RESEARCH ARTICLE

Bipolar Disorder as a Long-Term Risk Factor for Parkinson's Disease: A Nationwide Case–Control Study

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ABSTRACT: Background: Previous studies suggest an association between bipolar disorder (BD) and an increased risk of Parkinson's disease (PD), but the long-term temporal relationship remains unclear. Particularly, it is unclear whether the risk of PD is influenced by the duration since BD diagnosis.

Objective: The aim was to examine the association between BD and PD across time windows extending up to 35 years before PD diagnosis.

Methods: This nationwide, register-based, nested case–control study from Finland included 22,189 incident PD patients diagnosed between 1996 and 2015 and 148,009 age-, sex-, and region-matched controls. BD diagnoses from 1972 up to the PD diagnosis date (index date) were identified from health-care registers. Conditional logistic regression was used to estimate the association between BD and PD in various exposure windows with a 0- to 35-year lag. Main analyses considered BD diagnosed at least 8 years before the index date (8-year lag).

Results: BD was diagnosed before the index date in 172 (0.87%) PD patients and 509 (0.34%) controls. Elevated PD risk was evident already with a 20-year lag between BD and PD diagnoses, with a trend toward increased risk even at 30 years. In the main analysis using the 8-year lag, BD diagnosis was associated with over a twofold higher relative risk of PD (adjusted odds ratio, 95% confidence interval: 2.32, 1.85–2.91).

Conclusions: BD is associated with a significantly elevated risk of PD, observable decades before PD onset. These findings suggest that BD may reflect a long-term vulnerability to PD rather than a short-term prodromal state, emphasizing the need to explore shared pathophysiological mechanisms. © 2025 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: bipolar disorder; nested case–control study; Parkinson's disease; risk factor

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder defined by its cardinal motor symptoms, including bradykinesia, rigidity, and tremor, and neuropathologically by dopaminergic neuronal loss in the substantia nigra pars compacta and widespread deposition of α-synuclein-containing Lewy bodies.[1] In addition to its motor phenotype, PD patients have a wide range of non-motor symptoms, such as constipation, hyposmia, and depression, which can precede motor onset by

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years or even decades, reflecting the multisystem nature of PD pathology.[2]

Bipolar disorder (BD) is a chronic mental disorder that leads to repetitive episodes of either mania/hypomania or depression. Recent epidemiological studies have shown that people with BD have a higher likelihood of developing PD compared to the general population.[3] The BD–PD link is also supported by study on hypomanic manifestations in patients in different stages of PD.[4] Although the pathophysiology of BD remains incompletely understood, one potential link between BD and PD is dopaminergic dysregulation, as it has been suggested to occur also in BD.[5] Furthermore, BD and PD share certain clinical features, in both motor and psychiatric domains. Psychomotor symptoms of differing severity are relatively common in mood episodes of BD,[6] including various catatonic symptoms such as rigidity and mutism, as well as psychomotor retardation and even catatonic stupor in severe bipolar depression. In addition, depression itself is recognized as a possible prodromal feature of PD,[7] suggesting a potential shared neurobiological vulnerability. Throughout the course of PD, a wide range of psychiatric symptoms, such as hallucinations, psychosis, or apathy, further emphasize the complex interaction between psychiatric disorders and neurodegeneration in PD.[2] The topic is important, as based on a recent meta-analysis psychiatric comorbidity, including BD, is associated with poorer PD prognosis.[8]

Since the meta-analysis by Faustino and colleagues, which included three cross-sectional studies and four cohort studies,[3] the association between BD and PD has been further evaluated in four cohort studies[9-12] and one case–control study.[13] However, many of these studies were limited by relatively short follow-up durations, typically ≤10 years,[11,13,14] potentially underestimating the long-term risk trajectory. Additionally, other important methodological limitations remain. Some previous studies may have included broader diagnostic categories, such as parkinsonism of various etiologies, due to differences in case definitions or registry coding practices.[15-17] Although this does not necessarily reflect diagnostic error, it may partially explain the higher effect estimates reported in those studies compared to ours, where we applied exclusion criteria designed to increase diagnostic specificity for idiopathic PD. Another key challenge in PD risk factor research is the prodromal period, during which patients may exhibit subtle motor and nonmotor symptoms that do not yet meet diagnostic criteria of PD but may lead to increased health-care contact. This detection bias could result in higher prevalence of BD among PD patients, simply due to increased likelihood of diagnosis rather than a true etiological relationship. Longer follow-up studies are therefore needed to disentangle true risk factors from preclinical manifestations and confounding effects.

To address these limitations, we investigated the association between BD and subsequent PD in a large, nationwide, nested case–control setting. In particular, we examined the impact of different BD exposure periods, aiming to clarify the temporal dynamics of this association and to evaluate whether BD may represent a long-term risk factor.

Patients and Methods

Study Population and Identification of Patients and Controls

The Finnish Parkinson's disease study (FINPARK) is a case–control study nested into the population of Finland, including N = 22,189 incident PD patients diagnosed during 1996 to 2015 who were community dwelling at the time of diagnosis. The identification of cases was based on the national Special Reimbursement Register and Care Register for Health Care as described earlier.[18] The cases were identified based on eligibility to reimbursement for antiparkinsonian drugs, with PD (ICD-10 code G20) recorded as the reason for reimbursement. To be included, individuals had to be at least 35 years at the time of PD diagnosis and have no recorded diagnoses within the 2 years before or after the PD diagnosis that could mimic parkinsonian symptoms (eg, other neurodegenerative or movement disorders).[18] To be eligible for reimbursement, the PD diagnosis needs to be confirmed in specialist settings, and the diagnostic statements are centrally reviewed and confirmed in the Social Insurance Institution (Kela). During the case identification period, the PD diagnosis criteria were consistent with the UK Brain Bank criterion.[19] In the Finnish care guidelines for PD, a comprehensive clinical evaluation by a neurologist is required for diagnosis, with specific diagnostic criteria recommended (the UK Brain Bank Criteria until about 2015, MDS Clinical Criteria currently endorsed). Reimbursement for PD drugs requires a clinically verified diagnosis made by a neurologist, accompanied by a written confirmation from the diagnosing neurologist. Consequently, all PD patients in FINPARK were diagnosed by certified neurologists/neurology residents supervised by a certified neurologist.

On the date of PD diagnosis (index date), up to 7 age- (±1 year), sex- and region-matched controls per case (N = 148,009) were identified from the Kela database covering all residents in Finland. The controls were not allowed to have dopaminergic PD drug purchases (Anatomical Therapeutic Chemical classification ATC code N04B) or reimbursement code for PD drugs ever before the index date or 12 months after and during the month of index date. The exclusion criteria of

controls were otherwise identical to those of the patients, but controls with dementia due to PD (ICD-10 F02.3) were also excluded.

Data from Care Register for Health Care (1972–2015), Special Reimbursement Register (1972–2015) and Prescription Register (1995–2015), linked by pseudonymized personal identification numbers, were provided by the register maintainers. Permission for using the data was obtained from the National Health and Social Data Permit Authority Findata. The research team can access only pseudonymized data, and study participants were not contacted. Therefore, according to Finnish legislation separate ethics approval or informed consent was not needed.

BD Diagnosis

Information on diagnosed BD in specialized health-care settings was obtained from hospital discharges of Care Register for Health Care using ICD-8 codes (1972–1986), ICD-9 codes (1987–1995), and ICD-10 codes (1996–2015). Diagnoses during 1998 to 2015 were also retrieved from specialized health-care outpatient visits using ICD-10 codes. Specific diagnosis codes utilized in different time periods are presented in Table SS1. In addition to this diagnosis-based definition, we used lithium dispensing as a proxy marker for BD and conducted complementary analyses. Lithium is predominantly prescribed for the treatment of BD in psychiatric practice in Finland. Lithium use alone or as an adjuvant medication for unipolar depression or part of combination medications for psychotic disorders is relatively uncommon.[20] Therefore, lithium dispensing can be considered to provide an alternative indicator of BD. Data on lithium use between 1995 and 2015 were extracted from the Prescription Register using ATC code N05AN01. This register contains information on all reimbursed prescriptions dispensed in outpatient settings nationwide. However, it does not include medications administered in hospitals or long-term institutional care settings.

To avoid and to evaluate the impact of reverse causality and detection bias, we considered different exposure assessment periods, with BD diagnosed at least 8 years before the index date being the primary analysis. We performed sensitivity analyses for alternative exposure periods ranging from at least 35 years before to ever before the index date. Similar analyses were performed for BD definition based on recorded diagnosis or lithium dispensation.

Confounders

Potential confounding factors were identified using nationwide administrative registers. Information on comorbidities, occupational social class, and history of agricultural work based on employment history was extracted. Information on data sources and details on specific codes for data extraction are provided in Table SS1. Analyses were adjusted for cardiovascular diseases, diabetes, asthma, cancer, traumatic brain injury, substance abuse, admission with psychiatric comorbidity other than BD, and number of hospital days (any cause) since 1972 until 15 years before the index date. Occupational social class categorization was based on classification from Statistics Finland, and included the following categories: self-employed, upper-level employees, lower-level employees, manual workers, pensioners, and others. History of agricultural work was determined using the same data source.

Statistical Analyses

Association of BD and PD was investigated using conditional logistic regression, which accounts for matching. Patients with or without PD were matched for age, sex, and university hospital district. In addition to crude odds ratios (OR), we adjusted the analyses for comorbidities and occupational social class. Because inclusion of occupational social class and history of agricultural work introduced collinearity, we performed sensitivity analyses adjusting for agricultural work instead of occupational social class. As the confounder assessment period partially overlaps with the exposure assessment period and may result in adjustment for intermediates (and thus underestimation of association), we performed sensitivity analyses adjusting for confounders measured during the first 5 years of study period (1972–1976). To evaluate whether the association between BD and PD differed between sexes, we assessed by fitting a model with an interaction term in the fully adjusted main analysis. As there was no statistical evidence for a different association in men and women (P for BD*sex interaction term in a fully adjusted model with an 8-year lag of 0.864), sex-stratified analyses were not performed. Association between BD and age at PD diagnosis was assessed using linear regression. Analyses were conducted using Stata MP17.2.

Results

Characteristics of patients and controls are presented in Table 1. Altogether 172 people with PD (0.78%) and 509 (0.34%) controls had a BD diagnosis before the index date. Number and prevalence of BD diagnosis using different lag periods are presented in Table S2. The median age at BD diagnosis was 55.4 years for PD patients and 54.3 years for controls (Table 1). When the broader definition of BD was used (lithium purchase or diagnosis), the prevalence of BD increased to 225 (1.01%) in PD patients and 662 (0.45%) in

TABLE 1 *Characteristics of PD cases and controls*

Characteristic	PD patients n = 22,189	Controls n = 148,009	*P*-values
Age on index date, mean (SD)	70.9 (9.7)	70.5 (9.7)	Matched
Sex			Matched
Women	10,040 (45.2)	66,496 (44.9)	
Men	12,149 (54.8)	81,513 (55.1)	
Age at BD diagnosis, median (interquartile range)	55.4 (48.7–64.2)	54.3 (46.6–61.9)	0.37
Age at BD diagnosis/lithium initiation, median (interquartile range)	56.7 (49.2–65.0)	54.5 (47.1–61.9)	0.073
Occupational social class			<0.001
Self-employed	5274 (23.8)	33,938 (22.9)	
Upper-level employees	3888 (17.5)	22,541 (15.2)	
Lower-level employees	5337 (24.1)	34,608 (23.4)	
Manual worker	6237 (28.1)	45,104 (30.5)	
Pensioner	1146 (5.2)	8048 (5.4)	
Other	73 (0.3)	665 (0.4)	
Agricultural work	3693 (16.6)	23,401 (15.8)	0.012
Comorbidities			
Cardiovascular diseases (15 y before the index date)	4441 (20.0)	27,918 (18.9)	<0.001
Diabetes (15 y before the index date)	440 (2.0)	2507 (1.7)	0.002
Asthma/COPD (15 y before the index date)	781 (3.5)	4937 (3.3)	0.16
Cancer (15 y before the index date)	439 (2.0)	2791 (1.9)	0.35
Traumatic brain injury (15 y before the index date)	295 (1.3)	2003 (1.4)	0.77
Substance abuse (15 y before the index date)	274 (1.2)	2552 (1.7)	<0.001
Admission due to psychiatric comorbidity other than BD in 1972–1976	106 (0.5)	691 (0.5)	0.83
Hospital days in 1972–1976			0.46
None	15,184 (68.4)	101,877 (68.8)	
1–10	4314 (19.4)	28,662 (19.4)	
11–20	1484 (6.7)	9541 (6.4)	
≥21	1207 (5.4)	7929 (5.4)	

Note: Data are given as n (%) unless otherwise indicated.
Abbreviations: PD, Parkinson's disease; SD, standard deviation; BD, bipolar disorder; COPD, chronic obstructive pulmonary disease.

controls with approximately a 1-year increase in age at BD diagnosis in PD patients, whereas the median age in controls was not affected. History of agricultural work, cardiovascular diseases, and diabetes were more common in PD patients, whereas substance abuse was less common (Table 1). However, the differences were small. A similar pattern was observed for comorbidities assessed during the first 5 years of the study period (Table S3). PD patients with a history of BD were younger than those without BD (mean age, 95% CI: 67.9, 66.7–69.0 and 70.9, 70.8–71.0, for PD patients with and without BD, respectively, $P < 0.001$).

BD diagnosis was associated with higher risk of PD in the main analyses considering BD diagnosed at least 8 years before the index date (crude OR: 2.28, 95% CI: 1.82–2.86; Table 2). Similar results were observed with the exposure assessment period spanning a maximum of 5 years or until the index date. The association

TABLE 2 *Association between BD diagnosis and risk of PD with BD based on diagnosis only*

Assessment period for BD	Patients n = 22,189 n (%)	Controls n = 148,009 n (%)	Crude OR (95% CI)*	Comorbidity-adjusted OR (95% CI)**	Comorbidity- and occupational social class-adjusted OR (95% CI)***
At least 8 y before the index date					
No	22,087 (99.5)	147,706 (99.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	102 (0.5)	303 (0.2)	2.28 (1.82, 2.86)	2.35 (1.87, 2.95)	2.32 (1.85, 2.91)
At least 5 y before the index date					
No	22,059 (99.4)	147,622 (99.7)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	130 (0.6)	387 (0.3)	2.29 (1.88, 2.80)	2.35 (1.92, 2.87)	2.32 (1.85, 2.91)
Ever before the index date					
No	22,017 (99.2)	147,500 (99.7)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	172 (0.8)	509 (0.3)	2.31 (1.94, 2.75)	2.38 (1.99, 2.83)	2.36 (1.98, 2.81)

Note: Data are given as ORs with 95% CIs.
Abbreviations: BD, bipolar disorder; PD, Parkinson's disease; OR, odds ratio; CI, confidence interval.
*Accounts for matching factors: age, sex, and university hospital.
**Additional adjustment of crude model for cardiovascular diseases, diabetes, asthma, cancer, traumatic brain injury, substance abuse, admission with psychiatric comorbidity other than BD, number of hospital days (any cause).
***Additional adjustment of comorbidity-adjusted model for occupational social class.

remained after adjustment for comorbidities and occupational social class. Similar results were observed using a broader definition of BD (Table 3). Sensitivity analyses in which comorbidities were measured during the first 5 years of the study period provided similar results, as did adjustment for history of agricultural work instead of occupational social class (Tables S4 and S5).

When the crude ORs for exposure assessment periods with a 1-year interval ranging from 35 years before the index date through the index date were plotted, the association between BD diagnosis and higher risk of PD became apparent for BD diagnosed over 20 years before the index date, although the OR point estimates were suggestive of an increased risk for BD diagnoses recorded 30 years before the index date (Fig. 1A).

TABLE 3 *Association between BD diagnosis and risk of PD with BD based on diagnosis or lithium purchase*

Assessment period for BD	Patients n = 22,189 n (%)	Controls n = 148,009 n (%)	Crude OR (95% CI)*	Comorbidity-adjusted OR (95% CI)**	Comorbidity- and occupational social class-adjusted OR (95% CI)***
At least 8 y before the index date					
No	22,067 (99.5)	147,607 (99.7)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	122 (0.5)	402 (0.3)	2.06 (1.68, 2.53)	2.13 (1.73, 2.61)	2.11 (1.72, 2.59)
At least 5 y before the index date					
No	22,024 (99.3)	147,502 (99.7)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	165 (0.7)	507 (0.3)	2.22 (1.86, 2.64)	2.28 (1.91, 2.73)	2.26 (1.89, 2.70)
Ever before the index date					
No	21,964 (99.0)	147,347 (99.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	225 (1.0)	662 (0.4)	2.32 (1.99, 2.70)	2.39 (2.05, 2.79)	2.38 (2.04, 2.77)

Note: Data are given as ORs with 95% CI.
Abbreviations: BD, bipolar disorder; PD, Parkinson's disease; OR, odds ratio; CI, confidence interval.
*Matching factors age, sex, and university hospital district accounted for.
**Additional adjustment of crude model for cardiovascular diseases, diabetes, asthma, cancer, traumatic brain injury, substance abuse, admission with psychiatric comorbidity other than BD, number of hospital days (any cause).
***Additional adjustment of comorbidity-adjusted model for occupational social class.

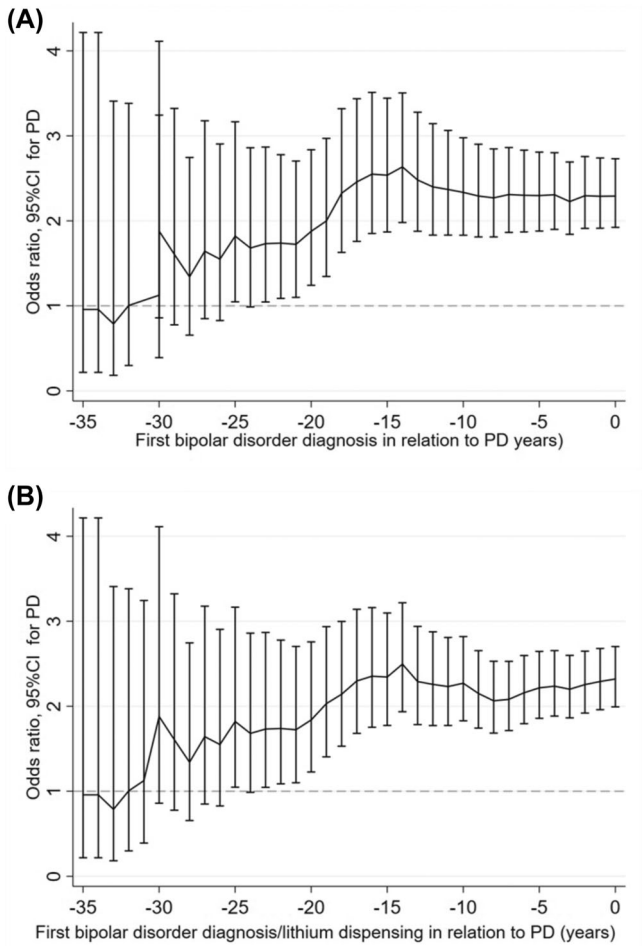

FIG. 1. Odds ratio and 95% CI (confidence interval) for the association between (**A**) bipolar disorder based on diagnosis and PD (Parkinson's disease) and (**B**) bipolar disorder based on diagnosis or lithium purchase using different exposure assessment windows.

Similar results were observed for the broader definition of BD diagnosis (Fig. 1B).

Discussion

The findings of this nationwide, nested, case–control study provide evidence for a significantly increased risk of PD among individuals with a prior diagnosis of BD. Particularly, the association was observed even when BD was diagnosed more than two decades before the PD diagnosis, suggesting that BD, or the treatment of BD, may leave a lasting neurobiological imprint—one that increases vulnerability to neurodegenerative processes later in life. To the best of our knowledge, this is the first study to assess PD risk among BD patients with exposure assessment period extending up to 35 years prior to the PD diagnosis.

Our results are in line with previous epidemiological studies reporting elevated PD risk in BD populations. The meta-analysis of Faustino and colleagues, which included four cohort and three cross-sectional studies, reported a pooled OR of 3.35 (95% CI: 2.00–5.60) for PD in individuals with BD.[3] Interestingly, studies with longer follow-up durations (>9 years) reported weaker associations (OR: 1.75, 95% CI: 1.36–2.26) compared to those with shorter follow-up or cross-sectional designs.[3] However, these earlier studies differed methodologically from ours. For instance, Marras and colleagues compared patients on lithium monotherapy to those on antidepressants, using medication as a surrogate for BD, whereas Nilsson and colleagues used comparison groups with osteoarthritis or diabetes and did not exclude secondary parkinsonism.[15,17] In contrast, our study utilized a median exposure assessment period of 35 years (range: 24–44 years), with strict exclusion criteria to increase diagnostic specificity for idiopathic PD. Consistent with earlier studies,[21] PD patients with BD history were diagnosed at an earlier age.

In a case–control study by Schrag and colleagues, the association between BD and PD was observed (OR: 3.80, 95% CI: 2.82–5.14), albeit with a shorter follow-up duration (mean: 6.0 years).[13] Similarly, a recent UK Biobank study showed that the hazard ratio (HR) for PD among BD patients was higher during the first 10 years of follow-up (HR: 2.93, 95% CI: 1.69–5.07), with a modest reduction after applying a 10-year lag (HR: 2.22, 95% CI: 1.41–3.49).[10] Our own findings using an 8-year lag (OR: 2.32, 95% CI: 1.85–2.91) are consistent with these results but provide stronger evidence for a long-term risk relationship. The weaker association observed in our study for analyses with no lag time, compared to earlier studies,[14,16,22] likely reflects differences in case determination. Mood symptoms, particularly depression or mixed affective episodes, may represent prodromal features of PD rather than an independent BD diagnosis. The impact of this is likely stronger in analyses and previous studies with a shorter lag time. However, the prodromal period of PD may extend up to two decades. The FINPARK study applied stringent diagnostic criteria, excluding individuals with secondary or atypical parkinsonism. In contrast, prior studies often relied on broader outcome definitions,[16] including self-reported PD diagnoses,[22] potentially inflating effect estimates due to broader definition.

The biological basis of the association between BD and PD remains unclear, but several plausible mechanisms merit consideration. First, dopaminergic dysregulation, central to both disorders, may represent a shared vulnerability. The dopamine hypothesis of BD suggests state-dependent dysregulation: dopaminergic downregulation during depressive phases and dopaminergic upregulation during mania.[5] Over time, this dysregulation could contribute to long-term alteration in dopaminergic tone, potentially increasing susceptibility

to nigrostriatal degeneration. Furthermore, PD patients may experience mood fluctuations resembling manic or depressive states during dopaminergic treatment cycles,[23] strengthening the role of dopamine in mood fluctuations. Even though BD neuropathology is poorly understood,[24] BD has increasingly been recognized as a neuroprogressive disorder,[25] with repeated mood episodes, particularly mania, associated with cumulative neural damage,[26] which could target basal ganglia circuitry increasing vulnerability for PD. Moreover, compulsive behaviors, which may be observed in certain phases of both BD and PD, including impulsivity, disinhibition, and affective instability, may reflect dysfunction in orbitofrontal and frontostriatal networks,[27] which are critically involved in decision-making and behavioral regulation. This aligns with the broader view of frontocortical vulnerability as a common substrate for both mood dysregulation and the emergence of compulsive or impulsive behaviors across these disorders. Another possibility is that the pharmacological treatment of BD influences PD risk. Some studies have suggested that medications used in BD, such as antipsychotics or mood stabilizers, may be an independent risk factor for the development of PD in BD.[10,28] Lithium may cause drug-induced parkinsonism, and Marras and colleagues found that patients using lithium are at increased risk of developing PD.[17] On the contrary, lithium has been thought to have neuroprotective effects,[25] and lithium use is positively associated with cortical thickness in BD.[29] However, in our analysis we did not observe differences in PD risk increase between BD patients based on BD diagnoses and lithium users, which suggests that lithium use does not explain the association. Comorbid medical conditions may further mediate the BD–PD link. BD patients often experience higher rates of cardiometabolic disorders, including diabetes or cardiovascular diseases,[30] which are associated with increased PD risk.[31] However, in our study the association remained after having been adjusted for these comorbidities. Finally, genetic pleiotropy may also play a role: certain genetic variants may increase susceptibility to both mood disorders and neurodegenerative disorders.[32] For example, a higher prevalence of family history of PD has been observed in patients with both BD and PD, suggesting potential shared heritable factors.[33]

An increased risk of PD has also been reported in other psychiatric disorders,[12,34-38] particularly major depression and schizophrenia. Depression affects up to 50% of PD patients and is now recognized as a potential prodromal symptom as well as an independent risk factor for PD.[35,36] Longitudinal studies have shown that depression may precede PD by up to 25 years,[37] and similar findings have been reported for schizophrenia, despite contrasting dopamine profiles in the two conditions.[38] Interestingly, BD appears to confer an even higher PD risk than major depression or schizophrenia. Huang and colleagues found a 51% greater risk of PD in BD patients compared to those with major depressive disorder.[12] Harrison and Luciano also reported higher PD risk in BD relative to both major depressive disorder (OR: 2.15, 95% CI: 1.99–2.33) and schizophrenia (OR: 1.26, 95% CI: 1.12–1.42), despite higher antipsychotic use in the schizophrenia group.[9] This pattern of elevated neurodegenerative risk in BD is not limited to PD. BD has also been associated with increased risk of dementia,[10] as have schizophrenia and major depression,[39,40] suggesting a broader vulnerability to neurodegeneration in severe mental illness. The cumulative burden of illness, repeated affective and psychotic episodes, and possible medication effects may contribute to long-term structural and functional brain changes.[29,41] It is plausible that BD patients with psychotic features, or those with prominent cognitive symptoms, represent a particularly high-risk subgroup for PD. According to the present study and earlier results,[21] the association between BD and PD is similar in men and women, but the literature studies are limited, and future studies are needed.

Strengths of our study include the use of a large, well-characterized, nationwide dataset; the long observational period; and adjustment for confounders, including socioeconomic position. We were able to evaluate the impact of BD on PD risk across multiple time windows and adjust for a range of potential confounders. However, some limitations should be acknowledged. BD diagnoses were available from 1972 onward, but before 1998, only inpatient data were recorded, potentially underestimating BD prevalence. Lithium prescription data were available only from 1995. Therefore, we may not have captured the earliest date for BD diagnoses, which would explain the relatively high age at BD diagnosis. Due to the high mortality in BD, including elevated suicide risk,[30,42] survivor bias may have led to underestimation of the true association. As a nested case–control study, our study is restricted to those people with BD who survived until their PD diagnosis/index date, which could partially explain why the prevalence of BD in our study population is slightly lower than the expected general BD prevalence that is more than 1%.[42] We were also unable to differentiate between BD type 1 and type 2, or evaluate the effects of possible psychotic symptoms or the predominance of manic or depressive mood episodes in medical history, which may have a different relationship with PD risk, and future cohort studies with more detailed clinical phenotyping are needed. In addition, studies assessing the impact of genetic factors, or with more detailed phenotyping, including dopamine transporter imaging data, could provide further insights into this association as these were not available in our study.

In conclusion, this study provides evidence for a long-term association between BD and increased risk of PD, with elevated risk observed even decades before PD onset. These findings suggest that BD may represent a predisposing state that reflects shared or interacting pathophysiological mechanisms with PD, rather than being merely a short-term consequence of diagnostic or treatment-related confounding. The temporal pattern of risk supports the hypothesis of a durable neurobiological vulnerability, potentially involving dopaminergic dysregulation, cumulative neuronal damage, or overlapping genetic or environmental factors. Further studies should aim to disentangle the relative contributions of these mechanisms and to identify specific subgroups of BD patients at the highest risk, which may provide important insights into early disease processes common to major psychiatric and neurodegenerative disorders.

Author Roles: (1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.
E.J.: 1A, 1B, 1C, 3A, 3B.
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V.K.: 1A, 1B, 1C, 2A, 3A, 3B.
J.H.: 1A, 1C, 3B.
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Data availability statement

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

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Supporting Data

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