# RESEARCH ARTICLE

# Increased Risk of Parkinson's Disease in Patients With Schizophrenia Spectrum Disorders

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**ABSTRACT: Background:** PD comorbid with schizophrenia has been considered rare because these diseases associate with opposite alterations in the brain dopamine system. The objective of this study was to investigate the risk of PD after a diagnosis of a schizophrenia spectrum disorder.

**Methods:** Regionally, this was a retrospective record-based case–control study. The cohort included 3045 PD patients treated 2004–2019 in southwestern Finland. Nationally this was a nested case–control study using registers to examine Finnish patients who received a clinically confirmed PD diagnosis 1996–2015 (n = 22,189). PD patients with previously diagnosed schizophrenia spectrum disorder (separate analysis for schizophrenia) were included. Comparable non-PD control groups were derived from both data sets. All PD diagnoses were based on individual clinical examinations by certified neurologists.

**Results:** In PD patients, the prevalence of earlier schizophrenia spectrum disorder was 0.76% in regional data and 1.50% in nationwide data. In age-matched controls, the prevalence in the regional and national data was 0.16% and 1.31%, respectively. The odds ratio for PD after schizophrenia spectrum disorder diagnosis was 4.63 (95% CI, 1.76–12.19; $P < 0.01$) in the regional data and 1.17 (95% CI, 1.04–1.31; $P < 0.01$) in the national data.

**Conclusions:** Schizophrenia spectrum disorder increases the risk of PD later in life. This association was observed in both individual patient data and nationwide register data. Therefore, despite the opposite dopaminergic disease mechanisms, schizophrenia spectrum disorder increases rather than decreases the risk of PD. The increased PD risk could be related to risk-altering effects of dopamine receptor antagonists or to the increased vulnerability of the dopamine system induced by illness phase-dependent dopamine dysregulation in schizophrenia/schizophrenia spectrum disorder. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

**Key Words:** Parkinson's disease; schizophrenia; comorbidity; dopamine

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Parkinson's disease (PD) and schizophrenia (SCZ) are associated with differential involvement of the brain dopamine (DA) system. PD is characterized by a prominent and progressive loss of mesostriatal DA,[1,2] whereas the original DA hypothesis of SCZ assumed an overactive DA system, especially in the mesolimbocortical DA pathways.[3–5] In addition, the primary pharmacotherapies for the 2 conditions appear contrasting: PD symptoms can be alleviated with DA receptor agonists, and SCZ is commonly treated with DA receptor antagonists.[6,7]

We now know that the involvement of DA in the neurobiology of PD as well as SCZ is far more complex than originally thought. Current views on the role of DA in SCZ assume a pathway-specific and partly state-dependent dysregulation of the DA system, which is combined with an imbalance of brain excitatory/inhibitory networks such as glutamate and GABA dysfunction.[3–5,8–12] Importantly, SCZ is an etiologically heterogeneous disorder, and DA dysregulation is not seen in all patients.[8–10,13] In fact, there may be a subgroup of "normodopaminergic" patients with schizophrenia[14] who are clinically nonresponsive to conventional DA D2 receptor antagonist drugs but may benefit from clozapine. Such a group represents up to 25%–30% of the patients with SCZ,[15] further complicating hypotheses on the involvement of DA in psychotic disorders.

It has been proposed that SCZ and PD could coexist in some patients because of differently affected dopaminergic system regions that act independently: overactive dopaminergic transmission in the nigrostriatal and mesolimbic pathways in SCZ and decreased dopaminergic transmission in the nigrostriatal pathway in PD.[16,17] On the other hand, given the opposite effects in the DA system, it could be hypothesized that the 2 diseases seldom coexist, assuming that major symptoms of one condition would neutralize the other via opposite dopaminergic effects in the brain. There are 2 reported register studies that have provided highly variable estimates of this comorbidity, with odds ratios (ORs) ranging from 3 to 48, suggesting the possibility of increased risk of PD in SCZ patients.[18,19] However, these studies did not exclude patients with drug-induced parkinsonism, which is a common condition in patients with SCZ who are treated with neuroleptics. Thus, the prevalence of comorbidity was likely inflated, and in general, the relevant literature mostly includes single case reports, underlining the rarity of PD and SCZ comorbidity.[16,17,20–33]

To obtain an accurate estimate, the psychotic symptoms as a manifestation of neurodegenerative diseases and parkinsonism as a manifestation of antipsychotic medications would need to be excluded from the analysis. A critical factor is the partially overlapping phenotypes of PD and SCZ. Advanced PD is often associated with psychotic symptoms,[34,35] and parkinsonism may be drug induced in patients with schizophrenia spectrum disorder (SCD). Therefore, in register studies, it is difficult to reliably differentiate concurrent SCD and PD diagnoses in a patient at a certain point.

We considered it possible that the risk of PD is altered in SCD patients because of putatively opposite dopaminergic disease mechanisms. We clarified this issue using 2 methodological approaches. In part I (regional data) of the present study (retrospective record-based case–control study), case by case we investigated individual patients who first developed SCD and later were diagnosed with PD, and we took into account misdiagnoses and drug treatments. In part II (national data), we performed a nationwide nested case–control study using national registers to examine clinically verified Finnish PD patients diagnosed with SCD across a 43-year exposure assessment time. Finally, we compared the results of the 2 methodologically different analyses.

## Material and Methods

### Part I: Regional Data

The study population consisted of all PD patients who were treated between January 1, 2004, and July 31, 2019, at Turku University Hospital district in southwestern Finland. PD patients were identified from the digital database on the basis of ICD-10 code G20*. The diagnostic criteria of PD are homogeneous in different parts of Finland and are based on the Finnish Current Care Guidelines of PD.[36] To receive drug reimbursement for PD, the diagnosis must be made by a certified neurologist using either the UK Brain Bank criteria or the MDS clinical criteria[37] on the basis of clinical examination, and primary symptoms and possible imagine findings must be reported. Thus, all diagnoses of PD in the present data (regional and national) were based on these criteria. Subsequently, we identified PD patients who had a concurrent diagnosis of SCD (ICD-10 code F2*, including schizotypal disorder, persistent delusional disorders, and schizoaffective disorders) and PD patients with a specific diagnosis of SCZ (ICD-10 code F20*). After identifying all patients with comorbidities, we manually reviewed each patient's electronic health records (EHRs) to exclude diagnosis coding errors and to confirm that the diagnoses were based on valid clinical symptoms and signs of PD and SCD. The control population was identified from the same digital database, and controls were age- and sex-matched (1:1 ratio) with the PD population. Patients with ICD-10 code F2* or F20* were identified from the control population, and their EHRs were similarly reviewed. Based on the information of EHRs, patients were excluded if the initial diagnosis of PD or SCD was considered incorrect or uncertain because of

the development of atypical clinical features as evaluated by a certified neurologist or a psychiatrist. In addition, patients were excluded if the SCD diagnosis was made after age 60 years or fewer than 6 years before the PD diagnosis. The age limit of 60 years was used to exclude very-late-onset SCD because psychotic symptoms among aged people are more likely to be associated with a prodromal phase of another neurodegenerative disease, such as Alzheimer's disease, frontotemporal degeneration, or Lewy body dementia (very late onset: onset after age 60).[38] To verify the results, we performed an additional analysis using the same exclusion criteria otherwise but excluding patients diagnosed with SCD/SCZ after age 45 years. The 6-year lag was used to exclude PD patients treated with antiparkinsonian drugs that could induce psychosis (such as DA agonists) before the formal diagnosis of PD and to exclude Lewy body disease spectrum patients who could experience early hallucinations and are misdiagnosed with SCD. The 6-year lag was also used to ensure that the 2 diagnoses were clearly chronologically separate episodes and to reduce the likelihood of including patients who had either PD with prominent psychiatric symptoms or SCD with prominent motor symptoms. The collected information from EHRs included age at PD diagnosis, age at onset of psychotic symptoms, sex, primary motor symptoms of PD, primary symptoms of SCZ/SCD, and last known neurological/psychiatric pharmacotherapy. If available in regional data, diagnostic brain imaging results, including dopamine transporter imaging ($[^{123}I]$FP-CIT SPECT), were also evaluated and recorded for patients who carried both SCD and PD diagnoses.

Logistic regression was used to compare the prevalence of SCD and SCZ diagnoses between the PD patient group and the control group. Statistical analyses were performed with SAS 9.4. for Windows (Cary, NC). The project received a registry study permit from the Turku University Hospital (T204/2019). Because the study did not involve patient contacts, approval from the Ethics Committee was not required.

## Part II: National Register Data

People who received drug reimbursement for PD between 1996 and 2015 and were community dwelling at the time of diagnosis were identified from the Special Reimbursement register. Therefore, some of the PD patients from regional data were also included in the national data. The diagnostic statements, which were centrally reviewed and confirmed in the Social Insurance Institution of Finland, contained anamnestic information and clinical evaluations of the patient's symptoms. Reimbursement can also be obtained for other PD-related conditions, but all PD diagnoses need to be made by a certified neurologist on the basis of

medical history and clinical examination using either UK Brain Bank criteria or MDS clinical criteria, as explained above in part I.

The original study population included 29,942 people who received drug reimbursement for PD. A total of 7753 patients (25.9%) were excluded for the following reasons: age at the time of PD diagnosis < 35 years (n = 53), special reimbursement for PD drugs for reasons other than PD (ICD-10 code for reimbursement other than G20; n = 1244) or possibility of misdiagnosis (n = 6456); see Figure 1. People who were within the 2-year time window of the diagnosis date (before and/or after) had exclusion diagnoses indicating diagnoses other than PD (including Alzheimer's disease, secondary parkinsonism, other neurodegenerative diseases, and movement disorders) as presented previously[39] were excluded.

For every PD patient, up to 7 matched controls without PD were identified from the register that includes all Finnish residents. The matching criteria were age (1-year caliper), sex, and hospital district within the country on the PD diagnosis date of the referent case (index date). Otherwise, the same exclusion criteria were used as for cases, but dementia from PD (ICD-10 code F02.3), resulting in 2–7 controls for each PD patient (n = 148,009).

Data on SCD were obtained from the Care Register for Health Care from 1972 until the index date. SCD diagnoses made after the age of 60 years or fewer than 6 years before the PD diagnosis (similar to part I) were not included in the analyses. As in part I, a confirmatory analysis of patients diagnosed with SCD/SCZ younger than age 45 years was performed. The validity of the SCZ diagnoses in this register is high.[40,41] SCZ was identified using ICD-10 codes F20* (excluding F20.4), ICD-9 codes 2950–2953, 2956, and 2959, and ICD-8 codes 2950–2953, 2956, 2958, and 2959. SCD was identified with ICD-10 codes F2*, ICD-9 codes 295, 297, 298, 3010, and 3012, and ICD-8 codes 295, 297, 298, 29,999, 3010, and 3012.

In addition, the data on the use of PD medications and antipsychotic medications were collected from the Special Reimbursement register on 3 times (2 years before PD diagnosis, 2 years after PD diagnosis, and 5 years after PD diagnosis) for patients with comorbidity of PD and SCD.

Associations between exposure and outcome were assessed with conditional logistic regression, which accounted for the matching of patients and controls, using Stata MP14.0.

## Results

### Part I: Regional Data

In PD patients (n = 3045), the prevalence of earlier SCZ was 0.46% (n = 14), and the prevalence of SCD
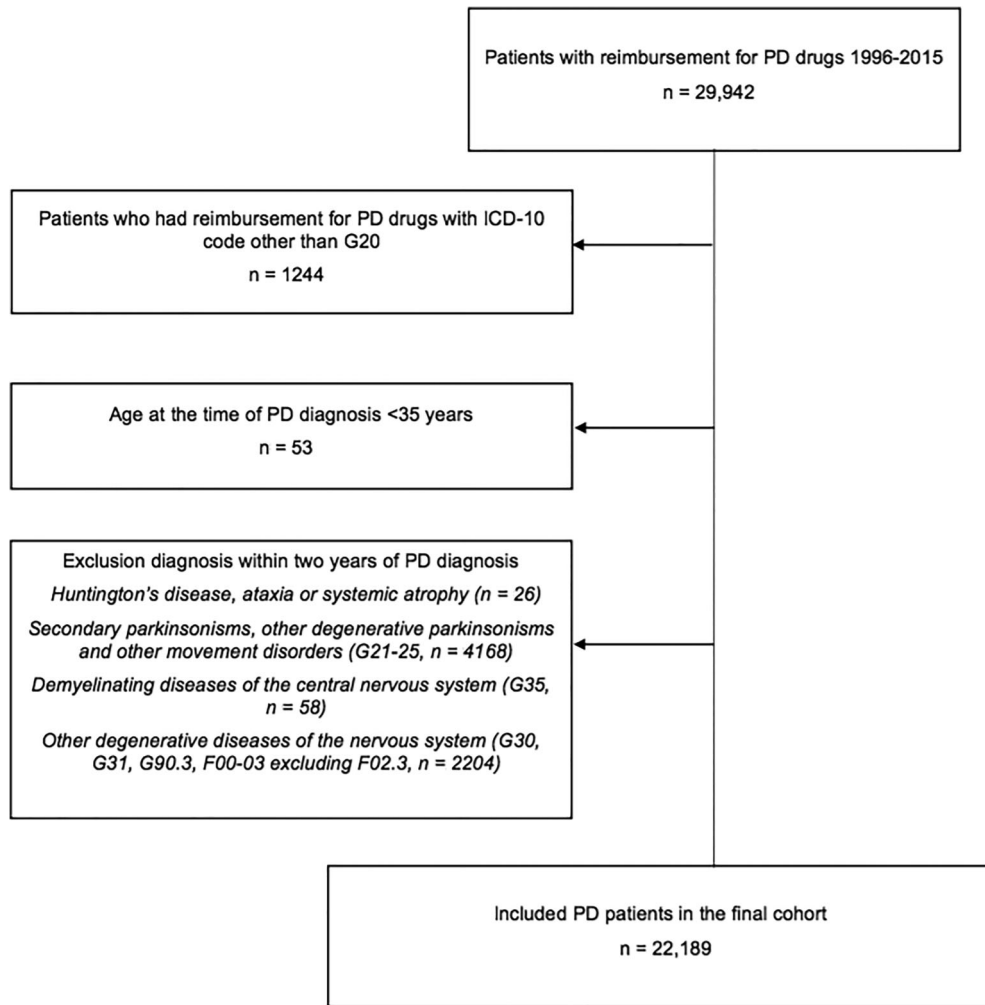
**FIG. 1.** Flow chart of study inclusion and exclusion in part II (national data)

**TABLE 1.** Sample sizes and odds ratios of PD risk in regional and national data

| | Regional data | | | National data | | |
|---|---|---|---|---|---|---|
| DG | PD patients (n = 3045), n (%) | Non-PD patients (n = 3045), n (%) | OR (95% CI), P | PD patients (n = 22,189), n (%) | Non-PD patients (n = 148,009), n (%) | OR (95% CI), P |
| F20 | 14 (0.46) | 3 (0.10) | 4.68 (1.35–16.31), P = 0.02 | 144 (0.65) | 902 (0.61) | 1.09 (0.91–1.30), P = 0.34 |
| F2* | 23 (0.76) | 5 (0.16) | 4.63 (1.76–12.19), P < 0.01 | 332 (1.50) | 1943 (1.31) | 1.17 (1.04–1.31), P < 0.01 |

DG, diagnosis; F20, schizophrenia; F2*, schizophrenia spectrum disorders; PD, Parkinson's disease; OR, odds ratio; CI, confidence interval.

was 0.76% (n = 23). In age- and sex-matched controls (n = 3045), the prevalence of SCZ and SCD was 0.10% (n = 3) and 0.16% (n = 5), respectively. The OR for PD after SCZ diagnosis and PD after SCD diagnosis was 4.68 (1.35–16.31, P = 0.02) and 4.63 (1.76–12.19, P < 0.01); see Table 1. The demographic characteristics of the patients and information about their drug therapies are presented in Table 2, and the clinical characteristics of the patients are presented in Table S1.

The original search identified 3045 PD patients, of whom 78 had concurrent SCD diagnoses. Fifty-five

patients were excluded. The reasons for exclusion are reported in Supplementary results. The mean ± SD age of the 23 included patients at the time of diagnosis of PD was 61.7 ± 10.7 years (median, 61 years), and the mean age of patients at the onset of psychotic symptoms was 36.7 ± 13.9 years (median, 38 years). Age at the onset of psychotic symptoms was not available for 3 patients, but EHR data indicated that the symptoms had appeared several years before PD diagnoses. Eleven of 23 patients had undergone diagnostic DA transporter imaging ([$^{123}$I]FP-CIT SPECT), and all of whom

**TABLE 2.** Demographic and clinical characteristics of Parkinson's disease and schizophrenia spectrum disorder patients in the regional data (part I) together with last known drug therapies for each condition

| | ID | Age at SCD | Age at PD | Sex (M/W) | Medication | | Striatal DAT binding | SCD diagnosis |
| | | | | | PD | SCD | | |
|---|---|---|---|---|---|---|---|---|
| PD+ | 1 | 22 | 44 | M | LCE, Rasagiline | Clozapine | Abnormal | Paranoid schizophrenia |
| | 2 | 23 | 60 | W | LC, LB | Quetiapine | — | Paranoid schizophrenia |
| | 3 | 29 | 70 | W | LC | Quetiapine | Abnormal | Paranoid schizophrenia |
| | 4 | 30 | 58 | W | Refused medical treatment | Olanzapine | Abnormal | Paranoid schizophrenia |
| | 5 | 38 | 71 | W | LC | — | — | Paranoid schizophrenia |
| | 6 | 46 | 58 | W | LCE | Olanzapine | — | Paranoid schizophrenia |
| | 7 | YA | 66 | M | LCE | Quetiapine | Abnormal | Paranoid schizophrenia |
| | 8 | 54 | 61 | M | LCE | Sulpiride, risperidone | — | Simple schizophrenia |
| | 9 | 47 | 53 | W | LCE, LC, Amantadine | Refused medical treatment | Abnormal | Delusional disorder |
| | 10 | 48 | 71 | M | LC, Selegiline | Quetiapine | Abnormal | Delusional disorder |
| | 11 | 49 | 66 | W | LC, LB | Quetiapine | — | Delusional disorder, UNP |
| | 12 | 55 | 77 | W | LC, LB | Quetiapine | — | Delusional disorder, UNP |
| | 13 | YA | 59 | M | LC, LB | Lithium, olanzapine, valproate | — | Hebephrenic schizophrenia |
| | 14 | 19 | 38 | W | LCE, LB, Pramipexole, Amantadine | Clozapine | — | Hebephrenic schizophrenia |
| | 15 | 19 | 66 | M | LC, Biperiden | Olanzapine, quetiapine | Abnormal | Hebephrenic schizophrenia |
| | 16 | NA[a,b] | 64 | W | LCE | Clozapine | Abnormal | Unspecified SCZ |
| | 17 | NA[a,c] | 52 | W | LC | — | Abnormal | Residual schizophrenia |
| | 18 | NA[a,b] | NA | M | LC | Thioridazine | — | Other acute predominantly delusional psychotic disorders |
| | 19 | YA | 52 | M | LB, Selegiline | Clozapine | Abnormal | SAD depressive type |
| | 20 | YA | 61 | M | LC | Clozapine | Abnormal | Schizotypal disorder |
| | 21 | YA | 79 | M | LC | — | — | UNP |
| | 22 | 21 | 52 | M | LC, LB | Quetiapine, clozapine | — | Acute schizophrenia-like psychotic disorder, UNP, recurrent depressive disorder, current episode severe with psychotic symptoms |
| | 23 | 51 | 79 | W | LC | Quetiapine | — | Unspecified schizophrenia, SAD depressive type |
| PD− | 24 | NA[c] | — | M | — | Quetiapine, perphenazine, olanzapine | | Paranoid schizophrenia |
| | 25 | YA | — | M | — | Quetiapine | | Unspecified schizophrenia |
| | 26 | YA | — | W | — | Olanzapine | | Unspecified schizophrenia |
| | 27 | 35 | — | M | — | Quetiapine, risperidone | | SAD, manic type; bipolar affective disorder, unspecified |
| | 28 | 41 | — | W | — | Risperidone | | SAD mixed type |

LB, levodopa-benserazide; LC, levodopa-carbidopa; LCE, levodopa-carbidopa-entacapone; NA, not available; PD, Parkinson's disease; SAD, schizoaffective disorder; SCD, schizophrenia spectrum disorder; SCZ, schizophrenia; UNP, unspecified nonorganic psychosis; YA, young adulthood.
Striatal dopamine transporter (DAT) binding refers to diagnostic brain [123I]FP-CIT SPECT.
[a]Several years before PD diagnosis.
[b]Younger than age 60.
[c]Younger than age 45.

had a striatal dopaminergic defect concordant with a diagnosis of PD (Table 2). Four patients without DA transporter imaging had used antipsychotic medications that can potentially cause drug-induced parkinsonism (Table 2; ID6, ID8, ID13, and ID18). However, all these patients had a long-term positive levodopa response (for several years), and PD diagnoses were confirmed repeatedly by a neurologists over years of clinical follow-up.

Twelve individuals with SCD diagnoses were identified from the non-PD control population, and 7 of these patients were excluded (the reasons for exclusion are reported in the Supplementary results). Three of the 5 SCD patients had specific diagnoses of SCZ, and the

other 2 patients had diagnoses of schizoaffective disorder. Psychotic symptoms started younger than age 40 years in 3 patients and at age 41 in 1 patient; data were not available for 1 patient.

After excluding patients who were diagnosed with SCD/SCZ after age 45 years, the prevalence of SCZ and SCD in PD patients was 0.33% (n = 10) and 0.46% (n = 14), respectively. In age- and sex-matched controls, the prevalence was 0.10% (n = 3) and 0.16% (n = 0.16%), respectively. The OR for PD after SCZ diagnosis and PD after SCD diagnosis was 3.34 (0.92–12.15, $P$ = 0.07) and 2.81 (1.01–7.81, $P$ = 0.048), respectively. If no patients had been excluded from the analysis, the search would have identified 78 PD patients with SCD diagnoses and 12 non-PD patients with SCD diagnoses, and the primary result would have been essentially the same (OR, 6.64; 95% CI, 3.61–12.23; $P < 0.01$).

## Part II: National Register Data

In PD patients (n = 22,189), the prevalence of earlier SCZ was 0.65% (n = 144), and the prevalence of SCD was 1.50% (n = 332). In non-PD patients (n = 148,009), the prevalence of earlier SCZ and SCD was 0.61% (n = 902) and 1.31% (n = 1943), respectively. The OR for PD after SCZ and PD after SCD was 1.09 (0.91–1.30, $P$ = 0.34) and 1.17 (1.04–1.31, $P < 0.01$), respectively (Table 1).

The mean age at the index date was 70.9 ± 9.7 years for PD patients and 70.5 ± 9.7 years for controls. In the PD population, the mean age at SCD diagnosis and SCZ diagnosis was 52.2 ± 16.3 years and 46.5 ± 15.1 years, respectively. In the control population, the mean age at SCD diagnosis and SCZ diagnosis was 49.1 ± 15.0 years and 45.7 ± 14.0 years, respectively. A total of 54.8% of PD patients and 55.1% of controls were men.

In PD patients, the prevalence of SCZ diagnosed younger than age 45 years was 0.44% (n = 97), and the prevalence of SCD diagnosed younger than age 45 years was 0.90% (n = 199). The corresponding prevalence in the control population was 0.39% (n = 574) and 0.75% (n = 1117), respectively. The OR for PD after SCZ and PD after SCD was 1.16 (0.94–1.44, $P$ = 0.18) and 1.23 (1.06–1.44, $P < 0.01$), respectively.

In PD patients with previously diagnosed SCD, the percentage of antipsychotic users was relatively constant over time, as 72.0% of patients (n = 239) used antipsychotic drugs 2 years before PD diagnosis, 67.8% (n = 225) 2 years after PD diagnosis, and 74.1% (n = 246) 5 years after PD diagnosis); see Table S2. The most commonly used antipsychotic drugs were quetiapine, olanzapine, and risperidone. However, 97.9% of patients (n = 325) used antiparkinsonian drugs 5 years after PD diagnosis, and 88.9% used levodopa-carbidopa or levodopa-benserazide, and also 17.5% used levodopa-carbidopa-entacapone after 5 years (Table S2).

## Discussion

The results of this study indicate that SCD increases the risk of PD later in life. The same association was seen in regional case–control data and in a nationwide nested case–control study with community-dwelling Finnish individuals as a source population. Therefore, despite putatively opposite dopaminergic disease mechanisms, SCD does not decrease the risk of PD but rather seems to increase the risk. Furthermore, the association was observed despite the increased mortality of patients with severe SCZ diluting the effect. We postulate that the results could be explained by the increased vulnerability of the DA system in the residual phases of SCD induced by an illness phase-dependent mechanism including DA dysregulation.

There are no previous case–control studies of the risk of PD in patients with SCZ or SCD. The 2 previously published register-based studies investigated a broad spectrum of comorbid diseases and conditions associated with SCZ, not specifically PD. The first study from Scotland suggested that viral hepatitis, constipation, and PD were overrepresented in patients with SCZ, but the study did not control for PD-specific confounding factors such as drug-induced parkinsonism in patients with SCZ.[18] The second study from Spain had the same limitation, but it pointed to an increased risk of infectious diseases, diabetes, and PD in patients with SCZ.[19] The OR for PD was exceptionally high (OR, 47.89; 95% CI, 44.49–51.55; $P < 0.001$), implying a large effect size.[42] Because PD and SCD have overlapping phenotypical features and because iatrogenic parkinsonism in SCD and psychotic symptoms in PD are common, we focused only on PD risk and used stringent exclusion criteria for patients, including the use of time limits for diagnoses/ages and the exclusion of patients with secondary parkinsonism. Although there remain sources of error in the register data, the diagnoses in regional analysis were individually confirmed or discarded. The combined results from more than 20,000 Finnish PD patients showed that there is an increased risk for PD among SCD patients. In SCZ, the increased risk was observed only in the more detailed regional data, which could be because of diagnostic classification: a diagnosis of SCD may often be the initial registered diagnosis in patients with SCZ.

It is important to note that the present results are related to an increased PD risk after SCD, not vice versa. In addition, the results are not related to the concurrent coexistence of the 2 conditions. Therefore, the results demonstrate the risk-altering effects of SCD that occur several years after the emergence of psychotic symptoms. SCZ is associated with increased mortality, and the life expectancy of SCZ patients is decreased by 15–25 years compared with the general population.[43,44] This effect is linked to an increased risk of

cardiovascular diseases, autoimmune diseases, infections, chronic obstructive pulmonary disease, and cancers in patients with SCZ.[44,45] Thus, patients with the most severe SCD were not included in our analyses because of premature death before the typical age of PD onset. Despite the diluting effect of increased mortality, the effect of increased PD risk was clearly observed. It is possible that the greater subcortical release of DA and D2 receptor augmentation[46] in the most severe cases of SCZ leads to a particularly increased PD risk over time, a risk that is neutralized by the increased mortality in the most severe cases. This theory could be tested in later studies by classifying and studying SCD patients according to the severity of their symptoms. Currently, the present results should be interpreted to suggest that late-life PD risk is increased in patients with mild/moderate SCD/SCZ. Increased risk of developing PD has also been reported in patients with bipolar disorder.[47,48]

Antipsychotic drugs induce parkinsonism by blocking postsynaptic dopaminergic receptors,[49,50] but it has been suggested that exposure to neuroleptic drugs could cause PD by inducing a long-term hypodopaminergic state that predisposes patients to nigral cell degeneration.[49] SCZ patients also appear to have lower tonic DA release throughout the disease, including oversensitive phasic DA release during psychotic episodes.[3,4] This could lead to a chronic hypodopaminergic state, as the frequency of psychotic episodes decreases, and negative and cognitive symptoms tend to dominate in later or residual phases of SCZ.[51] According to another hypothesis, neuroleptic drugs could predispose patients to the development of degenerative PD because of neurotoxic effects on dopaminergic neurons through the inhibition of the mitochondrial respiratory chain, an increase in DA turnover, and the enhanced production of neurotoxic free radicals[49]; there are also findings that support increased PD risk after neuroleptic exposure.[52,53] Therefore, the increased PD risk in patients with SCD could be related to neuroleptic exposure, to a chronic hypodopaminergic state after tonic-phasic dopaminergic fluctuations in active SCD, or to a combination of the two. Moreover, some SCZ patients respond poorly to conventional DA D2 receptor antagonists[14] but do respond to clozapine. It has been proposed that some of these patients are "normodopaminergic" and may not have a dysregulated DA system in the first place but rather an imbalance of glutamate/GABAergic systems.[15] It is possible that some of the patients treated with clozapine in our PD cohorts are putative normodopaminergic SCZ patients who developed PD later in life via progressive loss of mesostriatal DA.

A limitation in any register-based PD study is the suboptimal diagnostic accuracy. This was also clearly seen in our data, as we excluded 25% of PD patients from the regional data because of incorrect or uncertain PD diagnosis. However, if we assume that a similar level of diagnostic uncertainty is also the case for the main sample of 3045 patients, the effect would in fact be amplified. In particular, the possibility of drug-induced parkinsonism in some patients is a limitation of our study because a large proportion of patients were still medicated with antipsychotic drugs at the time of PD diagnosis (although mostly with atypical quetiapine/olanzapine/risperidone). However, it is important to note that nearly all PD patients (97.9%) with earlier SCD remained on levodopa or other PD medications 5 years after PD diagnosis. This suggests a long-term positive response to dopaminergic medications in these patients, supporting diagnoses of PD. Moreover and more importantly, all PD diagnoses in both regional and national data were based on individual clinical examinations by neurologists using diagnostic criteria reducing the possibility of drug-induced parkinsonism misdiagnosed as PD. It is also noteworthy that the prevalence of SCD and SCZ was lower in the regional data than in the national data. This is probably because of intrinsic differences in the data sets, as the regional cohort included patients from the university hospital database, whereas national data also included patients treated by general practitioners and private practitioners. The prevalence observed in our national data is consistent with the reported estimates of lifetime prevalence of SCZ (0.4%–1.3%).[54–57] The same intrinsic differences in the data sets may explain the difference in the mean ages of PD populations between regional and national data, as, for example, patients treated outside the university hospital are usually older and are included only in national data increasing the mean age of the PD population of national data compared with regional data. The OR for PD following diagnoses of SCZ and SCD was also larger in the regional data than in the national data. This may be because of the large difference in sample sizes between regional and national data, which can induce analytical bias in logistic regression.[58] However, the primary result of increased PD risk was clearly also observed in our considerably larger national data.

In summary, the results indicate an increased risk of hypodopaminergic PD after being diagnosed with hyperdopaminergic SCD. This increase could be associated with risk-altering dopamine receptor antagonists or disease-related neurobiological effects that increase vulnerability. Further studies are needed to investigate whether the severity of psychotic symptoms or the type or dosing of antipsychotic drugs impact the risk of PD.

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# Supporting Data

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