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Anxious Personality Predicts an Increased Risk of Parkinson's Disease

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Abstract

We studied the association of three personality traits related to neuroticism with the subsequent risk of Parkinson's disease (PD) using a historical cohort study. We included 7,216 subjects who resided within the 120-mile radius centered in Rochester, MN, at the time they completed the Minnesota Multiphasic Personality Inventory (MMPI) for research at the Mayo Clinic from 1962–1965. We considered three MMPI personality scales (pessimistic, anxious, and depressive traits). A total of 6,822 subjects (94.5%) were followed over 4 decades either actively or passively. During follow-up, 227 subjects developed parkinsonism (156 developed PD). An anxious personality was associated with an increased risk of PD (hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.16–2.27). A pessimistic personality trait was also associated with an increased risk of PD but only in men (HR = 1.92; 95% CI = 1.20–3.07). By contrast, a depressive trait was not associated with increased risk. Analyses combining scores from the three personality scales into a composite neuroticism score showed an association of neuroticism with PD (HR = 1.54; 95% CI = 1.10–2.16). The association with neuroticism remained significant even when the MMPI was administered early in life (ages 20–39 years). By contrast, none of the three personality traits was associated with the risk of non-PD types of parkinsonism grouped together. Our long-term historical cohort study suggests that an anxious personality trait may predict an increased risk of PD developing many years later.

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Keywords

Parkinson's disease; parkinsonism; anxious personality; pessimistic personality; neuroticism; Minnesota Multiphasic Personality Inventory

INTRODUCTION

Several studies have associated psychiatric symptoms or disorders with the later development of Parkinson's disease (PD), including psychoneurosis or psychosomatic disorders, anxiety, dysthymic disorder, and depression.¹⁻⁷ Other studies have documented a pre-morbid personality in PD patients, describing them as less novelty seeking and more rigid, cautious, conventional, and inflexible.^{4,8-11} However, the findings were inconsistent, and one study suggested that the specific personality characteristics of PD patients were not present in the pre-morbid stage.¹² Most of the existing studies were case-control studies, and the few cohort studies were limited by small samples or short length of follow-up.

We tested the hypothesis that certain pre-morbid personality traits related to neuroticism are associated with the later development of PD, using a large historical cohort study with long-term follow-up, namely the Mayo Clinic Cohort Study of Personality and Aging.^{13,14}

PATIENTS AND METHODS

Study Sample and Personality Testing

The Mayo Clinic Cohort Study of Personality and Aging is a geographically defined subset of a previously established Minnesota Multiphasic Personality Inventory (MMPI) cohort, as described extensively elsewhere.^{13,15,16} In brief, approximately 50,000 Mayo Clinic outpatients completed the MMPI from 1962–1965 for research purposes (not because of clinical indication). The study included ambulatory patients who came to the Mayo Clinic from anywhere in the U.S. for medical reasons other than an acute illness, a psychiatric disorder, a surgical procedure, or hospitalization. An effort was made to recruit all eligible patients in a consecutive manner, and the participation rate was 95%.¹⁵ We restricted the established cohort to 7,216 subjects who resided at the time of MMPI completion in 1 of 72 counties located approximately within a 120-mile radius centered in Rochester, MN, as described elsewhere.¹³

The MMPI includes 550 different statements concerning thoughts, feelings, attitudes, physical and emotional symptoms, and life experiences. The instrument is self-administered and the subject is asked to respond “true” or “false” to each statement.¹⁷ Hathaway and McKinley originally intended the MMPI to be used by physicians (primarily internists) to detect psychological symptoms in their medical practice. However, MMPI data also provide a standardized and quantitative measure of personality functioning.¹⁷

For this study, we selected three MMPI personality scales related to neuroticism (anxious, pessimistic, and depressive traits).^{14,18} The term neuroticism was described extensively by others.¹⁸ Details about the three MMPI scales and the new composite neuroticism score were reported elsewhere.^{13,14,19-21} In brief, we first used the anxious personality scale (historically called Scale 7 [Pt, Psychasthenia], 48 items with equal weight). An elevation on this scale indicates generalized feelings of anxiety and discomfort, and excessive rumination about personal inadequacies, either real or imagined.²¹ Second, we used the raw CoNeg scale as described by Colligan and colleagues to measure pessimistic personality.²⁰ An elevation on this scale is associated with feelings of negativity, pessimism, and a personality style consistent with the theory of learned helplessness (Seligman's theory).^{19,20} The 192

items on this scale and their corresponding weights were reported elsewhere (score range = 0–2,797).²⁰ Finally, we used the depressive personality scale (historically called Scale 2 [D, Depression], 60 items with equal weight). An elevation on this scale indicates feelings of depression, sadness, pessimism, guilt, passivity, and a tendency to give up hope easily. The items of the anxious and depressive personality scales were reported verbatim elsewhere.²¹ We tested the internal consistency of the three original scales in the current study using the Cronbach's coefficient alpha, and each of the three scales exhibited moderate to good values (anxious trait, $\alpha = 0.89$; pessimistic trait, $\alpha = 0.95$; depressive trait, $\alpha = 0.72$).¹⁴

Follow-up Procedures

All subjects were assessed by research team members who were kept uninformed of the results of the baseline MMPI using one active and two passive surveillance methods. The active method was a two-phase survey including individual screening of the subjects for parkinsonism via telephone and subsequent examination of those who screened positive (one screening contact for each person staggered over 2001–2006).^{22,23} To find the address of persons who moved since their last contact with the medical records-linkage system or with the Mayo Clinic, we used a combination of web-based tracking tools including Accurint (Seisist, Inc., West Palm Beach, FL), Switchboard (Switchboard, Inc., 1999), and Ancestry (MyFamily.com, Inc., 1998–2004). To identify proxies for deceased persons, we also used obituaries published in local newspapers and archived at state historical societies.

The telephone interview was made by one of six trained research assistants and was completed directly with the subject whenever possible; for deceased or otherwise incapacitated subjects (e.g., deaf, cognitively impaired, or terminally ill), we contacted a proxy informant. We initially identified contact persons from medical records or from other sources and asked them to judge who would be the most knowledgeable proxy. The best proxy was then invited to serve as the informant.

The verbatim text of the instruments used for direct or proxy screening has been reported elsewhere.²² Subjects screened positive if they had a previous diagnosis of PD, a previous treatment with levodopa, at least two of nine symptoms of parkinsonism, or “shaking” without other symptoms.²² We validated the screening instruments in three separate samples, and we observed sensitivity values of 97.3%, 88.0%, and 89.1% and specificity values of 43.8%, 63.8%, and 69.5%.^{22–24}

Subjects who were alive and screened positive were offered an examination by a movement disorders specialist either at the Mayo Clinic or at their home if they resided within a 5-state region including Minnesota, Iowa, Wisconsin, and North and South Dakota. If they resided outside of the 5-state region, they were examined only if they were willing to travel to the Mayo Clinic (with reimbursement of travel expenses). In addition, we obtained copies of medical records from care providers located anywhere in the US for subjects who screened positive but could not be examined or were deceased.

Independent of the contact described above, subjects who resided in Olmsted County, MN, were also followed passively through review of inpatient and outpatient medical records in the medical records-linkage system of the Rochester Epidemiology Project.²⁵ Similarly, subjects who resided outside of Olmsted County were followed passively by searching the Mayo Clinic records archive. Both the medical records-linkage system and the Mayo Clinic records archive maintain electronic indices of diagnostic codes (based on the International Classification of Diseases) that were searched for 53 specific codes related to parkinsonism.²⁶ The medical records of subjects with diagnostic codes of interest were abstracted manually by a specifically trained nurse and were adjudicated by a neurologist (J.H.B.) to confirm the diagnosis of parkinsonism or PD, as described elsewhere.²⁶

As a second passive surveillance method, we obtained death certificates for deceased subjects from the medical records-linkage system, the vital statistics offices of individual states, or from the National Death Index (NDI Plus; National Center for Health Statistics, Hyattsville, MD), as described elsewhere.^{14,27} We considered all causes of death to ascertain parkinsonism (underlying, intermediate, immediate, and other significant conditions). All study procedures and ethical aspects were approved by the institutional review boards of the Mayo Clinic and of Olmsted Medical Center. In addition, written informed consent was obtained from all subjects who were examined as part of the study.

Diagnostic Criteria

For subjects who were examined or had adequate medical record information, we used a set of previously published diagnostic criteria for parkinsonism and PD.²⁶ For subjects who could not be examined and had insufficient information in their medical records, parkinsonism or PD were defined as a previous diagnosis reported by the subject or by the proxy at interview, or listed on the death certificate. However, subjects who screened positive for parkinsonism but did not report a diagnosis of parkinsonism or PD were considered unaffected. Subjects with two or more sources of information about parkinsonism (e.g., medical record documentation and report by a proxy) were counted only for the source considered superior in the following hierarchical order: direct exam, medical record, direct interview, proxy interview, and death certificate.

Statistical Analysis

For all study subjects, we computed a follow-up time between the date of MMPI completion and one of the following endpoints, whichever came first: onset of parkinsonism (including PD), death, interview for the study, or time of last medical record entry. Cumulative incidence curves were drawn accounting for death as a competing risk, and hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards models.^{28,29} Cox models used age as the time scale to allow for complete age-adjustment and included sex (whenever appropriate). The assumption of proportional hazards was assessed by graphical methods and by introducing a time-dependent coefficient in the Cox models.²⁸

We partitioned the sample at baseline into quartiles of the distribution of scores for each of the MMPI scales, and used the lower three quartiles (quartiles 1–3) as reference. The quartiles were defined using sex-specific and age-specific distributions (by decades of age at the time of MMPI testing).¹³ We have shown previously that the top quartile cut-off corresponds to a clinically meaningful classification of the personality traits.¹³ Analyses were conducted overall, separately for men and women, and for three broad strata of age at the time of MMPI completion (20–39, 40–49, and 50–69 years).

We also conducted separate analyses adjusted for scores on the MMPI smoking proneness scale (quartile 4 vs. quartiles 1–3) as a surrogate for smoking (information not available), and analyses adjusted for the smoking proneness scale as well as for alcohol use and self-assessed general health (two specific MMPI questions).^{14,30} In addition, we conducted a set of secondary analyses adjusted for years of education as a marker of socioeconomic status (<9; 9–12; 13–16; >16 years of education) and for type of interview (direct vs. proxy). These analyses were restricted to the 4,261 cohort members who provided education information at interview. Finally, we performed analyses restricting the definition of outcome to subjects with a diagnosis of PD confirmed by in-person examination or by medical record review. All analyses were completed using SAS® (SAS Institute, Cary, NC), and tests of statistical significance were conducted at the two-tailed alpha level of 0.05.

RESULTS

Study sample

Fig. 1 shows a detailed flow-chart of the study. Of the 6,822 subjects (94.5%) included, 5,816 (85.3%) had complete follow-up because they met at least one of three criteria: 1) reached the outcome of parkinsonism or PD; 2) were interviewed directly or via proxy; or 3) had a medical contact with the medical records-linkage system or with the Mayo Clinic records archive within 3 years preceding death or the time of the study (mid-point = December 31, 2003). The remaining 1,006 subjects (14.7%) were followed for a number of years through the medical records-linkage system or the Mayo Clinic records database and were censored at the time of last contact. The median age at the time of MMPI completion for the overall cohort of 6,822 subjects was 48.3 years (range = 20–69 years by design), and the median length of follow-up was 29.2 years (range = <1–44.8 years). Of the 1,521 subjects who were alive and were screened directly, 508 screened positive for parkinsonism (33.4%), and 330 of them were examined in person (65.0%). Of the 2,894 subjects who were screened via proxy, 1,591 screened positive (55.0%), 102 of them were alive, and 31 of those alive were examined in person (30.4%; alive but incapacitated).

We found 227 subjects with parkinsonism of whom 156 had PD (68.7%). Of the 227 patients with parkinsonism, 25 were diagnosed directly by a study neurologist, 116 had medical record documentation, 8 reported parkinsonism during direct interview and 49 by proxy interview, and 29 had only death certificate documentation. Of 156 patients with PD, 15 were diagnosed directly by a study neurologist, 61 had medical record documentation, 8 reported PD during direct interview and 49 by proxy interview, and 23 had only death certificate documentation. The number of subjects with PD diagnosed via in-person examination or medical record review was similar to the number expected using published age- and sex-specific incidence rates from Olmsted County, MN (standardized incidence ratio = 0.94; 95% CI = 0.74–1.18; $P = 0.62$).²⁶

Risk of Parkinsonism or PD

Tables 1 and 2 show our cohort analyses for the three MMPI scales and the associated risk of parkinsonism or PD. We found a significant association of anxious personality with PD in overall analyses (HR = 1.63; 95% CI = 1.16–2.27) and in analyses restricted to men. We also found a significant association of pessimistic personality with PD but only in analyses restricted to men (HR = 1.92; 95% CI = 1.20–3.07). By contrast, no significant association was found for subjects scoring high on the depressive trait. The significant associations for parkinsonism of all types were due to the associations with PD. Indeed, none of the three personality traits was associated with the risk of non-PD types of parkinsonism grouped together (Tables 1 and 2, footnotes).

Analyses combining scores from the three MMPI scales into a composite neuroticism score showed an association of neuroticism with PD in overall analyses (HR = 1.54; 95% CI = 1.10–2.16) and in analyses restricted to men (Table 3). The association with neuroticism remained significant for PD even when the MMPI had been administered early in life (ages 20–39 years). Fig. 2 shows the cumulative incidence plots of PD for the anxious trait and for the composite neuroticism score (accounting for death as a competing risk; men and women combined).

Analyses stratified by sex and by age at time of MMPI testing did not reveal any significant interactions (Tables 1, 2, and 3, footnotes). Secondary analyses adjusting the HR for smoking proneness alone or for smoking proneness, alcohol use, and self-assessed general health yielded results consistent with the results of primary analyses (Tables 1–3, footnotes).

Similarly, analyses adjusting the HR for years of education and for type of interview yielded consistent results (data not shown).

DISCUSSION

This study showed a significant association of pre-morbid anxious personality with the later development of PD. The consistent but weaker association with the pessimistic personality trait may be due to the high correlation between scores for the pessimistic trait and for the anxious trait observed in our study at baseline.¹³ Indeed, in a model including both the anxious and the pessimistic traits, only the anxious trait remained significant (HR = 1.75; 95% CI = 1.07–2.86 for anxious trait, and HR = 0.91; 95% CI = 0.55–1.50 for pessimistic trait). The associations were consistently stronger in men than in women for the anxiety and pessimistic traits; however, these sex differences were not significant. We also found significant associations when scores from the three MMPI scales were combined into a composite neuroticism score. These findings provide more definitive evidence for the associations previously reported by our group and others.^{1,2,4,11}

There are at least three possible explanations for these associations. First, anxiety and neuroticism may be non-causally associated with PD. For example, the association may be caused by shared genetic or early-life environmental risk factors that predispose subjects to both PD and certain personality traits independently (confounding).¹¹ We previously reported that depressive disorders and anxiety disorders may share familial susceptibility factors with PD.³¹ However, our findings cannot confirm or exclude a possible confounding effect.

Second, anxiety and neuroticism may be early manifestations of the PD neurodegenerative process. Pathologic findings suggest that the degenerative process of PD may begin in the medulla oblongata and olfactory bulb, and then ascend the brainstem to involve components of the autonomic, limbic, and somatomotor systems.^{32,33} Thus, neuroticism could be a manifestation of this degenerative process involving non-nigral brainstem neurons (e.g., serotonergic or noradrenergic projection neurons). However, the association of anxiety and neuroticism with PD did not vary depending on the age of the subject at the time of MMPI testing, and remained significant for neuroticism measured at ages 20–39 years. Thus, for neuroticism to be an early manifestation, we would need to postulate a preclinical phase of 30–50 years before the onset of motor symptoms of PD.³⁴

Third, anxiety and neuroticism may be causal risk factors for PD. Stressful experiences may increase the secretion of glucocorticoids and may lead to neuronal death through the release of excitatory amino acids or the inhibition of neurogenesis. These mechanisms have been documented in the hippocampus.^{35–39} In addition, anxiety and neuroticism may be causally associated with PD because they prompt behaviors that confer risk (e.g., a particular diet or the use of certain medications). If this causal hypothesis were to be confirmed, treatment of anxiety with medications or cognitive behavioral therapies could become a primary prevention strategy for PD.^{40,41} Indeed, the HR for anxious personality was relatively modest (HR = 1.63); however, the population attributable risk may be quite large (13.6%) because exposure was defined as 25% of the population.

Our study has a number of strengths. First, it is a relatively large, historical cohort study using a well-defined and standard battery of 550 questions to measure personality. This design reduced recall bias and the confounding effect of personality changes that may follow the onset of parkinsonism. Because the MMPI was administered as part of a research project and not because of any medical condition, the confounding effect of pre-existing conditions was also reduced.

Second, because we restricted the cohort to subjects living within a 120-mile radius of Rochester, MN, we used the medical records-linkage system of the Rochester Epidemiology Project and the Mayo Clinic records archive to perform a passive follow-up in addition to the active follow-up. The use of both follow-up methods allowed for a more complete case ascertainment than using either method alone. Third, the long-term follow-up (median = 29.2 years) and the diverse age and sex composition of the sample at baseline make this study unique. Our cohort could be stratified into two sub-cohorts of approximately equal size for men and women and into three broad age sub-cohorts. Finally, our capture rate for incident cases of PD was comparable with published incidence rates using similar methods.²⁶

Our study also has limitations. First, the sample was not recruited from a well-defined population through randomization.¹³ On the other hand, efforts were made to recruit subjects coming to the Mayo Clinic sequentially, and 95% of the subjects who were asked to complete the MMPI participated. In addition, the age and sex patterns of scores found in our sample at baseline were similar to those observed in a population-based random sample.^{13,42,43}

Second, the diagnosis of PD was confirmed by in-person examination or by medical record review for only 48.7% of the patients. However, sensitivity analyses including only patients with more definite diagnoses of PD yielded similar results. In addition, because of financial restrictions, we were unable to examine in-person some of the subjects who screened positive but resided outside of the 5-state region. Fortunately, only 106 subjects (2.4%) resided outside of the 5-state region at the time of the follow-up interview.

Third, because parkinsonism is an aging-related disease, death may have acted as a competing outcome, and may have reduced the magnitude of the observed associations.¹⁴ However, our graphical representation of the cumulative incidence curves did account for death as a competing risk.²⁹ Fourth, our scale for the depressive trait had a lower internal consistency than the other two scales. This may have contributed in part to the lack of association with PD. Finally, it is possible that subjects with an anxious personality were more likely to seek care for their symptoms early in the course of PD resulting in an earlier diagnosis. However, our long-term follow-up should reduce this bias.

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Fig. 1.

Study contact and screening.

^aOf these 4,415 subjects, 4,309 (97.6%) resided within and 106 (2.4%) resided outside of the 5-state region at the time of the follow-up interview. Of the 106 subjects who resided outside of the 5-state region, 33 screened positive for parkinsonism, 32 of them were alive, and 7 were examined.

^bOf these 1,489 subjects, 1,211 (81.3%) had both medical record and death certificate information, 34 (2.3%) had only medical record information, 231 (15.5%) had only death certificate information, and the remaining 13 (0.9%) had neither.

Fig. 2.

Cumulative incidence of PD in men and women combined: comparison of subjects in the top quartile with subjects in quartiles 1–3 of the anxious personality trait (HR = 1.63; 95% CI = 1.16–2.27; $P = 0.004$) and of the composite neuroticism score (HR = 1.54; 95% CI = 1.10–2.16; $P = 0.01$). The graphic display accounts for death as a competing risk.²⁹

Table 1
Cohort analyses for anxious personality trait and risk of parkinsonism or Parkinson's disease

Cohort or stratum	Persons at risk	Person-years of follow-up	Parkinsonism			Parkinson's Disease		
			Persons with parkinsonism	Hazard ratio (95% CI) ^a	P	Persons with Parkinson's disease	Hazard ratio (95% CI) ^a	P
Overall ^b								
Quartiles 1–3	5,126	138,100	157	1.00 (reference)	---	105	1.00 (reference)	---
Quartile 4	1,696	43,097	70	1.49 (1.13–1.98)	0.005	51	1.63 (1.16–2.27) ^c	0.004
Men ^d								
Quartiles 1–3	2,463	63,106	81	1.00 (reference)	---	46	1.00 (reference)	---
Quartile 4	850	20,418	39	1.56 (1.06–2.28)	0.02	29	2.03 (1.28–3.24)	0.003
Women ^d								
Quartiles 1–3	2,663	74,994	76	1.00 (reference)	---	59	1.00 (reference)	---
Quartile 4	846	22,680	31	1.42 (0.93–2.15)	0.10	22	1.29 (0.79–2.10)	0.31
Ages 20–39 years at testing ^e								
Quartiles 1–3	1,464	49,767	24	1.00 (reference)	---	16	1.00 (reference)	---
Quartile 4	483	16,136	13	1.70 (0.86–3.33)	0.12	9	1.77 (0.78–4.01)	0.17
Ages 40–49 years at testing ^e								
Quartiles 1–3	1,331	39,485	46	1.00 (reference)	---	34	1.00 (reference)	---
Quartile 4	432	11,836	20	1.53 (0.91–2.59)	0.11	13	1.34 (0.71–2.54)	0.37
Ages 50–69 years at testing ^e								
Quartiles 1–3	2,331	48,848	87	1.00 (reference)	---	55	1.00 (reference)	---
Quartile 4	781	15,126	37	1.42 (0.96–2.08)	0.08	29	1.76 (1.12–2.75)	0.01

^aHR adjusted by age (used as the time scale) and sex.

^bTrend analyses for PD. Using quartile 1 as reference, the HR was 1.05 for quartile 2 (95% CI = 0.68–1.62; $P = 0.84$), 0.63 for quartile 3 (95% CI = 0.38–1.05; $P = 0.07$), and 1.46 for quartile 4 (95% CI = 0.96–2.21; $P = 0.08$).

^cWe performed a sensitivity analysis restricted to the 76 cases of PD who were diagnosed via in-person examination or medical record. The HR for quartile 4 compared with quartiles 1–3 was 1.71 (95% CI = 1.07–2.75; $P = 0.03$). The 80 cases of PD documented exclusively via direct or proxy interviews or via death certificates were included in analyses but censored as free of the outcome. Analyses including smoking proneness in the model (quartile 4 vs. quartiles 1–3) yielded an HR of 1.63 (95% CI = 1.17–2.29; $P = 0.004$); analyses including smoking proneness, alcohol use, and self-assessed general health yielded an HR of 1.62 (95% CI = 1.15–2.29; $P = 0.006$). The HR for non-PD types of parkinsonism grouped together was 1.22 (95% CI = 0.72–2.07; $P = 0.46$).

^dThere was no significant interaction between the anxious trait and sex ($P = 0.18$ for PD).

^eThere was no significant interaction between the anxious trait and age at time of MMPI administration ($P = 0.35$ for PD).

Table 2
Cohort analyses for pessimistic and depressive personality traits and risk of parkinsonism or Parkinson's disease

Cohort or stratum	Persons at risk	Person-years of follow-up	Parkinsonism			Parkinson's Disease		
			Persons with parkinsonism	Hazard ratio (95% CI) ^a	P	Persons with Parkinson's disease	Hazard ratio (95% CI) ^a	P
Pessimistic, overall ^b								
Quartiles 1–3	5,122	137,551	165	1.00 (reference)	---	110	1.00 (reference)	---
Quartile 4	1,700	43,647	62	1.23 (0.92–1.65)	0.16	46	1.37 (0.97–1.93) ^c	0.08
Pessimistic, men ^d								
Quartiles 1–3	2,493	63,771	83	1.00 (reference)	---	48	1.00 (reference)	---
Quartile 4	820	19,753	37	1.52 (1.03–2.24)	0.03	27	1.92 (1.20–3.07)	0.007
Pessimistic, women ^d								
Quartiles 1–3	2,629	73,779	82	1.00 (reference)	---	62	1.00 (reference)	---
Quartile 4	880	23,894	25	0.96 (0.61–1.50)	0.85	19	0.96 (0.57–1.61)	0.88
Depressive, overall ^e								
Quartiles 1–3	5,090	137,606	171	1.00 (reference)	---	116	1.00 (reference)	---
Quartile 4	1,732	43,592	56	1.11 (0.82–1.50)	0.51	40	1.16 (0.81–1.66) ^f	0.42
Depressive, men ^g								
Quartiles 1–3	2,465	63,189	95	1.00 (reference)	---	58	1.00 (reference)	---
Quartile 4	848	20,336	25	0.89 (0.58–1.39)	0.62	17	0.99 (0.58–1.70)	0.97
Depressive, women ^g								
Quartiles 1–3	2,625	74,418	76	1.00 (reference)	---	58	1.00 (reference)	---
Quartile 4	884	23,256	31	1.36 (0.90–2.07)	0.15	23	1.32 (0.81–2.14)	0.26

^aHR adjusted by age (used as the time scale) and sex.

^bTrend analyses for PD. Using quartile 1 as reference, the HR was 0.77 for quartile 2 (95% CI = 0.49–1.21; $P = 0.26$), 0.76 for quartile 3 (95% CI = 0.48–1.19; $P = 0.23$), and 1.16 for quartile 4 (95% CI = 0.77–1.75; $P = 0.48$).

^cWe performed a sensitivity analysis restricted to the 76 cases of PD who were diagnosed via in-person examination or medical record. The HR for quartile 4 compared with quartiles 1–3 was 1.31 (95% CI = 0.80–2.14; $P = 0.29$). The 80 cases of PD documented exclusively via direct or proxy interviews or via death certificates were included in analyses but censored as free of the outcome. Analyses including smoking proneness in the model (quartile 4 vs. quartiles 1–3) yielded an HR of 1.37 (95% CI = 0.97–1.94; $P = 0.07$); analyses including smoking proneness, alcohol use, and self-assessed general health yielded an HR of 1.35 (95% CI = 0.95–1.92; $P = 0.09$). The HR for non-PD types of parkinsonism grouped together was 0.96 (95% CI = 0.55–1.68; $P = 0.89$).

^dThere was no significant interaction between the pessimistic trait and sex ($P = 0.05$ for PD).

^eTrend analyses for PD. Using quartile 1 as reference, the HR was 1.12 for quartile 2 (95% CI = 0.74–1.71; $P = 0.59$), 0.69 for quartile 3 (95% CI = 0.43–1.13; $P = 0.14$), and 1.10 for quartile 4 (95% CI = 0.71–1.70; $P = 0.67$).

^fWe performed a sensitivity analysis restricted to the 76 cases of PD who were diagnosed via in-person examination or medical record. The HR for quartile 4 compared with quartiles 1–3 was 1.17 (95% CI = 0.70–1.94; $P = 0.55$). The 80 cases of PD documented exclusively via direct or proxy interviews or via death certificates were included in analyses but censored as free of the outcome. Analyses including smoking proneness in the model (quartile 4 vs. quartiles 1–3) yielded an HR of 1.16 (95% CI = 0.81–1.66; $P = 0.42$); analyses including smoking proneness, alcohol use, and self-assessed general health yielded an HR of 1.12 (95% CI = 0.76–1.65; $P = 0.57$). The HR for non-PD types of parkinsonism grouped together was 0.99 (95% CI = 0.57–1.73; $P = 0.98$).

^gThere was no significant interaction between the depressive trait and sex ($P = 0.47$ for PD).

Table 3
Cohort analyses for composite neuroticism score and risk of parkinsonism and Parkinson's disease

Cohort or stratum	Persons at risk	Person-years of follow-up	Parkinsonism			Parkinson's disease		
			Persons with parkinsonism	Hazard ratio (95% CI) ^a	P	Persons with Parkinson's disease	Hazard ratio (95% CI) ^a	P
Overall ^b								
Quartiles 1–3	5,131	138,677	160	1.00 (reference)	---	108	1.00 (reference)	---
Quartile 4	1,691	42,521	67	1.45 (1.09–1.94)	0.01	48	1.54 (1.10–2.16) ^c	0.01
Men ^d								
Quartiles 1–3	2,495	64,220	85	1.00 (reference)	---	49	1.00 (reference)	---
Quartile 4	818	19,304	35	1.45 (0.98–2.15)	0.06	26	1.87 (1.16–3.00)	0.01
Women ^d								
Quartiles 1–3	2,636	74,456	75	1.00 (reference)	---	59	1.00 (reference)	---
Quartile 4	873	23,217	32	1.45 (0.96–2.20)	0.08	22	1.27 (0.78–2.07)	0.34
Ages 20–39 years at testing ^e								
Quartiles 1–3	1,469	50,231	24	1.00 (reference)	---	15	1.00 (reference)	---
Quartile 4	478	15,672	13	1.82 (0.93–3.58)	0.08	10	2.27 (1.02–5.06)	0.04
Ages 40–49 years at testing ^e								
Quartiles 1–3	1,318	39,343	48	1.00 (reference)	---	36	1.00 (reference)	---
Quartile 4	445	11,978	18	1.32 (0.77–2.27)	0.32	11	1.07 (0.54–2.10)	0.85
Ages 50–69 years at testing ^e								
Quartiles 1–3	2,344	49,102	88	1.00 (reference)	---	57	1.00 (reference)	---
Quartile 4	768	14,872	36	1.42 (0.97–2.10)	0.07	27	1.64 (1.04–2.60)	0.03

^aHR adjusted by age (used as the time scale) and sex.

^bTrend analyses for PD. Using quartile 1 as reference, the HR was 0.96 for quartile 2 (95% CI = 0.62–1.49; $P = 0.86$), 0.71 for quartile 3 (95% CI = 0.44–1.15; $P = 0.16$), and 1.38 for quartile 4 (95% CI = 0.91–2.08; $P = 0.13$).

^cWe performed a sensitivity analysis restricted to the 76 cases of PD who were diagnosed via in-person examination or medical record. The HR for quartile 4 compared with quartiles 1–3 was 1.56 (95% CI = 0.96–2.53; $P = 0.07$). The 80 cases of PD documented exclusively via direct or proxy interviews or via death certificates were included in analyses but censored as free of the outcome. Analyses including smoking proneness in the model (quartile 4 vs. quartiles 1–3) yielded an HR of 1.54 (95% CI = 1.10–2.17; $P = 0.01$); analyses including smoking proneness, alcohol use, and self-assessed general health yielded an HR of 1.53 (95% CI = 1.08–2.18; $P = 0.02$). The HR for non-PD types of parkinsonism grouped together was 1.28 (95% CI = 0.76–2.16; $P = 0.36$).

^dThere was no significant interaction between the anxious trait and sex ($P = 0.25$ for PD).

^eThere was no significant interaction between the anxious trait and age at time of MMPI administration ($P = 0.34$ for PD).