Psychomotor retardation and risk of Parkinson's disease in unipolar depression: a retrospective cohort study

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Introduction

Previous cohort studies have identified a strong relationship between **depression** and subsequent **Parkinson's disease (PD)**. As a result, depression has been proposed as a prodromal symptom, or possibly a risk factor for PD[1]. However, to date no studies have focused on whether specific depressive psychopathology increases this risk.

Psychomotor retardation (or slowing) is a feature of depression and is defined as a slowing down of thought, and reduction of physical movements in an individual. **Psychomotor retardation** is often associated with more severe depressive or psychotic episodes, but is also a characteristic feature in **PD**.

We hypothesised that in individuals with depression, the presence of **psychomotor retardation**, is associated with a greater risk of incident **PD** diagnosis.

Aim

We conducted a retrospective cohort study using electronic patient record data to evaluate whether psychomotor retardation is associated with a greater risk Parkinson's disease amongst adults with major depressive disorder.

- Sample – Adults with an ICD-10 diagnosis of **F32 depressive episode** or **F33 recurrent depressive disorder** at age of diagnosis ≥40.
- Exposure – Presence of **psychomotor retardation**.
- Comparator – Any individuals with an ICD-10 diagnosis of **F32 depressive episode** or **F33 recurrent depressive disorder** without **psychomotor retardation** or with **psychomotor agitation**.
- Outcome – incident **Parkinson's disease** diagnosis (G20, F02.3).

Methods

The **South London and Maudsley Clinical Record Interactive Search (CRIS)** system was used to identify patients retrospectively from electronic health care record data **(02/01/2007 – 31/03/2023).**

Inclusion criteria were a **primary or secondary diagnosis of unipolar depression at age ≥40**. Participants were excluded if they had baseline PD. Diagnostic data was obtained from **CRIS** clinician-coded diagnoses as well as Medical Concept Annotation Tool (**MedCAT**) NLP diagnostic data, and Hospital Episode Statistics (**HES**) linkage. Censor refers to the earliest of the following three dates: end of study period, date of PD diagnosis, or date of death.

Descriptive data were extracted and primary analysis was a **Cox proportional hazards regression** adjusting for sex, ethnicity, antipsychotic use, neurological comorbidities, and psychiatric comorbidities. Antipsychotic use was defined as one or more mentions of any antipsychotic in the patient notes. Neurological comorbidities included: stroke, transient ischaemic attack, multiple sclerosis, and epilepsy. Psychiatric comorbidities included ICD-10 diagnoses coded F00-09 (organic, including symptomatic, mental disorders), and F20-29 (schizophrenia, schizotypal and delusional disorders).

Secondary analyses included **a linear mixed effects model** as per the approach described by Singh-Manoux et al.[2] to investigate the trajectory of psychomotor retardation in relation to PD diagnosis over time. Statistical analyses were conducted in R.

PMR	Total	Male	Age at Depression (mean)	Age at PMR +/- (mean)	Ethnicity - White	Ethnicity - Non-White	Neurological Comorbidities	Psychiatric Comorbidities
-ve	3925	1759 (44.8%)	56.92	58.00	2462 (62.7%)	1463 (37.3%)	146 (3.7%)	199 (5.1%)
+ve	2402	1040 (43.2%)	57.88	58.80	1425 (59.3%)	977 (40.3%)	54 (2.2%)	155 (6.5%)

PMR	Antipsychotic use	ECT	Deaths	Observation Time (years) (mean)	Cases of PD	Time until PD (years) (mean)	Age at Censor (mean)
-ve	1490 (38.0%)	95 (2.4%)	1072 (27.3%)	6.19	67 (1.7%)	4.90	64.20
+ve	1407 (58.6%)	240 (10.0%)	736 (30.6%)	6.57	72 (3.0%)	4.34	65.37

Table 1a & b: *Descriptive statistics of cohort. Censor refers to the earliest of the following three dates: end of study period, date of PD diagnosis, date of death. PMR = psychomotor retardation, ECT = electroconvulsive therapy.*

Results

Of all 24,973 patients diagnosed with depression at age ≥40, **2402** had a positive hit on the NLP app for psychomotor retardation, and **3925** without psychomotor retardation or with psychomotor agitation (Table 1a). Cox proportional hazard ratio for PD diagnosis was **1.43** (95% CI 1.01 – 2.01, **p = 0.04**) (Table 2). Sensitivity analyses (Lexis expansion for year-at-risk adjustment[3], excluding cases with a first psychomotor event within one year of censor date) supported the results of the primary analysis.

Running the linear mixed effects model with a quadratic time interaction, there was a significant negative interaction between time (as a linear variable) and Parkinson's disease status (**p = 0.03**). When depicted graphically there is a significant difference in psychomotor retardation incidence >10 years pre-PD.

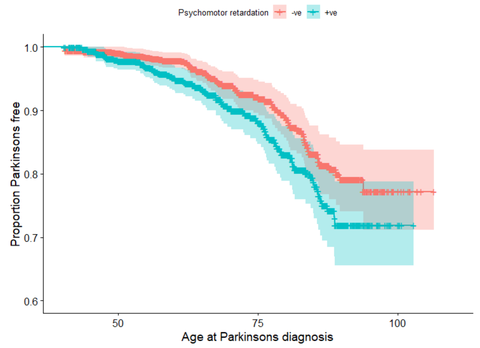

Figure 1: *Kaplan Meier curve for development of Parkinson's disease in depressed individuals with and without psychomotor retardation.*

Term	HR	P value	2.5% CI	97.5% CI
Psychomotor retardation	1.4264	0.04151*	1.0138	2.007
Sex	1.4925	0.02003*	1.0650	2.092
Ethnicity	1.1941	0.35622	0.8192	1.741
Antipsychotic use	1.6442	0.00532**	1.1590	2.332
Neurological comorbidity	1.8263	0.10097	0.8892	3.751
Psychiatric comorbidity	1.5102	0.14353	0.8693	2.624

Table 2: *Cox proportional hazard ratios for development of Parkinson's disease in depressed individuals with psychomotor retardation compared to those without.*

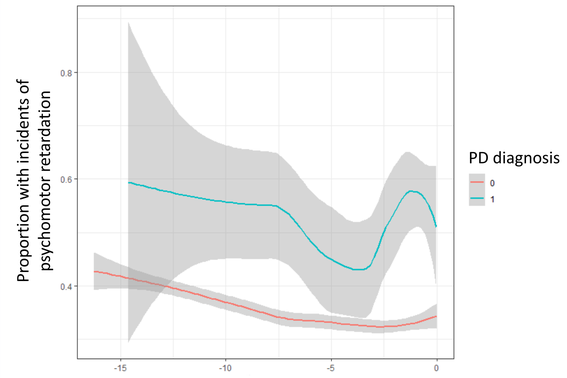

Figure 2: *Linear mixed effects model with quadratic time interaction for episodes of psychomotor retardation in individuals with or without Parkinson's disease*

Conclusion

These findings suggest that **psychomotor retardation in depression is associated with an increased risk of incident PD diagnosis, and therefore could serve as a prodromal factor.** Graphical modelling of the risk trajectory suggests that **this risk dates back to at least 10 years prior to PD diagnosis**, with a peak ~1 year prior to PD potentially indicative of misdiagnosis.

References

1. Gustafsson H, Nordström A, Nordström P. Depression and subsequent risk of Parkinson disease: A nationwide cohort study. Neurology. 2015; 84(24): 2422-9.

2. Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, Sabia S. Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. JAMA Psychiatry. 2017; 74: 712–8.

3. San H and Lewington S. Lexis expansion-age-at-risk adjustment for survival analysis. Brussels: Statistics and Pharmacokinetics Pharmaceutical Users Software Exchange conference. 2013. SP09.

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