

# Identification of Drugs Associated with Lower Risk of Parkinson's Disease Using a Systematic Screening Approach in a Nationwide Nested Case–Control Study

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**Introduction:** Drugs for other indications may be repurposable as disease-modifying drugs for Parkinson's disease (PD). A systematic hypothesis-free approach can enable identification of candidates for repurposing. We applied a hypothesis-free systematic approach to identify drugs associated with lower risk of PD to discover candidates with potential for repurposing as disease-modifying drugs for PD and to illustrate challenges in observational studies that simultaneously investigate multiple repurposing candidates.

**Methods:** The Finnish Parkinson's disease study (FINPARK), a nationwide nested case-control study, was randomized to screening (10,183 cases, 67,849 controls) and replication (10,184 cases, 67,754 controls) samples, including cases diagnosed in 1998–2015. After screening all univariable associations of register-derived exposure to individual-drug, group- and subgroup level since 1995 (exposure  $\geq 3$  years before outcome, threshold  $P = 0.1$ ), different exposure periods were used in confounder-adjusted replication analyses.

**Results:** In screening stage, the group-level (antipsoriatics and antigout preparations) and subgroup-level (cicatrizants, topical antipsoriatics, antigout preparations and mydriatics and cycloplegics) associations were mainly due to individual drugs. Seven other drugs (eg methotrexate, drugs for chronic obstructive pulmonary disease, COPD and/or asthma) were associated with lower risk. Associations of antigout preparations and antipsoriatics were replicated. COPD/asthma drugs, methotrexate and diabetes drugs were studied in separate, indication-restricted designs.

**Discussion:** The results reflect the known risk factors and the implied role of the immune system in PD pathogenesis and spurious associations. They underline the importance of controlling for confounding by indication, which is challenging to apply to systematic screening.

**Keywords:** Parkinson's disease, pharmacoepidemiology, drug repurposing, case–control study, indication bias

## Introduction

Recent therapeutic advances for Parkinson's disease (PD) have been modest and promising candidates have failed in trials. Currently, “almost an infinite number of targets and interventions” are being explored in preclinical models, but many of these leads are bound to be terminated due to lack of efficacy or safety issues in humans.<sup>1</sup> Consequently, candidates already clinically available for other indications have been proposed for delaying PD progression, based on their association with lower risk of PD.<sup>2–4</sup> The calcium channel blocker isradipine was associated with lower risk of PD in epidemiological studies,<sup>5</sup> and experimental studies supported neuroprotective effects.<sup>6</sup> However, the disease-modifying properties were not demonstrated in a trial on people with early-stage PD,<sup>7</sup> although a secondary analysis suggested slower progression among those with larger isradipine doses compared with placebo.<sup>8</sup> Preliminary trials with exenatide, a diabetes drug, were more promising, with

beneficial impacts on motor and cognitive symptoms in patients with PD.<sup>9,10</sup> Thus, other disease-modifying drugs may exist, but their identification would require a systematic and hypothesis-free approach in a study population with adequate exposure assessment time and verified PD diagnosis.

Long onset period of neurodegenerative diseases complicates etiological epidemiology studies. Prodromal symptoms may manifest long before the actual diagnosis and impact the exposure. Pharmacotherapies may be initiated or discontinued due to prodromal symptoms, or the ongoing disease process can increase the healthcare contacts, resulting to initiation or discontinuation of drugs for other conditions. This may be one explanation for challenges in replicating the observed associations between specific drugs and risk of PD. Recently, a self-controlled design was applied to identify drugs associated with lower risk of parkinsonism in US claims databases.<sup>3</sup> In that study, inhaled  $\beta$ -agonist albuterol and three central nervous system stimulants were associated with lower risk of parkinsonism. However, the self-controlled designs are often poorly suited to outcomes with a long onset period, likely to work better for transient effects which are unlikely for neurodegenerative outcomes, and may be sensitive to temporal exposure trends, such as increasing use of drugs for attention deficit hyperactivity disorder.<sup>11</sup>

Still, systematic, a hypothesis-free approach can be argued as a possibility to identify candidates for repurposing. Our aims were to identify drugs associated with lower risk of PD by systematic investigation of all individual prescription drugs and drug groups in a nationwide nested case-control study, and to illustrate challenges in this kind of study investigating multiple exposures at the same time. The findings were replicated in a separate sample so that timing of exposure was accounted for.

## Participants and Methods

### Study Population

The Finnish Parkinson's disease study (FINPARK) is a case-control study nested into the population of Finland. The PD cases (N=22,189) are community-dwelling residents of Finland with an incident, clinically confirmed PD diagnosis received between 1996–2015. Their identification was based on eligibility for reimbursement for anti-Parkinson drugs, with PD (ICD-10 code G20) as the reason for reimbursement, because these drugs can also be used for other indications. The cases had to be at least 35 years old on the date of diagnosis and they were not allowed to have diagnoses whose symptoms may be confused with PD within two years of PD diagnosis. The identification of cases has been described in detail earlier.<sup>12</sup> To be eligible for reimbursement, the PD diagnosis needs to be confirmed in specialist settings, and the diagnostic statements are centrally reviewed and confirmed in the Social Insurance Institution (Kela). The PD diagnosis criteria is consistent with the UK Brain Bank criterion.<sup>13</sup>

On the date of PD diagnosis (index date), up to seven age- ( $\pm 1$  year), sex- and region-matched controls per case (N=148,009) were identified from the Kela database covering all residents. The controls were not allowed to have dopaminergic PD drug purchases (Anatomical Therapeutic Chemical classification ATC code N04B) or reimbursement code for PD drugs ever before the index date or 12 months after and during the month of index date. The exclusion criteria of controls were otherwise identical to those of the cases, but controls with dementia due to PD (ICD-10 F02.3) were also excluded.

To ensure all participants had at least three-year exposure assessment time, the study was restricted to 20,367 cases and their 135,603 controls with index date from 1998 onwards. These case-control sets were randomly assigned to independent screening (10,183 cases, 67,849 controls) and replication (10,184 cases, 67,754 controls) sets per sex and diagnosis year.

Data from Care Register for Health Care (1972–2015), Special Reimbursement Register (1972–2015) and Prescription Register (1995–2015), linked by pseudonymized personal identification numbers, were provided by the register maintainers, who have approved the FINPARK study plan. Research team can only access pseudonymized data and study participants were not contacted. Therefore, according to Finnish legislation separate ethics approval or informed consent were not needed.

## Drug Exposure

Exposure data between 1995 (the beginning year of Prescription Register) and the index date were obtained from the Prescription Register, which contains data on reimbursed drug purchases, recorded by ATC codes. We investigated the associations on the level of groups (ATC therapeutic subgroups, three-character level, eg, A10 Drugs used in diabetes), subgroups (four-character level, eg, A10B Blood glucose lowering drugs, excluding insulins) and individual drugs (seven-character level, eg, A10BA02 metformin). Dopaminergic and antimentia drugs (ATC codes N04B and N06D, respectively) were excluded.

In screening, each exposure was categorised to binary variables indicating exposure at least three years before the index date (main analysis, average exposure assessment time 9.6 years) or ever before the index date (sensitivity analysis, average exposure assessment time 12.6 years). In replication, the exposure was categorised based on whether it was initiated at least three years before the index date or within the three-year time window immediately before the index date (lag). In addition, a five-year lag was used. The lag time was based on our earlier study demonstrating the increase in muscle relaxant use among persons with PD in this time window,<sup>14</sup> and applied to controls for outcome affecting the drug exposure by different mechanisms (changes in drug exposure due to prodromal symptoms of PD, or increased healthcare contact due to diagnostic process of PD or prodromal symptoms affecting drug exposure).

## Confounders

Replication analyses were adjusted for cardiovascular diseases, diabetes, stroke, asthma or chronic obstructive pulmonary disease (COPD), cancer, head injury and substance abuse since 1972 until three years before the index date, and information on non-steroidal anti-inflammatory drug use from 1995 to three years before the index date. Data sources and codes for data extraction are given in [Supplementary Table 1](#).

## Statistical Analyses

Univariable association of each exposure and PD was investigated with conditional logistic regression. Exposures with inverse association ( $\alpha=0.1$ ) were considered for replication. We applied a laxer significance level to avoid erroneously discarding less commonly used drugs.

In replication, the associations were assessed during different exposure windows (before three-year lag, only within the three-year lag vs no use, before five-year lag, only within the five-year lag vs no use, and ever use vs no use). Because implementation of indication-restricted screening was not feasible, the replication was conducted with an indication-restricted design when possible (the candidate was not the only available drug for the indication, or the candidate had a specific indication). The results of indicated-restricted replications have been reported earlier,<sup>15–17</sup> and thus only those replications that could not be confirmed in an indication-restricted setting are reported here.

Detectable odds ratios for screening and replication are summarized in [Supplementary Figure 1](#). We had 80% power to detect OR  $\leq 0.89$  for rare exposures (prevalence in controls, 5%) and  $\leq 0.95$  for common exposures (prevalence of exposure in controls, 50%). The detectable ORs in the replication phase ranged between 0.88 and 0.94 for the same scenarios.

## Results

The mean (SD) ages of PD cases and controls in the screening set were 70.8 (9.7) and 70.5 (9.6) years, respectively. Altogether, 55.23% of cases were men. These were similarly distributed in the replication set ([Supplementary Table 2](#)).

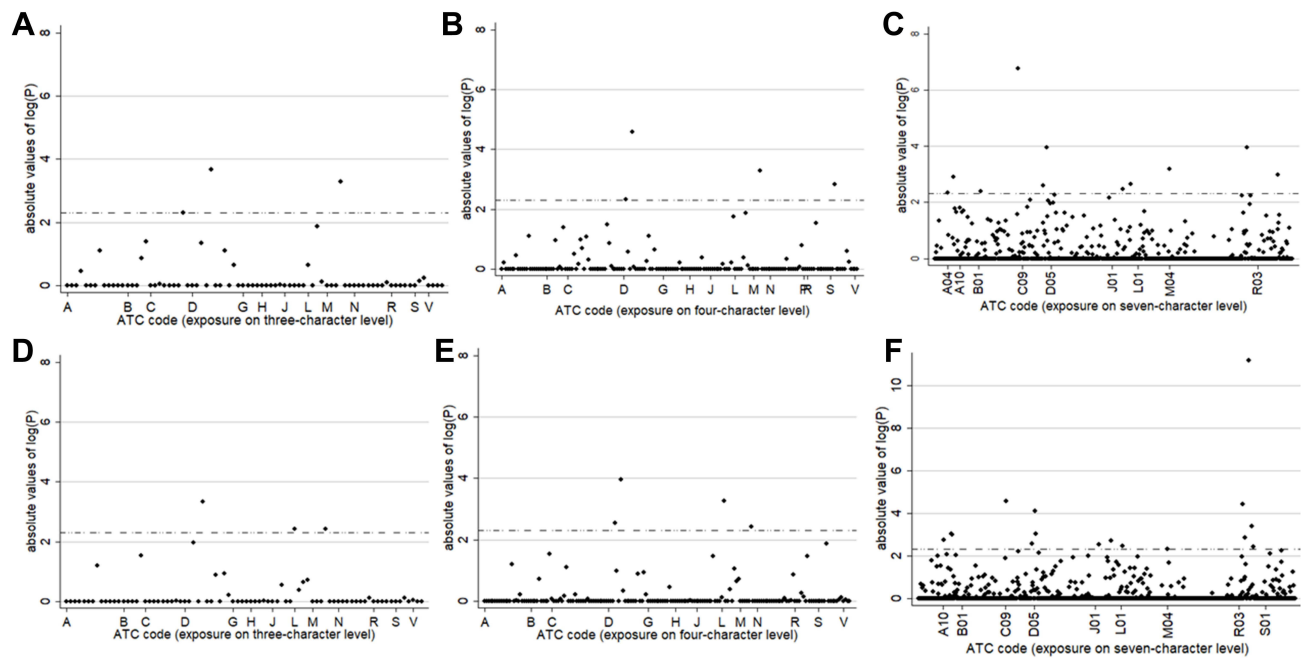
## Identification of Candidates in the Screening Phase

In the main analyses considering exposure that had occurred at least three years before the index date, the associations of 82 groups, 173 subgroups and 854 individual drugs were assessed. Of these, two groups (antipsoriaties D05 and antigout preparations M04) and four subgroups (cicatrizants D03A, antipsoriaties for topical use D05A, antigout preparations M04A and mydriatics and cycloplegics S01F) were associated with lower risk of PD and met the screening threshold ([Table 1](#)). The group-level associations of antipsoriaties and antigout preparations were mainly due to an individual drug

**Table 1** All Inverse Associations Observed in the Screening Data Set with P<0.1 Using Three-Year Lag Time (Main Analyses) or without Lag Time

Exposure (ATC Code)	Main Analyses (Exposure at Least Three Years Before Index Date)			Sensitivity Analyses (Any Exposure Before Index Date)		
	n (%) in Cases (N=10,183)	n (%) in Controls (N=67,849)	OR (95% CI)	n (%) in Cases (N=10,183)	n (%) in Controls (N=67,849)	OR (95% CI)
<i>Granisetron (A04AA02)</i>	5 (<0.1)	73 (0.1)	0.46 (0.19,1.15) <sup>a</sup>	16 (0.2)	154 (0.2)	0.69 (0.41,1.16)
<i>Prednisolone (A07EA01)</i>	6 (0.1)	89 (0.1)	0.44 (0.19,1.02) <sup>a</sup>	9 (0.1)	100 (0.1)	0.60 (0.30,1.18)
<i>Insulin lispro (A10AB04)</i>	19 (0.2)	178 (0.3)	0.71 (0.44,1.15)	24 (0.2)	239 (0.4)	0.67 (0.44,1.02) <sup>b</sup>
<i>Metformin and pioglitazone (A10BD05)</i>	0 (0)	22 (<0.1)	N.A	<5 (<0.1)	50 (0.1)	0.14 (0.02,0.98) <sup>b</sup>
<i>Metformin and vildagliptin (A10BD08)</i>	<5 (<0.1)	23 (<0.1)	0.29 (0.04,2.17)	<5 (<0.1)	65 (0.1)	0.31 (0.10,1.00) <sup>b</sup>
<i>Dabigatran etexilate (B01AE07)</i>	5 (<0.1)	72 (0.1)	0.46 (0.18,1.13) <sup>a</sup>	22 (0.2)	161 (0.2)	0.89 (0.57,1.39)
<i>Enalapril (C09AA02)</i>	999 (9.8)	7275 (10.7)	0.89 (0.83,0.95)	1256 (12.3)	8883 (13.1)	0.92 (0.86,0.98)
CICATRIZANTS (D03A)	6 (0.1)	78 (0.1)	0.50 (0.22,1.14)	7 (0.1)	91 (0.1)	0.50 (0.23,1.08)
<i>Cadexomer iodine (D03AX01)</i>	<5 (<0.1)	56 (0.1)	0.35 (0.11,1.11)	<5 (<0.1)	65 (0.1)	0.40 (0.15,1.11)
ANTIPSORIATICS (D05)	121 (1.2)	1005 (1.5)	0.80 (0.67,0.97)	156 (1.5)	1248 (1.8)	0.83 (0.71,0.99)
ANTIPSORIATICS FOR TOPICAL USE (D05A)	106 (1)	925 (1.4)	0.77 (0.63,0.94)	139 (1.4)	1150 (1.7)	0.81 (0.68,0.97)
<i>Calcipotriol (D05AX02)</i>	85 (0.8)	745 (1.1)	0.76 (0.61,0.96)	100 (1)	865 (1.3)	0.77 (0.63,0.95)
<i>Calcitriol (D05AX03)</i>	8 (0.1)	84 (0.1)	0.64 (0.31,1.32)	10 (0.1)	128 (0.2)	0.52 (0.27,1.00) <sup>b</sup>
<i>Dicloxacillin (J01CF01)</i>	6 (0.1)	78 (0.1)	0.51 (0.22,1.18)	8 (0.1)	100 (0.1)	0.53 (0.26,1.08) <sup>b</sup>
<i>Moxifloxacin (J01MA14)</i>	49 (0.5)	375 (0.6)	0.87 (0.64,1.17)	89 (0.9)	720 (1.1)	0.81 (0.65,1.01) <sup>b</sup>
<i>Fosfomycin (J01XX01)</i>	31 (0.3)	282 (0.4)	0.72 (0.50,1.04) <sup>a</sup>	42 (0.4)	331 (0.5)	0.83 (0.60,1.15)
ANTINEOPLASTIC AGENTS (L01)	41 (0.4)	299 (0.4)	0.90 (0.65,1.25)	61 (0.6)	503 (0.7)	0.79 (0.61,1.04) <sup>b</sup>
ANTIMETABOLITES (L01B)	14 (0.1)	134 (0.2)	0.68 (0.39,1.18)	22 (0.2)	230 (0.3)	0.63 (0.41,0.98) <sup>b</sup>
<i>Methotrexate (L01BA01)</i>	5 (<0.1)	76 (0.1)	0.44 (0.18,1.08)	7 (0.1)	91 (0.1)	0.51 (0.24,1.10)
ANTIGOUT PREPARATIONS (M04)	349 (3.4)	2569 (3.8)	0.89 (0.79,0.99)	485 (4.8)	3448 (5.1)	0.92 (0.83,1.01)
<i>Allopurinol (M04AA01)</i>	348 (3.4)	2556 (3.8)	0.89 (0.79,1.00)	484 (4.8)	3433 (5.1)	0.92 (0.83,1.02)
<i>Salmeterol and fluticasone (R03AK06)</i>	217 (2.1)	1601 (2.4)	0.89 (0.77,1.03)	312 (3.1)	2380 (3.5)	0.86 (0.76,0.97) <sup>b</sup>
<i>Fenoterol and ipratropium bromide (R03AL01)</i>	197 (1.9)	1415 (2.1)	0.91 (0.78,1.05)	255 (2.5)	1891 (2.8)	0.88 (0.77,1.00) <sup>b</sup>
<i>Tiotropium bromide (R03BB04)</i>	77 (0.8)	663 (1.0)	0.75 (0.59, 0.95)	127 (1.2)	1240 (1.8)	0.66 (0.55,0.80)
<i>Theophylline (R03DA04)</i>	218 (2.1)	1580 (2.3)	0.90 (0.78,1.04)	251 (2.5)	1892 (2.8)	0.86 (0.76,0.99) <sup>b</sup>
<i>Theophylline combinations (R03DA54)</i>	37 (0.4)	318 (0.5)	0.75 (0.54,1.06)	43 (0.4)	368 (0.5)	0.76 (0.55,1.04) <sup>b</sup>
MYDRIATICS AND CYCLOPLEGICS (S01F)	52 (0.5)	452 (0.7)	0.76 (0.57,1.01) <sup>a</sup>	64 (0.6)	510 (0.8)	0.83 (0.64,1.07)
<i>Atropine (S01FA01)</i>	11 (0.1)	131 (0.2)	0.54 (0.29, 1.00) <sup>a</sup>	14 (0.1)	143 (0.3)	0.63 (0.37,1.10)

Notes: <sup>a</sup>Association P≤0.1 in main analyses only (exposure at least three years before index date). <sup>b</sup>Association P≤0.1 in sensitivity analyses only (exposure any time before index date).



**Figure 1** Associations of individual exposures on (A) three-character level, (B) four-character level, (C) seven-character level in the main analyses (exposure at least three years before the index date, and in sensitivity analyses (any exposure before the index date) on (D) three-character level, (E) four-character level and (F) seven-character level. The dashed line represents the screening threshold (absolute value of natural logarithm of  $\alpha=0.1$ ).

(calcipotriol D05AX02 and allopurinol M04AA01, respectively). Similarly, the subgroup associations of cicatrizants and mydriatics and cycloplegics were driven by individual drugs (cadoxomer iodine D03AX01 and atropine S01FA01, respectively). This is also visualised in Figure 1, in which the associations of individual drugs (Figure 1C) in specific subgroups are not “elevated” as a whole, but only one individual drug per group meets the screening threshold.

In addition to the above-mentioned drugs with group-level associations, granisetron (A04AA02), prednisolone (A07EA01), dabigatran etexilate (B01AE07), enalapril (C09AA02), fosfomycin (J01XX01), methotrexate (L01BA01) and tiotropium bromide (R03BB04) were associated with lower risk of PD in the screening.

In sensitivity analyses considering any exposure prior to index date, 82 groups, 175 subgroups and 906 individual drugs were assessed. The results were mainly in line with those from the main analyses (Figures 1D–F, Table 1). The group- and subgroup-level associations observed in the main analyses were evident in the sensitivity analyses, except for mydriatics and cycloplegics. In addition, antineoplastic agents (L01) and their subgroup antimetabolites L01B associated with lower risk of PD. As in the main analyses, the group-level associations of cicatrizants and antigout preparations were due to individual drugs. In sensitivity analyses, calcitriol (D05AX03) in addition to calcipotriol (D05AX02) was associated with PD from the antipsoriatics group. Methotrexate was the only antineoplastic drug associated with lower risk of PD. In addition, three diabetes drugs (insulin lispro, combinations of metformin and pioglitazone A10BD05 and metformin and vildagliptin A10BD08), two antibiotics (dicloxacillin J01CF01 and moxifloxacin J01MA14) and five drugs for COPD (salmeterol and fluticasone R03AK06, fenoterol and ipratropium bromide R03AL01, tiotropium bromide R03BB04 and theophylline and its combinations R03DA04, R03DA54) were associated with lower risk of PD in sensitivity analyses, although a group-level association was not detected. Enalapril was associated with lower risk of PD in both sensitivity and main analyses. All results with  $OR < 1$  regardless of P-value are listed in [Supplementary Table 3](#) (main analyses) and [Supplementary Table 4](#) (sensitivity analyses).

## Choice of Replication Candidates

The associations of enalapril, antipsoriatics group and calcipotriol and antigout preparation group and allopurinol were assessed in the separate replication sample. The associations of diabetes drugs and drugs for obstructive airway diseases were assessed in studies restricted to people with diabetes and asthma/COPD, respectively, and are reported

elsewhere.<sup>16,17</sup> Methotrexate, the only associated drug from the antineoplastic group, is the first-line treatment for rheumatoid arthritis and therefore its association was assessed with an indication-restricted design.<sup>15</sup>

We did not attempt to replicate the associations of cicatrizants (wound treatment products), prednisolone (association observed only for rectal foam preparation of prednisolone) and ophthalmologic atropine because it is unlikely that they would affect the PD disease process. Granisetron (antiemetic) and dabigatran etexilate (direct oral anticoagulant) were not chosen for replication as their use was rare, associations weak, and no associations were observed with other drugs from the same groups. Associations of antibiotics were not replicated for the same reason. In addition, their association with PD risk has been investigated and reported earlier.<sup>18</sup>

## Replication in the Separate Data Set

Use of enalapril, an angiotensin-converting enzyme inhibitor, was associated with increased risk of PD in replication, also after adjusting for confounders (Table 2), but the associations were observed only for use in three-year lag (adjusted OR, 95% CI 1.28, 1.13–1.44) and five-year lag (adjusted OR, 95% CI 1.18, 1.08–1.30), not for use in the actual exposure assessment period.

In the adjusted analysis, use of antipsoriatics on a group level before the index date was associated with lower risk of PD (Table 3), also before the three- and five-year lag times. Similar associations were observed with antipsoriatics for topical use and calcipotriol.

Antigout preparations, and allopurinol as an individual drug associated with lower risk of PD in replication and associations were stronger for use that had occurred during the lag time than during the actual exposure assessment period (Table 4).

## Discussion

The findings from our systematic study to identify candidates for repurposing as disease-modifying drugs have several implications for these kind of studies. Although many signals were observed, the results appear, via indication bias, to reflect the known risk factors and the implied role of immune system in PD pathogenesis. Intuitively, identification of these biases is easier when multiple exposures are assessed at the same time, but they should also be considered in traditional single-exposure pharmacoepidemiological studies. Observational studies on simultaneous investigation of multiple repurposing candidates are gaining momentum,<sup>3,4</sup> but indication bias is challenging to control in these kind of settings. Although the findings regarding candidates for repurposing were modest, they support the hypothesis on immune system involvement in PD disease process.<sup>19</sup>

In this study, we replicated only those candidates that could not be replicated in an indication-restricted design. For example, allopurinol is the first-line drug for gout, and other drug treatment is initiated only if adequate symptom control is not achieved with allopurinol or in cases of allopurinol intolerance. For the candidates whose replication was performed in an indication-restricted design, ie, methotrexate,<sup>15</sup> diabetes drugs<sup>16</sup> and COPD/asthma drugs,<sup>17</sup> the results were strongly supportive of indication as the cause for association. On the other hand, some other drugs were associated with lower risk of PD in these indication-restricted replication studies, although they did

**Table 2** Associations of Enalapril (ATC Code C09AA02) in the Replication Data Set

Time window	Frequency in Cases (N=10,184) n (%)	Frequency in Controls (N=67,754) n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
No use	8714 (85.57)	58,767 (86.74)	1.00 (reference)	1.00 (reference)
Any use before index date	1470 (14.43)	8987 (13.26)	1.09 (1.03–1.16)	1.06 (1.00–1.13)
Use in three-year lag time only	337 (3.31)	1753 (2.59)	1.29 (1.14–1.45)	1.28 (1.13–1.44)
Use before three-year lag	1133 (11.13)	7234 (10.68)	1.04 (0.97–1.12)	1.01 (0.94–1.08)
Use in five-year lag time only	547 (5.37)	3067 (4.53)	1.20 (1.09–1.32)	1.18 (1.08–1.30)
Use before five-year lag	923 (9.06)	5920 (8.74)	1.04 (0.96–1.12)	1.00 (0.92–1.08)

**Note:** <sup>a</sup>Adjusted for cardiovascular diseases, diabetes, stroke, asthma or chronic obstructive pulmonary disease (COPD), cancer, head injury, substance abuse and non-steroidal anti-inflammatory drug use.

**Table 3** Associations of Antipsoriatic Drugs (ATC Code D05), Antipsoriatics for Topical Use (ATC Code D05A) and Calcipotriol (D05AX02) in the Replication Data Set

Exposure (ATC Code) and Time Window	Frequency in Cases (N=10,184), n (%)	Frequency in Controls (N=67,754), n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
<b>Antipsoriatic drugs (D05)</b>				
No use	10,018 (98.37)	66,466 (98.10)	1.00 (reference)	1.00 (reference)
Any use before index date	166 (1.63)	1288 (1.90)	0.86 (0.73–1.01)	0.84 (0.71–0.99)
Use in three-year lag time only	42 (0.41)	261 (0.39)	1.08 (0.78–1.50)	1.06 (0.76–1.47)
Use before three-year lag	124 (1.22)	1027 (1.52)	0.80 (0.67–0.97)	0.79 (0.66–0.96)
Use in five-year lag time only	73 (0.72)	463 (0.68)	1.06 (0.82–1.35)	1.05 (0.82–1.34)
Use before five-year lag	93 (0.91)	825 (1.22)	0.75 (0.61–0.93)	0.74 (0.60–0.92)
<b>Antipsoriatics for topical use (D05A)</b>				
No use	10,030 (98.49)	66,570 (98.25)	1.00 (reference)	1.00 (reference)
Any use before index date	154 (1.51)	1184 (1.75)	0.87 (0.73–1.03)	0.85 (0.72–1.00)
Use in three-year lag time only	41 (0.40)	245 (0.36)	1.12 (0.81–1.57)	1.10 (0.79–1.54)
Use before three-year lag	113 (1.11)	939 (1.39)	0.80 (0.66–0.98)	0.79 (0.65–0.96)
Use in five-year lag time only	70 (0.69)	431 (0.64)	1.09 (0.84–1.40)	1.08 (0.84–1.39)
Use before five-year lag	84 (0.82)	753 (1.11)	0.74 (0.59–0.93)	0.74 (0.59–0.92)
<b>Calcipotriol (D05AX02)</b>				
No use	10,069 (98.87)	66,889 (98.72)	1.00 (reference)	1.00 (reference)
Any use before index date	115 (1.13)	865 (1.28)	0.89 (0.73–1.09)	0.87 (0.71–1.06)
Use in three-year lag time only	20 (0.20)	113 (0.17)	1.20 (0.75–1.94)	1.18 (0.73–1.90)
Use before three-year lag	95 (0.93)	752 (1.11)	0.85 (0.68–1.05)	0.83 (0.67–1.03)
Use in five-year lag time only	40 (0.39)	232 (0.34)	1.17 (0.84–1.64)	1.16 (0.83–1.62)
Use before five-year lag	75 (0.74)	633 (0.93)	0.79 (0.62–1.01)	0.78 (0.61–0.99)

**Notes:** <sup>a</sup>Adjusted for cardiovascular diseases, diabetes, stroke, asthma or chronic obstructive pulmonary disease (COPD), cancer, head injury, substance abuse and non-steroidal anti-inflammatory drug use.

**Table 4** Associations of the Antigout Preparations (ATC Code M04) and Allopurinol (ATC Code M04AA01) in the Replication Data Set

Exposure and Time Window	Frequency in Cases (N=10,184), n (%)	Frequency in Controls (N=67,754), n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
<b>Antigout preparations (M04)</b>				
No use	9691 (95.16)	64,027 (94.50)	1.00 (reference)	1.00 (reference)
Any use before index date	493 (4.84)	3727 (5.50)	0.86 (0.78–0.95)	0.81 (0.74–0.90)
Use in three-year lag time only	123 (1.21)	1104 (1.63)	0.72 (0.60–0.87)	0.70 (0.58–0.84)
Use before three-year lag	370 (3.63)	2623 (3.87)	0.92 (0.82–1.03)	0.88 (0.78–0.98)
Use in five-year lag time only	206 (2.02)	1775 (2.62)	0.75 (0.65–0.87)	0.73 (0.63–0.84)
Use before five-year lag	287 (2.82)	1952 (2.88)	0.96 (0.84–1.09)	0.92 (0.81–1.04)
<b>Allopurinol (M04AA01)</b>				
No use	9694 (95.19)	64,042 (94.52)	1.00 (reference)	1.00 (reference)
Any use before index date	490 (4.81)	3712 (5.48)	0.86 (0.78–0.95)	0.81 (0.73–0.89)
Use in three-year lag time only	123 (1.21)	1101 (1.62)	0.72 (0.60–0.87)	0.70 (0.58–0.84)
Use before three-year lag	367 (3.60)	2611 (3.85)	0.92 (0.82–1.02)	0.87 (0.78–0.98)
Use in five-year lag time only	206 (2.02)	1768 (2.61)	0.76 (0.65–0.88)	0.73 (0.63–0.85)
Use before five-year lag	284 (2.79)	1944 (2.87)	0.95 (0.84–1.08)	0.91 (0.80–1.04)

**Notes:** <sup>a</sup>Adjusted for cardiovascular diseases, diabetes, stroke, asthma or chronic obstructive pulmonary disease (COPD), cancer, head injury, substance abuse and non-steroidal anti-inflammatory drug use.

not meet the screening threshold in this study. For example, chloroquine and hydroxychloroquine were associated with lower risk of PD in persons with rheumatoid arthritis,<sup>15</sup> and thiazolidinediones with lower risk of PD in people with diabetes.<sup>16</sup>

Antipsoriatic and antigout drugs were associated with lower risk of PD on a group level, and in both cases the association was due to a single drug. Earlier studies have also reported lower risk of PD among allopurinol users,<sup>4,20</sup> and individuals with gout who received any antigout drug.<sup>18</sup> As 87% of persons with gout used allopurinol in that study, those findings also reflect the association between allopurinol and PD.<sup>18</sup> In contrast, two studies found no association between risk of allopurinol<sup>21</sup> or any antigout drug use<sup>22</sup> and PD. Although Lai et al 2018 did not find an association between allopurinol use and risk of PD, they initially hypothesized that allopurinol might reduce the risk of PD by inhibition of xanthine oxidase,<sup>21</sup> and higher xanthine oxidase activity among people with PD has been reported.<sup>23</sup> Allopurinol also has semantic similarity to compounds that have been demonstrated to reduce aggregation of  $\alpha$ -synuclein in experimental models,<sup>4</sup> but at present there are no experimental studies with allopurinol.

The lower risk of PD among antigout drug users has been suggested to result from confounding by indication because initiation of antigout drugs indicates severe gout and high uric acid levels,<sup>24</sup> which have been associated with lower risk of PD. Cortese et al 2018 reported that the lowest risk of PD was observed within the years prior to initiation of antigout medication.<sup>20</sup> On the other hand, a meta-analysis concluded that gout is not associated with a lower risk of PD, although the statistical heterogeneity was high ( $I^2=87\%$ ),<sup>25</sup> and differences in, eg, study designs and follow-up times can contribute to conflicting results. Two individual studies reported decreased risk of PD,<sup>26,27</sup> two an increased risk of PD in persons with gout<sup>24,28</sup> and three observed no association.<sup>21,29,30</sup> The increased risk of PD among people with gout likely reflects surveillance bias, as Pakpoor et al noted that the risk of PD was detected in the early years (<1 year or 1–4 years) after hospitalization for gout,<sup>24</sup> and the other study also had short median follow-up time (2.1 years) from diagnosis of gout to incident PD.<sup>28</sup> Thus, it is unclear whether gout is associated with PD, and whether lower uric acid levels in PD are a cause or a consequence of the disease.<sup>24</sup> Interestingly, a meta-analysis of studies on persons with PD reported lower uric acid levels among persons in middle stage, compared to those in early stage of the disease.<sup>31</sup> In addition, lower serum uric acid levels have been associated with freezing of gait,<sup>32</sup> and nonmotor symptoms (dysphagia, anxiety, depression, apathy), cognitive dysfunction and whole-brain gray matter volume<sup>33</sup> in cross-sectional studies of persons with PD.

To our knowledge, calcipotriol or antipsoriatics have not been linked to PD before. The association between psoriasis and risk of PD is currently unclear, and the earlier studies are hampered by duration of exposure assessment. Two cohort studies with relatively short follow-ups, maximum 5 years<sup>34</sup> and average of 3.4 years,<sup>35</sup> reported an increased risk of PD in patients with psoriasis and one study found no excess risk of PD one or five years after hospitalization for psoriasis.<sup>36</sup> No association was observed in a case-control study with psoriasis diagnosed at least five years before the outcome.<sup>37</sup> Only one study evaluated the effect of systemic treatment of psoriasis, defined as at least one prescribed systemic agent more than once.<sup>35</sup> The higher risk of PD was not observed among those with systematic treatment for psoriasis, but this may be explained by small number of users of systemic therapy, and their younger age and shorter mean follow-up time compared with those without systemic therapy. Due to limited and conflicting findings, the association of treatment of psoriasis and risk of PD is unclear and more large-scale population-based studies with appropriate methods are needed.

The strengths of the study data arise from systematic data collection. The Finnish healthcare system is organized according to a national framework. All citizens/residents are covered by the tax-supported public health service and have access to health services, regardless of socioeconomic status. Data on purchased prescription drugs and use of healthcare services on an individual level are routinely collected on national registers, enabling a nationwide study with long exposure assessment. The internal validity, coverage and accuracy of Finnish administrative registers have been confirmed previously.<sup>38–40</sup> Diagnosis of PD and its differential diagnostics is challenging, and false diagnoses are common in the early phase.<sup>41,42</sup> The proportion of excluded persons in FINPARK (25.9%) is in line with estimated proportion of misdiagnosed PD,<sup>41–44</sup> supporting the validity of outcome. It should be noted that the PD diagnoses were from nearly 20 consecutive years (1998–2015), and it is possible that there may have been variations in clinical diagnostic process. However, there have not been significant changes in the Kela criterion during the study period. In addition, the assessment period for confounders partially overlapped with the exposure assessment period in the replication analysis. Therefore, the adjusted results should be interpreted as the association between exposure and PD, independent of measured comorbidities and NSAID use, regardless of whether these factors act as confounders or are

part of the pathway between exposure and outcome. According to power calculations, we had power to detect clinically meaningful associations for drugs with >5% exposure in controls. However, we acknowledge that our approach was simplistic, and further modifications, such as more extensive cross-validation in screening stage, would be helpful to prune out some spurious associations, such as those observed with enalapril.

In conclusion, although use of real-world databases for identifying repurposing candidates may seem like a promising approach, there are pitfalls that should be addressed and considered. Confounding by indication is likely easier to identify and suspect when screening is implemented with traditional frequentist methods, but it should be acknowledged also in studies with more advanced methods, and single-exposure pharmacoepidemiological studies.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author but restrictions apply to the availability of these data, and so they are not publicly available. Data are however available from the authors upon reasonable request and with permission of the register maintainers.

## Ethics Approval and Consent to Participate

Register maintainers have approved the FINPARK study plan. Data were pseudonymized before submission to the research team and study participants were not contacted. Therefore, according to Finnish legislation (including Personal Data Act 23/1999, Act on the Openness of Government Activities 621/1999 and Act on the Secondary Use of Health and Social Data 552/2019, and previous Act on the National Healthcare registers [no official English translation as this is not available] 556/1989), the study has been granted an exemption from requiring ethics approval or informed consent.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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