1 years and more than 10 years post index date, and was the strongest in 1 to 2 years following the index date, adjusted HR 1.64 (1.30, 2.06).

Associations between sleep apnea and gout were similar across 2 to 5 and 5 to 10 years following the index date.

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In the normal BMI category, the risk of incident gout 2 to 5 years after index date among those with OSA was over twice the risk among those without OSA, 2.02 (1.13, 3.62), however no significant differences were found for other time points, despite the HR being the highest in 1 to 2 years post index date (Table 3). For those overweight, the hazard ratio peaked in the period 1 to 2 years after index date (1.73 (1.02, 2.96)), and for those who are obese significant HRs were observed in time periods 1 to 2, 2 to 5 and 5 to 10 years post index date, with HR being the highest in the shorter term (1 to 2 years 1.70 (1.18, 2.43)).

A sensitivity analysis to assess the effect of unmeasured confounding showed that adjustment for a confounder with a difference in prevalence of <20% (as seen for diabetes and hypertension for example) would result in a reduction in the bias of the estimate of the hazard ratio, but that the significant association between OSA and gout would remain.

The effect of restricting analyses to those with complete data on all covariates (i.e. complete case analysis) generally had minimal impact on our findings, as did using data on BMI and alcohol use recorded at any time point.

Findings of all sensitivity analyses may be found in the Supplementary Appendix.

The proportional hazards assumption was satisfied throughout.

Discussion

The novelty of this study lies in assessing both the short and long term association of OSA with incident gout in a large primary care based population. It has previously been shown that people with OSA have a higher risk of developing gout in the first year after OSA diagnosis (13). We have shown that this increased risk persists beyond the first year after OSA diagnosis, with overall risk peaking one to two years after index date. This

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statistically significant finding was seen in patients with normal BMI as well as those who were overweight or obese; however, the risk of incident gout in patients with OSA relative to those without OSA was greater in those with normal BMI than those overweight or obese.

Whilst there is potential for misclassification of OSA, this is a diagnosis that is unlikely to be made solely in primary care and as such will only be entered into the patient's record after a diagnosis has been made by a respiratory specialist in secondary care.

Indeed, previous studies have shown that when a general practitioner records a diagnosis for OSA, this diagnosis is usually correct (6,22,23). It is therefore likely that those identified as having OSA do indeed have the condition, but that OSA may be unrecognised in some patients (6,23,24), which could potentially bias our findings towards the null. Similarly, there is the possibility of misclassification of gout where the GP diagnosis is not entirely accurate, however previous studies have indicated that this is unlikely to occur frequently in CPRD (25,26). Furthermore a recent study by Meier and Jick reported the positive predictive value of a gout diagnosis in CPRD to be 90% (27). Possible misclassification of confounding comorbidities may occur but is expected to occur at random therefore not affecting our findings.

BMI may not be the best correlate for OSA, neck and waist circumference may be better suited as they take into account obesity distribution and are therefore associated with visceral obesity which is associated with risk of OSA among others. However these measures are not routinely collected in CPRD (28,29).

It is important to know how reliable our estimates are. It is possible that the significant adjusted relationship between OSA and gout could be a result of residual confounding, due to possible exposure misclassification as explained above and/or omission of

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important confounders such as genetic factors and dietary components that may be associated with both OSA and gout, but are unmeasurable or are not routinely recorded in primary care in the UK. We have tested the sensitivity of our overall estimated HR on the presence of some unobserved confounder (or a selection of confounders subsequently split into binary low/high risk) *strongly* associated with gout in both exposure groups, and found that it is robust provided that the absolute difference in the prevalence of such a confounder between exposed and unexposed is approximately <20%. If however the prevalence among the exposed is much higher, then it is possible that adjustment for such a confounder would have attenuated the observed association in this study. This should not take away from the importance of our findings, but rather be seen as a necessary component of any analysis using observational data, especially when medical record data are involved as they may be prone to incomplete and imprecise recording.

A wide time range was chosen for identification of OSA, namely from 1st January 1990 until 31st December 2010 in order to allow sufficient time to detect potential confounders prior to OSA diagnosis and for gout to develop after this index date.

Our study confirms the findings of earlier studies that people with OSA are at increased risk of incident gout. The most likely mechanism to explain this association is that, along with catecholamine surges and sustained hypertension (30), intermittent hypoxia increases nucleotide turnover which enhances endogenous uric acid production (11), raising the question as to whether correction of hypoxia in OSA by treatment with continuous positive airways pressure (CPAP) lowers serum uric acid levels. This could theoretically both reduce the risk of incident gout and treat existing gout. However, whilst observational studies have suggested that CPAP treatment leads to reduction in serum uric acid levels (31), a secondary, albeit underpowered, analysis of data from a

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small randomised controlled trial of obese men with OSA and type II diabetes mellitus but not gout did not show any beneficial urate-lowering effect of CPAP compared with sham CPAP (32).

The risk of incident gout in patients with OSA persisted in all three BMI strata.

However, the risk differed according to BMI with those having normal BMI being at greater risk of gout than those overweight or obese. This suggests that the contribution of OSA to the risk of hyperuricaemia and gout is independent of BMI and clinicians should consider the possibility of gout in patients with sleep apnea regardless of obesity. The effect of CPAP to lower urate and hence prevent or treat gout in patients with OSA remains unclear and further adequately-powered randomized controlled trials are required to investigate the potential therapeutic urate-lowering effect of CPAP.

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Author contributions

All authors contributed to the conception of the study. MBB designed analysis plan, performed statistical analyses and drafted the initial manuscript. SM wrote the initial ISAC application form. All authors participated in the design of the study, interpretation of data, drafting of manuscript. All authors read and approved the final manuscript.

Declaration of interests

The authors have no conflicts of interest to declare.

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Table 1: Patient characteristics (covariates) at index date

Covariates	OSA	No OSA	p-value
	(15,879)	(63,296)	
	N (%)	N (%)	
Age, mean (SD) years	52.2 (1.2)	52.2 (12.2)	0.949
Male	12,108 (76)	48,260 (76)	0.986
BMI			<0.001
Normal	1,272 (8)	13,148 (21)	
Overweight	3,279 (21)	14,830 (23)	
Obese	8,059 (51)	8,857 (14)	
Missing	3,269 (20)	26,461 (42)	
<i>BMI, mean (SD)</i>	<i>34.0 (8.1)</i>	<i>27.4 (5.1)</i>	
Alcohol			<0.001
No	1,748 (11)	4,968 (8)	
Ex-drinker	372 (2)	854 (1)	
Current drinker	9,841 (62)	31,823 (50)	
Missing	3,918 (25)	25,651 (41)	
Diabetes	2,168 (14)	3,669 (6)	<0.001
Ischemic heart disease	741 (5)	1,691 (3)	<0.001
Hypertension	4,667 (29)	10,299 (16)	<0.001
Hyperlipidemia	2,288 (14)	4,942 (8)	<0.001
Diuretic use	4,499 (28)	7,587 (12)	<0.001

Frequencies (percentages) given unless otherwise stated; OSA obstructive sleep apnea; SD standard deviation

Table 2: Incidence rate and risk of gout by BMI category

Sample	Number of events	Incidence rate per 1000 person-years (95% CI)		Unadjusted HR (95%CI)	Adjusted HR (95%CI)
		OSA	No OSA		
All[†] (79,175)	2433	7.83 (7.29, 8.39)	4.03 (3.84, 4.23)	1.94 (1.78, 2.12)	1.42 (1.29, 1.56)
BMI[‡]					
Normal (14,420)	222	4.16 (2.99, 5.80)	2.24 (1.94, 2.59)	1.84 (1.28, 2.64)	1.76 (1.22, 2.53)
Overweight (18,109)	608	6.76 (5.74, 7.96)	5.00 (4.57, 5.48)	1.34 (1.11, 1.62)	1.27 (1.06, 1.54)
Obese (16,916)	808	9.77 (8.83, 10.61)	6.70 (6.03, 7.44)	1.44 (1.25, 1.66)	1.40 (1.21, 1.61)

OSA obstructive sleep apnea; HR hazard ratio; CI confidence interval;

[†]Adjusted HR: adjusted for for age, gender, BMI, alcohol, diabetes mellitus, ischemic heart disease, hypertension, hyperlipidaemia and use of diuretics drugs;

[‡]Adjusted HR: further adjusted for sleep apnea*BMI interaction (Wald test p-value for the interaction < 0.001)

Table 3: Adjusted risk of gout at different time points after index date by BMI category

Group	Years after index date				
	HR (95%CI)				
	0 to 1	1 to 2	2 to 5	5 to 10	>10
All [†]	1.22 (0.97, 1.53)	1.64 (1.30, 2.06)	1.46 (1.25, 1.70)	1.44 (1.22, 1.70)	1.27 (0.95, 1.70)
BMI[‡]					
Normal	1.75 (0.67, 4.54)	2.11 (0.71, 6.26)	2.02 (1.13, 3.62)	1.65 (0.82, 3.32)	0.96 (0.29, 3.22)
Overweight	1.22 (0.73, 2.04)	1.73 (1.02, 2.96)	1.05 (0.75, 1.48)	1.38 (0.98, 1.93)	1.31 (0.77, 2.25)
Obese	1.24 (0.88, 1.77)	1.70 (1.18, 2.43)	1.42 (1.12, 1.79)	1.41 (1.08, 1.85)	0.82 (0.46, 1.44)

Reference category in each case is no obstructive sleep apnea; HR hazard ratio; CI confidence interval;

[†]Adjusted for sleep apnea*time interaction, age, gender, BMI, alcohol, diabetes mellitus, ischemic heart disease, hypertension, hyperlipidaemia and use of diuretics drugs (Wald test p-value for interaction < 0.001);

[‡]Further adjusted for three-way sleep apnea*BMI*time interaction (Wald test p-value for interaction < 0.001)

Figure 1: Selection of exposed and unexposed patients

UTS=up to standard date