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GOUT AND THE RISK OF PARKINSON'S DISEASE IN DENMARK

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There is growing evidence that oxidative stress plays a major role in Parkinson's Disease (PD) etiology [1, 2]. Importantly, uric acid has been shown in experimental studies to have an antioxidant effect on neurons [3, 4]. Recently, several observational studies have also evaluated associations between serum uric acid levels and PD risk and have consistently reported a lower risk of PD among individuals with the highest levels of serum uric acid [5–10]. The most common metabolic disorder underlying hyper-uricemia is gout. Thus, if hyperuricemia decreases the risk of PD, gout should also be negatively associated with PD risk. Two studies, to date, have evaluated the association between gout and PD risk and both reported an inverse association [11, 12], although the association was only observed among men in one of the two studies [11].

Using Danish population registers, we aimed to confirm the findings from these two previous observational studies. We investigated whether a history of use of anti-gout prescription medications was associated with PD risk. From nationwide Danish in- and outpatient Hospital Register records, we identified 4,484 patients with a first time diagnosis of PD between 2001–2008 and a diagnosis confirming PD medication history according to the Danish National Prescription Registry (DNPR) that records all prescription in Denmark since 1995 [13]. We randomly selected 22,416 population controls from the Danish Civil Registration System [14], density-matched by birth year and sex. We extracted information about the use of anti-gout drugs from the DNPR for all study participants. Exposure was defined as at least one prescription of anti-gout drugs prior to the first diagnosis of PD for the cases or the corresponding date (index date) for their matched controls. Prescriptions included Anatomical Therapeutic Chemical (ATC) group M04 anti-gout preparations

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(M04AA preparations inhibiting uric acid production (e.g., allopurinol), M04AB preparations increasing uric acid excretion (e.g., benzbromarone), M04AC preparations with no effect on uric acid metabolism (e.g., colchicine), and M04AX (other anti-gout preparations, e.g., urate oxidase). Odds ratios (OR) were estimated using logistic regression models adjusted for age, sex, and chronic obstructive pulmonary disease as an indicator of smoking. Further details of the study and methods, including baseline characteristics of the study population, have been provided elsewhere [15].

We found no associations between the use of anti-gout medications and risk of PD. This lack of an association did not differ by gender or age at onset of PD (Table 1). Results were similar when we excluded PD cases that occurred within 2 or 5 years after first use of anti-gout drugs. Similarly, adjustment for use of diuretic medications or of non-steroidal antiinflammatory drugs did not alter our findings.

Limitations of our study include the potential for exposure misclassification, which may have biased our results towards the null, and that we were unable to control for possible confounders such as smoking habits and caffeine intake; however, we did adjusted for COPD as a surrogate for heavy smoking. Main strength of our study is that it included four times the number of PD patients compared to the previous studies.

In sum, data from this large case-control study did not provide support for an inverse association between anti-gout medication intake in the decade before PD onset and risk of PD. This suggests that uric acid levels in those using anti-gout medications may not have been high enough to protect from PD or that it is not adequate to use gout treatment prescription records as indicators of high uric acid levels, even though both previous epidemiologic studies used similar record systems and reported that the PD risk reduction was strongest among treated gout patients. Our data also preserve the possibility that there may not be an important effect of hyperuricaemia on PD in humans.

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Table 1

Association between gout and Parkinson's disease*

	Cases (n=4,484)	Controls (n=22,416)	Odds Ratio (95% CI)†
Overall			
No	4,299	21,537	1.0
Yes	185	879	1.06 (0.90–1.25)
Men			
No	2,540	12,729	1.0
Yes	136	649	1.06 (0.88–1.28)
Women			
No	1,759	8,808	1.0
Yes	49	230	1.07 (0.79–1.47)
Early Onset (<60y at PD diagnosis)			
No	651	3,252	1.0
Yes	15	76	0.99 (0.56–1.73)
Late Onset (≥60y at PD diagnosis)			
No	3,648	18,285	1.0
Yes	170	803	1.07 (0.91–1.27)

*Diagnosis of gout based on any prescription of anti-gout drugs (ATC codes M04AA, M04AB, M04AC, M04AX)

†adjusting for age, sex, and COPD (lagged 5 years)