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Identifying Drugs Associated With Parkinson's Disease Risk Using Machine Learning

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ABSTRACT

Machine learning (ML)–based methods have been proposed as a potential approach for identifying candidate drugs to be repurposed as disease-modifying treatments for Parkinson's disease (PD). We applied an ML-based signal detection method to identify drugs associated with PD and evaluated the method's generalizability. An algorithm combining subsampling and lasso logistic regression was implemented in a case–control study of 12 257 PD cases and 81 103 matched controls identified in Finnish registers. Drug exposure was defined at the subgroup and drug substance levels of the Anatomical Therapeutic Chemical (ATC) classification, considering the frequency of dispensation over 2 years, starting 10 years before the index date (8-year lag). Three subgroups and two individual drugs were associated with reduced PD risk. Inhalant anticholinergics, in particular tiotropium bromide, showed the most robust signal. Other signals included antimalarial drugs (aminoquinolines) and the antibiotic subgroup lincosamides. Several drugs were associated with increased PD risk, as expected. In addition to direct pharmacological effects, observed associations could be due to treatment of prodromal symptoms of PD, increased comorbidity in individuals later diagnosed with PD or a combination of these factors. These results support the feasibility of the approach. Associations of decreased PD risk observed should be further investigated in view of drug repurposing.

1 | Introduction and Background

There is a growing interest in repurposing existing drugs for Parkinson's disease (PD) treatment, offering a faster and more cost-effective alternative to de novo drug development [1, 2]. In 2024, a total of 136 clinical trials for symptomatic (76 trials) and disease-modifying (60 trials) therapies in PD were registered, of which 52 were for repurposed drugs [3].

Many of the ongoing trials are motivated by observational pharmacoepidemiological studies reporting a lower risk of PD among users of a specific drug. More systematic approaches for candidate drug identification, such as hypothesis-free systematic screening utilizing traditional epidemiological methods, have been proposed [4, 5], in addition to machine learning (ML)–based methods, which can more efficiently handle vast amounts of data and variables. Recently, a French study implemented an ML-based signal detection method to identify potential candidates for repurposing [6]. The study comprised 40 760 incident PD patients and 176 395 controls. They identified six drug subgroups associated with a lower risk of PD.

Reverse causation represents a challenge in pharmacoepidemiological studies of PD due to prodromal symptoms that can

Summary

We used a machine learning (ML)–based method to identify drugs associated with the risk of Parkinson's disease (PD) in Finnish register data. We compared the use of different prescription drugs 10 years before PD diagnosis between people with PD and a control group. Three subgroups and two individual drugs were associated with a lower risk of PD. These findings may help in developing new treatments for PD. Several drugs were associated with increased PD risk, and this is likely because they are used to treat prodromal symptoms of PD, which may already have occurred years before the disease can be diagnosed.

lead to changes in drug prescriptions in the years before PD. Therefore, using an appropriate exposure assessment period is necessary. We applied the novel ML method developed in the French study to Finnish nationwide data with the following aims: (i) to identify drugs associated with a lower risk of PD, (ii) to identify drugs associated with a higher risk of PD, (iii) to study the transferability of the ML approach and whether it produces similar or different findings compared to our previous study using traditional analysis methods within the same Finnish dataset [4].

2 | Materials and Methods

2.1 | Study Population

The study population was identified from the Finnish Parkinson's Disease study (FINPARK), including 22 189 community-dwelling residents of Finland who received a clinically confirmed PD diagnosis between 1996 and 2015 and up to seven matched controls for each PD case ($n = 148\,009$). Matching criteria were age (±1 year), sex and region. PD cases were identified from the Special Reimbursement Register maintained by the Social Insurance Institution of Finland (KELA). To get special reimbursement entitlement for PD medication, KELA requires a statement from the neurologist who has confirmed the PD diagnosis. The date of special reimbursement entitlement was used as an index date. During the study period, diagnosis criteria were consistent with the UK Parkinson's Disease Society Brain Bank criteria [7]. The formation of the FINPARK study and the exclusion criteria have been described in detail previously [8].

To ensure all participants have a full drug exposure period, this study was restricted to 12 257 persons receiving incident PD diagnosis in 2006–2015 and 81 103 matched controls.

2.2 | Drug Exposure

Drug exposure data were obtained from the Prescription Register, which contains data on reimbursed prescription medicine purchases with Anatomical Therapeutic Chemical (ATC) classification codes and date of dispensing. The same analyses were conducted in the penultimate level of ATC classification (Level 4), corresponding to the chemical, pharmacological or therapeutic subgroup of drugs and in the finest ATC classification level (Level 5) corresponding to an active drug substance.

The study design is illustrated in Figure S1. In the main analyses, an 8-year lag before the index date was applied, and drug exposure in a 2-year exposure period before the lag was considered similar to the former French study [6]. In sensitivity analyses, 5-year lag and 5-year drug exposure periods were considered to capture more users and purchases for each drug.

We counted the number of drug dispensations from community pharmacies for each drug during the exposure period using the same categorization as in the French study [6]. For each drug, three binary embedded variables were derived to describe the frequency of exposure using the method of variable coding developed by Schneeweiss et al. [9]: (1) 'ever' if the drug was delivered at least once, (2) 'sporadic' if the number of times the drug was delivered was greater than or equal to the median number of deliveries of that drug among exposed controls and (3) 'frequent' if the number of times the drug was delivered was greater than or equal to the 75th percentile of the number of deliveries among exposed controls. Each of the three binary variables had a specific exposure cut-off. If two exposure cut-offs were the same, only the binary variable associated with the lowest cut-off was created. For example, if the median number of dispensations is equal to 1, cut-offs for the 'ever' and 'sporadic' variables are the same, and only the variable 'ever' is created. Details are described in the Supporting Information of the French study [6].

2.3 | Covariates

Sociodemographic covariates included age at the index date (continuous), sex (men/women), university hospital district on the index date (categorical 6-level), the highest occupational social class before the exposure period as an indicator of socioeconomic position (ordinal 6-level) and occupational exposure to pesticides before the exposure period (binary).

Other covariates considered were long-term diseases (Table S1), and the diagnoses of hospital stays and outpatient visits in specialist health care during the exposure period. Data on long-term diseases were extracted from the Special Reimbursement Register. Eleven binary covariates were included in the analysis, considering the most common diseases and grouping some of them.

The Care Register for Health Care contains diagnoses of day visits to specialist health care and hospital stays coded according to the International Classification of Diseases and Related Health Problems 10th revision (ICD-10). We considered the ICD codes in three-digit blocks, for example, A00–A09, and counted the number of hospital days of ICD blocks for each study participant. All registered ICD codes were included, and day visits were counted as 1 day. Each ICD block was coded with up to three binary variables (ever, sporadic and frequent) in the same way as the drug exposure.

2.4 | Statistical Methods

We implemented a signal detection strategy that combines multiple sample splitting and lasso logistic regression analysis as described previously [6]. All analyses were adjusted for age, sex, region, occupational social class and occupational exposure to pesticides. Binary variables with fewer than 50 occurrences were removed because they could cause instability. Due to computational constraints, conditional logistic regression could not be implemented.

The analysis had three steps: (1) data splitting into two equal-sized groups D1 and D2 so that cases and their matched controls were retained in the same group; (2) a lasso logistic regression analysis with fivefold cross-validation in D1 so that cases and their matched controls were in the same fold. In this step, we identified a variable set S associated with PD status. Sociodemographic variables, including matching factors (age, sex and region), were forced to be included in S by setting the penalty factor of sociodemographic variables to zero; (3) unpenalized logistic regression in D2 including the variables in S. All three steps were repeated 500 times, resulting in 500 regression coefficients (β) for each drug binary variable. If the drug variable was not in the set S, its regression coefficient was set to 0. We used the same selection percentage (SP) threshold value as the original signal detection paper and considered as signals drug binary variables with $SP \geq 50\%$ over the 500 replications [6]. Distributions of SPs are illustrated in Figure S2. The strength of association of these signals with PD was determined from their average beta estimated over the 500 repetitions.

2.5 | Ethics and Approvals

According to Finnish legislation, ethics committee approval or informed consent is not needed because the included persons cannot be identified due to pseudonymized register data, and the persons were not contacted. The study was conducted in accordance with the 'Basic & Clinical Pharmacology & Toxicology Policy for Experimental and Clinical Studies' [10].

3 | Results

The characteristics of 12 257 patients with PD and their matched controls are described in Table S2. The mean (SD) ages of PD cases and controls were 71.3 (9.7) and 70.8 years (9.6), respectively, and 57% of participants were men.

Potential covariates (Table S3) in the main analyses included 11 long-term diseases, 141 diagnoses coded with 329 binary variables from health care and 13 sociodemographic characteristics. We screened 241 drug subgroups coded with 515 binary variables.

In the main analysis (8-year lag, 2-year exposure period) at the penultimate ATC level, only one signal corresponded to antimalarial drugs aminoquinolines, with ever exposure (P01BA_ever, $SP = 52.2\%$, $\overline{\beta} = -0.192$) associated with a lower risk of PD being detected, while 23 signals were associated with increased risk and involved 21 subgroups (Table 1). These 21 subgroups were mainly related to gastrointestinal, urological and cardiovascular conditions and drugs for the central nervous system.

At the finest level of the ATC classification, 465 drug substances were coded with 939 binary variables. The analysis included 1292 variables (Table S3). In this analysis, no signals were associated with a lower risk of PD while 23 signals were associated with increased risk and involved 22 drugs (Table 2). Twenty drugs belonged to 18 of the 21 subgroups identified in the subgroup analyses (Figure S3a), including drugs for gastrointestinal, urological and cardiovascular conditions and the central nervous system. Antithrombotic low-dose acetylsalicylic acid and acetazolamide were observed here, but not in subgroup-level analyses. There were no signals for dermatological antifungals for topical use, other antiepileptics and antipsychotic thioxanthene derivatives as in the subgroup level.

Sensitivity analyses were conducted in the same study population with a 5-year exposure period and a 5-year lag. Potential covariates (Table S4) in the sensitivity analyses included 11 long-term diseases, 166 diagnoses from health care coded with 415 binary variables and 13 sociodemographic characteristics. We screened 267 drug subgroups coded with 603 binary variables.

In sensitivity analysis at the penultimate ATC level, two signals, frequent exposure to lincosamides (J01FF_frequent, $SP = 58.8\%$, $\overline{\beta} = -0.178$) and ever exposure to anticholinergics (R03BB_ever, $SP = 59.2\%$, $\overline{\beta} = -0.116$), were associated with a lower risk of PD. There were no signals for antimalarial drugs aminoquinolines (P01BA_ever, $SP = 33.2\%$, $\overline{\beta} = -0.054$). In total, 26 signals were associated with increased risk of PD and involved 22 subgroups (Table 3). Of these subgroups, 17 were the same as in the main analysis and involved drugs related to gastrointestinal, urological and cardiovascular conditions and drugs for the central nervous system (Figure S3b). Five signals were observed here, but not in the main analysis. They corresponded to bile acids and derivatives, antimycotics for systemic use, anticholinergic tertiary amines, chemotherapeutics for topical use and lithium.

At the finest level of the ATC classification, 535 drug substances were coded with 1156 binary variables. The sensitivity analysis included 1595 variables (Table S4). In this analysis, two signals, frequent exposure to diazepam (N05BA01_frequent, $SP = 50.6\%$, $\overline{\beta} = -0.180$) and ever exposure to tiotropium bromide (R03BB04_ever, $SP = 75.8\%$, $\overline{\beta} = -0.296$), were associated with a lower risk of PD (Table 4). The signal for diazepam was weak ($SP = 50.6\%$), while for tiotropium bromide, it was stronger ($SP = 75.8\%$) and also detected at the subgroup level. There were 28 signals for increased risk involving 25 drugs (Table 4). Of these drugs, 23 belonged to 18 of the 22 subgroups highlighted in the sensitivity analysis at the penultimate ATC level, while the benign prostatic hypertrophy drug finasteride and antiarrhythmic drug flecainide were the signals not detected at the subgroup level (Figure S3c). No individual signals from the subgroups of propulsives, bile acids and derivatives, urological androgens and antipsychotic

TABLE 1 | Characteristics of detected signals in the penultimate level of ATC classification grouped according to indication or the organ system.

Drug subgroup	Drug binary variable (ATC code + frequency of exposure)	Exposed cases (%)	Exposed controls (%)	Exposure cut-off	Selection percentage	Average beta	Average OR
Drugs for gastric acid–related disorders							
Proton pump inhibitors	A02BC_ever	12.83	10.78	1	90.8	0.097	1.10
Other drugs for peptic ulcer and gastro-oesophageal reflux disease	A02BX_ever	0.58	0.32	1	56.6	0.139	1.15
	A02BX_frequent	0.29	0.12	2	67.0	0.348	1.42
Drugs for constipation and functional gastrointestinal disorders							
Propulsives	A03FA_ever	1.93	1.37	1	61.6	0.082	1.09
Bulk-forming laxatives	A06AC_ever	2.24	1.43	1	96.8	0.348	1.36
Osmotically acting laxatives	A06AD_ever	1.29	0.82	1	77.0	0.190	1.21
Drugs for the cardiovascular system							
Organic nitrates	C01DA_ever	11.89	10.06	1	80.0	0.088	1.09
Beta-blocking agents, non-selective	C07AA_ever	4.24	3.19	1	94.2	0.210	1.23
Urologicals							
Androgens: 3-Oxoandrosten (4) derivatives	G03BA_ever	0.73	0.41	1	65.8	0.249	1.28
Drugs for urinary incontinence	G04BD_ever	2.02	1.34	1	87.0	0.252	1.29
Drugs for benign prostate hyperplasia: Alpha-adrenoreceptor antagonists	G04CA_ever	5.55	4.08	1	99.8	0.258	1.29
Drugs affecting the central nervous system							
Antiepileptics: Fatty acid derivatives	N03AG_ever	0.62	0.14	1	67.2	0.421	1.52
	N03AG_sporadic	0.16	0.05	6	60.0	0.305	1.36
Other antiepileptics	N03AX_sporadic	0.16	0.05	6	59.8	0.303	1.35
Antipsychotics: Thioxanthene derivatives	N05AF_ever	0.75	0.40	1	71.2	0.219	1.25
Benzamides	N05AL_sporadic						
Long-acting benzodiazepines	N05BA_ever	7.07	5.65	1	68.2	0.038	1.04
Antidepressants: Non-selective monoamine reuptake inhibitors	N06AA_frequent	0.78	0.49	7	55.8	0.127	1.14
Antidepressants: Selective serotonin reuptake inhibitors	N06AB_ever	5.74	4.42	1	90.0	0.137	1.15

(Continues)

TABLE 1 | (Continued)

Drug subgroup	Drug binary variable (ATC code + frequency of exposure)	Exposed cases (%)	Exposed controls (%)	Exposure cut-off	Selection percentage	Average beta	Average OR
Antivertigo preparations	N07CA_sporadic	0.75	0.44	6	73.0	0.316	1.37
Other subgroups							
Dermatological antifungals for topical use: Imidazole and triazole derivatives	D01AC_ever	3.01	2.41	1	50.2	0.057	1.06
Thyroid hormones	H03AA_ever	5.12	4.11	1	64.2	0.087	1.09
Antimalarials: Aminoquinolines	P01BA_ever	0.46	0.68	1	52.0	−0.191	0.83
Corticosteroids (nasal preparations)	R01AD_ever	8.10	6.68	1	81.4	0.104	1.11

thioxanthene derivatives were observed. Compared to the main analysis results in ATC Level 5, there were 14 identical drugs involving drugs for gastrointestinal, urological and cardiovascular conditions and the central nervous system (Figure S3d).

4 | Discussion

We applied a novel ML method recently described by Courtois et al. [6] to evaluate its transferability and effectiveness in identifying drugs associated with the risk of PD using Finnish nationwide data. We identified three subgroups and two individual drugs associated with a lower risk of PD and 26 subgroups and 32 individual drugs with a higher risk. In general, the results were robust for modification of the exposure assessment window. The identified signals were largely supported by previous epidemiological literature, supporting the feasibility of this approach.

We identified five previous pharmacoepidemiological screening studies on PD based on various routinely collected healthcare data sources, in addition to Courtois et al.'s study [6] (Table S5). Maclagan et al. first identified candidate drugs based on their AI-predicted capacity to reduce aggregation of alpha-synuclein, followed by a case–control study of the shortlisted compounds [11]. None of the preselected candidates in that study overlapped with the inverse associations observed in our analyses. Similarly, no comparable signals were observed in the self-controlled study design by Cepeda et al. [12]. Koponen et al. [4] conducted a nested case–control study, and Romanowska et al. [5] a cohort study, both applying traditional statistical methods. Wei et al. performed a meta-analysis of two nested case–control studies conducted in Sweden and France [13].

Overall, the comparison of these screening studies is not straightforward due to differences in analysis methods, study design and study population (Table S5). The key differences relate to the use of lag time and adjustment for confounders. Most of the previous studies adjusted for few confounders, most commonly age and sex, while the present study, alongside Courtois et al. [6], was able to account for multiple data-driven confounders on a case-by-case basis for each candidate. Similarly, these two studies had the longest lags. Some of the studies did not use lag time, and results may therefore reflect reverse causality. In addition, Koponen et al. did not report results of ATC Level 4, whereas Romanowska et al. and Wei et al. reported results at ATC Level 2, which also poses challenges to direct comparison of results. So far, the use of ML methods in screening studies has been rare.

Inverse associations with PD were detected within the same drug subgroups that were associated with a lower risk of PD in previous studies of the FINPARK study population using traditional methods. In the main analysis at ATC Level 4, aminoquinolines were associated with a decreased risk of PD. We have previously reported an inverse association between aminoquinolines and PD in a study restricted to PD cases and controls with rheumatoid arthritis in FINPARK [14]. Interestingly, in Koponen et al.'s screening study with a traditional statistical method, the association of hydroxychloroquine (aminoquinoline) and PD was not statistically significant but suggestive of lower risk (OR 0.91, 95% CI 0.75–1.11) [4]. The Norwegian screening study examined drugs in ATC Level 2 and found an inverse association between the P01 subgroup (antiprotozoals) and PD [5]. Inhalant anticholinergic tiotropium bromide (R03BB04) was inversely associated with the risk of PD in sensitivity analyses at both subgroup and drug substance levels in this ML-based study. A similar association was observed in a previous systematic screening study in FINPARK [4], as well as in the sensitivity analysis of the French ML-based signal detection study [6]. The results of the R03 subgroup vary, while Romanowska et al. found an inverse association [5]. However, in Wei et al.'s meta-analysis, no association was found [13]. It should be noted that an inverse association could be explained by unmeasured confounding by, for example, smoking. Tiotropium bromide is indicated in chronic

TABLE 2 | Characteristics of detected signals in the finest level of ATC classification grouped according to indication or the organ system.

Drug	Drug binary variable (ATC code + frequency of exposure)	Exposed cases (%)	Exposed controls (%)	Exposure cut-off	Selection percentage	Average beta	Average OR
Drugs for gastric acid–related disorders							
Lansoprazole	A02BC03_ever	4.32	3.48	1	50.8	0.050	1.05
Sucralfate	A02BX02_ever	0.57	0.30	1	76.2	0.344	1.41
Drugs for constipation and functional gastrointestinal disorders							
Cisapride	A03FA02_ever	1.09	0.72	1	59.0	0.122	1.13
Ispaghula	A06AC01_ever	2.24	1.43	1	96.2	0.328	1.39
Lactulose	A06AD11_ever	1.28	0.80	1	78.6	0.225	1.25
Drugs for the cardiovascular system							
Acetylsalicylic acid	B01AC06_frequent	0.42	0.25	4	51.0	0.162	1.18
Glyceryl trinitrate	C01DA02_ever	8.00	6.48	1	89.0	0.142	1.15
Propranolol	C07AA05_ever	2.28	1.49	1	93.0	0.317	1.37
Urologicals							
Testosterone	G03BA03_ever	0.73	0.41	1	64.0	0.256	1.29
Tolterodine	G04BD07_ever	1.09	0.69	1	64.6	0.168	1.18
Solifenacin	G04BD08_ever	0.22	0.09	1	59.8	0.332	1.39
Alfuzosin	G04CA01_ever	1.21	0.83	1	55.4	0.125	1.13
Tamsulosin	G04CA02_ever	4.66	3.40	1	99.4	0.262	1.30
Drugs affecting the central nervous system							
Valproic acid	N03AG01_ever	0.62	0.26	1	73.8	0.311	1.37
	N03AG01_sporadic	0.42	0.14	6	66.8	0.415	1.51
Sulpiride	N05AL01_sporadic	0.16	0.05	4	66.8	0.523	1.69
Alprazolam	N05BA12_ever	1.65	1.13	1	73.2	0.164	1.18
Doxepin	N06AA12_frequent	0.37	0.20	7	50.6	0.219	1.25
Fluvoxamine	N06AB08_sporadic	0.18	0.07	3	56.2	0.383	1.47
Betahistine	N07CA01_sporadic	0.75	0.44	2	69.8	0.301	1.35
Other drugs							
Levothyroxine sodium	H03AA01_ever	5.12	4.11	1	58.6	0.081	1.08
Mometasone	R01AD09_ever	3.61	2.94	1	53.2	0.057	1.06
Acetazolamide	S01EC01_frequent	0.16	0.07	7	50.6	0.398	1.49

obstructive pulmonary disease, whose major risk factor is smoking, which has been consistently associated with reduced PD risk in several studies [15–18].

Another signal associated with lower PD risk in our sensitivity analysis at the drug subgroup level was the antibiotic subgroup lincosamides. Lincosamides, studied together with the antibiotic subgroup macrolides in a previous Finnish study, were associated with increased risk of PD, although the association in that study was no longer significant after correction for false discovery rate [19]. Results of subgroup J01 (antibacterials for systemic use) have been inconsistent. While the Norwegian study found an inverse association, in the meta-analysis of two countries, no association was found [5, 13].

Several drugs were associated with an increased risk of PD. Results could reflect overall morbidity, reverse causation due to prodromal PD symptoms, direct pharmacological effect of drugs

TABLE 3 | Characteristics of detected signals in sensitivity analysis at the penultimate level of ATC classification grouped according to indication or the organ system.

Drug subgroup	Drug binary variable (ATC code + frequency of exposure)	Exposed cases (%)	Exposed controls (%)	Exposure cut-off	Selection percentage	Average beta	Average OR
Drugs for gastric acid–related disorders							
Proton pump inhibitors	A02BC_ever	24.52	21.45	1	61.2	0.028	1.03
	A02BC_sporadic	16.23	13.71	2	60.6	0.032	1.03
Drugs for constipation and functional gastrointestinal disorders							
Propulsives	A03FA_ever	3.14	2.32	1	50.8	0.034	1.04
Bulk-forming laxatives	A06AC_ever	4.46	2.89	1	100.0	0.284	1.33
Osmotically acting laxatives	A06AD_ever	2.98	1.85	1	98.8	0.287	1.33
Drugs for the cardiovascular system							
Organic nitrates	C01DA_ever	17.92	15.48	1	78.6	0.074	1.08
Beta-blocking agents, nonselective	C07AA_ever	5.96	4.26	1	97.4	0.210	1.23
Dermatologicals							
Dermatological antifungals for topical use: Imidazole and triazole derivatives	D01AC_ever	5.69	4.62	1	62.2	0.062	1.06
Chemotherapeutics for topical use	D06BX_ever	1.58	1.13	1	72.0	0.176	1.19
Urologicals							
Androgens: 3-Oxoandrosten (4) derivatives	G03BA_frequent	0.37	0.18	9	52.0	0.170	1.19
Drugs for urinary incontinence	G04BD_ever	4.54	2.91	1	100.0	0.320	1.38
Drugs for benign prostate hyperplasia: Alpha-adrenoreceptor antagonists	G04CA_ever	10.68	8.09	1	100.0	0.231	1.26
Anti-infectives for systemic use							
Antibacterials for systemic use: Lincosamides	J01FF_frequent	0.55	0.78	2	58.8	−0.178	0.84
Antimycotics for systemic use: Triazole and tetrazole derivatives	J02AC_frequent	3.71	2.72	2	92.6	0.208	1.23
Drugs affecting the central nervous system							
Antiepileptics: Fatty acid derivatives	N03AG_ever	1.02	0.44	1	84.2	0.271	1.31
	N03AG_sporadic	0.63	0.23	7	50.6	0.069	1.07
	N03AG_frequent	0.42	0.12	16	82.4	0.497	1.64

(Continues)

TABLE 3 | (Continued)

Drug subgroup	Drug binary variable (ATC code + frequency of exposure)	Exposed cases (%)	Exposed controls (%)	Exposure cut-off	Selection percentage	Average beta	Average OR
Anticholinergic agents: Tertiary amines	N04AA_ever	0.42	0.16	1	74.4	0.257	1.33
Antipsychotics: Thioxanthene derivatives	N05AF_ever	1.02	0.53	1	75.2	0.192	1.21
Antipsychotics: Benzamides	N05AL_frequent	0.16	0.04	9	76.2	0.790	2.20
Antipsychotics: Lithium	N05AN_ever	0.42	0.15	1	78.8	0.361	1.44
Long-acting benzodiazepines	N05BA_ever	10.35	7.93	1	82.6	0.068	1.07
Antidepressants: Selective serotonin reuptake inhibitors	N06AB_ever	9.96	7.21	1	100.0	0.208	1.23
Drugs for the respiratory system							
Corticosteroids (nasal preparations)	R01AD_ever	14.11	12.00	1	72.0	0.053	1.05
	R01AD_frequent	4.72	3.62	4	72.0	0.053	1.05
Anticholinergics (inhalants)	R03BB_ever	1.50	1.79	1	59.2	−0.116	0.89
Other subgroups							
Bile acids and derivatives	A05AA_ever	0.16	0.08	1	50.8	0.271	1.31
Thyroid hormones	H03AA_ever	6.86	5.65	1	58.6	0.059	1.06

or a combination of these factors. As this is a signal detection study, it is difficult to disentangle which of the aforementioned mechanisms explains each of the associations. To further investigate the mechanisms at work, pharmacoepidemiological studies with a specific design for each signal generated would be necessary. Although the method accounts for multiple comorbidities, it may not fully capture multimorbidity, and residual confounding may remain. Multimorbidity has been associated with a higher risk of PD, which could be explained by the increased chronic inflammation, increased oxidative stress and exposure to the medicines used to treat multimorbidity [20]. Despite the lag (8 or 5 years) before the index date to avoid reverse causation bias, many of these drugs associated with increased risk of PD may have been used to treat prodromal symptoms of PD that can occur more than a decade earlier, with some non-motor symptoms such as constipation even occurring ≥20 years before PD diagnosis [21–23]. Signals of increased risk were found in drugs for constipation (ispaghula, lactulose), reflux (omeprazole, lansoprazole, sucralfate), tremor (propranolol) and urinary problems (alfuzosin, tamsulosin, finasteride), which could have been used for early symptoms of PD. Benzodiazepines may have been used for anxiety symptoms and sleeping difficulties, and antidepressants doxepin, fluvoxamine, escitalopram and citalopram for depressive symptoms, which are also possible prodromal symptoms of PD [23]. Tolterodine and solifenacin have an anticholinergic action mechanism, and these kinds of drugs have been associated with an increased risk of cognitive impairment in older adults [24–26]. The association of valproic acid, sulpiride and lithium with increased risk of PD could be consistent with earlier findings that people with epilepsy, bipolar disorder or schizophrenia have a higher risk of PD [23, 27–31]. These drugs, especially sulpiride, can cause drug-induced parkinsonism [32], and according to a systematic review, the proportion of false diagnoses in administrative databases varies significantly [33]. However, the case identification was based on special reimbursement decisions, which require neurologist-confirmed diagnosis, and exclusion of drug-induced parkinsonism as a cause of the symptoms. A person is eligible for special reimbursement of PD drugs after a neurologist at KELA reviews and accepts the statement from a neurologist. In addition, we attempted to mitigate the impact of false diagnoses by using stringent exclusion criteria, including diagnoses of drug-induced parkinsonism within 2 years of PD diagnosis.

In general, the findings with increased risk of PD at subgroup and individual drug levels were similar, with benzodiazepines being the only exception. Ever exposure to the subgroup of benzodiazepines was associated with a higher risk of PD. Among benzodiazepines, a strong signal (SP 94.0%) for increased risk was observed for alprazolam. Benzodiazepines are recommended only for short-term use because of several adverse effects, especially in long-term use and dependence risk [34], and alprazolam is especially problematic with respect to physical dependence and withdrawal reactions [35, 36]. Conversely, a weak

TABLE 4 | Characteristics of observed signals in sensitivity analysis at the finest level of ATC classification grouped according to indication or the organ system.

Drug	Drug binary variable (ATC code + frequency of exposure)	Exposed cases (%)	Exposed controls (%)	Exposure cut-off	Selection percentage	Average beta	Average OR
Drugs for gastric acid–related disorders							
Omeprazole	A02BC01_ever	6.56	5.25	1	78.4	0.084	1.09
Drugs for constipation							
Ispaghula	A06AC01_ever	4.35	2.81	1	100.0	0.294	1.34
Lactulose	A06AD11_ever	2.96	1.84	1	98.6	0.303	1.35
Drugs for the cardiovascular system							
Flecainide	C01BC04_ever	0.87	0.58	1	50.2	0.121	1.13
Glyceryl trinitrate	C01DA02_ever	12.96	10.88	1	81.0	0.097	1.10
Propranolol	C07AA05_ever	3.72	2.31	1	97.2	0.267	1.31
	C07AA05_sporadic	2.08	1.16	3	67.0	0.082	1.09
Dermatologicals							
Imidazoles/ triazoles in combination with corticosteroids	D01AC20_ever	3.73	2.90	1	67.8	0.104	1.11
Metronidazole	D06BX01_ever	1.58	1.13	1	65.8	0.160	1.17
Urologicals							
Tolterodine	G04BD07_ever	2.60	1.57	1	99.4	0.333	1.40
Solifenacin	G04BD08_ever	0.80	0.44	1	55.4	0.136	1.15
	G04BD08_sporadic	0.51	0.24	2	52.4	0.186	1.20
Alfuzosin	G04CA01_ever	3.05	2.21	1	78.2	0.151	1.16
Tamsulosin	G04CA02_ever	8.60	6.54	1	99.8	0.205	1.23
Finasteride	G04CB01_ever	4.93	3.78	1	55.0	0.044	1.05
Drugs affecting the central nervous system							
Valproic acid	N03AG01_ever	1.02	0.43	1	85.0	0.284	1.33
	N03AG01_frequent	0.42	0.12	16	82.0	0.525	1.69
Biperiden	N04AA02_ever	0.41	0.15	1	74.0	0.284	1.33
Sulpiride	N05AL01_frequent	0.16	0.04	9	71.0	0.705	2.02
Lithium	N05AN01_ever	0.42	0.15	1	75.4	0.340	1.41
Diazepam	N05BA01_frequent	0.56	0.66	8	50.6	−0.180	0.84
Alprazolam	N05BA12_ever	2.60	1.66	1	94.0	0.215	1.24
Citalopram	N06AB04_ever	5.43	3.81	1	98.2	0.181	1.20
Fluvoxamine	N06AB08_ever	0.41	0.20	1	53.8	0.201	1.22
Escitalopram	N06AB10_ever	1.81	1.18	1	67.4	0.146	1.16
Drugs for the respiratory system							
Fluticasone	R01AD08_ever	4.38	3.50	1	60.4	0.076	1.08

(Continues)

TABLE 4 | (Continued)

Drug	Drug binary variable (ATC code + frequency of exposure)	Exposed cases (%)	Exposed controls (%)	Exposure cut-off	Selection percentage	Average beta	Average OR
Mometasone	R01AD09_ever	8.09	6.79	1	70.4	0.063	1.07
Tiotropium bromide	R03BB04_ever	0.69	0.99	1	75.8	−0.296	0.74
Other drugs							
Levothyroxine sodium	H03AA01_ever	6.86	5.65	1	55.8	0.056	1.06
Fluconazole	J02AC01_frequent	2.51	1.85	2	56.2	0.086	1.09

signal, barely above the selection threshold, for a lower risk of PD for frequent diazepam use (SP 50.8%) was found, which could be a chance discovery. The findings on subgroup N05 (psycholeptics) were consistent in previous studies, showing an increased risk of PD [5, 13]. The direct comparison of the results to the French study using the same method [6] is hampered by differences between the French and Finnish study populations, including case definition and sample sizes and differences in treatment and prescription practices and reimbursement in these two countries. Study size differences were considered by changing the threshold for removing the least prevalent binary variable from 100 to 50 occurrences. PD cases were identified in France from 2016 to 2018 using a validated algorithm. In Finland, cases were identified from 2006 to 2015 based on eligibility for special reimbursement of PD drugs. Therefore, the exposure assessment years differ between the two studies, and drugs that came to the market more recently are not fully captured in the present study. Risk-increasing associations were not reported in the French study [6]. On the other hand, the association of tiotropium bromide was observed in both of these ML-based studies.

The strengths of our study arise from longitudinal, nationally representative data, which enabled us to assess drug exposure 8 years before the outcome and adjust for comorbidities and socio-economic position. The validity of Finnish national registers in epidemiological and pharmacoepidemiological research has been described previously [37–39]. The PD definition is based on clinical diagnoses by neurologists. However, the diagnosis of PD and its differential diagnostics are challenging, and especially in the early phase, false diagnoses are common [40–43]. The proportion of excluded persons in FINPARK (25.9%) is in line with the proportion of assumed false diagnoses [33, 40, 41, 44] and supports the validity of the outcome. The ML-based methodology applied in the current study allows convenient and flexible confounder adjustment.

The ML method employed is a hypothesis-free approach capable of uncovering unexpected associations, potentially paving the way for further studies to identify novel targets for disease-modifying treatment in PD. On the other hand, the identified signals should be interpreted cautiously until confirmed in further studies. Similarly, the associations with increased risk should be interpreted carefully as they may reflect the treatment of prodromal symptoms of PD or overall multimorbidity despite the covariate adjustment. Indications are not recorded in our data sources and, as with other pharmacoepidemiological studies utilizing administrative healthcare data, drug exposure is inferred from dispensing records, assuming that the dispensed drugs were subsequently used. Nonetheless, dispensed prescriptions provide a more accurate reflection of actual drug use compared to written prescriptions alone. The inclusion of candidates would also be affected by the selection threshold; therefore, we utilized a low threshold and reported the exact SP for each signal that met the prespecified threshold. Limitations also include the lack of direct adjustment for potential confounders related to lifestyle factors such as smoking and physical activity. Further, although the applied confounder adjustment method is able to flexibly select the exposure-specific set of confounders, the ability to account for confounders may vary. It should be noted that the matching of cases and controls was retained in the split to training and validation samples, but penalized conditional logistic regression could not be implemented due to computational constraints. This may increase the risk of Type 1 error, although the matching factors age, sex and region were forced as adjusting covariates.

To conclude, our results support the generalizability of the applied ML method in identifying pharmacoepidemiological risk or protective factors. We found two drug subgroups, aminoquinolines and inhalant anticholinergics, particularly tiotropium bromide, associated with lower PD risk as in our previous studies with different study methods. The signals found with the inverse association should be further investigated.

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Conflicts of Interest

E.P.: Michael J. Fox Foundation for Parkinson's Research (MJFF) (Grant 023918).

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A.P.: Nothing to declare.

S.H.: Nothing to declare.

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Data Availability Statement

The data used in this study are not publicly available due to restrictions by the register maintainers and Finnish legislation. Data access requires a data permit from the Finnish National Health and Social Data Permit authority Findata.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Study design. **Figure S2:** Distribution of selection percentages (SPs) in analyses. **Figure S3:** Venn diagrams of the drugs associated with increased PD risk. **Table S1:** Long-term diseases captured from special reimbursement registers using Finnish special reimbursement codes. **Table S2:** Characteristics of incident Parkinson's disease cases and controls extracted from the Finnish Parkinson's Disease study (FINPARK). **Table S3:** Number of binary variables in the main analyses before and after removing the least prevalent variables (< 50 occurrences). **Table S4:** Number of binary variables in sensitivity analyses before and after removing the least prevalent variables (< 50 occurrences). **Table S5:** Comparison of pharmacoepidemiological screening studies on PD and signals of drugs associated with a lower risk of PD (relative risks and 95% confidence intervals) in this study compared with the earlier screening studies. Reference numbers as in the manuscript.