ARTICLE

Use of β2-adrenoreceptor agonist and antagonist drugs and risk of Parkinson disease

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Abstract

Objective
To verify the previously reported association between long-term use of β2-adrenoreceptor (β2AR) agonist and antagonist with reduced and increased risk of Parkinson disease (PD), respectively.

Methods
We obtained odds ratios (ORs) associating time of β2AR agonist and antagonist use with PD risk in nationwide Danish health registries.

Results
We included 2,790 patients with PD and 11,160 controls. Long-term β2AR agonist use was associated with reduced PD risk (OR 0.57, 95% confidence interval [CI] 0.40–0.82) in this cohort. Unexpectedly, short-term β2AR agonist use was equally associated (OR 0.64, 95% CI 0.42–0.98). Because β2AR agonists are prescribed mostly for chronic obstructive pulmonary disease (COPD), often caused by long-term nicotine abuse, we analyzed other markers of smoking. Diagnosis of COPD (OR 0.51, 95% CI 0.37–0.69) and use of inhaled corticosteroids (OR 0.78, 95% CI 0.59–1.02) or inhaled anticholinergics (OR 0.41, 95% CI 0.25–0.67) were also inversely associated with PD. Increased PD risk was not found for all β2AR antagonists but only for propranolol and metoprolol. Associations were markedly stronger for short-term than long-term use.

Conclusion
We confirmed β2AR agonist use to be associated with reduced PD risk and β2AR antagonist use with increased PD risk. However, our data indicate the association of β2AR agonists to be indirectly mediated by smoking, which is repeatedly associated with reduced risk of PD. The association of β2AR antagonists indicates reverse causation, with PD symptoms triggering their prescription rather than β2AR antagonists causing PD. Thus, current epidemiologic data do not support a causal link between β2AR agonists and antagonists and PD risk.

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Glossary

β2AR = β2-adrenoreceptor; **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **DDD** = defined daily dose; **ICD-8** = *International Classification of Diseases, 8th revision*; **ICD-10** = *International Classification of Diseases, 10th revision*; **OR** = odds ratio; **PD** = Parkinson disease.

The etiopathogenesis of sporadic Parkinson disease (PD), the most common form of parkinsonism, is complex with varying contributions of genetic and environmental factors. However, the pathomechanism leading to PD is only partially understood.

Recently, an epidemiologic study reported that the use of the β2-adrenoreceptor (β2AR) agonist salbutamol was associated with a dose-dependent decreased risk of PD.[1] The authors provided biochemical evidence supporting such a relation by demonstrating that β2AR modulation bidirectionally regulates the expression of α-synuclein, the accumulation of which is the pathologic hallmark of PD. They also showed a β2AR agonist to protect against neuronal cell loss in a mouse model of PD. Consistently, this study[1] showed long-term use of β2AR antagonists, for example, propranolol, to be associated with increased risk of PD in their epidemiologic substudy. A more recent epidemiologic study examined the risk of β2AR agonist and antagonist on PD.[2] The authors replicated the finding of an increased risk of PD with the use of β-antagonists, while use of β2-agonists was associated with reduced risk of PD.[2] If 2 essential, commonly used, and well-tolerated drug classes such as β2AR agonists and antagonists would be confirmed to possess disease risk–modulating properties, it would have profound public health implications. First, PD would have to be considered a potential adverse event of β2AR antagonists, challenging the application of this drug class. Second, β2AR agonists might be considered candidates for disease-modifying therapeutic trials in PD. Because of these far-reaching health consequences, we sought to replicate and expand the epidemiologic evidence presented by the previous study[1] in an independent cohort. Thus, we conducted a case-control study of incident PD cases in the even larger Danish nationwide health registries.[3,4]

Methods

The analysis was conducted as a case-control study of incident cases of idiopathic PD in Denmark (population 5.6 million) between January 1, 2000, and December 31, 2012, among Danes born in 1950 or before. We compared the use of β2AR agonists and antagonists among PD cases to that among disease-free population controls to obtain the odds ratios (ORs), as an estimate of the incidence rate ratio, associating use of β2AR agonists and antagonists with the risk of PD. To avoid bias, we handled cases and controls the same way according to standard epidemiologic principles. Therefore, controls would have been eligible for sampling as cases if they had developed the disease.

Main analysis

The analysis followed a standard matched case-control approach. Descriptive statistics were expressed as frequencies and proportions of cases and controls within each category of the exposure and covariates. We used conditional logistic regression to calculate crude and adjusted ORs for PD associated with the use of β2AR agonists and antagonists while controlling for covariates. The a priori defined main analyses comprised the OR for PD associated with having cumulatively used ≥3 years of (any) β2AR agonists and antagonists. Further analyses were carried out by looking at never/ever use and strata of cumulative use and for the single drugs individually.

Data sources

In Denmark, virtually all medical care is provided by public health authorities, which, in combination with the extensive Danish health registries, allows population-based studies covering all inhabitants of Denmark. Since 1968, all Danish residents have been assigned a unique civil registration number that encodes sex and date of birth. The civil registration number enables simple and correct record linkage across Danish medical and administrative registries.[5] In this study, data from 3 sources were used: the Danish National Registry of Patients, the Danish National Prescription Registry, and the Danish Person Registry. Information on all hospital contacts is recorded in the Danish National Patient Registry[3] (admissions since 1977, outpatient and emergency department visits since 1995). Diagnoses are coded according to the ICD (ICD-8 in 1977–1993, ICD-10 since 1994). The Danish National Patient Registry is continuously undergoing internal validation and is internationally considered to be the most comprehensive registry of its kind.[3]

The Prescription Registry[4] holds information on all prescriptions for drugs dispensed at Danish community pharmacies since 1995. For each prescription, the date the drug was dispensed and a full account of the dispensed product are recorded, including the Anatomical Therapeutic Chemical code and the quantity in defined daily doses (DDDs).[6] Information on dosing instruction and the indication for prescribing are not included in the Prescription Registry. The Danish Person Registry[5] contains data on vital status (date of death) and migrations into and out of Denmark. This allowed us to extract controls and to calculate risk time for all participants. All linkage was performed within Statistics Denmark, which is a governmental institution that collects and maintains electronic records for a broad spectrum of statistical and scientific purposes. Further information on the Danish registries has been previously described in detail elsewhere.[7]

Cases

As the base study population, we used data material covering all Danes born before January 1, 1950, and living in Denmark April 2, 1968, or later. From this population, cases were identified as individuals with a hospital contact with a primary diagnosis code of PD 2000 and 2011. This ensures a minimum of 5 years of follow-up from the start of the Prescription Register in 1995.[8] To increase the validity of the case definition, we further required that cases had filled ≥2 prescriptions of anti-PD medication in the following year[4] while excluding those receiving their PD diagnosis during use of antipsychotics (defined as a fill <180 days from date of diagnosis). To only include incident cases of PD, we excluded cases who had any previous record of a PD diagnosis, including nonprimary diagnoses or any previous use of anti-PD medication, if these diagnoses preceded the case defining diagnosis by >1 month. Cases with any record of a diagnosis of atypical or secondary forms of parkinsonism or essential tremor were also excluded. Lastly, patients who were not inhabitants in Denmark at the index date or who had any history of migration within 5 years before their index date were excluded to ensure sufficient follow-up on all patients.

Controls

Using a risk-set sampling strategy, we extracted 4 controls randomly from the study population for each case. Controls were matched by sex and birth year and assigned an index date identical to the corresponding case. Furthermore, controls who fulfilled any of the exclusion criteria described for cases or had any history of PD before their index date were excluded. We allowed participants to be selected as controls before they became cases. We also allowed participants to be selected as controls more than once. The generated OR is therefore an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study based on the same source population.[9]

Drug exposure

For both cases and controls, we obtained information on use of all inhaled β2AR agonists between January 1, 1995, and July 1, 2012. Exposure was categorized both as never/ever use and as cumulative duration of use, measured as the estimated number of days of exposure to β2AR agonists before the index date while allowing noncontinuous use. Cumulative duration of exposure was preferred over cumulative amount because β2AR agonists are used extensively as part of combination products (often in combination with corticosteroids), for which a DDD value of 1 DDD per puff is assigned to all drugs, thus precluding meaningful assessment of cumulative doses. Because the prescribed duration of a prescription is not recorded in the Prescription Registry, durations had to be estimated. To this end, we modeled exposure durations using the parametric waiting time distribution,[10,11] specified by the single drug substance or combination product, including in the model age (continuous), sex, and number of packages dispensed (1, 2, and ≥3) as covariates and using a cutoff of 80% in the interarrival density.[11]

Table 1 Characteristics of cases with idiopathic PD and their matched controls

	Cases (n = 2,790)	Controls (n = 11,160)
Sex, n (%)		
Men	1,638 (58.7)	6,552 (58.7)
Women	1,152 (41.3)	4,608 (41.3)
Age		
Median (IQR), y	73 (66–79)	73 (67–79)
<65 y, n (%)	528 (18.9)	1,996 (17.9)
65–79 y, n (%)	1,623 (58.2)	6,420 (57.5)
≥80 y, n (%)	639 (22.9)	2,744 (24.6)
Drugs, n (%)		
Statins	680 (24.4)	2,582 (23.1)
Psycholeptic drugs, any	1,379 (49.4)	4,602 (41.2)
Antipsychotics	224 (8.0)	537 (4.8)
Anxiolytics	938 (33.6)	2,900 (26.0)
Hypnotics and sedatives	890 (31.9)	2,969 (26.6)
Selective serotonin reuptake inhibitors	909 (32.6)	1,620 (14.5)
Nonsteroidal anti-inflammatory drugs	1,906 (68.3)	7,363 (66.0)
History of, n (%)		
Asthma	54 (1.9)	238 (2.1)
Myocardial infarction	180 (6.5)	839 (7.5)
Stroke	234 (8.4)	758 (6.8)
Depression	160 (5.7)	174 (1.6)
Alcohol-related disease	81 (2.9)	352 (3.2)
Charlson Comorbidity Index, n (%)		
0	1,393 (49.9)	6,113 (54.8)
1	604 (21.6)	1,988 (17.8)
≥2	793 (28.4)	3,059 (27.4)
Highest achieved education, n (%)		
Short (7–10 y)	1,102 (39.5)	4,419 (39.6)
Medium (11–13 y)	123 (4.4)	491 (4.4)
Long (>13 y)	1,310 (47.0)	5,181 (46.4)

Abbreviations: IQR = interquartile range; PD = Parkinson disease.

Analytical variables

Potential confounders were incorporated into the analyses: (1) use of antipsychotics, statins, and nonsteroidal anti-inflammatory drugs because these drugs are suspected to modify the risk of parkinsonism; (2) diseases and drugs that served as markers of general health, including asthma, myocardial infarction, stroke, depression, alcohol-related diseases,

Table 2 Association between β2AR agonists and antagonists and risk of idiopathic PD

	Cases, n	Controls, n	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
β2AR agonists	108	550	0.77 (0.62–0.95)	0.66 (0.52–0.85)
Short-acting	74	346	0.83 (0.64–1.08)	0.76 (0.56–1.02)
Salbutamol	38	148	0.97 (0.67–1.40)	0.84 (0.56–1.26)
Terbutaline	35	204	0.69 (0.48–1.00)	0.70 (0.47–1.05)
Long-acting	53	295	0.68 (0.50–0.92)	0.57 (0.40–0.82)
Salmeterol	28	169	0.62 (0.41–0.93)	0.54 (0.34–0.86)
Formoterol	22	125	0.67 (0.42–1.06)	0.59 (0.35–1.00)
β2AR antagonists	407	1,488	1.29 (1.13–1.46)	1.28 (1.10–1.47)
Propranolol	46	94	2.46 (1.64–3.69)	2.26 (1.48–3.46)
Sotalol	25	92	1.37 (0.84–2.24)	1.29 (0.76–2.19)
Metoprolol	247	841	1.37 (1.16–1.61)	1.35 (1.12–1.62)
Atenolol	47	233	1.00 (0.71–1.40)	1.04 (0.73–1.49)
Bisoprolol	17	99	0.68 (0.40–1.17)	0.67 (0.38–1.19)

Abbreviations: β2AR = β2-adrenoreceptor; CI = confidence interval; OR = odds ratio; PD = Parkinson disease.
[a] Adjusted for age, sex, and calendar time (by matched design and conditional analysis).
[b] Fully adjusted model: (1) use of antipsychotics, statins, and nonsteroidal anti-inflammatory drugs because these drugs are suspected to modify the risk of parkinsonism; (2) diseases and drugs that served as markers of general health, including myocardial infarction, stroke, depression, alcohol-related diseases, anxiolytics, hypnotics and sedatives, and selective serotonin reuptake inhibitors; (3) Charlson Comorbidity Index; and (4) highest achieved education (as a crude measure of socioeconomic status).

anxiolytics, hypnotics and sedatives, and selective serotonin reuptake inhibitors; (3) Charlson Comorbidity Index[12]; and (4) highest achieved education (as a crude measure of socioeconomic status). Any confounding effects from age, sex, and calendar time were fully adjusted for by the matching procedure and were therefore not included in the regression. A full definition of all covariates can be obtained from the corresponding author on request.

Table 3 Association between β2AR agonist use and risk of idiopathic PD

	Cases, n	Controls, n	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Exposure group				
Nonuse	2,428	9,412	1.0 (Referent)	1.0 (Referent)
Ever use	362	1,748	0.80 (0.71–0.91)	0.73 (0.63–0.85)
Long-term use	108	550	0.77 (0.62–0.95)	0.64 (0.42–0.98)
Cumulative use, y				
0–1	181	896	0.77 (0.65–0.91)	0.69 (0.57–0.82)
1–3	73	302	0.95 (0.73–1.24)	0.96 (0.70–1.31)
3–5	35	153	0.91 (0.62–1.33)	0.70 (0.40–1.22)
5–8	32	187	0.69 (0.47–1.02)	0.59 (0.30–1.18)
≥8	41	210	0.72 (0.51–1.02)	0.64 (0.28–1.42)
Incremental (per year)	362	1,748	$p = 0.71$	$p = 0.97$

Abbreviations: β2AR = β2-adrenoreceptor; CI = confidence interval; OR = odds ratio; PD = Parkinson disease.
[a] Adjusted for age, sex, and calendar time (by matched design and conditional analysis).
[b] Fully adjusted model: (1) use of antipsychotics, statins, and nonsteroidal anti-inflammatory drugs because these drugs are suspected to modify the risk of parkinsonism; (2) diseases and drugs that served as markers of general health, including myocardial infarction, stroke, depression, alcohol-related diseases, anxiolytics, hypnotics and sedatives, and selective serotonin reuptake inhibitors; (3) Charlson Comorbidity Index; and (4) highest achieved education (as a crude measure of socioeconomic status).

Table 4 Association between use (≥3 y) of β2AR agonist, inhaled corticosteroids, and inhaled anticholinergics or having received an in-hospital COPD diagnosis and risk of idiopathic PD

	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]
β2AR agonists	0.77 (0.62–0.95)	0.66 (0.52–0.85)	0.64 (0.42–0.98)
Inhaled corticosteroids	0.84 (0.66–1.06)	0.78 (0.59–1.02)	1.56 (0.97–2.50)
COPD diagnosis	0.61 (0.46–0.82)	0.51 (0.37–0.69)	0.61 (0.43–0.85)
Inhaled anticholinergics	0.47 (0.29–0.76)	0.41 (0.25–0.67)	0.56 (0.32–0.97)

Abbreviations: β2AR = β2-adrenoreceptor; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio; PD = Parkinson disease.
[a] Adjusted for age, sex, and calendar time (by matched design and conditional analysis).
[b] Fully adjusted model: (1) use of antipsychotics, statins, and nonsteroidal anti-inflammatory drugs because these drugs are suspected to modify the risk of parkinsonism; (2) diseases and drugs that served as markers of general health, including myocardial infarction, stroke, depression, alcohol-related diseases, anxiolytics, hypnotics and sedatives, and selective serotonin reuptake inhibitors; (3) Charlson Comorbidity Index; and (4) highest achieved education (as a crude measure of socioeconomic status).
[c] Adjusted as in above with additional adjustment for markers of smoking, including inhaled corticosteroids, inhaled anticholinergics, and a diagnosis of COPD.

Supplementary and sensitivity analyses

We carried out a number of preplanned supplementary and sensitivity analyses. First, long- and short-acting and individual inhaled β2AR agonists were analyzed. Second, similar analyses were performed for inhaled corticosteroids, inhaled anticholinergics, and oral β2AR antagonists. Third, in addition to adjustment for baseline comorbidity, we repeated the main analyses adjusting for markers of smoking (inhaled corticosteroids, inhaled anticholinergics, diagnosis of chronic obstructive pulmonary disease [COPD]).[13] Fourth, we restricted the analysis to or excluded the last 5 years' exposure before sampling to investigate whether timing of use relative to diagnosis provided different effect estimates. Fifth, we carried out a "new user" analysis by excluding users of any inhaled medication during 1995 to 1996 (i.e., the first 2 years of available prescription data), with the rationale that the remaining cohort was less likely to have had a substantial use of inhaled β2AR agonists before 1995. Lastly, we performed similar analyses for β2AR antagonists.

In post hoc analyses, we excluded ever users of antipsychotics to ensure no misclassification of secondary parkinsonism from antipsychotic use. Acknowledging the uncertainty in PD onset, we also performed an analysis characterizing cases and controls in terms of covariates 5 years before sampling instead of at the date of sampling. Lastly, acknowledging the large proportion of cases excluded on the basis of previous nonprimary diagnoses or previous treatment, we performed analyses allowing such to occur within 1 year from the index diagnosis (compared to 30 days in the main analysis).

All analyses were performed with Stata Release 14.2 (StataCorp, College Station, TX). The study was approved by the Danish Data Protection Agency.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

We identified a total of 9,042 patients with a primary diagnosis of PD. After exclusion of 1,865 cases with previous nonprimary PD diagnosis and 2,842 with previous PD treatment, 1,072 without ≥2 prescriptions for PD treatment in the year after diagnosis, 238 with previous history of a secondary PD diagnosis, 232 with current use of antipsychotics, and 3 with recent migrations, we obtained 2,790 eligible patients with PD (58.7% men, median age 73 years) and 11,160 matched controls (table 1).

We found an inverse association between long-term use of β2AR agonists (≥3 years) and risk for PD (OR 0.66; 95% confidence interval [CI] 0.52–0.85). Decreased risks were seen for both short- and long-acting β2AR agonists (OR 0.76 and 0.57, respectively) and individual β2AR agonists (OR 0.54–0.84) (table 2). However, an association was also found for short-term use (<1 year), and a formal test for trend (risk reduction per year of exposure) was negative (p_{trend} = 0.97) (table 3). Furthermore, we found protective associations with markers of smoking (COPD diagnosis [OR 0.51], long-term use of inhaled corticosteroids [OR 0.78], inhaled anticholinergics [OR 0.41]). In analyses simultaneously adjusted for these 4 factors, associations disappeared for corticosteroids, were attenuated for β2AR agonist use and COPD diagnosis, and remained for use of anticholinergics (table 4).

Results similar to those of the main analyses were found when we considered only the past 5 years before sampling and when we ignored the last 5 years before sampling (table 5). The analysis applying different lag times (up to 5 years) did not lead to materially different estimates, as did applying a new user design (data not shown).

Use of β2AR antagonists was associated with an increased risk of PD, which was markedly stronger for short-term use (<1 year; OR 1.97, 95% CI 1.70–2.28) compared to long-term use (≥3 years; OR 1.28, 95% CI 1.10–1.47) (table 6). In a comparison of different β2AR antagonists, the association was

Table 5 Association between β2AR agonist and risk of idiopathic PD when either ignoring or restricting to the single individual's last 5 years of exposure history

	Cases (n = 4,088), n	Controls (n = 16,352), n	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Ignoring the last 5 y of exposure				
Nonuse	2,546	10,058	1.0 (Referent)	1.0 (Referent)
Ever use	244	1,102	0.87 (0.76–1.01)	0.79 (0.67–0.92)
Long-term use	60	282	0.84 (0.63–1.11)	0.82 (0.59–1.14)
Cumulative use				
0–1 y	134	604	0.87 (0.72–1.06)	0.79 (0.65–0.97)
1–3 y	50	216	0.93 (0.68–1.27)	0.81 (0.58–1.13)
3–5 y	31	122	1.04 (0.69–1.55)	1.04 (0.67–1.61)
5–8 y	19	119	0.62 (0.38–1.01)	0.64 (0.38–1.10)
≥8 y	10	41	0.91 (0.45–1.85)	0.94 (0.44–2.03)
Incremental (per year)	244	1,102	$p = 0.72$	$p = 0.85$
Restricting to the last 5 y of exposure				
Nonuse	2,510	9,758	1.0 (Referent)	1.0 (Referent)
Ever use	280	1,402	0.78 (0.68–0.89)	0.68 (0.58–0.79)
Long-term use	83	437	0.75 (0.59–0.95)	0.68 (0.52–0.89)
Cumulative use				
0–1 y	134	681	0.76 (0.63–0.92)	0.67 (0.54–0.81)
1–3 y	63	284	0.86 (0.65–1.14)	0.71 (0.53–0.96)
3–5 y	83	437	0.75 (0.59–0.95)	0.68 (0.52–0.89)
5–8 y	n < 5	n < 5		—
≥8 y	n < 5	n < 5		—
Incremental (per year)	280	1,402	$p = 0.58$	$p = 0.66$

Abbreviations: β2AR = β2-adrenoreceptor; CI = confidence interval; OR = odds ratio; PD = Parkinson disease.
[a] Adjusted for age, sex, and calendar time (by matched design and conditional analysis).
[b] Fully adjusted model: (1) use of antipsychotics, statins, and nonsteroidal anti-inflammatory drugs because these drugs are suspected to modify the risk of parkinsonism; (2) diseases and drugs that served as markers of general health, including myocardial infarction, stroke, depression, alcohol-related diseases, anxiolytics, hypnotics and sedatives, and selective serotonin reuptake inhibitors; (3) Charlson Comorbidity Index; and (4) highest achieved education (as a crude measure of socioeconomic status).

particularly pronounced for propranolol (table 2), which showed a statistically significant inverse dose-response pattern (OR going from 5.14 to 1.48, $p_{trend} < 0.001$) (table 7).

In post hoc analyses, restriction to never users of antipsychotics returned estimates virtually unchanged compared to the main analysis, as did assessment of baseline covariates 5 years before sampling. Allowing nonprimary PD diagnoses or previous PD treatment within 1 year from the index diagnosis led to ≈25% more cases being included but virtually unchanged estimates (data not shown).

Discussion

While we replicated the association between β2AR agonist use and a decreased risk of PD, our findings can be explained by an indirect association caused by smoking. Smoking is known to be associated with reduced risk of PD.[14,15] In addition, smoking is the main cause of COPD,[16] which is treated with inhaled β2AR agonists, corticosteroids, and anticholinergics. Thus, smoking possibly constitutes the causal factor underlying the inverse association between these inhaled medications and risk of PD. This interpretation is supported by 2 findings. First, the observed risk reduction was not specific for β2AR agonists but was observed for all other markers of smoking, in particular inhaled anticholinergics and inhaled steroids. Second, incremental duration of β2AR agonists use did not correlate with corresponding reductions of the ORs, and short-term use (<1 year) already showed a strong inverse association with PD risk, which is unlikely to reflect true disease modification because neurodegeneration in PD is known to progress for many years before the clinical manifestation.[17]

Table 6 Association between β2AR antagonists and risk of idiopathic PD

	Cases, n	Controls, n	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Exposure group				
Nonuse	1,754	8,051	1.0 (Referent)	1.0 (Referent)
Ever use	1,036	3,109	1.55 (1.42–1.69)	1.58 (1.43–1.74)
Long-term use	407	1,488	1.29 (1.13–1.46)	1.28 (1.10–1.47)
Cumulative use				
0–1 y	400	934	1.97 (1.72–2.26)	1.97 (1.70–2.28)
1–3 y	229	687	1.52 (1.29–1.80)	1.53 (1.27–1.85)
3–5 y	143	516	1.31 (1.06–1.61)	1.33 (1.06–1.67)
5–8 y	150	500	1.40 (1.14–1.72)	1.41 (1.12–1.76)
8+ y	114	472	1.21 (0.96–1.52)	1.17 (0.91–1.50)
Incremental (per year)	1,036	3,109	$p < 0.001$	$p < 0.001$

Abbreviations: β2AR = β2-adrenoreceptor; CI = confidence interval; OR = odds ratio; PD = Parkinson disease.
[a] Adjusted for age, sex, and calendar time (by matched design and conditional analysis).
[b] Fully adjusted model: (1) use of antipsychotics, statins, and nonsteroidal anti-inflammatory drugs because these drugs are suspected to modify the risk of parkinsonism; (2) diseases and drugs that served as markers of general health, including myocardial infarction, stroke, depression, alcohol-related diseases, anxiolytics, hypnotics and sedatives, and selective serotonin reuptake inhibitors; (3) Charlson Comorbidity Index; and (4) highest achieved education (as a crude measure of socioeconomic status).

As for the association between β2AR antagonist use and increased risk of PD, the observation of a significantly stronger effect for short-term use compared to longer-term use is compatible with reverse causation.[18] That is, the association is likely driven by the use of β2AR antagonists for symptoms of early (yet undiagnosed) PD such as tremor.[19] In line with this interpretation, propranolol, a noncardioselective β2AR antagonist and the drug of choice for symptomatic tremor treatment,[20] showed by far the strongest association.

The primary strength of our study is the use of nationwide Danish health registries, considered to be of high validity and

Table 7 Association between propranolol and risk of idiopathic PD

	Cases, n	Controls, n	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Exposure group				
Nonuse	2,453	10,781	1.0 (Referent)	1.0 (Referent)
Ever use	337	379	4.25 (3.57–5.06)	4.18 (3.48–5.02)
Long-term use	46	94	2.46 (1.64–3.69)	2.26 (1.48–3.46)
Cumulative use				
0–1 y	219	212	5.09 (4.07–6.37)	5.14 (4.06–6.50)
1–3 y	72	73	4.28 (2.94–6.21)	4.21 (2.85–6.22)
3–5 y	28	41	3.34 (1.90–5.85)	2.95 (1.64–5.30)
5–8 y	11	25	2.17 (0.98–4.83)	2.10 (0.91–4.85)
8+ y	7	28	1.48 (0.59–3.71)	1.48 (0.58–3.82)
Incremental (per year)	337	379	$p < 0.001$	$p < 0.001$

Abbreviations: CI = confidence interval; OR = odds ratio; PD = Parkinson disease.
[a] Adjusted for age, sex, and calendar time (by matched design and conditional analysis).
[b] Fully adjusted model: (1) use of antipsychotics, statins, and nonsteroidal anti-inflammatory drugs because these drugs are suspected to modify the risk of parkinsonism; (2) diseases and drugs that served as markers of general health, including myocardial infarction, stroke, depression, alcohol-related diseases, anxiolytics, hypnotics and sedatives, and selective serotonin reuptake inhibitors; (3) Charlson Comorbidity Index; and (4) highest achieved education (as a crude measure of socioeconomic status).

used extensively for research.[3,4] A limitation is the lack of data on smoking history, precluding direct assessment of the hypothesis that smoking is in fact the underlying causal factor. Another limitation is the difficulty in identifying PD onset from registry-based resources, as evident from the large number of cases excluded due to history of nonprimary PD diagnoses or treatment. Reassuringly, less stringent inclusion criteria led to a higher number of eligible cases but results similar to the those of the main analyses.

Of note, the recently published case-control study[2] replicating the initial finding leveraged data on smoking history and did not find that smoking was the factor explaining the apparent associations. However, analyses comparable to those presented here, that is, associations for other inhaled drugs (anticholinergics, steroids) on PD risk, were not provided. Future studies on the interaction of smoking and medication use with PD risk are needed to clarify these discrepancies. Furthermore, it is important to emphasize that our analyses do not contradict the laboratory findings provided by the previous study[1] However, our findings offer an alternative explanation for the epidemiologic findings, and at present, the available epidemiologic data are not sufficient to infer any causal relationship between use of these essential medicines and risk of PD.[21]

Author contributions

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Disclosure

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References

1. Mittal S, Bjornevik K, Im DS, et al. Beta2-adrenoreceptor is a regulator of the alpha-synuclein gene driving risk of Parkinson's disease. Science 2017;357:891–898.
2. Gronich N, Abernethy DR, Auriel E, Lavi I, Rennert G, Saliba W. Beta2-adrenoceptor agonists and antagonists and risk of Parkinson's disease. Mov Disord 2018;33:1465–1471.
3. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 2015;7:449–490.
4. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. Int J Epidemiol 2017;46:798–798f.
5. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39:22–25.
6. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment 2011. Oslo: World Health Organization; 2010.
7. Sortsø C, Thygesen LC, Brønnum-Hansen H. Database on Danish population-based registers for public health and welfare research. Scand J Public Health 2011;39:17–19.
8. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38–41.
9. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
10. Støvring H, Pottegård A, Hallas J. Determining prescription durations based on the parametric waiting time distribution. Pharmacoepidemiol Drug Saf 2016;25:1451–1459.
11. Støvring H, Pottegård A, Hallas J. Refining estimates of prescription durations by using observed covariates in pharmacoepidemiological databases: an application of the reverse waiting time distribution. Pharmacoepidemiol Drug Saf 2017;26:900–908.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
13. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017;389:1931–1940.
14. Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. Arch Neurol 2007;64:990–997.
15. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016;15:1257–1272.
16. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet 2012;379:1341–1351.
17. Rascol O. "Disease-modification" trials in Parkinson disease: target populations, endpoints and study design. Neurology 2009;72:S51–S58.
18. Csizmadi I, Collet JP, Boivin JF. Bias and confounding in pharmacoepidemiology. In: Pharmacoepidemiology. New York: John Wiley & Sons, Ltd; 2007:791–809.
19. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591–1601.
20. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. Lancet Neurol 2011;10:148–161.
21. WHO Expert Committee. The Selection and Use of Essential Medicines. Oslo: World Health Organization; 2017.

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