Increased Risk of Depressive and Anxiety Disorders in Relatives of Patients With Parkinson Disease

Gennarina Arabia, MD, MSc; Brandon R. Grossardt, MS; Yonas E. Geda, MD, MSc; Justin M. Carlin, BA;
James H. Bower, MD; J. Eric Ahlskog, PhD, MD; Demetrius M. Maraganore, MD; Walter A. Rocca, MD, MPH

Context: Relatives of patients with Parkinson disease (PD) have an increased risk of PD and other neurologic disorders; however, their risk of psychiatric disorders remains uncertain.

Objective: To study the risk of depressive disorders and anxiety disorders among first-degree relatives of patients with PD compared with first-degree relatives of controls.

Design, Setting, and Participants: In a population-based, historical cohort study, we included 1000 first-degree relatives of 162 patients with PD and 850 first-degree relatives of 147 controls. Both patients with PD and controls were representative of the population of Olmsted County, Minnesota.

Main Outcome Measures: Documentation of psychiatric disorders was obtained for each relative separately through a combination of telephone interviews with the relatives (or their proxies) and review of their medical records from a records-linkage system (family study method). Psychiatric disorders were defined using clinical criteria from the *DSM-IV* or routine diagnoses.

Results: We found an increased risk of several psychiatric disorders in first-degree relatives of patients with PD compared with first-degree relatives of controls (hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.21-1.95; $P<.001$). In particular, we found an increased risk of depressive disorders (HR, 1.45; 95% CI, 1.11-1.89; $P=.006$) and anxiety disorders (HR, 1.55; 95% CI, 1.05-2.28; $P=.03$). The results were consistent in analyses that adjusted for type of interview, excluded relatives who developed parkinsonism, or excluded relatives who developed both a depressive disorder and an anxiety disorder.

Conclusion: These findings suggest that depressive disorders and anxiety disorders may share familial susceptibility factors with PD.

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Author Affiliations:
Department of Health Sciences Research, Divisions of Epidemiology (Drs Arabia, Geda, and Rocca) and Biostatistics (Messrs Grossardt and Carlin), Department of Psychiatry and Psychology (Dr Geda), and Department of Neurology (Drs Bower, Ahlskog, Maraganore, and Rocca), Mayo Clinic College of Medicine, Rochester, Minnesota. Dr Arabia was on leave from the Institute of Neurological Sciences, Italian National Research Council, Cosenza, Italy, at the time of the study.

DEPRESSIVE DISORDERS AND anxiety disorders are common in patients with Parkinson disease (PD), particularly in patients affected by the akinetic-rigid form of PD.[1-6] In addition, symptoms of depression and anxiety not only occur after the onset of motor symptoms but also may develop many years, even decades, before the onset of PD.[7-9] One possible interpretation of these findings is that depressive disorders and anxiety disorders are not simply reactions to the disability caused by PD, but they share genetic susceptibility factors with PD.[8] If we assume that there are shared genetic factors, we would expect relatives of patients with PD to have a higher risk of these psychiatric disorders than relatives of controls. Therefore, as part of the Mayo Clinic Family Study of Parkinson's Disease,[10-15] we investigated the risk of depressive disorders and anxiety disorders among first-degree relatives of patients with PD compared with first-degree relatives of controls.

METHODS

STUDY DESIGN

This study included 2 cohorts of relatives: (1) first-degree relatives of patients with incident PD from Olmsted County, Minnesota, and (2) first-degree relatives of controls free of PD, parkinsonism, or tremor from the same Olmsted County population. The first-degree relatives from both cohorts were followed up from birth to onset of psychiatric disorders, death, telephone interview for the study, or last medical record information. Documentation of psychiatric disorders was obtained through telephone interviews and review of medical records (family study method). Details about the overall study design were reported elsewhere.[10,12] All aspects of the study that in-

volved contact with participants were approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center. Relatives examined as part of the study (to assess neurologic outcomes) signed an informed consent form. Most relatives included in this study classified themselves as white when presented with the standard US Census options.[12] Information on ethnicity was collected because it was considered related to genetic or nongenetic familial susceptibility factors.

PATIENTS WITH PD AND CONTROLS

The medical records–linkage system of the Rochester Epidemiology Project was used to identify all individuals who resided in Olmsted County who developed PD from 1976 through 1995. Details about the study population, the identification of incident cases, and the diagnostic criteria for PD are reported elsewhere.[16,17] Our clinical classification of patients with PD through medical record review was found to be valid compared with a direct examination by a movement disorders specialist.[18] Each patient with PD was individually matched by age (±1 year) and sex to a general population control who resided in Olmsted County and was free of PD, other parkinsonism, or tremor of any type in the index year (year of onset of PD in the matched case). Records of potential controls were reviewed by a neurologist (D.M.M.) to confirm their eligibility. Our exclusion of parkinsonism in controls through medical record review was found to be valid compared with a direct examination by a movement disorders specialist.[18] The presence of dementia or other neurologic diseases was not an exclusion criterion. Similarly, the presence of depressive disorders, anxiety disorders, or other psychiatric disorders was not an exclusion criterion. Further details about the selection of controls have been reported elsewhere.[12,18]

We asked patients with PD and controls (or their proxies) to provide a full listing and contact information of all first-degree relatives.[12] For some of the families who resided in Olmsted County and who had no available informant, the pedigree composition was obtained from the obituaries archived at the Olmsted County Historical Society and the records-linkage system, as described elsewhere.[12,19] Because the 2 cohorts of relatives were originally designed to investigate the risk of parkinsonism and because parkinsonism is rare in individuals younger than 40 years, we excluded relatives who were younger than 40 years at the time of the study. However, for those relatives who were included, we studied the onset of psychiatric disorders at any time from birth onward. In addition, we excluded stepparents, stepsiblings, and adopted relatives because they were not biologically related. We also excluded half-siblings.

ASCERTAINMENT OF PSYCHIATRIC DISORDERS AMONG RELATIVES

Psychiatric disorders were ascertained using a combination of 2 methods: (1) telephone interviews and (2) review of medical records from a records-linkage system. The telephone contact was made by 1 of 3 specifically trained research assistants and was direct whenever possible; for deceased or otherwise incapacitated relatives (eg, deaf, cognitively impaired, or terminally ill), we contacted the best available proxy (most knowledgeable person in the family).[12]

The interview included a structured questionnaire for depressive disorders. We first asked, "Have you ever suffered (Did he or she ever suffer) from a depression that interfered with your (his or her) work or daily activities?" Relatives or their proxies who reported depression were asked details about age at occurrence, treatments (drugs or electroconvulsive therapy), and hospitalizations. Information about other psychiatric diseases, including anxiety disorders, was collected through an open-ended question: "Have you ever had (has he or she ever had) any psychiatric disease or psychiatric problem?" We also administered the Geriatric Depression Scale (GDS; short version with 15 items) to all relatives interviewed directly. This scale has been previously validated.[20]

Independent of the interview described herein, relatives who had resided in Olmsted County for part or all of their life were studied through review of inpatient and outpatient medical records in the records-linkage system of the Rochester Epidemiology Project.[12,19] In addition, for relatives who resided outside Olmsted County and reported a psychiatric disease (directly or by proxy), we obtained written authorization, and we requested copies of their pertinent medical records from physicians or medical institutions throughout the United States to strengthen the diagnostic certainty. All medical records from within or outside the records-linkage system were abstracted by a trained neurologist (G.A.) with the assistance of a board-certified psychiatrist (Y.E.G.).

The relatives (or their proxies), the 3 telephone interviewers, and both physicians (G.A. and Y.E.G.) involved in medical records abstracting were kept uninformed of the relation of relatives to patients with PD or controls to prevent bias (masking). In particular, the scripted introductory telephone conversation between the interviewers and the relatives (or their proxies) described the study only in general terms ("a family study of neurological diseases"), specified that the study involved relatives of individuals both with and without neurologic diseases, and did not reveal whether the individuals were or were not affected by a neurologic disease (to protect confidentiality within the family and to maintain masking). Similarly, the abstracting of medical records was kept masked by involving a study coordinator who organized the abstracting.

DIAGNOSTIC CRITERIA FOR PSYCHIATRIC DISORDERS

For depressive disorders, we required that the psychiatric symptoms documented in the medical records of the patient met the criteria of the *DSM-IV* for major depressive disorder, dysthymic disorder, or depressive disorder not otherwise specified or that the physician had made an explicit diagnosis of depression or dysthymia.[21] For anxiety disorders, we required that the psychiatric symptoms documented in the medical records of the patient met *DSM-IV* criteria for 1 specific type of anxiety disorder or that the physician had made 1 of the following descriptive diagnoses: anxiety neurosis, anxiety state, anxiety reaction, nervous tension, nervous exhaustion, tension state, generalized anxiety disorder, psychoneurosis, nervousness, obsessive-compulsive disorder or neurosis, phobias of any type, and panic attacks or disorder. These terms were used historically by physicians involved in the records-linkage system to describe anxiety disorders.[8] For other psychiatric disorders, we required that the psychiatric symptoms documented in the medical records of the patient met *DSM-IV* criteria or that the physician had made an explicit diagnosis of schizophrenia, somatoform disorder, personality disorder, dissociative disorder, or adjustment disorder.

For individuals who had no pertinent medical record, psychiatric disorders were defined as a previous diagnosis reported by the individual or proxy at interview. As markers of severity of the psychiatric symptoms, we obtained information on diagnosis by a psychiatrist and on use of specific medications (eg, antidepressants). For relatives with multiple sources of information, the final diagnosis was based on the best available evidence. For relatives with positive information from both the interview and medical record, we gave priority to the medical record; however, for relatives with discordant information, a positive report was given priority regardless of source.

RELIABILITY AND VALIDITY

The ascertainment of depressive disorders relied on both medical records and interviews (**Table 1**). To assess the reliability of our method to ascertain depressive disorders (a combination of telephone interview and medical records), all relatives who resided within driving distance (a 120-mile radius centered in Rochester, Minnesota) and were 60 years or older at the time of interview were invited to undergo an independent clinical examination (at Mayo Clinic or at home).[12] One of 3 neurologists (J.H.B., J.E.A., and D.M.M.) who were kept unaware of the psychiatric diagnosis assigned by our method examined 139 relatives, of whom 132 were previously interviewed directly and 7 via proxy. Both current and past depression were investigated during the clinical examination. The agreement between our method and a direct examination was adequate (agreement=83.5%; κ=0.51; 95% confidence interval [CI], 0.34-0.68). The agreement was similar when considering relatives of patients with PD and relatives of controls separately.

In addition, agreement on the diagnosis of depressive disorders between telephone interview (direct or proxy) and independent review of medical records from the records-linkage system was 80.7% (κ=0.32; 95% CI, 0.23-0.42) in a sample of 610 relatives who had both sources of data. The limited agreement was partly due to the inadequacy of some medical records to document current depression. However, the agreement was similar when considering relatives of patients with PD and relatives of controls separately.

Finally, we compared the performance on the GDS (score ≥6) with our method of ascertainment of depressive disorders (a combination of telephone interview and medical records) in 320 relatives with adequate information. Although the overall agreement was good (85.3%), the κ was only 0.15 (95% CI, 0.005-0.30). The disagreement was partly due to the ascertainment of past depression by our method but not by the GDS. Therefore, we did not use the GDS score to define depressive disorders.

Contrary to depressive disorders, the ascertainment of anxiety disorders was based almost completely on the review of medical records (98.9% in relatives of patients with PD and 100.0% in relatives of controls; Table 1). Therefore, a comparison of methods of ascertainment could not be performed.

STATISTICAL ANALYSIS

First-degree relatives of patients with PD or controls were included in the analyses from birth through the onset of a specific psychiatric disorder (eg, depressive disorder), death, telephone interview for the study, or last medical record information, whichever came first. For 56 relatives of patients with PD and 32 relatives of controls with unknown age at onset of depressive disorders and for 1 relative of a patient with PD with unknown age at onset of anxiety disorders, we used age at death, age at telephone interview, or age at last medical record information (carry-forward imputation).

We obtained cumulative incidence curves of psychiatric disorders using the Kaplan-Meier method and estimated hazard ratios (HRs) and their 95% CIs using Cox proportional hazards models with age as the time scale.[22] Because the study outcomes clustered in some of the families of patients with PD or controls, we accounted for the clustering in all statistical models.[23] The proportionality assumption in the Cox proportional hazards models was tested graphically and by introducing a time-dependent coefficient.[22] Primary analyses were conducted on the overall sample and in strata defined by age at onset of patients with PD (in tertiles), clinical type of PD (tremor-dominant vs akinetic-rigid), presence of depressive disorders

or anxiety disorders, type of relative, and sex of the relative. Stratification by clinical type of PD was prompted by findings from previous studies[5,6] and was based on clinical features abstracted from medical records, as detailed elsewhere.[24]

We also conducted secondary analyses restricted to outcomes confirmed by a psychiatrist or that required treatment as well as several sets of sensitivity analyses. Data were analyzed with SAS statistical software, version 8.2 (SAS Institute Inc, Cary, North Carolina), and all statistical testing was performed at the conventional 2-tailed α level of .05.

RESULTS

Details about the participation of the 162 patients with PD and the 147 controls in the construction of pedigrees and the identification of first-degree relatives have been reported elsewhere.[12] Table 1 gives details about the inclusion of first-degree relatives of patients with PD and

Table 1. Inclusion of First-Degree Relatives in the Study and Documentation of Psychiatric Diagnoses

Variable	No. (%) of Patients		P Value
	Patients With PD	Controls	
Inclusion of first-degree relatives			
All relatives identified	1278 (100.0)	1207 (100.0)	
Relatives included[a]	1000 (78.2)	850 (70.4)	<.001
Direct interview	412 (41.2)	274 (32.2)	<.001
With medical records	362 (36.2)	227 (26.7)	<.001[b]
Without medical records	50 (5.0)	47 (5.5)	...
Proxy interview	506 (50.6)	491 (57.8)	.002
With medical records	226 (22.6)	231 (27.2)	...
Without medical records	280 (28.0)	260 (30.6)	...
Only medical records	82 (8.2)	85 (10.0)	...
Documentation of psychiatric diagnoses among first-degree relatives			
All relatives with depression[c]	200 (100.0)	125 (100.0)	
Medical records	88 (44.0)	45 (36.0)	.26[d]
Only direct interview	65 (32.5)	51 (40.8)	...
Only proxy interview	47 (23.5)	29 (23.2)	...
All relatives with anxiety[c]	90 (100.0)	52 (100.0)	
Medical records[e]	89 (98.9)	52 (100.0)	.45

Abbreviation: PD, Parkinson disease.

[a] We explored the variables that influenced the inclusion of relatives in the study with multivariable stepwise logistic regression models. We considered family size (≤7 members vs otherwise), sex of relative, vital status of relative (dead vs alive), relationship of relative (parent, sibling, or offspring), age of patient with PD or control (in tertiles), year of birth of patient with PD or control (in tertiles), and relative of patient with PD or relative of control status. The final model showed higher inclusion for relatives from smaller families, women relatives, living relatives, siblings and offspring (compared with parents), and relatives of younger patients. Even after accounting for all of these variables, relatives of patients with PD were included more frequently than relatives of controls (odds ratio, 1.37; 95% confidence interval, 1.13-1.68; P=.002).

[b] P value comparing frequencies of relatives with direct interview with medical records, direct interview without medical records, proxy interview with medical records, proxy interview without medical records, and relatives with only medical records.

[c] For the documentation of psychiatric diagnoses, medical records were given priority. For relatives with diagnoses from both record and interview, only record was counted.

[d] P value comparing frequencies of diagnoses confirmed by medical records, with only direct interview, or with only proxy interview.

[e] Only 1 relative of a patient with PD and no relatives of controls had anxiety disorders documented only via interview (direct interview).

Table 2. Risk of Psychiatric Disorders Among First-degree Relatives of Patients With PD Compared With Relatives of Controls

| | No. (%) of Events | | | |
	Relatives of Patients With PD (n=1000)	Relatives of Controls (n=850)	HR (95% CI)	P Value
Psychiatric Disorder				
Any psychiatric disorder	257 (25.7)	154 (18.1)	1.54 (1.21-1.95)	<.001
Any mood disorder	207 (20.7)	129 (15.2)	1.46 (1.12-1.90)	.005
Depressive disorders[a]	200 (20.0)	125 (14.7)	1.45 (1.11-1.89)	.006
Bipolar disorders	7 (0.7)	4 (0.5)	1.53 (0.37-6.37)	.56
Anxiety disorders	90 (9.0)	52 (6.1)	1.55 (1.05-2.28)	.03
Schizophrenia	12 (1.2)	4 (0.5)	2.64 (0.88-7.90)	.08
Somatoform disorders	18 (1.8)	4 (0.5)	3.93 (1.36-11.36)	.01
Personality disorders	13 (1.3)	7 (0.8)	1.63 (0.61-4.37)	.33
Dissociative disorders	1 (0.1)	0	NA[b]	. . .
Adjustment disorders	24 (2.4)	10 (1.2)	2.16 (1.04-4.50)	.04

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available; PD, Parkinson disease.
[a] Depressive disorders included major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified. Results were consistent after excluding depressive disorder not otherwise specified (HR, 1.41; 95% CI, 1.02-1.94; *P*=.04).
[b] The HR could not be estimated because no relatives of controls had a dissociative disorder.

Table 3. Risk of Depressive Disorders Among First-degree Relatives of Patients With PD Compared With Relatives of Controls

Type of Relatives	No. of Relatives at Risk	No. (%) With Depressive Disorders	HR (95% CI)	P Value
Analyses stratified by type of diagnosis[a]				
Relatives of controls, all diagnoses	850	125 (14.7)	1 [Reference]	. . .
Relatives of patients with PD, all diagnoses	1000	200 (20.0)	1.45 (1.11-1.89)[b]	.006
Relatives of controls, by psychiatrist	850	22 (2.6)	1 [Reference]	. . .
Relatives of patients with PD, by psychiatrist	1000	47 (4.7)	1.87 (1.11-3.17)	.02
Relatives of controls, ever treated	850	53 (6.2)	1 [Reference]	. . .
Relatives of patients with PD, ever treated	1000	91 (9.1)	1.53 (1.03-2.27)	.04
Analyses stratified by relatives of patients with PD with the following characteristics:[c]				
Onset ≤66 y[d]	344	83 (24.1)	1.95 (1.36-2.78)	<.001
Onset from 67-75 y	324	62 (19.1)	1.43 (0.98-2.07)	.06
Onset >75 y	332	55 (16.6)	1.06 (0.76-1.48)	.74
Tremor-dominant type[e]	754	150 (19.9)	1.41 (1.06-1.89)	.02
Akinetic-rigid type	246	50 (20.3)	1.57 (1.06-2.32)	.02
Depressive disorders[f]	212	41 (19.3)	1.39 (0.95-2.03)	.09
No depressive disorders	731	153 (20.9)	1.54 (1.15-2.06)	.004
Analyses stratified by type of relative				
Parents of controls	174	14 (8.1)	1 [Reference]	. . .
Parents of patients with PD	217	29 (13.4)	1.81 (0.96-3.43)	.07
Siblings of controls	425	45 (10.6)	1 [Reference]	. . .
Siblings of patients with PD	457	84 (18.4)	1.84 (1.22-2.77)	.004
Offspring of controls	251	66 (26.3)	1 [Reference]	. . .
Offspring of patients with PD	326	87 (26.7)	1.04 (0.72-1.49)	.85

Abbreviations: CI, confidence interval; HR, hazard ratio; PD, Parkinson disease.
[a] Analyses were conducted including all relatives with all levels of diagnostic certainty and were repeated including only diagnoses confirmed by a psychiatrist or only relatives ever treated with antidepressant medications.
[b] Analyses adjusted by type of interview (direct, proxy, or only medical record) were consistent (HR, 1.30; 95% CI, 1.00-1.69; *P*=.05). A sensitivity analysis that excluded the 72 relatives who developed PD or parkinsonism (43 relatives of patients with PD and 29 relatives of controls) was consistent (HR, 1.47; 95% CI, 1.12-1.94; *P*=.006). A sensitivity analysis that removed the 80 relatives who had both depression and anxiety was also consistent (HR, 1.44; 95% CI, 1.07-1.94; *P*=.02). Finally, a sensitivity analysis that removed the 88 relatives with unknown age at onset of depressive disorders yielded an HR of 1.41 (95% CI, 1.04-1.91; *P*=.03).
[c] Relatives of patients with PD stratified by age at onset of PD (in tertiles), clinical type of PD, or presence of depressive disorders were compared with the overall group of relatives of controls (reference).
[d] Results of a test for linear trend in the log HRs were statistically significant (*P*<.001).
[e] Results of a formal test of interaction were not statistically significant (*P*=.60).
[f] Relatives of patients with PD with a history of depressive disorders preceding the onset of motor symptoms.[8] Depression status was unknown for 7 patients with PD (with 57 relatives). Results of a formal test of interaction were not statistically significant (*P*=.59).

controls via interview or medical record review. First-degree relatives of patients with PD were included more frequently (78.2% vs 70.4%; *P*<.001) and had more direct interviews (41.2% vs 32.2%; *P*<.001) than first-degree relatives of controls. In a multivariable logistic regression model, we found higher inclusion in the study

Table 4. Risk of Anxiety Disorders Among First-degree Relatives of Patients With PD Compared With Relatives of Controls

Type of Relatives	No. of Relatives at Risk	No. (%) With Anxiety Disorders	HR (95% CI)	P Value
Analyses stratified by type of diagnosis[a]				
Relatives of controls, all diagnoses	850	52 (6.1)	1 [Reference]	
Relatives of patients with PD, all diagnoses	1000	90 (9.0)	1.55 (1.05-2.28)[b]	.03
Relatives of controls, by psychiatrist	850	8 (0.9)	1 [Reference]	
Relatives of patients with PD, by psychiatrist	1000	32 (3.2)	3.49 (1.63-7.48)	.001
Relatives of controls, ever treated	850	30 (3.5)	1 [Reference]	
Relatives of patients with PD, ever treated	1000	49 (4.9)	1.45 (0.88-2.38)	.15
Analyses stratified by relatives of patients with PD with the following characteristics:[c]				
Onset ≤66 y[d]	344	29 (8.4)	1.55 (0.90-2.67)	.12
Onset 67-75 y	324	34 (10.5)	1.86 (1.14-3.04)	.01
Onset >75 y	332	27 (8.1)	1.29 (0.78-2.14)	.33
Tremor-dominant type[e]	754	70 (9.3)	1.58 (1.05-2.36)	.03
Akinetic-rigid type	246	20 (8.1)	1.45 (0.76-2.76)	.26
Anxiety disorders[f]	432	50 (11.6)	2.00 (1.26-3.16)	.003
No anxiety disorders	511	38 (7.4)	1.29 (0.82-2.03)	.27
Analyses stratified by type of relative				
Parents of controls	174	0	1 [Reference]	
Parents of patients with PD	217	12 (5.5)	NA[g]	. . .
Siblings of controls	425	26 (6.1)	1 [Reference]	
Siblings of patients with PD	457	38 (8.3)	1.42 (0.83-2.43)	.20
Offspring of controls	251	26 (10.4)	1 [Reference]	
Offspring of patients with PD	326	40 (12.3)	1.19 (0.73-1.96)	.48

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available; PD, Parkinson disease.

[a] Analyses were conducted including all relatives with all levels of diagnostic certainty and were repeated including only diagnoses confirmed by a psychiatrist or only relatives ever treated.

[b] Analyses adjusted by type of interview (direct, proxy, or only medical record) were consistent (HR, 1.46; 95% CI, 1.00-2.13; P=.05). A sensitivity analysis that excluded the 72 relatives who developed PD or parkinsonism (43 relatives of PD patients and 29 relatives of controls) was consistent (HR, 1.58; 95% CI, 1.05-2.36; P=.03). A sensitivity analysis that removed the 80 relatives who had both anxiety and depression was also consistent (HR, 1.64; 95% CI, 0.96-2.82; P=.07).

[c] Relatives of patients with PD stratified by age at onset of PD (in tertiles), by clinical type of PD, or by presence of anxiety disorders were compared with the overall group of relatives of controls (reference).

[d] Results of a test for linear trend in the log HRs were statistically significant (P=.03).

[e] Results of a formal test of interaction were not statistically significant (P=.81).

[f] Relatives of patients with a history of anxiety disorders preceding the onset of motor symptoms.[8] Anxiety status was unknown for 7 patients with PD (with 57 relatives). Results of a formal test of interaction were not statistically significant (P=.07).
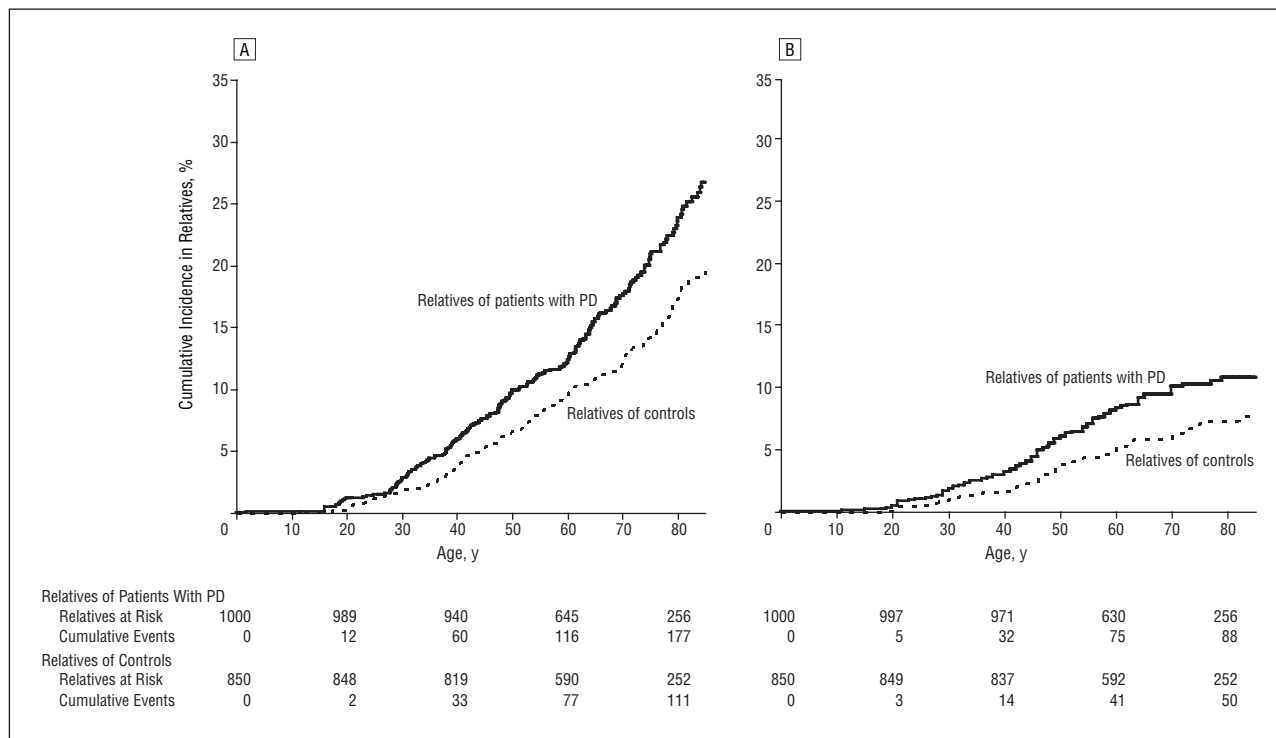
[g] The HR could not be estimated because no parents of controls had an anxiety disorder.

for relatives from smaller families, women relatives, living relatives, siblings and offspring (compared with parents), and relatives of younger patients (Table 1, footnote a). Even after accounting for all of these variables, relatives of patients with PD were included more frequently than relatives of controls (odds ratio, 1.37; 95% CI, 1.13-1.68; P=.002). Table 1 also gives the degree of clinical information obtained for relatives affected by depressive disorders or anxiety disorders.

The size of families of patients with PD (median, 8 relatives; interquartile range, 5-10 relatives) was similar to that of controls (median, 7 relatives; interquartile range, 6-11 relatives; P=.48). We investigated the clustering of depressive and anxiety disorders in families of patients with PD or controls. For the controls, we observed 125 relatives affected by depressive disorders clustered within 76 families (51.7% of all 147 families). A total of 43 families had 1 relative affected, 20 had 2, and 13 had 3 or more relatives affected. Similarly, we observed 52 relatives affected by anxiety disorders clustered within 37 families (25.2% of all 147 families). A total of 25 families had 1 relative affected, 9 had 2, and 3 had 3 relatives affected. For the patients with PD, we observed 200 relatives af-

fected by depressive disorders clustered within 96 families (59.3% of all 162 families). A total of 38 families had 1 relative affected, 30 had 2, and 28 had 3 or more relatives affected. Similarly, we observed 90 relatives affected by anxiety disorders clustered within 63 families (38.9% of all 162 families). A total of 44 families had 1 relative affected, 12 had 2, and 7 had 3 or more relatives affected.

Tables 2, **3**, and **4**, and the **Figure** show our results. We found an increased risk of several psychiatric disorders in relatives of patients with PD compared with relatives of controls. In particular, we found an increased risk of depressive disorders, anxiety disorders, somatoform disorders, and adjustment disorders. Results for depressive disorders and anxiety disorders were consistent after restricting the analyses to disorders diagnosed by a psychiatrist or ever treated. Because PD aggregates in families[11] and because depression and anxiety are more frequent in patients with PD than in the general population,[9,25-27] we also performed sensitivity analyses that excluded the 72 relatives who developed PD or parkinsonism. The associations did not change noticeably (Table 3 and Table 4, footnotes).

Relatives of Patients With PD									
Relatives at Risk	1000	989	940	645	256	1000	997	971	630	256
Cumulative Events	0	12	60	116	177	0	5	32	75	88
Relatives of Controls									
Relatives at Risk	850	848	819	590	252	850	849	837	592	252
Cumulative Events	0	2	33	77	111	0	3	14	41	50

Figure. Cumulative incidence of disorders among first-degree relatives of patients with Parkinson disease compared with first-degree relatives of controls. A, Depressive disorders. B, Anxiety disorders.

Relatives of patients with younger age at onset of PD (first tertile) had a particularly increased risk of depressive disorders, and we found a trend of increasing risk of depressive disorders in relatives with decreasing age at onset of PD in the patients (test for linear trend of the log HRs; $P<.001$; Table 3). However, the trend for anxiety disorders in relatives was less pronounced ($P=.03$; Table 4). We did not find statistically significant differences in HRs for depressive disorders (interaction $P=.83$) or anxiety disorders (interaction $P=.29$) comparing male relatives with female relatives (data not shown). Results were consistent in several sets of sensitivity analyses (Table 3 and Table 4, footnotes). In particular, because anxiety disorders and depressive disorders may occur in the same person,[28,29] we repeated our analyses after removing all relatives who had both outcomes. The results were consistent.

The risk of depressive disorders or anxiety disorders in relatives did not vary across strata of relatives of patients with PD with the tremor-dominant or the akinetic-rigid form. Similarly, the risk did not vary across strata of relatives of patients with PD with or without depressive disorders or anxiety disorders (Table 3 and Table 4).

COMMENT

We observed an increased risk of depressive disorders and anxiety disorders in first-degree relatives of patients with PD compared with first-degree relatives of controls. Interestingly, the increased risk of depressive disorders or anxiety disorders was not restricted to those families of patients with PD who had experienced depressive disorders or anxiety disorders before the onset of their motor symptoms. In addition, we observed an increased risk of somatoform disorders and adjustment disorders among relatives of patients with PD; however, our analyses for those conditions had limited statistical power.

Our findings are novel because evidence is limited for the occurrence of psychiatric disorders in relatives of patients with PD. We are aware of only 1 previous study that addressed the association from a different perspective. Fahim et al[30] compared the family history of PD in patients with self-reported depression with that in controls without depression and found inconclusive results. Another study[31] that focused on dementia showed a higher frequency of family history of major depression in patients with Alzheimer disease and depression compared with patients with Alzheimer disease but no depression. Therefore, our findings cannot be directly compared with previous data. We discuss several comparisons based on the assumption that clinical and demographic characteristics associated with a higher risk of anxiety disorders or depressive disorders in patients with PD are also associated with a higher risk of psychiatric disorders among relatives.

First, we found the risk of depressive disorders to be particularly increased for relatives of patients with younger age at onset of PD (≤ 66 years, first tertile). These findings are consistent with a study[32] that showed a higher risk of depression in patients with younger age at onset of PD (ie, before 50 years of age). Second, some studies[33,34] showed no difference in the frequency of depression in men and women with PD, whereas other studies[35] showed a preponderance in women. We observed a higher frequency of depressive disorders and anxiety disorders in women than in men in both relatives of pa-

tients with PD and relatives of controls. However, the HRs were similar in men and women (data not shown).

Third, 2 studies showed a higher frequency of depression in patients with a postural instability-gait difficulty type of PD compared with tremor-dominant patients[5] or in patients with akinetic-rigid PD compared with the tremor-dominant type.[6] By contrast, we did not observe a higher risk of depressive disorders or anxiety disorders among relatives of patients with the akinetic-rigid type of PD compared with relatives of patients with the tremor-dominant type of PD.

This study has several strengths. First, using a population-based sample of patients with incident PD and controls, we avoided possible biases related to survival (incidence-prevalence bias) and to selection of cases and controls for inclusion in the study (referral bias).[36] Second, we used the medical records-linkage system of the Rochester Epidemiology Project to increase the assessment of psychiatric disorders via passive surveillance follow-up. Third, we used a family study method and confirmed the presence of psychiatric disorders in a large proportion of relatives (Table 1).[10,37,38] As evidence for the completeness of our outcome assessment, the crude frequency of depressive disorders among relatives of controls (14.7%) was almost identical to the frequency observed among the controls themselves in a previous case-control study (14.8%).[8] We also observed some degree of familial clustering of depressive disorders or, separately, of anxiety disorders in families of controls. These findings confirm previous evidence of the familial aggregation of depressive disorders or anxiety disorders in the general population.[39-41]

However, our study has several limitations, and not all potential biases could be controlled. First, despite our ability to supplement a traditional family study method with access to a records-linkage system, first-degree relatives of patients with PD were included more frequently and had more direct interviews than first-degree relatives of controls. In addition, living relatives were included more frequently than deceased relatives for both patients with PD and controls (Table 1, footnote a). However, the overall mortality was similar for relatives of patients with PD and relatives of controls (HR, 1.00; 95% CI, 0.88-1.14; P =.98; data not shown). In addition, analyses adjusted for type of interview (direct, proxy, or only medical record) yielded consistent results. Finally, to address the approximately 8% lower participation rate of relatives of controls compared with relatives of patients with PD, we conducted a sensitivity analysis in which we imputed a corresponding number of relatives of controls, assuming that they had the same risk as relatives of patients with PD (worst-case scenario). The results remained consistent in 500 repeated random simulations.

Second, our structured telephone interview to detect psychiatric disorders had limitations. In particular, some relatives with a diagnosis of psychiatric disorders documented only via proxy interview may have been misclassified. In addition, the open-ended question about other psychiatric disorders may have caused some underreporting of less severe psychiatric disorders. However, the misclassification should be similar for relatives of patients with PD and relatives of controls. In fact, analyses

restricted to relatives with a diagnosis confirmed by a psychiatrist or to relatives who were treated for their psychiatric disorder were consistent. For approximately 28% of relatives of patients with PD and 26% of relatives of controls with depressive disorders, the age at onset was unknown, and we used a carry-forward imputation. However, a sensitivity analysis that excluded all relatives with missing age at onset yielded consistent results.

Third, we considered ineligible relatives who were younger than 40 years at the time of the study; however, most relatives excluded were sons or daughters, and we excluded both relatives of patients with PD and relatives of controls in a symmetric way. The percentage of relatives excluded because they were younger than 40 years was 9.7% for relatives of patients with PD and 9.3% for relatives of controls (P =.74). Fourth, despite the large number of first-degree relatives studied, the number of outcome events was small for rare psychiatric disorders and in some stratified analyses, and the study had limited power. On the other hand, some of the significant findings may be due to chance (multiple testing).

This study provides evidence that first-degree relatives of patients with PD have an increased risk of depressive disorders and anxiety disorders. These associations are primarily driven by relatives of patients with younger age at onset of PD. Our findings suggest that depressive disorders and anxiety disorders may share familial susceptibility factors (genetic or nongenetic) and common pathogenetic mechanisms with PD. If confirmed, these findings may have both clinical and research implications.

Correspondence: Walter A. Rocca, MD, MPH, Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (rocca@mayo.edu).

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