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Original research

Neuroanatomical and prognostic associations of depression in Parkinson's disease

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ABSTRACT

Background Depression is reported as a risk factor, prodromal feature and late consequence of Parkinson's disease (PD). We aimed to evaluate the timing, neuroanatomy and prognostic implications of depression in PD.

Methods We used data from 434 023 participants from UK Biobank with 14.1 years of follow-up. Multivariable regression models established associations of depression with incident PD and regional brain volumes. Cox proportional hazards models assessed prognostic associations of depression in PD with incident dementia and all-cause mortality.

Results Of 2632 individuals with incident PD, 539 (20.5%) were diagnosed with depression at some point. Depression was associated with an increased risk of subsequent PD (risk ratio 1.53, 95% CI 1.37 to 1.72). Among incident PD cases, depression prevalence rose progressively from 10 years pre-PD diagnosis (OR 2.10, 95% CI 1.57 to 2.83) to 10 years postdiagnosis (OR 3.51, 95% CI 1.33 to 9.22). Depression severity in PD was associated with reduced grey matter volume in structures including the thalamus and amygdala. Depression prior to PD diagnosis increased risk of dementia (HR 1.47, 95% CI 1.05 to 2.07) and mortality (HR 1.30, 95% CI 1.07 to 1.58).

Conclusions This large-scale prospective study demonstrated that depression prevalence increases from 10 years before PD diagnosis and is a marker of cortical and subcortical volume loss. Depression before PD diagnosis signals a worse prognosis in terms of dementia and mortality. This has clinical implications in stratifying people with poorer cognitive and prognostic trajectory in PD.

INTRODUCTION

Parkinson's disease (PD) is associated with a range of neuropsychiatric features including disorders of affect, motivation and perception.¹ The most common among these is depression, which is estimated to affect 35% of individuals with PD.² Depression has been shown to become more prevalent in advanced PD³ and is sometimes interpreted as a reactive consequence of motor disability. However, depression has also been shown to be common at the time of PD diagnosis and longitudinal cohort studies have suggested that it can occur prior to the onset of motor symptoms as a consequence of early neuropathological changes.⁴ An alternative view is that depression might be a causal risk factor for PD^{5,6} which reflects neurodegenerative changes. In

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Depression has been reported as a risk factor, prodromal feature and consequence of Parkinson's disease (PD).

WHAT THIS STUDY ADDS

⇒ We evaluated the timing, neuroanatomical associations and prognostic implications of depression in PD. This large-scale prospective study of 2632 people with PD demonstrated that the prevalence of depression increases from 10 years prior to PD diagnosis and is associated with cortical and subcortical volume loss. Depression prior to PD diagnosis signals a worse prognosis in terms of dementia and mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Depression in PD is associated with poorer prognosis and neurodegeneration; this has clinical implications in stratifying people with poorer cognitive and prognostic trajectory in PD.

support of this hypothesis, neuroimaging studies have demonstrated an association between depression in PD and loss of white matter connectivity in specific networks.^{7,8}

Depression has a substantial impact on people with PD and, in some patients, is the largest determinant of quality of life.⁹ There is some evidence to suggest that depression is associated with poorer PD prognosis¹⁰ including neurological outcomes (eg, motor severity),¹¹ disability,¹² cognitive decline¹³ and death.¹⁴ However, the temporal relationship between depression in PD and the effect this has on disease prognosis has not been comprehensively evaluated in a large longitudinal cohort study. Additionally, few studies have included neuroimaging data when evaluating prognostic and temporal associations of depression in PD.

We aimed to comprehensively evaluate the timing, neuroanatomical associations and prognostic implications of depression in PD in a large prospective longitudinal population cohort. We identified a nested cohort of participants with PD, and hypothesised that within this cohort; depression would be associated with reduced regional brain volumes; become increasingly common in the years prior to PD diagnosis; that depression would be associated



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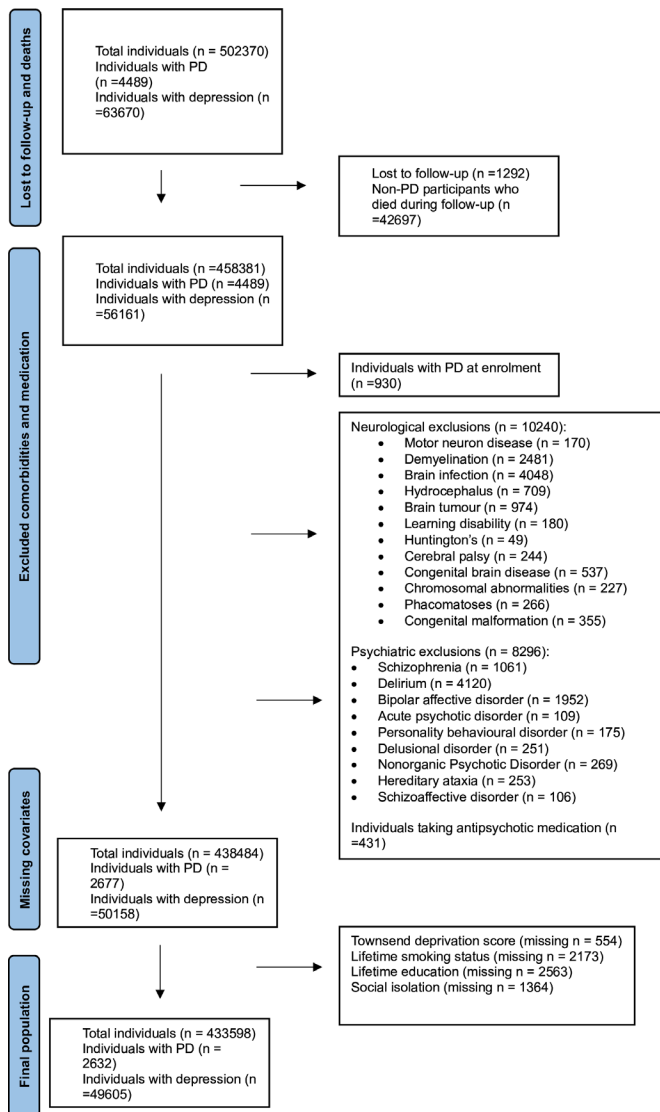


Figure 1 Participant flow chart. The figure shows the inclusion and exclusion decisions with relative numbers of participants at each stage and detailed reasons for exclusion. PD, Parkinson's disease.

with greater intensity and extent of neurodegenerative change as indexed by regional brain volumes; that depression would signal increased risk of dementia and death among those with PD.

METHODS

The separate analyses used have been described in online supplemental table 1.

Cohort

UK Biobank is a national cohort study including over 500 000 participants in the UK, recruited between 2006 and 2010, the detailed methods of which have been described elsewhere.¹⁵ Data were extracted on 10th March 2023 and included a mean follow-up duration of 14.1 years. Individuals with PD at baseline, psychiatric comorbidity other than depression and anxiety (which is frequently comorbid with depression and shares similar risk factors¹⁶), neurological comorbidity other than PD and those taking antipsychotic medication (as defined in Pillinger *et al*¹⁷) were excluded (see figure 1 for a detailed breakdown). For the analysis evaluating the association between

depression in PD and subsequent dementia, individuals who developed dementia prior to PD were excluded. A sensitivity analysis excluding cases of PD diagnosed within 2 years of enrolment was also conducted (online supplemental materials) to address the possible issue of prevalence spill-over. To ascertain the neuroanatomical correlates of depression symptom severity, all individuals with PD with complete MRI brain imaging data and who completed depressive symptom severity questionnaires at the time of imaging were included.

Exposure and outcome definitions

Depression, PD and dementia diagnoses, and date of diagnoses, were ascertained through linked primary healthcare records, inpatient hospital records, self-report and death certificate registration (see online supplemental table 2). A sensitivity analysis was conducted where only primary healthcare and inpatient hospital records were used to define depression diagnosis (online supplemental materials). Death was ascertained through death certificate registration. Depression symptom severity at enrolment was assessed as per Lyall *et al*,¹⁸ which is an abridged version of the Patient Health Questionnaire-9 (PHQ-9) depression assessment tool, and uses four questions to probe key depressive symptoms:

‘Over the past 2 weeks, how often have you...

- ▶ ... felt down, depressed or hopeless?’
- ▶ ... had little interest or pleasure in doing things?’
- ▶ ... felt tense, fidgety or restless?’
- ▶ ... felt tired or had little energy?’

Responses could be graded ‘not at all’, ‘several days’, ‘more than half days’ and ‘nearly every day’. Questions were combined into a depressive symptom score from 0 to 12. Cut-off scores for depression severities were translated from the corresponding scores on the full PHQ-9, resulting in the following thresholds:

- ▶ Subthreshold depressive symptoms <2.22.
- ▶ Mild depressive symptoms <4.44.
- ▶ Moderate depressive symptoms <6.66.
- ▶ Moderately-severe depressive symptoms <8.8.
- ▶ Severe depressive symptoms >8.88.

To ascertain the neuroanatomical correlates of depression in PD, a total of 273 image-derived phenotypes (IDPs) were analysed from T1-weighted images, which were preprocessed by the UK Biobank imaging pipeline.¹⁹ These included regional grey matter volumes derived from FSL FAST, subcortical volumes derived from FSL FIRST and subcortical FreeSurfer subsegmentation. Of 159 individuals with PD and complete imaging data, 5 were missing depression severity questionnaire data at the time of imaging, consequently brain imaging analysis was possible for 154 participants with PD.

Statistical analysis

Statistical analysis was performed in R V.4.2.2 (R Project for Statistical Computing). Data wrangling was performed in both R V.4.2.2 and MATLAB V.23.2 R2023b (MathWorks). This research utilised Queen Mary's Apocrita HPC facility, supported by QMUL Research-IT (<http://doi.org/10.5281/zenodo.438045>).

Analyses and study designs used for the respective questions have been summarised in online supplemental table 1.

To ascertain whether depression was associated with an increased risk of PD, risk ratios (RRs) and 95% CIs were calculated using multivariable logistic regression with depression (diagnosed prior to PD) as the exposure, PD diagnosis following enrolment as the outcome and adjusting for age (at enrolment),

Table 1 Baseline characteristics of the UK Biobank sample among participants who went on to develop PD and those who did not

	Individuals who developed PD (n=2632)	Individuals who did not develop PD (n=430 966)	Test statistic; p value; 95% CI
Age (median, IQR)	64.0 (60.0–67.0)	57.0 (49.0–63.0)	T=62.8 <0.001 (6.47 to 6.88)
Sex (female)	1030 (39.1%)	240 537 (55.8%)	$\chi^2=294.3$ <0.001
Ethnicity	2522 (95.8%) white, 48 (1.8%) Asian 21 (<1%) black, 10 (<1%) mixed, 18 (<1%) other, 13 (<1%) not reported	406 193 (94.3%) white, 9904 (2.3%) Asian, 7014 (1.6%) black, 2590 (<1%) mixed, 3942 (<1%) other, 1347 (<1%) not reported	$\chi^2=23.8$ <0.001
Townsend socioeconomic status	Quintile 1 (least deprived): 1108 (42.1%) Quintile 2: 945 (35.9%) Quintile 3: 423 (16.1%) Quintile 4: 153 (5.8%) Quintile 5 (most deprived): 3 (<1%)	Quintile 1 (least deprived): 173 655 (40.3%) Quintile 2: 157 543 (36.6%) Quintile 3: 70 455 (16.3%) Quintile 4: 26 913 (6.2%) Quintile 5 (most deprived): 2400 (<1%)	$\chi^2=12.6$ 0.014
Education level	College: 1150 (43.7%) Secondary education: 802 (30.5%) No secondary education: 680 (25.9%)	College: 210 610 (48.9%) Secondary education: 150 253 (34.9%) No secondary education: 70 103 (16.3%)	$\chi^2=175.6$ <0.001
Smoking status across lifetime (ever smoker)	1585 (60.1%)	255 216 (59.2%)	$\chi^2=1.04$ 0.307
Depression prevalence	539 (20.5%)	49 066 (11.4%)	$\chi^2=212.6$ <0.001
Depression severity	None: 1046 (39.7%) Subthreshold: 879 (33.4%) Mild: 383 (14.6%) Moderate: 127 (4.8%) Moderately severe: 52 (2.0%) Severe: 43 (1.6%)	None: 166 206 (38.6%) Subthreshold: 148 874 (34.5%) Mild: 66 874 (15.5%) Moderate: 19 390 (4.5%) Moderately severe: 8608 (2.0%) Severe: (1.5%)	$\chi^2=4.44$ <0.488

PD, Parkinson's disease.

age², age³, sex, socioeconomic status (Townsend Deprivation Score), lifetime smoking status, education, social isolation and family history of PD. Education level was measured according to individuals who had a college degree, secondary education or lack of secondary education. There were very low levels of missing data: among individuals who developed PD (n=2677), missing covariate data were highest for education n=26 (0.97%), lifetime smoking status n=20 (0.75%) and socioeconomic status n=4 (0.15%). In all analyses, complete-case analysis was used as there were low levels of missingness (online supplemental table 3).

To ascertain the temporal relationship between depression and PD, a nested case–control design and survival analysis was used to calculate ORs. PD cases (who developed PD after enrolment in UK Biobank) were matched to their nearest neighbour controls on age, socioeconomic status (Townsend Deprivation Score), lifetime smoking status, education and were matched exactly on sex and enrolment year, using the MatchIt program in R (R Project for Statistical Computing). This resulted in an average of six matched controls per case with at least one match per case. For the survival analysis, the age at PD diagnosis in cases was used as the index date for the relevant matched controls. The outcome was depression diagnosis and participants who were not diagnosed with depression were censored if they died or were lost to follow-up. For the survival analysis, the time variable was measured as the minimum interval between PD diagnosis (or matched date of diagnosis in controls) and depression, death or completion of follow-up. HRs and 95% CIs intervals for depression prior to PD diagnosis were calculated.²⁰ A flexible parametric model with 3 df was used to graphically display

the trajectory of HRs for depression diagnosis in PD cases compared with matched controls relative to the index date.²¹

A multivariable linear regression model was used to ascertain the neuroanatomical correlates of depression in PD. Depression symptom severity was assessed using the severity scores described above but assessed at the same follow-up session as neuroimaging assessment. Neuroanatomical correlates were assessed using the 273 normalised IDP volumes. This was adjusted for intracranial volume, MRI centre, age, age², age³, interval from PD diagnosis to enrolment in the study and corrected for multiple testing using the false discovery rate with alpha 0.05.²²

To ascertain the relationship between depression and PD prognosis, RRs and 95% CIs were calculated using multivariable logistic regression in a sample of individuals who developed PD following enrolment. For the mortality analysis, depression (diagnosed prior to PD) was the exposure and all-cause mortality was the outcome, adjusting for age, sex, education, socioeconomic status, cardiovascular disease, obesity, diabetes mellitus and smoking. For the dementia analysis, individuals who developed dementia prior to PD were excluded. Depression (diagnosed prior to PD) was the exposure and dementia (following PD diagnosis) was the outcome, adjusting for age, sex, education, socioeconomic status and smoking. To explore the temporality of the relationship between depression and PD prognosis, a Cox proportional HR was used, adjusting for the same covariates as per the multivariable logistic regression and displayed graphically.

All variable definitions are specified in more detail in online supplemental table 4.

Table 2 ORs for depression diagnosis in Parkinson's disease (PD) cases relative to matched controls at different time periods relative to PD diagnosis

Time period (years relative to PD diagnosis)	OR of depression diagnosis (in PD group vs matched controls)	Lower CI	Upper CI	P value
<-20	1.38	1.11	1.70	0.003
-20 to -15	1.35	0.95	1.90	0.094
-15 to -10	1.65	1.23	2.23	<0.001
-10 to -5	2.10	1.57	2.83	<0.001
-5 to 0	2.70	2.06	3.53	<0.001
0 to 5	3.01	2.26	4.02	<0.001
5-10	2.35	1.41	3.91	0.001
>10	3.51	1.33	9.22	0.011

RESULTS

Descriptive statistics

We identified a total of 2632 individuals with incident PD, after excluding individuals who had PD at baseline (n=930), had a psychiatric comorbidity other than depression (n=873), used an antipsychotic medication (n=9) or were missing important covariate data (n=45) (see figure 1 for detailed reasons for exclusions). PD diagnosis was predominately through hospital and primary care records (n=2188 hospital, n=284 primary care, n=51 death records, n=109 self-report). The median age at PD diagnosis was 72.4 (IQR 67.9–76.1), and median interval from enrolment to PD diagnosis was 9.40 years (IQR 6.51–11.8). Ethnicity was reported in 2619 incident PD cases, 2522 (95.8%) were white, 48 (1.8%) Asian, 21 (<1%) black, 10 (<1%) mixed, 18 (<1%) other and 13 (<1%) not reported (table 1). The prevalence of depression among individuals with incident PD was 20.5% (539/2632).

Temporal association between depression and PD

Considering the cohort as a whole, diagnosis of depression was associated with an increased risk of developing PD during the follow-up period (RR 1.53, 95% CI 1.37 to 1.72, $p<0.001$), after controlling for age, sex, socioeconomic status, education, life-time smoking status, social isolation and family history of PD. Case-control analysis of the time of depression diagnosis in PD cases compared with matched controls showed that the risk of depression began to increase in the years approaching PD diagnosis and continued to increase in the years following PD diagnosis, up to the last date of follow-up (table 2). This can be visualised using the flexible parametric model of HRs over time for depression diagnosis in PD cases compared with matched controls (figure 2).

Depression symptom severity also increased in the years prior to PD diagnosis. Average depression score was highest in the 1 year preceding PD diagnosis 1.98 (95% CI 1.54 to 2.42), compared with matched controls (1.36 (95% CI 1.20 to 1.52)) (online supplemental figure 1).

Depressive symptom severity at baseline was associated with risk of incident PD in a dose-dependent manner, after adjusting for age, sex, socioeconomic status, education, life-time smoking status, social isolation and family history of PD (online supplemental table 5, figure 3). Severe depression was associated with an RR of 2.04 (95% CI 1.50 to 2.80) and mild depression was associated with an RR of 1.34 (95% CI 1.19 to 1.51). There was a significant trend in the RRs with worsening depression severity (Z: 24.0, $p<0.001$, 4 df), measured with the Cochran-Armitage test of trend.

Grey matter associations of depressive symptoms in PD

Among individuals with PD, greater depression symptom severity was associated with reduced grey matter volume in 18 brain regions, distributed bihemispherically and predominantly comprising subcortical structures including

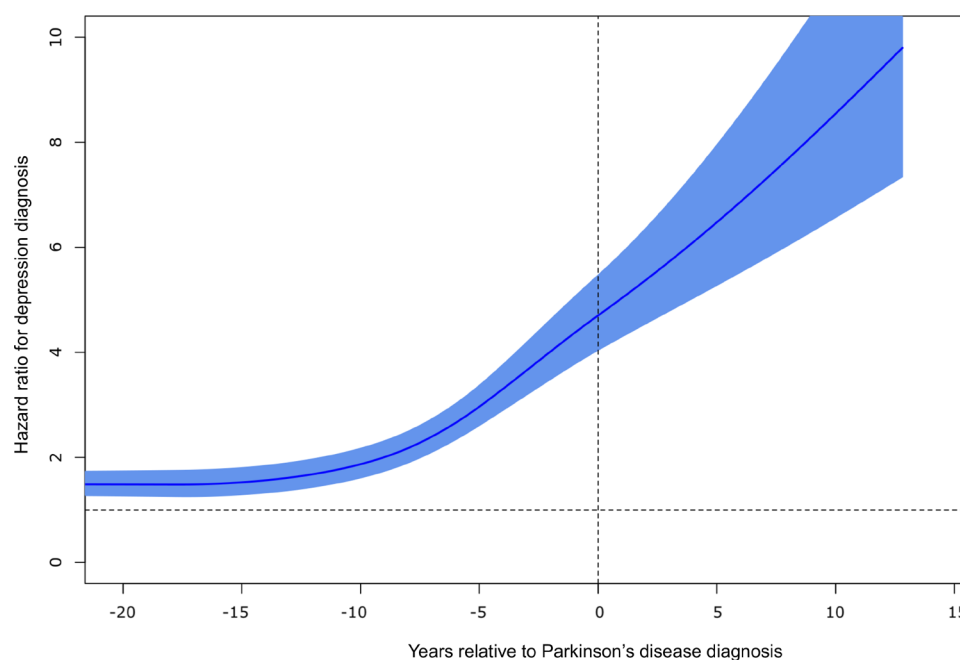


Figure 2 Trajectory of HRs for depression diagnosis over time in Parkinson's disease cases compared with matched controls. The figure shows a flexible parametric model of HRs for depression in those with Parkinson's disease relative to those without, aligned to year of Parkinson's disease diagnosis (or age-matched year for healthy controls). The shaded area represents a 95% CI.

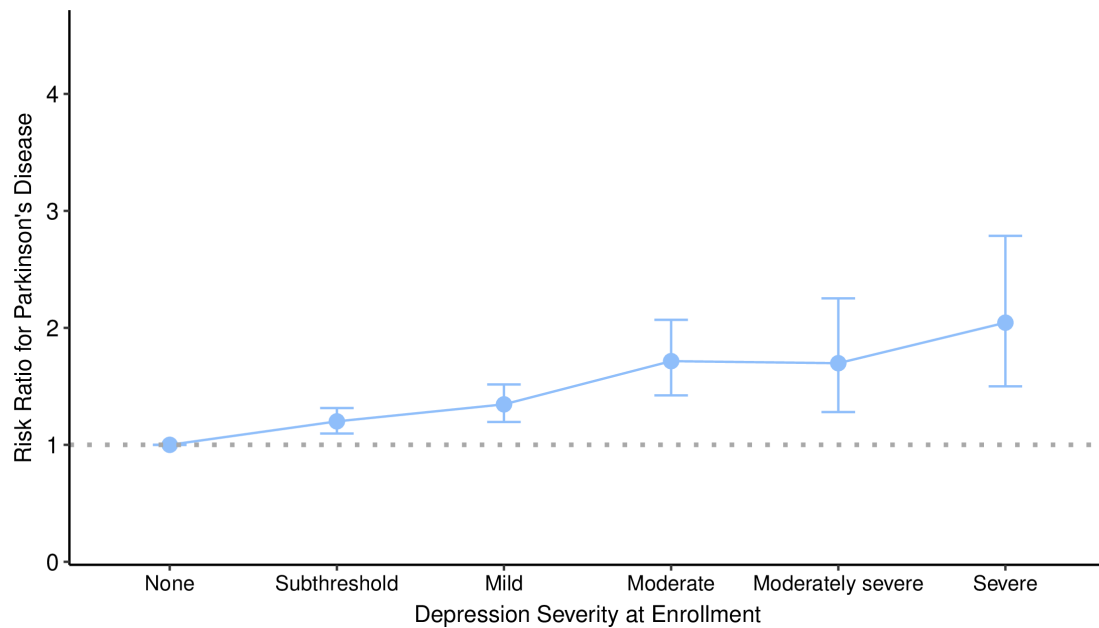


Figure 3 Depression severity at enrolment and risk ratio for incident Parkinson's disease (PD). The figure shows the risk ratio of varying depression symptom severity at enrolment and subsequent PD diagnosis, adjusting for age, age², age³, sex, socioeconomic status (Townsend deprivation score), lifetime smoking status, and education, social isolation and family history of PD. The width represents the 95% CI.

the thalamus and amygdala but also several cortical regions (frontal pole, occipital pole, temporal gyrus), after adjusting for intracranial volume, MRI centre, age, age², age³ and interval from PD diagnosis to enrolment in the study (table 3, figure 4).

Association of all-cause mortality with the presence of depression preceding PD diagnosis

The presence of depression occurring before the time of PD diagnosis was associated with an increased risk of all-cause mortality (RR 1.40, 95% CI 1.09 to 1.80), after controlling for age, sex, education, socioeconomic status, cardiovascular disease, obesity, diabetes mellitus and smoking). The risk

of mortality was highest among individuals who developed depression in the 3 years immediately prior to PD onset (RR 4.01 (95% CI 2.22 to 7.24)) (online supplemental table 6). Depression diagnosis following PD diagnosis was not associated with an increased risk of mortality (RR 1.40 (95% CI 0.91 to 2.16)); consequently only depression diagnosis in the immediate period preceding PD diagnosis conferred a higher mortality risk.

The Cox proportional HR for depression (onset prior to PD) and mortality was 1.30 (95% CI 1.07 to 1.58), when adjusting for age, sex, education, socioeconomic status, cardiovascular disease, obesity, diabetes mellitus and

Table 3 Grey matter associations of depression symptom severity among individuals with Parkinson's disease

Grey matter region (UK Biobank field ID):	beta	SE	t	P _{FDR} *
Left temporal pole (2579)	-0.221	0.049	-4.490	0.004
Left lateral posterior thalamic nucleus (26687)	-0.204	0.053	-3.866	0.023
Left central lateral thalamic nucleus (26681)	-0.172	0.054	-3.203	0.043
Right anterior superior temporal gyrus (25799)	-0.172	0.052	-3.271	0.043
Right frontal pole (25783)	-0.171	0.049	-3.476	0.043
Right ventral lateral posterior nucleus (26707)	-0.168	0.053	-3.153	0.043
Right amygdala (26619)	-0.168	0.050	-3.368	0.043
Right occipital pole (25877)	-0.167	0.051	-3.256	0.043
Right basal nucleus (26611)	-0.167	0.050	-3.319	0.043
Right lateral nucleus (26610)	-0.164	0.050	-3.251	0.043
Right occipitotemporal fusiform cortex (25859)	-0.162	0.052	-3.097	0.043
Left lateral nucleus (26600)	-0.159	0.052	-3.077	0.043
Left amygdala (26609)	-0.157	0.051	-3.069	0.043
Right corticoamygdala transition zone (26617)	-0.156	0.050	-3.146	0.043
Right planum-polare (25869)	-0.156	0.050	-3.136	0.043
Left frontal pole (25782)	-0.154	0.050	-3.109	0.043
Right posterior superior temporal gyrus (25801)	-0.152	0.050	-3.052	0.043
Right accessory basal nucleus (26612)	-0.149	0.049	-3.007	0.047

*FDR correction.
FDR, false discovery rate.

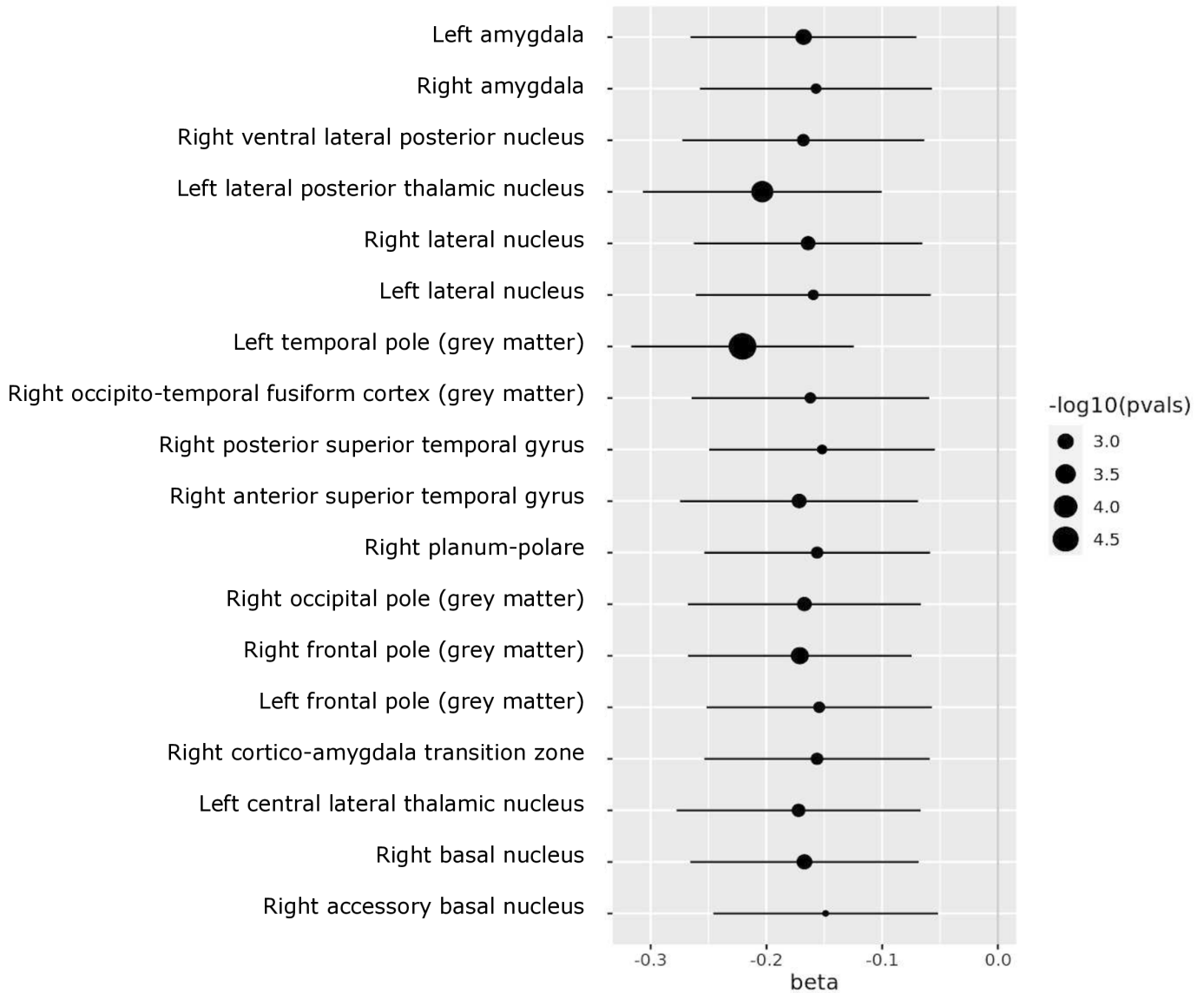


Figure 4 Grey matter associations of depression symptom severity among individuals with Parkinson’s disease (PD). The figure shows individual brain regions (image derived phenotypes) and the association (beta regression coefficient) with depression symptom severity (measured at the MRI visit) in people with PD, adjusting for intracranial volume, MRI centre, age, age², age³ and interval from PD diagnosis to enrolment in the study, with FDR correction. Error bars represent 95% CIs and the size of the dot represents the FDR adjusted p value. FDR, false discovery rate.

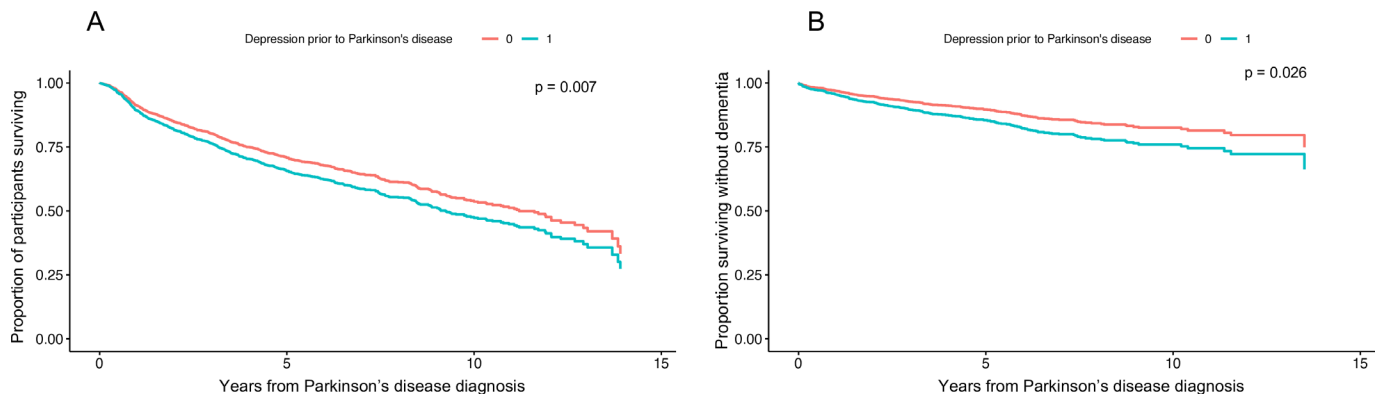


Figure 5 (A) Cox proportional hazards model of depression prior to Parkinson’s disease (PD) and risk of all-cause mortality. The figure shows the Cox proportional hazards model of depression diagnosis (prior to PD) and risk of all-cause mortality, in people with PD over time (years from PD diagnosis). (B) Cox proportional hazards model of depression prior to PD and risk of dementia. The figure shows the Cox proportional hazards model of depression diagnosis (prior to PD) and risk of dementia, in people with PD over time (years from PD diagnosis).

smoking. The Cox model is displayed graphically over time from Parkinson's diagnosis in figure 5.

Association of incident dementia risk with depression occurring prior to a PD diagnosis

Depression occurring prior to PD diagnosis was associated with an increased risk of subsequent incident dementia, RR 1.49 (95% CI 1.07 to 2.05), after controlling for age, sex, education, socioeconomic status and smoking. The risk of dementia was highest among patients who developed depression more than 5 years prior to PD onset RR 1.73 (95% CI 1.16 to 2.58).

The Cox proportional HR for depression (onset prior to PD) and subsequent dementia was 1.47 (95% CI 1.05 to 2.07), when adjusting for age, sex, education, socioeconomic status and smoking. The Cox model is displayed graphically over time from PD in figure 5.

In the first sensitivity analysis, PD cases diagnosed within 2 years of enrolment in UK Biobank (n=111) were excluded to prevent prevalence spillover. The associations detected remained significant (online supplemental materials).

In the second sensitivity analysis, only primary healthcare and inpatient hospital records were used to define depression diagnosis. The associations detected also remained significant (online supplemental materials).

DISCUSSION

Here, we have shown using a large-scale prospective population cohort that depression becomes progressively more common in PD from 10 years prior to diagnosis, and prevalence continues to rise in the years following diagnosis. Depressive symptom severity in people with PD was associated with predominantly subcortical grey matter volume loss (including the bilateral thalami and amygdalae). Prediagnostic depression was associated with increased risk of dementia and all-cause mortality.

The increased risk of PD among those with depression, and the increasing risk with more severe depression symptoms that we have shown are in line with previous population studies in other countries. For example, a large-scale longitudinal cohort study from Sweden, which demonstrated an increased risk of PD in people with depression, found that risk of PD was highest in the 5 years following depression diagnosis.⁵ Similar to our findings, a dose-dependent relationship with depression severity and subsequent PD was also shown. Temporal and dose-dependent associations have been used to evaluate whether depression is an early prodromal symptom or causal risk factor in PD.⁵ Causal risk factors would exert a greater effect on the outcome with more prolonged exposure. In contrast, the association between depression and PD was greatest when depression occurred just prior to PD diagnosis. This suggests that the epidemiological association is predominantly due to depression being caused by prediagnostic PD rather than depression as a causal risk factor for PD. The subsequent continued increase in prevalence after PD diagnosis is consistent with longitudinal cohort studies of PD demonstrating an increase in neuropsychiatric disorders up to 5 years following PD diagnosis⁴ and in the later stages of PD.³

Our findings of increased incident dementia risk and mortality provide high-quality longitudinal evidence that depression in PD indicates an adverse prognosis, without the risk of recall bias inherent in disease cohort studies. This amplifies previous evidence associating depression in PD with a range of prognostic outcomes in smaller cohorts, including motor complications,²³ care home admission,²⁴ disability²⁵ and mild cognitive

impairment.²⁶ Reports of associations between depression and mortality in PD have been inconsistent and are based on heterogeneous populations and small numbers of subjects.^{14 26 27} Our finding that increased mortality risk continued to widen up to the end of follow-up suggests that larger and longer cohort studies are required to reveal the true magnitude of this effect.

More specifically, our survival analyses found that depression developing within a few years prior to PD diagnosis conferred a poorer prognosis in terms of incident dementia and all-cause mortality, whereas more long-standing depression or depression developing following PD diagnosis did not show the same prognostic associations. This suggests that prodromal depression might be signalling the presence of specific patterns of underlying disease biology that expedite these outcomes. However, we could have been underpowered to find an association between postdiagnostic depression and poorer prognosis. The regional brain volume associations suggest two possible mechanisms: the distributed grey matter atrophy might suggest that depression is indexing neurodegenerative intensity more broadly, whereas the association with limbic structures such as the amygdala raises the possibility that depression might be a consequence of neurodegeneration in a specific brain network that regulates affect. This is consistent with structural neuroimaging studies of major depressive disorder (outside of PD), where limbic regions including the amygdala and distributed cortical regions (mainly cingulate) have been implicated.²⁸

The setting for this study provides both strengths and limitations. The size, follow-up length, prospective nature and population basis of the UK Biobank cohort mean that the analysis was powered to show novel temporal and prognostic associations without risk of recall bias. However, there would be greater certainty in the reliability of PD, depression and dementia diagnoses in a more intensively phenotyped disease cohort. This also precludes adjustment for PD-specific assessment measures in our analyses. Depression severity was assessed using a previously adopted method,¹⁸ which has not been comprehensively validated and it could have been affected by antidepressant medication which was not accounted for in these analyses. There is also a risk that the UK Biobank cohort is over-representative of healthier and wealthier members of the population from which it was drawn, which might have introduced bias into some of the associations. Additionally, these results could be liable to survival and collider bias. Future work should focus on combining this large longitudinal population cohort approach with biomarkers that would help to further disentangle the underlying mechanisms of depression in PD. For example, corroboration of underlying neuropathological change with specific markers of alpha-synuclein and Alzheimer's disease pathology.

CONCLUSION

This large-scale prospective study found that depression is a common prediagnostic feature in PD, is a marker of cortical and subcortical volume loss and signals a poor prognosis in terms of incident dementia and all-cause mortality. From a clinical standpoint, this study underscores the importance of screening for depression in PD, and the role that depression might play in guiding stratification and individualised counselling in patients with PD.

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Contributors JBB completed the data analysis and manuscript write-up. AP contributed to data analysis and manuscript write-up. BMJ contributed to data analysis and manuscript write-up. AJN provided advice on the analysis plan and manuscript. CRM obtained funding, conceptualised the study, contributed to

manuscript write-up, provided advice on the analysis plan and manuscript, and is the guarantor of the work. SW completed data wrangling, contributed to data analysis and manuscript write-up.

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Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data may be obtained from a third party and are not publicly available. Data include a range of demographic, clinical and neuroimaging information on over 500 000 participants recruited from across the UK. These data are held by the UK Biobank (<https://www.ukbiobank.ac.uk/>) and access is available to any bona fide researcher proposing a health-related project that is in the public's interest. Researchers must be registered with the UK Biobank's Access Team.

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