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Risk of Parkinson's disease in people with New Onset Anxiety over 50 years - Incidence and Associated Features

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Abstract

Background: Anxiety has been identified as a prodromal feature of Parkinson's disease (PD). The prospective risk of PD in those newly presenting with anxiety and factors that increase the risk of PD in patients with anxiety have not been investigated.

Aim: To investigate the incidence of PD in people with anxiety above the age 50 years and clinical features associated with later diagnosis of PD in people with anxiety.

Design and Setting: Retrospective cohort study using UK primary care data of people between 2008 and 2018 who had new onset anxiety over the age of 50 years.

Method: We fitted Weibull survival regression models and estimated hazard ratios (HR) for modelling time-to-PD in those with and without anxiety and when determining the risk of developing PD in those with anxiety. Results were adjusted for sociodemographic and lifestyle factors and relevant physical and mental health conditions.

Results: The risk of PD was increased 2-fold compared to the non-anxiety group after adjustment for age, sex, social deprivation, lifestyle factors, severe mental illness, head trauma and dementia HR 2.1 (CI: 1.9-2.4). In those with anxiety, the presence of depression, hypotension, tremor, rigidity, balance impairment, constipation, sleep disturbance, fatigue, and cognitive impairment were associated with an increased risk of developing PD.

Conclusion: The risk of developing PD was at least doubled in people with anxiety compared to those without. The clinical features of those who developed PD can help identify patients presenting with anxiety who are in the prodromal phase of PD.

Keywords: Anxiety, Parkinson's, incidence, electronic health records

How this fits in:

Presence of anxiety is known to be increased in the prodrome of Parkinson's.

We investigated the risk of developing Parkinson's in people with anxiety compared to those without anxiety, accounting for a number of confounding variables.

Our results suggest that there is a strong association between anxiety and later diagnosis of Parkinson's in patients over the age of 50 years who present with a new diagnosis of anxiety.

This provides evidence for anxiety as a prodromal presentation of Parkinson's.

Introduction

Anxiety disorders are common in older adults, affecting at least 10-20% of adults over the age of 50 years (1). Age of onset of anxiety disorders is typically in earlier life and incidence in older age has been reported to be associated with subjective memory complaints as well as subsequent cognitive decline (2,3,4).

Parkinson's Disease (PD) is the second most common neurodegenerative condition worldwide, and it is estimated that it will affect 14.2 million people by 2040, mostly due to an increase in life expectancy (5). Patients with PD can be affected by a range of motor and non-motor symptoms (6) and may present with non-motor symptoms such as constipation, depression and olfactory symptoms years before motor symptoms develop (7). Presence of anxiety is known to be increased in the prodrome of PD, but the prospective risk of PD in those with onset of anxiety over age 50 years is not known. In addition, it is unclear whether other prodromal features of PD are present in this population, that may help improve early recognition and elucidate progression of underlying pathology. One population-based cohort study of 174,776 adults below the age of 100 without neurological conditions found that after adjusting for age, sex, medications and comorbidities, patients with a recorded diagnosis of anxiety or an anxiolytic prescription were more likely to develop PD than those without (HR 1.38; CI: 1.26-1.51); and those with more severe anxiety were at greater risk (8). However, this study did not take into consideration important factors, such as lifestyle factors or socioeconomic status, and other prodromal features were not examined.

The Health Professionals Follow-Up Study is a cohort study that used the Crown-Crisp Phobic Anxiety index in 35,815 men aged between 40 and 75 years old and investigated the incidence of PD over 12 years in those with the highest and lowest levels of anxiety (9). There were 189 new cases of PD and after adjusting for age, smoking and caffeine intake the relative risk of PD among men with the highest level of anxiety was 1.5 (CI: 1.0-2.1, p=0.01) compared to men with the lowest level of anxiety. A limitation of this study was that it only focused on male healthcare professionals, who were mostly White Caucasian.

In addition, amongst 156 people who developed PD over a period of 40 years in a cohort study of 7,216 people between 20 and 79 years in Rochester, Minnesota, an anxious personality was associated with an increased risk of PD (HR 1.63, CI: 1.16-2.27) (10).

None of the above studies examined clinical features that could help predict risk of PD. In addition, variables known to be associated with anxiety such as lifestyle factors,

socioeconomic status or presence of comorbidities such as dementia and head injury were not considered. The aim of this study was therefore to investigate the risk for developing PD in people with anxiety compared to those without anxiety, accounting for a number of confounding variables. Furthermore, we sought to identify risk factors for later diagnosis of PD in people presenting with anxiety over the age of 50 years.

Methods

Data source

The data source was The IQVIA Medical Research Database (IMRD) database, which include de-identified data from The Health Improvement Network (THIN), a large UK primary care dataset which provides routinely collected electronic health records that are using the In Practice Systems (IPS), also called Vision GP. Data is recorded using Read Codes, such as diagnoses, symptoms referrals. THIN data includes about 15.6 million patients, of which 3 million are active patients, from 711 practices whose medical records can be prospectively followed (11). There are two main quality markers for these data: 1) the acceptable computer usage (ACU), which is reached when a general practice has, on average, at least two therapy records, one medical record and one additional health data record per patient in a year (12). 2) acceptable mortality reporting (AMR), which is reached when mortality records in a general practice are consistent with the official national statistics (13). We only included data from general practices from when they met the criteria for ACU and AMR in this study. THIN data broadly represents the UK in terms of demographics, social deprivation and chronic diseases (14).

Cohort Identification

Within THIN, we identified all people aged between 50 and 99 years who were registered with a participating practice between 1st January 2008 and 31 December 2018 and had at least one anxiety record in the GP database after at least one year of no previous records of anxiety. We excluded those under 50 years as the population with younger onset Parkinson's may have different characteristics and associations with anxiety. At the time of first record of anxiety, each person was matched with four other unexposed persons based on their sex and age. This selection process ran forward in time, from the initiation until the end of the observation period, setting the matching date for unexposed persons as their index date. An incidence and dynamic cohort study was used, where people can initially act as a control for someone else but can eventually become exposed (i.e. if they later develop anxiety. This approach is known as Exposure Density Sampling (EDS) and has been

validated elsewhere (15). The codelist for defining anxiety cases is provided in Supplementary Box S1.

Outcomes, covariates and analysis

For the main analysis of comparing the risk of developing PD between people with and without anxiety, we fitted Weibull survival regression models for modelling time-to-event for PD, estimating hazard ratios (HR). First, HR estimates were unadjusted, followed by HR estimates adjusted for sociodemographics, i.e., sex, age and social deprivation measured with Townsend index, from least (1) to most (5) deprived quintile (model 1). Townsend score was calculated at lower-layer super output areas (LSOA) level using national census data, grouping into quintile based on the deprivation score. The sociodemographics and lifestyle covariates (smoking, alcohol drinking, body mass index) were included in model 2, while sociodemographics, lifestyle covariates, and relevant physical and mental health conditions were included in model 3. We built the models stepwise to explore the associations accounting for sociodemographic factors only, then the addition of life-style factors and then adding in health conditions which might confound the relationships. All covariates were measured at baseline (i.e., date of anxiety record for each exposed person and their matched controls). A directed acyclic graph (DAG) is shown in Supplementary Figure S1 demonstrating the associations between variables considered as potential confounders in the analysis (16). We used the survival predictions for visualising the trajectory of people with and without anxiety (i.e., survival figures), for both the unadjusted and model 3 estimates. In these figures, we call event-free survival (or PD-free survival) when a person has not presented the outcome at a given time point of follow up.

In order to determine which factors contribute to the prediction of PD in people with incident anxiety from the incident and dynamic cohort described above, we evaluated several risk factors for developing PD (i.e., risk of developing PD given an incident anxiety diagnosis). We examined the presence of risk and prodromal features of PD at any time point between the anxiety diagnosis date up to one year before the date of PD diagnosis. The one-year interval before diagnosis of PD was chosen to account for diagnostic delays for PD. For each risk factor, we determined the risk of developing PD, unadjusted and adjusted for the other risk and prodromal features. For survival models, we evaluated the proportional hazard assumption graphically. Missing data on covariates were handled by multiple imputation with chained equations. Imputation models included one auxiliary variable (i.e., systolic blood pressure) and a Nelson-Aalen estimator. We imputed twenty datasets, specifying 100 iterations for the burn-in period for each chain (one chain per imputation). The survival models were fitted in each of the twenty datasets and their estimates summarised applying

Rubin's rules. Multiple imputation codes are reported in Supplementary Box S2. All estimates were given with 95% confidence intervals (C.I.) using robust standard errors to consider clustering by practice. The statistical analyses were performed using Stata/MP version 16.1 for Windows (17).

Results

Comparing the risk of developing PD in people with and without anxiety

There were 38,510 men and 70,925 women who were diagnosed with a first episode of anxiety; and 324,670 men and 553,586 women in the unexposed group. In the anxiety group, sleep problems, depression, fatigue and constipation were prodromal features that were more common (Table 1).

Of those who had anxiety, 331 developed PD during the follow up period. The median time to diagnosis of PD after the first recorded episode of anxiety was 4.9 years (interquartile range = 5.6).

The incidence of PD in those with and without anxiety was 1.02 (95% CI 0.92-1.13) and 0.49 (95% CI 0.47-0.52) per 1,000 person-years, respectively (Table 2). The risk of PD in people with anxiety was 2-fold the risk of people without, even after adjustment for age, sex, social deprivation, lifestyle factors, severe mental illness, head trauma and dementia (HR 2.1 (95% CI 1.9 – 2.4) (Table 2). Also, people without anxiety survived for a longer period of time without developing a PD event compared to those with anxiety (Figure 1). We also report the absolute risk of having Parkinson's per age band for those with and without anxiety (Supplementary Table S1). This may be helpful for clinicians having discussions with their patients about their risk of Parkinson's, considering their specific age group.

Identifying risk factors for developing PD in people with anxiety

Women (HR 0.4 CI: 0.34-0.50) and those in the most deprived socioeconomic group (HR 0.60 CI: 0.40-0.91) were less likely to be diagnosed with PD. When lifestyle factors were included in the model (smoking, alcohol use and BMI), they were not found to be associated with developing PD. The following symptoms were associated with developing PD in people with anxiety: depression (HR 1.7 CI: 1.1-2.5), sleep disturbance (HR 2.2 CI: 1.5-3.2), fatigue (HR 1.8 CI: 1.3-2.6), cognitive impairment (HR 1.8 CI: 1.1-3.1), hypotension (HR 4.0 CI: 1.7-9.7), tremor (HR 21.3 CI: 14.4-31.5), rigidity (HR 5.1 CI: 1.2-21.2), balance impairment (HR

4.2 CI: 2.1-8.3), constipation (HR 2.6 CI: 1.9-3.6), but not shoulder pain, dizziness, erectile dysfunction and urinary dysfunction (Table 3).

Discussion

Summary

Our results suggest that there is a strong association between anxiety and later diagnosis of PD in patients over the age of 50 years who present with a new diagnosis of anxiety. In people with anxiety, we confirmed that depression, sleep disturbance, fatigue, cognitive impairment, hypotension, tremor, rigidity, balance impairment, and constipation are risk factors for developing PD.

Comparison with existing literature

Our findings are in line with results from previous studies reporting an increased risk of PD in people with previous anxiety (HR 1.38 CI: 1.26-1.51; HR 1.5 CI: 1.0-2.1, HR 1.63 CI: 1.16-2.27) (8,9,10) in a population that is broadly representative of the UK population, even when adjusting for socioeconomic factors, lifestyle factors and confounding conditions such as severe mental illness, head trauma and dementia. It was important to include these conditions, as they have been shown to be associated with both anxiety and PD (18-29). Of note, smoking has consistently negatively been associated with PD, whereas it has been positively associated with anxiety. In this study in patients with anxiety, smoking status was not associated with PD when alcohol use and BMI was also accounted for.

In keeping with PD overall, older people, those in a less deprived socioeconomic group and male individuals with anxiety were at greater risk of a diagnosis of PD. This is similar to the general population, as incidence of a PD diagnosis is known to be higher in older people, males and those from higher socioeconomic groups (30,31). Anxiety, on the other hand, is more common in females and tends to start earlier in life (32). However, mental health is under-reported and under-recognised, including in older people (33), in part due to stigma and negative media portrayal (34). Primary care doctors also under-record anxiety symptoms and diagnoses, sometimes because they do not want to give patients a mental health label (35). It is therefore possible that only more severe forms of anxiety were recorded.

The pattern of clinical features associated with later PD was similar to that reported in the general population previously (36), including motor features (tremor, rigidity, balance

impairment), autonomic features (constipation and hypotension), sleep disturbance, cognitive impairment, and fatigue (37). However, the previously reported features that were not associated with an increased risk of PD were erectile dysfunction, urinary dysfunction, dizziness and shoulder pain. This may be due to these symptoms masking an association of specific presentations such as postural hypotension with later diagnosis of PD, or due to underreporting of these symptoms in general practice. However, as they were previously shown to be associated with later diagnosis of PD in a similar study design, it may also suggest that patients with PD who present with initial anxiety have a specific clinical phenotype with fewer autonomic features. It has been suggested that PD can begin with different phenotypes, reflecting differences in progression pathways.

The condition has been divided using subtyping systems, including according to age-at-onset categories, motor phenotypes and by non-motor symptoms (38), for example the neuropsychiatric subtype, where defining symptoms are anxiety and depression, postural instability, and gait disturbances (39, 40). There are also subtypes according to whether symptoms do or do not start in the brain (brain and body first subtypes) (41). There is increasing evidence for specific non-motor dominant PD phenotypes and subtyping may help guide research and clinical practice, although this may be challenging as PD is highly heterogenous and subtypes are likely to overlap (42). One specific hypothesis suggests that there is a 'brain first' subtype of PD, which starts in the brain and spreads to the peripheral autonomic nervous system, and a 'body first' PD pathology that starts in the enteric or peripheral autonomic nervous system and spreads to the brain (41), leading to presentations with orthostatic hypotension, constipation and olfactory symptoms (43). Onset of PD with anxiety as first presentation may fit into this model of the 'brain first' subtype, with less involvement of peripheral autonomic structures and greater involvement of serotonergic structures involved in early stages (44). Other features of PD that are thought to be related to serotonergic deficits include fatigue, poor sleep and depression (45) which the study also found to be associated with an increased the risk of later PD.

Strengths and limitations

This study used a large electronic health record database which is broadly representative of the UK population. We also included important factors such as socioeconomic status, lifestyle factors and confounding conditions, such as severe mental illness and our results therefore add to what is already known in this area. However, our results are limited by the information entered in the medical records by healthcare professionals, which is primarily added for clinical purposes and not research. Mental health is under-recorded in electronic

health records including in older people (33, 35), in part due to stigma and negative media portrayal (34). It is therefore possible that the true impact of anxiety on subsequent PD incidence is therefore not fully captured in our results due to under-reporting and under-recording.

Implications for research and/or practice

Anxiety is not as well researched as other prodromal features of PD, such as depression. Further research should explore anxiety in relation to other prodromal symptoms and how this symptom complex is associated with the incidence of PD. This may lead be earlier diagnosis and better management of PD. It could also explore if incidence is affected by severity of anxiety and we recommend that further studies are needed to explore why there is an increased risk of PD in people with anxiety over the age of 50.

Conclusion

There was a twofold increase in risk of PD in patients with first presentation of anxiety over the age of 50 years. The clinical features of those who developed PD can help identify patients presenting with anxiety who are in the prodromal phase of PD.

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Ethical approval

No ethical approval was needed as this study analysed data routinely collected from primary care. The Health Improvement Network (THIN) data, also known as IQVIA Medical Research Data, have a REC Reference 18/LO/0441, as visible on the NHS Health Research Authority website. Scientific approval to undertake this study was received from the South East Medical Research Scientific Review Committee at IQVIA (SRC Protocol Number: 21-003). The IQVIA SRC did not request extra participants' consent for this study, and IQVIA counts with all permissions requested by the NHS Health Research Authority. All research methods were carried out in accordance with the NHS Health Research Authority guidelines and regulations.

Competing interest

There are no competing interests to declare.

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Tables

Table 1: Characteristics of people with and without Anxiety (N=987,691)

	Non-Anxiety Cohort (N=878,256)		Anxiety Cohort (N=109,435)	
Characteristic	n	%	n	%
Sex				
men	324670	36.97	38510	35.19
women	553586	63.03	70925	64.81
Age				
50-55	343552	39.12	41794	38.19
55-60	129533	14.75	16288	14.88
60-65	121250	13.81	14869	13.59
65-70	89183	10.15	11056	10.10
70-75	75715	8.62	9724	8.89
75-80	59062	6.72	7656	7.00
80-85	36504	4.16	4868	4.45
85-90	18298	2.08	2505	2.29
90-95	4481	0.51	603	0.55
95-99	678	0.08	72	0.07
deprivation				
least deprived	242499	27.61	28260	25.82
2	214063	24.37	25610	23.40
3	184065	20.96	22803	20.84
4	143140	16.30	19225	17.57
most deprived	94489	10.76	13537	12.37
alcohol				
non drinker	372292	42.39	53538	48.92
ex drinker	175477	19.98	28113	25.69
normal drinker	55944	6.37	9539	8.72
heavy drinker	26271	2.99	5209	4.76
very heavy drinker	864	0.10	183	0.17
missing	247408	28.17	12853	11.74
smoking				
never smoker	372370	42.40	53540	48.92
ex smoker	182842	20.82	29382	26.85
current smoker	128077	14.58	22808	20.84
missing	194967	22.20	3705	3.39

body mass index				
mean(sd)	27.94 (5.61)		27.73 (5.72)	
missing	280128	31.90	13868	12.71
cognitive impairment	16578	1.89	3369	3.10
erectile dysfunction	18767	2.14	2152	2.00
sleep problems	29989	3.41	8813	8.10
balance impairment	3365	0.38	606	0.55
constipation	42838	4.88	9251	8.45
depression	24820	2.83	9900	9.05
dizziness	40392	4.60	6464	5.91
fatigue	51740	5.89	12330	11.27
hypotension	2877	0.33	393	0.36
rigidity	978	0.11	140	0.13
shoulder pain	43297	4.93	4002	3.66
tremor	3445	0.39	703	0.64
urinary dysfunction	3006	0.34	468	0.43

Table 2. Incidence of Parkinson's disease in patients with and without Anxiety (N=987,691).

Group	Incidence (95% CI)*	Unadjusted HR (95% CI)	Model I - HR (95% CI)	Model II - HR (95% CI)	Model III - HR (95% CI)
Non-Anxiety	0.49 (0.47-0.52)	reference	reference	reference	reference
Anxiety	1.0 (0.92-1.1)	2.5 (2.3-2.8)	2.7 (2.4-2.9)	2.7 (2.4-3.0)	2.1 (1.9-2.4)

(*) Incidence per 1000 person-years

*Model I is a Weibull survival model adjusted for **sex, age and deprivation** and for clustering by practice using robust standard errors.*

*Model II is a Weibull survival model adjusted for sex, age and deprivation, **alcohol, smoking, BMI** and for clustering by practice using robust standard errors.*

*Model III is a Weibull survival model adjusted for sex, age and deprivation, alcohol smoking, BMI, **SMI, Head Trauma, Dementia** and for clustering by practice using robust standard errors.*

Table 3. Parkinson's disease risk factors in people with Anxiety (N=109,435).

Variable		Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
sex				
	men	reference	reference	
	women	0.42 (0.35-0.52)	0.40 (0.33-0.49)	0.41 (0.34-0.50)
age				
	50-55	reference	reference	
	55-60	3.4 (2.1-5.4)	3.3 (2.1-5.3)	3.2 (2.0-5.2)
	60-65	4.4 (2.9-6.9)	4.4 (2.8-6.8)	4.0 (2.6-6.3)
	65-70	8.1 (5.3-12.6)	7.9 (5.1-12.2)	7.0 (4.5-11.1)
	70-75	10.2 (6.7-15.7)	9.7 (6.3-14.9)	8.0 (5.1-12.4)
	75-80	8.5 (5.4-13.5)	7.9 (5.0-12.5)	6.5 (4.0-10.6)
	80-85	8.3 (4.9-14.1)	7.5 (4.4-12.9)	6.7 (3.8-11.6)
	85-90	4.4 (1.8-10.6)	3.8 (1.6-9.4)	3.4 (1.4-8.3)
	90-95	11.8 (3.5-39.0)	9.9 (3.0-32.9)	9.8 (2.9-32.8)
	95-99	0 (0-0)	0 (0-0)	0 (0-0)
deprivation				
	least deprived	reference	reference	
	2	0.89 (0.66-1.2)	0.91 (0.68-1.2)	0.91 (0.68-1.2)
	3	1.1 (0.82-1.4)	1.1 (0.86-1.5)	1.1 (0.86-1.5)
	4	0.89 (0.66-1.2)	0.98 (0.72-1.3)	0.97 (0.72-1.3)
	most deprived	0.54 (0.36-0.81)	0.61 (0.40-0.92)	0.60 (0.40-0.91)
alcohol				
	non drinker		reference	
	ex drinker		0.73 (0.21-2.5)	0.73 (0.20-2.6)
	normal drinker		0.77 (0.17-3.5)	0.77 (0.16-3.7)
	heavy drinker		0.68 (0.15-3.2)	0.64 (0.13-3.2)
	very heavy drinker		0 (0-9.1)	0 (0-28.2)
smoking				
	never smoker		reference	
	ex smoker		0.99 (0.30-3.4)	0.99 (0.27-3.6)
	current smoker		0.63 (0.15-2.7)	0.63 (0.14-2.9)
body mass index			0.99 (0.97-1.0)	0.99 (0.97-1.0)
cognitive impairment				1.8 (1.1-3.1)
erectile dysfunction				0.96 (0.42-2.2)

sleep problems	2.2 (1.5-3.2)
balance impairment	4.2 (2.1-8.3)
constipation	2.6 (1.9-3.6)
depression	1.7 (1.1-2.5)
dizziness	0.56 (0.29-1.1)
fatigue	1.8 (1.3-2.6)
hypotension	4.0 (1.7-9.7)
rigidity	5.1 (1.2-21.2)
shoulder pain	0.86 (0.41-1.8)
tremor	21.3 (14.4-31.5)
urinary dysfunction	1.8 (0.44-7.5)

We performed multiple imputation (20 datasets) for bias correction.

Model 1 is a Weibull survival model adjusted for ***sex, age and deprivation*** *and for clustering by practice using robust standard errors.*

Model 2 is a Weibull survival model adjusted for sex, age and deprivation, ***alcohol, smoking, BMI*** *and for clustering by practice using robust standard errors.*

Model 3 is a Weibull survival model adjusted for sex, age and deprivation, alcohol smoking, BMI, ***cognitive impairment, erectile dysfunction, sleep problems, balance impairment, constipation, depression, dizziness, fatigue, hypotension, rigidity, shoulder pain, tremor, urinary dysfunction,*** *and for clustering by practice using robust standard errors.*

Figures

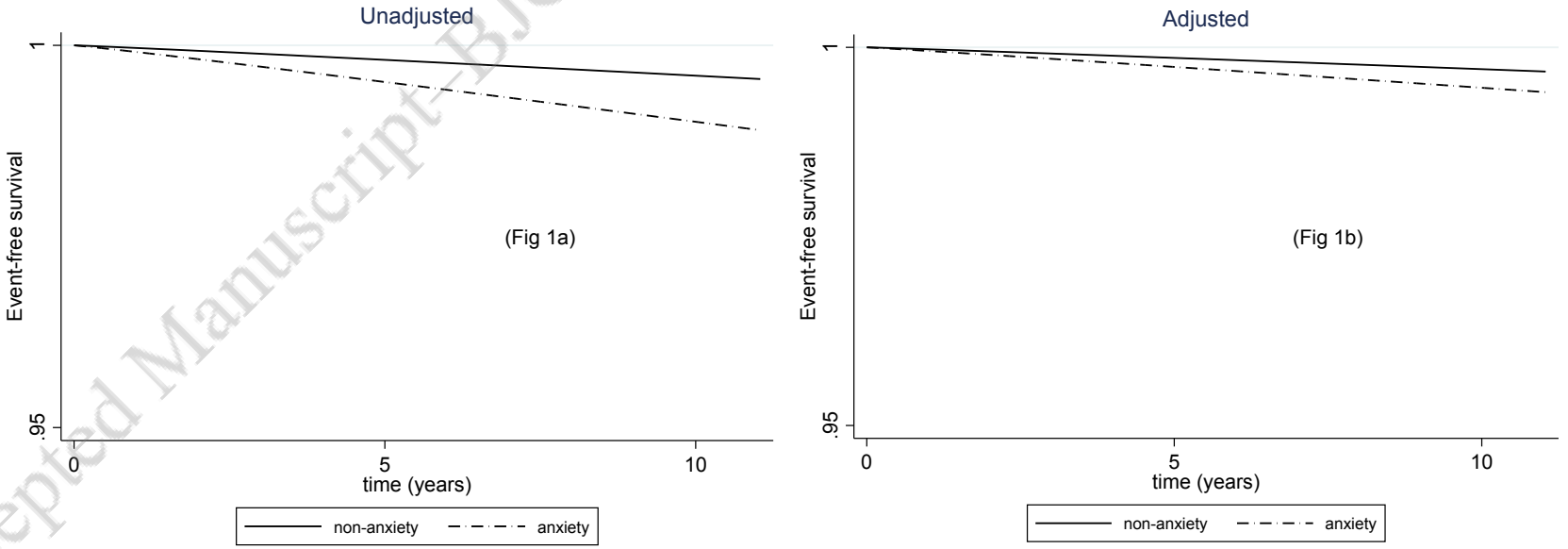

Figure 1. Predicted Parkinson's Disease-free survival for people with and without anxiety

Adjusted for sex, age and deprivation, alcohol smoking, BMI, cognitive impairment, erectile dysfunction, sleep problems, balance impairment, constipation, depression, dizziness, fatigue, hypotension, rigidity, shoulder pain, tremor, urinary dysfunction, and for clustering by practice (using robust standard errors).