

Depression preceding and following the diagnosis of Parkinson's disease and Lewy body dementia

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ABSTRACT

Background Depression is a common comorbidity in Parkinson's disease (PD) and Lewy body dementia (LBD). However, studies examining the rate of incident depression in the period preceding and following the diagnosis of PD and LBD are lacking in the literature.

Aims To quantify the incidence of depression in the period preceding and following the diagnosis of PD and LBD.

Methods We conducted a retrospective case-control study. Specifically, we used Danish registers to identify all patients with a diagnosis of PD or LBD in the period from 2007 to 2019. These patients were matched by age, calendar year of diagnosis and sex with up to three patients diagnosed with rheumatoid arthritis (RA), chronic kidney disease (CKD) or osteoporosis, respectively. The outcome was incident depression. The incidence of depression was assessed for up to 10 years before and up to 10 years after the diagnosis of PD or LBD. Hazard rates of incident depression for patients with PD or LBD, both before and after diagnosis, were compared with those for patients with RA, CKD or osteoporosis using a Cox-proportional hazards model.

Results We identified 17 711 patients with PD or LBD. Their median age was 74.98 (68.10–80.85) years, and 39.92% were females. These patients were matched to 19 556, 40 842 and 47 809 patients with RA, CKD and osteoporosis, respectively. From 7 to 8 years before diagnosis to 5 years after diagnosis, patients with PD and LBD consistently had higher hazard rates of incident depression than all comparator groups.

Conclusions These findings are compatible with depression being an early manifestation of the neurodegenerative changes eventually leading to PD and LBD and imply that incident depression at a late age should raise awareness of potential PD and LBD.

INTRODUCTION

Depression commonly occurs comorbid to Parkinson's disease (PD) and Lewy body dementia (LBD), with an estimated prevalence of approximately 30%–40%.^{1 2} In the context of PD, comorbid depression is associated with cortical and subcortical volume loss, disease progression, cognitive impairment, disability, suicide and increased overall mortality.^{3–6}

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Depression is a common comorbidity in Parkinson's disease (PD) and Lewy body dementia (LBD). However, it is unknown whether the incidence of depression in the years preceding and following the diagnosis of PD or LBD is higher than that observed in other chronic conditions.

WHAT THIS STUDY ADDS

⇒ Patients with PD or LBD had substantially higher hazard rates of incident depression compared with matched patients with rheumatoid arthritis, chronic kidney disease and osteoporosis, respectively. Elevated depression rates were present as early as 8 years before the diagnosis of PD or LBD and remained higher up to 5 years after the diagnosis.

HOW THIS STUDY AFFECTS RESEARCH, PRACTICE OR POLICY

⇒ These findings (i) are compatible with depression being an early manifestation of the neurodegenerative changes eventually leading to PD and LBD, (ii) imply that incident depression at a relatively late age should raise awareness of potential PD and LBD and (iii) highlight the importance of detecting and treating depression in patients with PD and LBD.

The progressive neurodegenerative changes observed in PD and LBD have been proposed to be linked to the development of depression.^{3 7} Supporting this, previous studies have shown an increased risk of depression in the prodromal phase of PD.^{8–11} Indeed, a recent study found that, compared with matched controls, depression was more common in patients with PD up to a decade before the diagnosis of PD, suggesting that early PD-related neurodegenerative changes could cause depression.³ An alternative explanation is that the impairment due to prodromal/undiagnosed PD/LBD^{12–14} could lead to depression, as is likely also to be the case for the prodromal/undiagnosed phase of other chronic medical conditions, such

as rheumatic arthritis (RA) and chronic kidney disease (CKD).^{15 16}

This study aimed to quantify the incidence of depression in the period preceding and following the diagnosis of PD and LBD and to compare it to the depression incidence for the same period for RA, CKD and osteoporosis. Here, RA and CKD act as ‘active control’ chronic medical conditions, as these diseases are associated with substantial disability but are not neurodegenerative, like PD and LBD.¹⁷ In contrast, osteoporosis acts as a ‘passive control’ (concerning detection bias in particular) as it is associated with less disability^{18 19} but still requires routine contact with the healthcare system. If the incidence rate of depression is found to be substantially higher among patients with PD and LBD, particularly in the prediagnostic phase, this would suggest that depression may be a manifestation of the neurodegenerative changes responsible for PD and LBD. It would also imply that incident depression in late life should raise awareness of the potential for PD and LBD.

METHODS

We conducted a retrospective case-control study. The study was approved by Statistics Denmark and the Danish Health Data Authority. It is registered on the internal list of research projects with Aarhus University as data steward. As per Danish law, register-based studies are exempt from informed consent requirements and ethical review board approval.

Data sources

This study is based on data from the nationwide Danish registers.²⁰ Specifically, we used the Danish Civil Registration System (DCRS) to obtain information on date of birth and vital status.²¹ The DCRS includes a unique personal identifier that allows linkage across multiple registers for all individuals living in Denmark. Data on diagnoses assigned at contacts with Danish psychiatric hospitals, including emergency visits, admissions and outpatient contacts, were obtained from the Danish Psychiatric Central Research Register (DPCRR).²² Data on diagnoses from all non-psychiatric hospital contacts were obtained from the Danish National Patient Register (DNPtR).²³ Data on redeemed prescriptions were obtained from the Danish National Prescription Register (DNPreR), which contains information on prescriptions redeemed at Danish pharmacies since 1995.²⁴

Study population

We used the DNPtR to identify all patients with a first-time diagnosis of PD (International Classification of Diseases, 10th revision (ICD-10) code: G20) or LBD (ICD-10: G318E) from 1 January 2007 to 1 January 2019. We also used the DNPtR to identify patients with RA (ICD-10: M05, M06), CKD (ICD-10: N18) and osteoporosis (ICD-10: M80, M81). Specifically, each case of PD or LBD was matched with up to three patients diagnosed

with osteoporosis, RA or CKD, respectively. The patients were matched on sex, age at diagnosis and calendar year of diagnosis. Patients could be included in more than one chronic condition group if they had more than one of the diagnoses included in this study.

Incident depression

The majority of individuals with depression in the Danish healthcare system are treated by general practitioners or private practising psychiatrists,²⁵ who do not report diagnoses to the DNPtR or DPCRR. Therefore, we defined incident depression based on the first-ever redemption of a prescription for an antidepressant (Anatomical Therapeutic Chemical (ATC-code): N06A) with a listed indication of depression (ie, antidepressants prescribed for treatment of, eg, anxiety disorders, obsessive-compulsive disorder or post-traumatic stress disorder, etc were not included) or the first recorded psychiatric hospital contact with a diagnosis of depression (ICD-10: F32–F33), whichever occurred first. This operationalisation of depression is regularly used in studies based on the same data,^{26 27} and the recorded indication in the DNPtR is generally considered valid for research purposes.²⁸

Statistical analyses

The earliest start of follow-up for depression (both for prediagnostic and post-diagnostic depression concerning PD, LBD, RA, CKD and osteoporosis) was 1 January 2006, due to the limited coverage of the prescription indication variable in the DNPreR before this year.²⁵ Patients were followed until death, incident depression or 1 March 2019, whichever occurred first. The time of diagnosis served as time point zero. We covered the incidence of depression over 20 years, extending from 10 years before the diagnosis to 10 years following the diagnosis of PD, LBD, RA, CKD and osteoporosis, respectively. Patients contributed with follow-up only for the years they remained under observation. Thus, while the study period spans 10 years before and 10 years after diagnosis, no individual patient was observed for this entire 20-year window.

First, we employed hazard rate graphs to visualise the incidence of depression relative to the onset of PD, LBD, RA, CKD and osteoporosis. Second, we used Cox proportional hazards models with time since diagnosis as the underlying time scale to compare the rate of incident depression for PD with that of LBD, RA, CKD and osteoporosis for each year preceding and following diagnosis. Models were stratified by sex in secondary analyses.

Since the group of patients with RA was younger and more likely to be female (as not all patients with PD or LBD could be matched with patients with RA of similar age and sex), we performed a sensitivity analysis that included only those patients with PD or LBD who were successfully matched to three patients with RA, along with their matched RA counterparts.

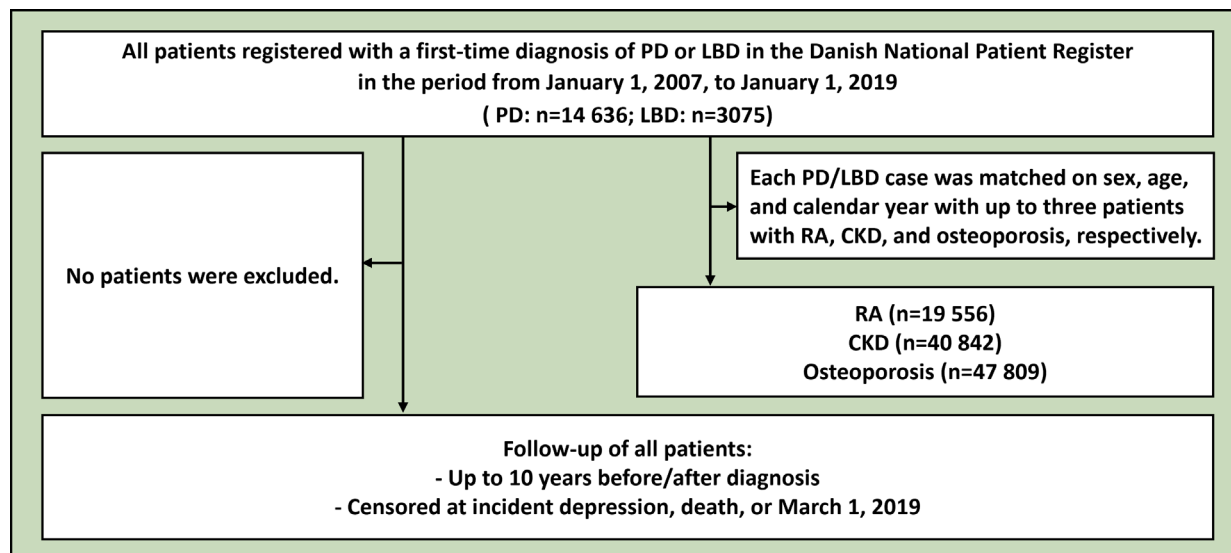


Figure 1 Study flowchart. CKD, chronic kidney disease; LBD, Lewy body dementia; PD, Parkinson's disease; RA, rheumatoid arthritis.

RESULTS

We identified 17 711 patients with PD or LBD (14 636 with PD and 3075 with LBD). Their median age was 74.98 years (25%–75%: 68.10–80.85), and 39.92% were female. These patients were matched to 19 556, 40 842 and 47 809 patients with RA, CKD and osteoporosis, respectively (figure 1). The age and sex distribution of the patients with CKD and osteoporosis were similar to that of the patients with PD/LBD (see table 1), while the patients with RA were younger (median age, 69.35 years; 25%–75%: 61.22–76.56) and more likely to be female (58.16%).

In the 10 years preceding diagnosis, 1918 (13.10%) patients with PD and 520 (16.91%) patients with LBD experienced incident depression (median pre-diagnostic

observation time, 6.7 years; 25%–75%: 3.8–9.3). For comparison, 1087 (5.56%), 3192 (7.82%) and 3460 (7.24%) patients with RA (median pre-diagnostic observation time, 6.4 years; 25%–75%: 3.7–9.2), CKD (median pre-diagnostic observation time, 7.0 years; 25%–75%: 4.2–9.6) and osteoporosis (median pre-diagnostic observation time, 6.9 years; 25%–75%: 4.1–9.6) experienced incident depression in the 10-year pre-diagnostic period. For patients with PD, LBD, RA, CKD and osteoporosis who developed depression, respectively, 362 (18.87%), 100 (19.23%), 191 (17.57%), 490 (15.35%) and 519 (15.00%) had a pre-diagnostic psychiatric hospital contact leading to a depression diagnosis.

In the 10 years following diagnosis, 1160 (7.93%) patients with PD and 261 (8.49%) patients with LBD

Table 1 Characteristics of patients with PD, LBD, RA, CKD and osteoporosis

	PD or LBD	RA	CKD	Osteoporosis
Number of patients	Overall: 17 711 PD: 14 636 LBD: 3075	19 556	40 842	47 809
Females (%)	Overall: 7071 (39.92) PD: 5889 (40.24) LBD: 1182 (38.44)	11 374 (58.16)	15 800 (38.69)	21 197 (44.34)
Median age (25%–75%)	Overall: 74.98 (68.10–80.85) PD: 74.84 (67.88–80.70) LBD: 75.76 (69.36–81.43)	69.35 (61.22–76.56)	75.09 (67.57–81.44)	74.55 (67.42–80.73)
Year of diagnosis (%)				
2007–2010	5357 (30.25)	6667 (34.09)	11 449 (28.03)	14 254 (29.81)
2011–2014	6648 (37.54)	7377 (37.72)	16 023 (39.23)	18 018 (37.69)
2015–2018	5706 (32.22)	5512 (28.19)	13 370 (32.74)	15 537 (32.50)

CKD, chronic kidney disease; LBD, Lewy body dementia; PD, Parkinson's disease; RA, rheumatoid arthritis.

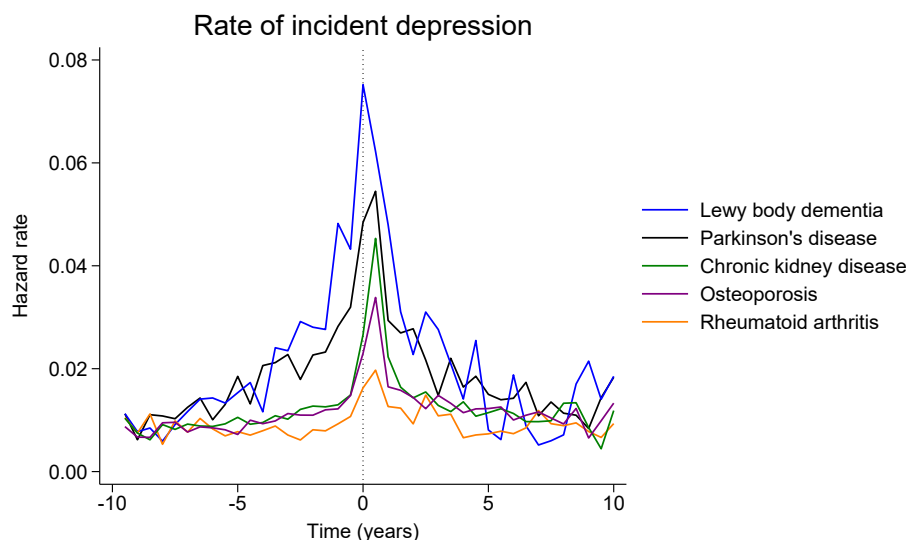


Figure 2 Hazard rate of incident depression preceding and following diagnosis of Parkinson's disease, Lewy body dementia, rheumatoid arthritis, chronic kidney disease and osteoporosis. '0' represents the date of diagnosis of Parkinson's disease, Lewy body dementia, rheumatoid arthritis, chronic kidney disease and osteoporosis.

experienced incident depression (median post-diagnostic observation time, 3.1 years; 25%–75%: 1.3–5.7). For comparison, 992 (5.07%), 2240 (5.48%) and 2911 (6.09%) patients with RA (median post-diagnostic observation time; 4.7 years; 25%–75%: 2.3–7.7), CKD (median post-diagnostic observation time, 2.6 years; 25%–75%: 0.8–5.1) and osteoporosis (median post-diagnostic observation time, 3.8 years; 25%–75%: 1.7–6.6) experienced incident depression in the 10-year post-diagnostic period. For patients with PD, LBD, RA, CKD and osteoporosis who developed depression, respectively, 241 (20.78%), 45 (17.24%), 170 (17.14%), 344 (15.36%) and 519 (17.83%) had a post-diagnostic psychiatric hospital contact that led to a depression diagnosis.

Figure 2 and table 2 show that from 8 years before the diagnosis, patients with PD and LBD had substantially and statistically significantly higher hazard rates of depression compared with patients with RA, CKD and osteoporosis—especially in the 3 years leading up to PD or LBD diagnosis. Figure 2 and table 3 show that the elevated risk persisted up to 5 years after diagnosis. Notably, from 3 years before diagnosis to 3 years after the diagnosis, the incidence rate of depression was substantially and statistically significantly higher for LBD than for PD (with the exception of the period 1–2 years post-diagnosis). The analyses stratified by sex yielded similar results (see online supplemental figure 1).

The results from the sensitivity analysis, which included only patients with PD or LBD (median age, 63.64 years; 25%–75%: 55.76–70.55) who were successfully matched to three patients with RA (median age, 63.60 years; 25%–75%: 55.81–70.55), were similar to those from the primary analyses (see online supplemental figure 2).

DISCUSSION

Main findings

In this nationwide register-based study, we found that patients with PD or LBD had substantially higher hazard rates of incident depression preceding and following diagnosis compared with matched patients with other chronic conditions (RA, CKD and osteoporosis). Specifically, compared with the depression incidence in patients with RA, CKD and osteoporosis, it was elevated already 7 to 8 years prior to the diagnosis of PD/LBD and remained elevated for 5 years after the diagnosis. Notably, during the period surrounding the time of diagnosis, the incidence of depression was markedly higher in patients with LBD compared with those with PD.

Implications

Our findings align with those from prior studies, the majority of which have also observed increased prevalence and incidence of depression both prior to and following the diagnosis of PD and LBD.^{3 8–11 29 30} However, most of these studies, with exceptions,^{31 32} have used control groups consisting of healthy individuals. Our comparison with other chronic conditions should, at least to some extent, control for the disability associated with the development and manifestation of PD and LBD. Consequently, by controlling for 'disability-associated depression', the results of the present study support that depression in PD and LBD is a key manifestation of these diseases and is likely to be related to the underlying neurodegenerative processes.^{3 7 33} However, this study cannot fully determine whether the excess risk of depression reflects a direct manifestation of underlying neurodegenerative processes or arises secondarily from the disability associated with prodromal PD and LBD, such as subtle motor impairments, autonomic dysfunction and sleep disturbances.

Table 2 Comparisons of hazard rates of incident depression preceding diagnosis of PD, LBD, RA, CKD and osteoporosis

Period before diagnosis	Rate of incident depression per 1000 years of follow-up (95% CI, p value*)				
	PD	LBD	RA	CKD	Osteoporosis
10–9 years	8.50 (6.05 to 11.96, ref.)	9.38 (4.88 to 18.04, p=0.796)	8.86 (6.52 to 12.03, p=0.854)	8.81 (7.24 to 10.72, p=0.859)	7.64 (6.28 to 9.28, p=0.593)
<9–8 years	10.93 (8.43 to 14.17, ref.)	7.10 (3.70 to 13.65, p=0.230)	8.04 (6.11 to 10.58, p=0.111)	7.76 (6.48 to 9.29, p=0.034)	8.16 (6.93 to 9.61, p=0.062)
<8–7 years	11.44 (9.13 to 14.35, ref.)	10.48 (6.51 to 16.86, p=0.743)	8.70 (6.89 to 10.98, p=0.098)	8.75 (7.52 to 10.16, p=0.053)	8.59 (7.46 to 9.90, p=0.036)
<7–6 years	12.11 (9.91 to 14.81, ref.)	14.20 (9.74 to 21.72, p=0.467)	9.28 (7.57 to 11.38, p=0.068)	8.82 (7.70 to 10.12, p=0.011)	8.59 (7.37 to 9.79, p=0.005)
<6–5 years	15.87 (13.47 to 18.69, ref.)	14.36 (10.10 to 20.42, p=0.614)	7.37 (5.97 to 9.10, p<0.001)	9.93 (8.81 to 11.20, p<0.001)	7.65 (6.73 to 8.70, p<0.001)
<5–4 years	16.98 (14.62 to 19.71, ref.)	14.41 (10.29 to 20.16, p=0.383)	7.53 (6.19 to 9.15, p<0.001)	9.38 (8.35 to 10.54, p<0.001)	9.64 (8.66 to 10.74, p<0.001)
<4–3 years	21.99 (19.40 to 24.93, ref.)	23.78 (18.46 to 30.63, p=0.587)	7.96 (6.66 to 9.52, p<0.001)	10.52 (9.47 to 11.69, p<0.001)	10.58 (9.60 to 11.67, p<0.001)
<3–2 years	20.33 (17.93 to 23.04, ref.)	28.61 (22.82 to 35.88, p=0.010)	7.16 (5.98 to 8.57, p<0.001)	12.42 (11.31 to 13.64, p<0.001)	10.97 (10.00 to 12.05, p<0.001)
<2–1 years	25.76 (23.13 to 28.69, ref.)	37.96 (31.27 to 46.09, p=0.001)	8.61 (7.35 to 10.08, p<0.001)	12.79 (11.69 to 13.98, p<0.001)	12.09 (11.12 to 13.17, p<0.001)
<1–0 year	40.11 (36.81 to 43.70, ref.)	58.98 (50.41 to 68.99, p<0.001)	13.49 (11.92 to 15.26, p<0.001)	20.72 (19.32 to 22.21, p<0.001)	18.87 (17.64 to 20.18, p<0.001)

*Comparing the incidence rate of depression before the diagnosis of Parkinson's disease with the rate of depression before the diagnosis of the other disorders.

CI, confidence interval; CKD, chronic kidney disease; LBD, Lewy body dementia; PD, Parkinson's disease; RA, rheumatoid arthritis; ref., reference.

While RA and CKD served as comparator conditions associated with substantial disability, they may not fully capture the specific functional decline and uncertainty characteristic of the prodromal phase of neurodegenerative disease. Thus, our interpretation that depression represents an early non-motor feature of PD/LBD should be considered alongside these alternative explanations.

In PD and LBD, comorbid depression is thought to result from disruptions in several monoaminergic systems, including serotonin, norepinephrine and dopamine, which play key roles in mood regulation. Additionally, cholinergic dysfunction, a hallmark of PD and LBD, may further contribute to the mood disturbances. Indeed, loss of cholinergic innervation in areas such as the hippocampus and prefrontal cortex can impair emotional regulation and cognitive function,³⁴ potentially exacerbating depressive symptoms. However, other contributing factors may include predisposing traits (eg,

personality), psychological aspects (eg, coping styles) and social influences (eg, isolation).³⁵ The more aggressive disease course and frequent medical and social challenges in LBD may contribute to a higher allostatic load, contributing to the finding of increased pre- and post-diagnostic rates of depression in LBD compared with PD. Future studies should explore the mechanistic underpinnings of this finding, potentially guiding more targeted interventions for mood disturbances in PD and LBD.⁷

The present findings also have implications for the early detection of PD and LBD. In the prodromal phase, the marked increase in incident depression—observed as early as 8 years before diagnosis and peaking 3 years prior—suggests that late-onset depression (with a median age of PD/LBD diagnosis at 75 years) should alert physicians to the possibility of prodromal or even manifest PD/LBD.^{36,37} This may enable earlier detection of both non-motor and motor symptoms in developing PD or LBD.

Table 3 Comparisons of hazard rates of incident depression following diagnosis of PD, LBD, RA, CKD and osteoporosis

Period following diagnosis	Rate of incident depression per 1000 years of follow-up (95% CI, p value*)				
	PD	LBD	RA	CKD	Osteoporosis
0 to <1 year	42.51 (38.78 to 46.60, ref.)	55.42 (46.38 to 66.23, p=0.009)	16.26 (14.42 to 18.34, p<0.001)	34.56 (32.52 to 36.73, p<0.001)	25.48 (23.95 to 27.11, p<0.001)
1 to <2 years	27.34 (24.11 to 30.99, ref.)	27.14 (20.45 to 36.01, p=0.961)	10.85 (9.30 to 12.66, p<0.001)	15.42 (13.93 to 17.08, p<0.001)	15.13 (13.87 to 16.50, p<0.001)
2 to <3 years	18.42 (15.55 to 21.82, ref.)	29.43 (21.67 to 39.96, p=0.009)	12.92 (11.11 to 15.01, p=0.002)	14.25 (12.65 to 16.04, p=0.015)	13.46 (12.18 to 14.88, p=0.002)
3 to <4 years	19.39 (16.13 to 23.32, ref.)	17.78 (11.34 to 27.88, p=0.723)	8.96 (7.38 to 10.88, p<0.001)	12.55 (10.88 to 14.48, p<0.001)	12.41 (11.06 to 13.92, p<0.001)
4 to <5 years	16.88 (13.51 to 21.11, ref.)	17.45 (10.33 to 29.46, p=0.911)	7.23 (5.72 to 9.13, p<0.001)	11.09 (9.32 to 13.19, p=0.004)	12.22 (10.75 to 13.89, p=0.014)
5 to <6 years	14.10 (10.66 to 18.66, ref.)	11.92 (5.68 to 25.00, p=0.673)	7.63 (5.93 to 9.80, p=0.001)	11.79 (9.70 to 14.35, p=0.302)	11.37 (9.79 to 13.21, p=0.186)
6 to <7 years	14.33 (10.38 to 19.78, ref.)	7.18 (2.32 to 22.26, p=0.249)	10.09 (7.91 to 12.86, p=0.087)	9.71 (7.53 to 12.54, p=0.064)	11.26 (9.49 to 13.36, p=0.194)
7 to <8 years	12.53 (8.40 to 18.69, ref.)	6.52 (1.63 to 26.06, p=0.374)	9.14 (6.84 to 12.20, p=0.209)	11.40 (8.59 to 15.13, p=0.706)	9.89 (8.01 to 12.22, p=0.306)
8 to <9 years	9.80 (5.69 to 16.88, ref.)	18.99 (7.13 to 50.59, p=0.248)	8.71 (6.16 to 12.31, p=0.723)	11.27 (7.88 to 16.12, p=0.679)	9.68 (7.50 to 12.49, p=0.970)
9 to 10 years	16.11 (9.54 to 27.20, ref.)	15.99 (4.00 to 63.93, p=0.997)	7.83 (4.99 to 12.27, p=0.040)	7.61 (4.32 to 13.41, p=0.058)	11.38 (8.50 to 15.24, p=0.257)

*Comparing the rate of depression after the diagnosis of Parkinson's disease with the rate of depression after the diagnosis of the other disorders.

CKD, chronic kidney disease; LBD, Lewy body dementia; PD, Parkinson's disease; RA, rheumatoid arthritis ; ref., reference.

However, it is important to emphasise that the potential benefits of earlier PD/LBD detection do not necessarily extend to initiating dopaminergic treatment at an earlier stage. Indeed, dopamine replacement therapy carries substantial risks, including dyskinesia, hallucinations and impulse control disorders, particularly when used over prolonged periods.³⁸ Therefore, early recognition should primarily be seen as an opportunity to monitor symptoms more closely, manage psychiatric comorbidities more effectively and potentially enrol patients in trials of disease-modifying therapies—once such treatments become available—rather than to accelerate symptomatic dopaminergic treatment.³⁹

Following a diagnosis of PD or LBD, the persistent higher incidence of depression highlights the need for heightened clinical awareness and systematic screening for depressive symptoms in these patients. Given the established associations between depression, cognitive decline and accelerated disease progression, early detection and

treatment of depression in this patient population may be crucial.^{3,4} Integrating mental health assessments into routine neurological care may facilitate the timely initiation of antidepressant therapy or other appropriate interventions, which may improve PD and LBD prognosis in patients with concomitant depression.^{40,41}

Limitations

Some limitations should be acknowledged. First, we included osteoporosis with the intention of it acting as a passive control, based on the assumption that it would be associated with less disability than RA and CKD and hence less depression. However, the hazard rates of incident depression were in fact higher for patients with osteoporosis than for patients with RA, especially in the period surrounding the time of diagnosis. We believe that this is due to our operationalisation of osteoporosis based on hospital diagnoses. Specifically, patients are often referred for hospital-based osteoporosis assessment following a

fracture, a time when pain and disability—both associated with depression—are at their peak.^{18 19 42 43} Thus, in hindsight, osteoporosis was likely more of an ‘active control’ in this context.⁴⁴ This has important implications for interpretation. In the period preceding diagnosis, the elevated depression incidence observed in PD/LBD relative to osteoporosis is likely to be a conservative estimate, as the comparator group itself experienced a transient spike in depression risk. Thus, our main conclusion—that PD/LBD are associated with a marked excess depression risk preceding and following diagnosis when compared with other chronic conditions—remains valid. Danish patients with RA, on the other hand, seem to be somewhat undertreated when it comes to depression,⁴⁵ questioning its role as ‘active control’ in the context of this study. Second, depression may be a causal risk factor for the development of osteoporosis,^{46 47} whereas this appears less likely for PD, LBD, CKD, and RA. This difference may help explain the relatively high incidence of depression observed around the time of osteoporosis diagnosis. Third, due to our operationalisation of PD and LBD via hospital diagnoses, there is likely a bias towards more severe cases, as those diagnosed and treated solely by private practising neurologists are not included. As such, assuming that the more severe the PD/LBD, the higher the risk of depression, the reported rates of incident depression may not be representative (ie, overestimated) for the entire population/severity spectrum of PD/LBD. From the comparative perspective, however, this is less of a problem as the same severity bias is likely in play with regard to the chronic medical conditions used as disability controls. Fourth, the operationalisation of incident depression does not cover those receiving non-pharmacological treatment by, for example, general practitioners, private practising psychiatrists or psychologists. In addition, although we used antidepressants with a listed indication for depression as a proxy for depression, misclassification bias may remain. However, this misclassification is expected to be non-differential across groups, thus not affecting relative comparisons. Fifth, although we included chronic medical conditions as controls, it remains possible that the development and manifestation of PD and LBD symptoms lead to more frequent healthcare contacts, thereby increasing the likelihood of detecting depression (detection bias). Sixth, while it is important to improve our understanding of whether (late onset) depression appearing in the context of PD/LBD differs phenomenologically and biologically from ‘normal’ depression, and from depression occurring in the context of other neurological conditions, for example, Alzheimer’s disease,^{48 49} the registers providing data for this study do not hold sufficiently fine-grained data to inform such research. Seventh, our analyses involved multiple comparisons across several time windows. This increased the likelihood of type 1 errors, especially in the early prediagnostic and late post-diagnostic periods, where estimates are based on fewer patients and outcomes. However, the more consistent and robust excess depression risk observed in the

years immediately surrounding diagnosis for PD/LBD is unlikely to be attributable to chance. Finally, although our study did not estimate cumulative incidences of depression but rather compared hazard rates of depression over time between PD/LBD and comparison groups, death might act as a competing risk. This is especially true in the late follow-up periods, because of higher mortality in PD and LBD than the comparison groups, meaning that patients with PD and LBD in the later follow-up might represent a selectively surviving subgroup. As a result, the hazard rates observed towards the end of follow-up may be influenced by selective survival and should be interpreted with caution.

CONCLUSIONS

According to this study, patients with PD or LBD had substantially higher pre- and post-diagnostic rates of incident depression compared with matched patients with RA, CKD and osteoporosis, respectively. Elevated depression rates were present as early as 8 years before the diagnosis of PD or LBD and remained higher up to 5 years after the diagnosis. These findings (i) are compatible with depression being an early manifestation of the neurodegenerative changes eventually leading to PD and LBD, (ii) imply that incident depression at a relatively late age should raise awareness of potential PD and LBD and (iii) emphasise the need for detecting and treating depression among patients with PD and LBD.

Contributors The study was designed by CR, MLC and SDØ. SDØ procured the data. The statistical analyses were carried out by CR. All authors contributed to the interpretation of the results. CR and SDØ wrote the first draft of the manuscript, which was subsequently revised for important intellectual content by all authors. All authors approved the final version of the manuscript prior to submission. CR is the guarantor.

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Ethics approval This study involved individual-level data from registers. As per Danish law, register-based studies are exempted from informed consent requirements and ethical review board approval.

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Data availability statement The data used for this study cannot be shared according to Danish Law. Access to the data can be achieved for researchers affiliated with Danish institutions upon application to Statistics Denmark and the Danish Health Data Authority.

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