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Neuroticism and risk of Parkinson's Disease: A meta-analysis

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Abstract

Background: Neuroticism is linked to mood disorders and Alzheimer's disease, but fewer studies have tested the prospective association with Parkinson's disease.

Objectives: To examine the association between neuroticism and risk of Parkinson's disease in a large cohort and a meta-analysis of prospective cohort studies.

Method: Participants from the UK Biobank (N = 490,755) completed a neuroticism scale in 2006-2010. Incident Parkinson's disease was ascertained using electronic health records or death records up to 2018. The systematic search and meta-analysis followed the MOOSE guidelines.

Results: During 11.91 years of follow-up (mean = 8.88 years; 4,360,105 person-years) 1,142 incident Parkinson's disease cases were identified. Neuroticism was associated with higher risk of incident Parkinson's disease, both as continuous (HR = 1.28; 95%CI: 1.21–1.36) and categorical

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variable (top vs. bottom quartiles: HR = 1.88; 95%CI: 1.60–2.22). The association remained significant after accounting for age, sex, smoking, physical activity, anxiety, and depressed mood, and after excluding cases that occurred within the first five years of follow-up. The associations were similar for women and men and across levels of socioeconomic status. Random-effect meta-analysis of four prospective studies (N = 548,284) found neuroticism associated with increased risk of incident Parkinson's disease (HR = 1.82; 95%CI: 1.59–2.08; $p = 7.31^{-19}$). There was no evidence of heterogeneity across studies with follow-ups ranging from one to four decades.

Conclusions: The results from the large UK biobank and meta-analysis of prospective studies indicate that neuroticism is consistently associated with a higher risk of incident Parkinson's disease.

Keywords

Neuroticism; Parkinson's disease; Prospective study; Meta-analysis

Introduction

Neuroticism is a personality trait that measures individual differences in the tendency to experience negative emotions, vulnerability to stress, inability to resist urges, and self-consciousness. Neuroticism is one of the five major personality traits known as the big five or Five-Factor Model of personality¹, and one of the most studied psychological dispositions for its relevance spanning from normal to abnormal emotional functioning. Individuals who score high in neuroticism are at higher risk for poor health outcomes across the lifespan, particularly in the domain of mental health²⁻⁴ and neurodegenerative diseases, including Alzheimer's disease and related dementias.⁵⁻⁹ Relatively less is known about the association between neuroticism and Parkinson's disease (PD),^{10, 11} a multifactorial neurodegenerative disorder characterized by bradykinesia, resting tremor, rigidity, and may include autonomic dysfunctions, cognitive deficits, and mood disorders.¹² The prevalence of PD is about 1% in older adults,¹³ and globally, it is estimated that over 6 million individuals have PD.¹⁴ Several studies indicate that patients with PD tend to report a higher level of neuroticism as compared to healthy controls, but past research has relied mainly on cross-sectional or retrospective methods.^{10, 11, 15} The scope of this study was to examine whether self-ratings of neuroticism in healthy community-dwelling adults are prospectively associated with the risk of receiving a diagnosis of PD at follow-up. Similar to other biomedical and behavioral risk factors, this research is needed to better understand the role of neuroticism in modulating risk of developing PD. Thus, the primary aim of this study was to test the hypothesis that neuroticism is prospectively associated with the risk of PD in one of the largest samples to date. We examined the robustness of the association in sensitivity analyses; these included testing whether the effect of neuroticism was independent from other PD risk factors, including measures of physical activity, smoking, anxiety, and depression.¹⁶ We also tested whether the association was moderated by sex or socioeconomic status. Finally, we conducted a meta-analysis of the present and previous prospective studies to provide a quantitative synthesis of the current evidence.

Methods.

Participants.

The UK Biobank (<http://www.ukbiobank.ac.uk>) is a large biomedical study that recruited over 500,000 individuals across the UK between 2006 and 2010. Participants were registered with the UK National Health Service (NHS) and were aged 40 to 69 years at recruitment. The overall protocol for the study is available online (<http://www.ukbiobank.ac.uk>). Figure S1 presents the flow chart of the study participants. The study complies with the principles of the Declaration of Helsinki, the protocol was approved by the local institutional review board (North West Multicenter Research Ethics Committee), and all participants gave informed consent. This research has been conducted using the UK Biobank Resource under Application Number 57672.

Personality assessment.

Neuroticism was assessed using the short form of the Eysenck Personality Questionnaire-Revised (EPQ-R)¹⁷. The scale included 12 items (e.g., “Are you a worrier?”) with the response options, Yes, No, Do not know, or Prefer not to answer. Participants who responded Yes (1) or No (0) to at least nine items were included in the analyses (11.7% had one missing response, 4.5% had two missing responses, and 2% had three missing responses; sensitivity analyses that used only the 81.7% of participants who responded yes/no to all 12 items generated the same pattern of results). The neuroticism score was the average across the 12 items and was next transformed into z-scores for the continuous analyses and into quartiles for categorical analyses. The UK Biobank did not assess other major personality traits besides neuroticism.

Parkinson's disease.

Incident PD was ascertained through linked National Health Service hospital inpatient records or death records. We used PD diagnosis and dates generated by the UK Biobank Outcome Adjudication Group (March 2018).¹⁸ Most incident cases (98.4%) were the earliest known relevant International Classification of Diseases (ICD; ICD 9 Code 332.0, ICD 10 Code G20) code in the electronic health records. A small proportion of cases (1.6%) were ascertained from death register records. For those participants, the date of death was used as the date of ascertainment. Participants with a relevant ICD code in the electronic health records before recruitment or self-reported diagnosis at recruitment were excluded from the analyses.

Covariates and Moderators.

The following covariates were included to evaluate the association between neuroticism and risk of PD while accounting for demographic and other risk/protective factors for PD. Sex and an index of socioeconomic status were tested as moderators.

Demographic.—Age (in years) and sex (0 = male, 1 = female) were assessed at baseline and included in all analyses.

Socioeconomic status.—The Townsend deprivation index was used as a proxy for socioeconomic status and assigned to participants based on their postcodes. The Townsend deprivation index is based on unemployment, non-home ownership, non-car ownership, and household overcrowding in a geographic area.

Tobacco smoking.—Never smokers were compared to current and former smokers based on questions about current ("Do you smoke tobacco now?") and past ("In the past, how often have you smoked tobacco?") tobacco smoking.

Physical activity.—Physical activity was measured using the International Physical Activity Questionnaire.¹⁹ We used a physical activity score computed from the average of three items: "In a typical WEEK, on how many days did you walk for at least 10 minutes at a time?", "In a typical WEEK, on how many days did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at normal pace? (Do not include walking)", and "In a typical WEEK, how many days did you do 10 minutes or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)".

Depressive symptoms.—Two items from the Patient Health Questionnaire-2 ("Over the past two weeks, how often have you had little interest or pleasure in doing things?" and "Over the past two weeks, how often have you felt down, depressed or hopeless?") were used to assess depressed mood. Scores ≥ 3 were used as likely depressed cases.²⁰

Anxiety.—The UK Biobank did not include a standardized anxiety scale at baseline, but participants were asked, "Have you ever seen a psychiatrist for nerves, anxiety, tension or depression?" with response options no (0) and yes (1).

Statistical analyses.

Descriptive statistics for the study variables at baseline were computed as means and standard deviations (SD) or proportions in the full sample and by PD outcome. The primary analyses used Cox proportional hazard regression models with neuroticism as predictor of incident PD. Similar to previous studies²¹⁻²³, neuroticism was tested as a continuous variable and as a categorical variable split in quartiles. The reference group was the quartile with the lowest neuroticism scores. Time was coded in years from the date of the personality assessment (2006-2010) up to the date of the first PD report in the electronic health record, death record, or censoring date. The basic model included age and sex as covariates. Because smoking, physical activity, anxiety, and depressed mood are risk/protective factors for PD^{16, 24}, a follow-up model included these risk/protective factors as covariates along with age and sex. We also tested two moderators. First, previous studies^{22, 23} found inconsistent sex differences and we tested the interaction of sex*neuroticism and reported the association separately for women and men. Second, some studies found that socioeconomic status interacts with personality traits in predicting risk of cognitive impairment²⁵; we tested a similar interaction of the deprivation index*neuroticism to evaluate whether the association between neuroticism and risk of PD varies by socioeconomic status. We conducted additional sensitivity analyses. First, we

excluded incident PD cases within the first five years of follow-up to reduce the likelihood that participants already had PD at baseline. Second, we examined whether the results were dependent on the ascertainment method (health vs. death records) by excluding PD cases ascertained from death records. Third, we excluded individuals with dementia at baseline (ascertained through linked National Health Service hospital inpatient records or self-reported). Lastly, we examined models with age as the underlying time scale instead of time from the personality assessment.

Literature search and Meta-Analysis.

The MOOSE guidelines for meta-analyses of observational studies were followed.²⁶ The protocol was not preregistered. We included studies that measured neuroticism or a neuroticism-related trait at baseline and prospectively followed participants to identify incident cases of PD. We excluded work with cross-sectional or retrospective study designs. We excluded one study that used a parkinsonism rating scale and not the diagnosis of PD²⁷. Of note, the study found a significant association between neuroticism and the parkinsonism rating scale.²⁷ We had no other exclusion criteria. A systematic literature search covering all years from inception up to January 2021 was conducted using PubMed and Web of Science. We used the terms *neuroticism* AND *Parkinson*. The literature search was conducted independently by two researchers (AT and DA). We screened the titles and abstracts of each article for eligibility. Next, the full-text articles were assessed for inclusion, and the data extracted from selected studies. Google Scholar was used to conduct a similar search and to identify additional studies through forward searches. The identified studies and systematic reviews^{10, 11} on personality and PD were further used to ‘hand search’ for relevant studies. We had no contact with the authors. All identified studies had similar designs and data quality. When multiple models were reported, we selected the model that accounted for age and sex for consistency across studies. Of note, the effects were essentially the same in models that accounted for additional covariates.²¹ The association findings from the UK biobank and the identified studies were meta-analyzed using random-effects models. Heterogeneity was assessed using Q , I^2 , and τ . Potential publication biases were examined by inspecting funnel plot asymmetry and Egger’s test.

Results

UK Biobank.

Descriptive statistics for the full sample and separately by PD status are reported in Table 1. At baseline, 491,653 participants completed the neuroticism scale, of whom 898 had PD at baseline (labeled as prevalent PD) and 490,755 did not. During up to 11.91 years of follow-up (average = 8.88 years, SD = 1.23), 4,360,105 person-years, 1,142 individuals received the PD diagnosis (labeled as incident PD). Figure 1 illustrates the neuroticism age and sex-adjusted marginal means across groups. Consistent with past research,¹¹ participants with a diagnosis of PD at baseline scored higher on neuroticism compared to those without a PD diagnosis ($p = .007$; Cohen $d = 0.09$). Participants without PD at baseline but who were diagnosed during the follow-up had the highest score on neuroticism, compared to both those with no PD ($p < .001$; Cohen $d = 0.23$) and those with PD at baseline ($p = .002$; Cohen $d = 0.14$).

Table 2 presents the Hazard Ratios (HRs) and 95% confidence interval (CIs) for incident PD associated with 1 SD difference in neuroticism (continuous) and across quartiles of neuroticism (categorical). In the primary model that accounted for age and sex, high neuroticism was associated with a higher risk of PD, as either a continuous (HR = 1.28; 95%CI: 1.21 – 1.36) or categorical variable (top vs. bottom quartiles: HR = 1.88; 95%CI: 1.60 – 2.22). In the model that further included smoking, physical activity, anxiety, and depressed mood as covariates, neuroticism remained significantly associated with risk of PD as a continuous (HR = 1.20; 95%CI: 1.13 – 1.28) and as a categorical variable (top vs. bottom quartiles: HR = 1.62; 95%CI: 1.36 – 1.93). The results were essentially the same for women and men (Table 2), with no significant sex*neuroticism interaction ($p = .98$), and similar across levels of socioeconomic status (deprivation index*neuroticism; $p = .16$).

The sensitivity analyses supported the main findings. First, we excluded cases that were diagnosed within the first 5 years of follow-up. Neuroticism remained a significant predictor of incident PD in models that accounted for age and sex and with neuroticism as either a continuous (HR = 1.25; 95%CI: 1.17 – 1.35) or categorical variable (HR = 1.72; 95%CI: 1.41 – 2.11). Second, the results were also unchanged when 18 participants with PD ascertained from death records were excluded (HR = 1.28; 95%CI: 1.21 – 1.36; top vs. bottom quartiles: HR = 1.89; 95%CI: 1.60 – 2.23). Third, the results were unchanged when we excluded 207 individuals with dementia at baseline (HR = 1.28; 95%CI: 1.21 – 1.36; top vs. bottom quartiles: HR = 1.87; 95%CI: 1.58 – 2.20). Lastly, similar results were obtained in models with age as the time scale (HR = 1.34; 95%CI: 1.26 – 1.42; top vs. bottom quartiles: HR = 2.09; 95%CI: 1.77 – 2.46).

Meta-Analysis.

The systematic literature search (see Figure S2) identified three published studies²¹⁻²³ that reported prospective associations between neuroticism and risk of PD. Table 3 presents the descriptive information for the studies included in the meta-analysis. The four studies (3 previously published and current UK Biobank) included 548,284 participants at baseline and 1,670 incident PD cases over the follow-up (range from 7.9 to 36.8 years). Most PD diagnoses were based on health records. When there was a combination of ascertainment methods, the effect sizes did not depend on the method used^{21, 22}. Two of the four studies did not report the necessary data to conduct a meta-analysis with the continuous neuroticism score,^{22, 23} but all four studies reported the association results for the categorical neuroticism. Figure 2 presents a forest plot with the effects from each sample and the overall meta-analytic effect (HR = 1.82; 95%CI: 1.59 – 2.08; $Z = 8.87$, $p = 7.31 \times 10^{-19}$), indicating that individuals within the higher neuroticism category had over 80% higher risk of developing PD compared to those in the lower neuroticism category. The effects were highly consistent across studies, all within the range of HR ~1.5 to ~2.0, and low heterogeneity statistics ($Q = 1.76$, $p = 0.62$, $I^2 = 0\%$; $\tau = 0$). The leave-one-out analysis indicates that the association was significant without the UK Biobank, and the effect was not dependent on any single study. There was no funnel plot asymmetry (Figure 2) or evidence of small-studies effect (e.g., Egger's regression intercept = $-.073$, $p = 0.54$) that could suggest potential publication biases. However, the number of studies included in the meta-analysis was only four and inferences about heterogeneity and publication biases should be made with caution.

Discussion

In the largest cohort to date and a meta-analysis of prospective studies, we found consistent evidence that scoring higher on neuroticism is associated with a higher risk of incident PD. More specifically, adults who scored in the top quartile of neuroticism had more than 80% greater risk of incident PD as compared to those who scored lower on neuroticism. The association was found with neuroticism as both continuous and categorical variables. The effects were similar across women and men and socioeconomic strata. Furthermore, the association was virtually unchanged in models that excluded incident cases within the first five years of follow-up and remained significant in models that accounted for demographic variables and other risk factors, including smoking, physical activity, anxiety, and depression. The meta-analysis confirmed the association of neuroticism and >80% increased risk of incident PD and found no significant heterogeneity across the four large studies that span from one to four decades.

The association we found for neuroticism should be evaluated as compared to other risk factors for PD. An umbrella review of meta-analyses evaluated the strength of the evidence in support of the association between 75 risk factors and PD¹⁶. The following criteria were used to evaluate ‘convincing’ or ‘Class I’ evidence: more than 1000 PD cases, $p < 10^{-6}$ by random-effects, not large heterogeneity, 95% prediction interval excluding the null value, and absence of hints for small-study effects and excess significance bias. Out of 75 risk factors included in the review, only constipation and physical activity met these criteria. Although more studies are needed to better evaluate excess significance bias and heterogeneity, our current meta-analytic findings meet all of the umbrella review criteria¹⁶ for ‘convincing’ or ‘Class I’ evidence and suggest that neuroticism should be considered among one of the most robust risk factors for incident PD.

Neuroticism is a well-established risk factor for anxiety and mood disorders,² which in turn are related to a higher PD risk and are common comorbid conditions in patients with PD.²⁸⁻³¹ A meta-analysis of two cohort studies^{28, 29} that examined the association between mood disorders and PD risk (HR = 1.79; 95%CI: 1.72 – 1.86)²⁴ found an effect size remarkably similar to the one we observed in our meta-analysis for neuroticism. Of note, the association of neuroticism and PD risk remained significant in models that accounted for current depressive symptoms and ever seen a psychiatrist for anxiety or depression. This latter finding suggests that the association between neuroticism and PD risk is likely to be independent of, and broader than, the effect of anxiety and depression. This pattern has clinical implications. The findings indicate that a higher neuroticism score increases risk of neurodegenerative diseases even among people who do not meet the clinical criteria for psychiatric disorders. With the progression of PD, patients who score higher on neuroticism are also at higher risk of developing comorbid anxiety and mood disorders, higher risk of dementia,⁹ and experience worse quality of life.³² The findings have also implications for research and resonate with the National Institutes of Health emphasis on the research domain criteria framework.³³ In particular, neuroticism can bridge knowledge across the normal to abnormal spectrum of emotional functioning.

While the data suggest a ‘convincing’ association between neuroticism and PD’s risk, high neuroticism could be a prodromal sign more than a PD risk factor. Similar to other risk factors, such as physical activity or mood disorders, reverse causality may contribute to the observed association. The underlying neuropathology that leads to PD is thought to start years before the motor and non-motor symptoms become noticeable. Although unlikely, loss of dopaminergic (e.g., from substantia nigra) or serotonergic neurons (e.g., from dorsal raphe nucleus) could impact fundamental psychological functioning and lead to increases in neuroticism before the emergence of motor symptoms. Unrecognized PD symptoms may also lead to anxiety and distress that could similarly increase neuroticism before the diagnosis. Of note, new knowledge on the early signs of PD in the preclinical and prodromal phases is tremendously valuable to understand the early manifestations of this neurodegenerative disease. Multiple lines of evidence, however, suggest that neuroticism is likely to be a risk factor more than an emerging symptom of PD. First, previous prospective studies had follow-ups that spanned up to 36.8 years, and the associations were even stronger among study participants who completed the neuroticism scale between the ages of 20 and 39.²² Second, contrary to the reverse causality hypothesis, the UK Biobank participants who were later diagnosed with PD had higher neuroticism compared to individuals who already had PD at baseline and neuroticism remained a significant predictor in the sensitivity analysis that excluded incident cases within the first five years of follow-up. Third, the results were essentially unchanged in models that included physical activity, anxiety, and depression measures, which presumably would be impacted by the underlying neurodegeneration¹⁶ more than a stable personality trait.³⁴ Lastly, for other neurodegenerative diseases, a long-term longitudinal study found no increases in neuroticism in the preclinical phase of Alzheimer’s disease, which provides additional evidence against the reverse causality hypothesis.³⁵

The above findings make reverse causality less likely. However, longitudinal studies are needed to thoroughly examine whether there are increases in neuroticism in the preclinical phases of PD that could explain the observed association between neuroticism and PD. Importantly, further research is needed to identify the mechanisms that link neuroticism to the risk of PD. By definition, people with high neuroticism experience more frequent and intense negative emotions, are more vulnerable to stress, and have maladaptive coping skills.³⁶⁻³⁸ From early in life, neuroticism is associated with health-risk behaviors, including physical inactivity and substance use and abuse.³⁹⁻⁴¹ High neuroticism has also been associated with poor motor function, as indexed by slow walking speed,^{42, 43} and worse biomarker profiles, including lower levels of brain-derived neurotrophic factor (BDNF)^{44, 45}. In part through these emotional, behavioral, and physiological vulnerabilities, high neuroticism can undermine brain health and increase the risk of neurodegenerative diseases. The association of neuroticism and incident PD could also partly reflect shared genetic liability⁴⁶. It is worth noting that the largest genome-wide association study of neuroticism⁴⁷ found top hits in the microtubule-associated protein tau (*MAPT*) gene, which is also implicated in PD.⁴⁸⁻⁵⁰

Limitations.

First, because of delays in the diagnosis of PD and because some cases may remain undiagnosed, both the medical and death records may under detect the true number of incident PD cases. In addition, the UK Biobank sample is relatively young, and the study did not account for the use of dopaminergic therapy, which could lead to under or overestimation of PD. However, the lower sensitivity of the ascertainment method is likely to underestimate the actual association between neuroticism and the risk of PD. Furthermore, studies that assessed participants at follow-up with the Unified Parkinson's Disease Rating Scale have reported a similar association between neuroticism and a higher risk of incident parkinsonism.²⁷ Second, some individuals high in neuroticism are hypochondriac and more likely to seek medical care,^{23, 51} which could result in an earlier PD diagnosis. However, Sieurin and colleagues²³ adjusted for the total number of hospital visits for causes other than PD and found that such adjustment did not influence the association of neuroticism and incident PD. Third, our analyses did not account for influential PD related factors, such as REM sleep behavior disorder,⁵² poor olfactions,⁵³ or apathy.⁵⁴ Although our analyses included an item on whether participants had ever seen a psychiatrist for anxiety- or depression-related states, the item was not specific to anxiety. This lack of specificity is a limitation because anxiety is highly related to both neuroticism and PD risk. Fourth, the meta-analytic findings are based on four samples and thus the heterogeneity and publication bias statistics should be interpreted with caution. Fifth, the current literature relies on samples from high-income countries. Research in middle and low-income communities and countries is needed to examine the generalizability of the findings. Of note, the findings in the UK Biobank were not moderated by a socioeconomic deprivation index.

Conclusions.

In summary, data from a large cohort and meta-analysis of prospective studies provide consistent evidence that high neuroticism is associated with a higher risk of incident PD. These findings advance knowledge of the psychological risk factors for PD. More research is needed to assess whether neuroticism can contribute to the early diagnosis of PD. Furthermore, neuroticism is related to the risk of mood disorder and cognitive impairment in the general population, and similar associations are likely to exist among patients with PD. As the disease progresses, neuroticism is also associated with functional status⁵⁵ and quality of life.³²

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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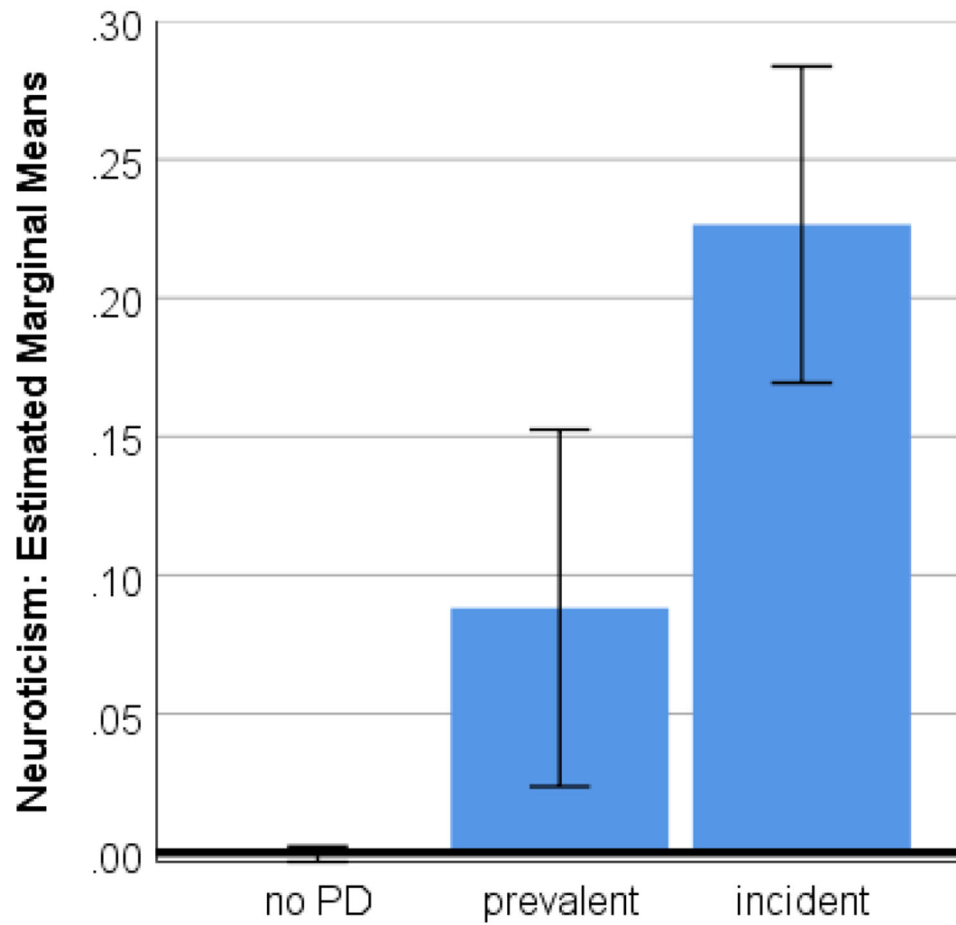
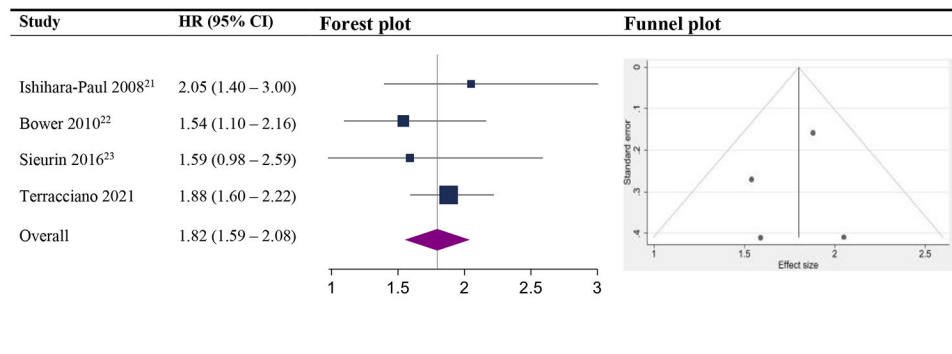


Figure 1.
Neuroticism scores by Parkinson's disease status.

Notes. Age and sex-adjusted means for neuroticism for participants with no diagnosis of Parkinson's disease (no PD; $n = 489,613$), with a diagnosis of Parkinson's disease at baseline (prevalent; $n = 898$), and for those who received the diagnosis of Parkinson's disease during the follow-up (incident; $n = 1,142$).

**Figure 2.**

Forest and funnel plots of the prospective association between neuroticism and the risk of incident Parkinson's disease.

Notes. Ishihara-Paul and colleagues²¹ categorical results were reported by tertiles and the HR and its confidence intervals were taken from a figure. Bower and colleagues²² reported the HR of the top quartile vs. quartile 1-3.

Table 1.

Descriptive statistics for the full sample and by incident Parkinson's disease.

	Total	No PD	Incident PD
N	490,755	489,613	1,142
Neuroticism	0.00 (1.00)	0.00 (1.00)	0.10 (1.04)
Age, years	56.53 (8.09)	56.52 (8.09)	63.42 (5.25)
Follow-up, years	8.88 (1.23)	8.89 (1.22)	5.64 (2.10)
Sex (Women)	267,465 (54.5%)	267,012 (54.5%)	453 (39.7%)
Deprivation Index	-1.32 (3.08)	-1.32 (3.08)	-1.29 (3.13)
Smoking (never)	268,985 (54.8%)	268,405 (54.8%)	580 (50.8%)
Physical Activity	3.65 (1.64)	3.65 (1.64)	3.69 (1.72)
Depressed mood	28,029 (5.7%)	27,953 (5.7%)	76 (6.7%)

Notes: In parenthesis are SD or %. PD = Parkinson's disease. The Deprivation Index is the Townsend deprivation index. Physical Activity is the average number of days participants engaged in walking, moderate, or vigorous activities for at least 10 minutes. Depressed mood is the proportion of participants with Patient Health Questionnaire-2 score ≥ 3 .

Table 2.

Cox regression results of neuroticism predicting the risk of incident Parkinson's disease in the entire cohort and by sex

	Full sample		Women		Men	
	At-risk/PD	HR (95% CI)	PD	HR (95% CI)	PD	HR (95% CI)
Continuous	490755/1142	1.28 (1.21-1.36)	453	1.30 (1.18-1.42)	689	1.27 (1.18-1.37)
Quartile 1	122853/261	-	69	-	192	-
Quartile 2	111084/244	1.14 (0.96-1.36)	94	1.21 (0.89-1.65)	150	1.10 (0.89-1.37)
Quartile 3	134071/304	1.33 (1.13-1.58)	134	1.40 (1.05-1.88)	170	1.30 (1.06-1.60)
Quartile 4	122747/333	1.88 (1.60-2.22)	156	1.92 (1.45-2.55)	177	1.88 (1.53-2.31)

Notes: At-risk/PD refers to the number at risk and the number of incident Parkinson's disease. Quartile 1 (lowest neuroticism score) is the reference group.

Table 3.

Characteristics of samples included in the meta-analysis.

Study	Country	<i>Ntot</i>	<i>NPD</i>	Mean age	Follow-up	Female	Measure
Ishihara-Paul 2008 ²³	UK	20855	175	58.8	7.9	56.5%	EPI
Bower 2010 ²²	USA	6822	156	48.3	29.2	51.4%	MMPI
Sieurin 2016 ²¹	Sweden	29852	197	30.2	36.8	52.4%	EPI
Terracciano 2021	UK	490755	1142	56.5	8.8	54.5%	EPQ-R

Ntot = total sample size; *NPD* = number of incident Parkinson's disease cases; EPI = Eysenck Personality Inventory; MMPI = Minnesota Multiphasic Personality Inventory; EPQ-R = Eysenck Personality Questionnaire-Revised. Follow-up is the mean or median^{22, 23} follow-up. All studies included age and sex as covariates, and Sieurin¹⁸ further included smoking.