The impact of psychiatric comorbidity on Parkinson's disease outcomes: a systematic review and meta-analysis

Ella Burchill,[a,q,*] Cameron James Watson,[b,c,q] Jack B. Fanshawe,[d,e] James Brunton Badenoch,[f] Emma Rengasamy,[g] Dory Anthony Ghanem,[h] Constantine Holle,[h] Isabella Conti,[b] Mohammed Ahmed Sadeq,[i] Aman Saini,[h] Abdelilah Lahmar,[j] Ben Cross,[k] Gareth McGuigan,[l] Amar Nandrha,[h] Edward J. Kane,[c] Julia Wozniak,[h] Reem Mohamed Farouk Ghorab,[i] Jia Song,[m] Andrew Sommerlad,[a,m] Andrew Lees,[n] Michael S. Zandi,[n] Anthony S. David,[a,o] Glyn Lewis,[a] Ben Carter,[p] and Jonathan P. Rogers[a]

[a]Division of Psychiatry, University College London, London, UK
[b]Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[c]South London and Maudsley NHS Foundation Trust, UK
[d]Department of Psychiatry, University of Oxford, Oxford, UK
[e]Oxford Health NHS Foundation Trust, Oxford, UK
[f]Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[g]Department of Public Health and Primary Care, University of Cambridge, UK
[h]Medical School, University College London, London, UK
[i]Faculty of Medicine, Misr University for Science and Technology, 6th of October City, Egypt
[j]Faculty of Medicine, Mohamed First University, Oujda, Morocco
[k]Mersey Care NHS Foundation Trust, Liverpool, UK
[l]Ayrshire & Arran NHS Foundation Trust, Scotland, UK
[m]Camden and Islington NHS Foundation Trust, London, UK
[n]UCL Queen Square Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
[o]UCL Institute of Mental Health, University College London, London, UK
[p]Department of Biostatistics and Health Informatics, King's College London, London, UK

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Summary

Background The burden of psychiatric symptoms in Parkinson's disease includes depression, anxiety, apathy, psychosis, and impulse control disorders. However, the relationship between psychiatric comorbidities and subsequent prognosis and neurological outcomes is not yet well understood. In this systematic review and meta-analysis, in individuals with Parkinson's disease, we aimed to characterise the association between specific psychiatric comorbidities and subsequent prognosis and neurological outcomes: cognitive impairment, death, disability, disease progression, falls or fractures and care home admission.

Methods We searched MEDLINE, Embase, PsycINFO and AMED up to 13th November 2023 for longitudinal observational studies which measured disease outcomes in people with Parkinson's disease, with and without specific psychiatric comorbidities, and a minimum of two authors extracted summary data. Studies of individuals with other parkinsonian conditions and those with outcome measures that had high overlap with psychiatric symptoms were excluded to ensure face validity. For each exposure-outcome pair, a random-effects meta-analysis was conducted based on standardised mean difference, using adjusted effect sizes–where available–in preference to unadjusted effect sizes. Study quality was assessed using the Newcastle–Ottawa Scale. Between-study heterogeneity was assessed using the I^2 statistic and publication bias was assessed using funnel plots. PROSPERO Study registration number: CRD42022373072.

Findings There were 55 eligible studies for inclusion in meta-analysis (n = 165,828). Data on participants' sex was available for 164,514, of whom 99,182 (60.3%) were male and 65,460 (39.7%) female. Study quality was mostly high (84%). Significant positive associations were found between psychosis and cognitive impairment (standardised mean difference [SMD] 0.44, [95% confidence interval [CI] 0.23–0.66], I^2 30.9), psychosis and disease progression (SMD 0.46, [95% CI 0.12–0.80], I^2 70.3%), depression and cognitive impairment (SMD 0.37 [95% CI 0.10–0.65], I^2 27.1%), depression and disease progression (SMD 0.46 [95% CI 0.18–0.74], I^2 52.2), depression and disability (SMD 0.42 [95% CI 0.25–0.60], I^2 7.9%), and apathy and cognitive impairment (SMD 0.60 [95% CI 0.02–1.19], I^2 27.9%). Between-study heterogeneity was moderately high.

*Corresponding author. Division of Psychiatry, University College London, London, W1T 7BN, UK.
E-mail address: e.burchill@ucl.ac.uk (E. Burchill).
[q]These authors contributed equally.

Interpretation Psychosis, depression, and apathy in Parkinson's disease are all associated with at least one adverse outcome, including cognitive impairment, disease progression and disability. Whether this relationship is causal is not clear, but the mechanisms underlying these associations require exploration. Clinicians should consider these psychiatric comorbidities to be markers of a poorer prognosis in people with Parkinson's disease. Future studies should investigate the underlying mechanisms and which treatments for these comorbidities may affect Parkinson's disease outcomes.

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Keywords: Parkinson's disease; Neuropsychiatry; Depression; Psychosis; Systematic review; Meta-analysis

Research in context

Evidence before this study

Non-motor symptoms in Parkinson's disease are common, with neuropsychiatric symptoms in particular constituting a major disease burden in people with the disease. There is evidence to suggest that psychiatric conditions in Parkinson's disease detrimentally affect quality of life, but their association with outcomes and overall disease prognosis has never been systematically evaluated. We searched MEDLINE, Embase, PsycInfo and AMED from inception to January 18th, 2024, with the following search terms in all fields without limits: 'parkinson and psychiatric and (outcome or cognit* or dementia or death or mortality or disabilty or progression or fall or fracture or "care home" or "residential home") and "systematic review"'. This search identified 255 articles, but none systematically reviewed the relationship between a range of psychiatric comorbidity and subsequent outcomes in Parkinson's disease.

Added value of this study

This systematic review and meta-analysis indicates that common psychiatric comorbidities in Parkinson's disease (such as psychosis, depression, and apathy) are all associated with at least one adverse outcome, including cognitive impairment, disease progression and disability.

Implications of all the available evidence

As well as being common and disabling, psychiatric comorbidities in Parkinson's disease can be considered markers of a poorer prognosis. These comorbidities warrant further study to evaluate the potential mechanisms underlying their associations with these adverse neurological outcomes at an individual and epidemiological level, and whether effective treatments can affect disease outcome. The temporality of symptom presentation also deserves attention, as a combination of non-motor and psychiatric symptoms may identify a prodromal Parkinson's disease phenotype.

Introduction

Parkinson's disease is a chronic neurodegenerative disorder, affecting more than 1% of adults 65 years of age and older.[1] Parkinson's disease is defined in terms of its motor presentation, namely bradykinesia, rigidity and tremor,[2] and results from the loss of dopaminergic neurons in the substantia nigra. However, in recent years, it has become increasingly evident that non-motor symptoms, in particular neuropsychiatric ones, form an important part of the overall disease burden.[3]

These neuropsychiatric comorbidities can be categorised into broad clusters: disorders of affect (e.g. depression and anxiety), perception and thinking (e.g. hallucinations and other psychotic experiences), and motivation (e.g. impulse control disorders and apathy).[4] These comorbidities are very common in patients with Parkinson's disease, with studies showing the point prevalence to be as high as 70–89%,[5] and both the prevalence and severity of psychiatric comorbidities have been shown to increase over time. Longitudinal cohort studies examining mortality in Parkinson's disease have shown that death is not directly related to Parkinson's disease itself in most patients; pneumonia and cancer are commonly implicated, highlighting the need to consider medical complications, comorbidities (including psychiatric) and cognitive impairment.[6] Cognitive impairment can include mild cognitive impairment and Parkinson's disease dementia, the latter appearing on average 10 years after diagnosis.[7] Psychiatric comorbidity in Parkinson's disease has been linked to poorer quality of life,[8] but it is not currently clear whether it has an impact on neurological outcomes, including cognitive impairment, disease progression, disability and overall prognosis. We sought to better understand the complex relationship between distinct psychiatric comorbidities and the overall disease

course of Parkinson's disease, hypothesising that specific psychiatric conditions (e.g. depression, psychosis, apathy) may be associated with worse overall disease outcomes such as motor progression, cognitive impairment and care home admission.

In this study, in individuals with Parkinson's disease, we aimed to ascertain the association between specific psychiatric comorbidities and subsequent prognostic and neurological outcomes: cognitive impairment, death, disability, disease progression, falls or fractures and care home admission.

This systematic review addresses an important clinical question, expanding on current literature in the field, which has thus far been largely limited by examining psychiatric comorbidities in Parkinson's disease in isolation, without comparison between comorbidities. By limiting our eligibility criteria to those studies which include a control group (i.e. no psychiatric comorbidity), we intend to delineate and better understand the role psychiatric comorbidities play in Parkinson's disease, in relation to neurological outcomes and overall disease prognosis.

Methods

We conducted a systematic review and meta-analysis, registered on PROSPERO (CRD42022373072). This manuscript follows the PRISMA 2020 reporting guidelines[9] and the PRISMA checklist is in Supplementary Table S1.

Search strategy and selection criteria

The full selection criteria are stated in the PECOS format in Table 1. Our overriding principle in designating conditions as exposures and outcomes was to consider conventionally defined psychiatric disorders as the exposures and markers of neurological progression as outcomes. Dementia and other neurocognitive disorders (including mild cognitive impairment, dementia with Lewy bodies and Parkinson's disease dementia) might fall into either category but were designated as outcomes, as they tend to be conceived as processes that occur later in the disease course.[10] Some prognostic measures (such as the Non-Motor Symptom Scale and the SF-36[11,12]) have multiple elements that directly measure psychiatric symptoms, so these were excluded in order to avoid a bias in which associations were inflated by a conceptual overlap in the measurement of exposures and outcomes.

Searches were conducted on Ovid using Medline All, Embase Classic + Embase, PsycINFO and AMED from inception to 27/10/2022, subsequently updated to 13/11/2023. The search strategy, which was limited to humans, used keywords and structured headings to combine terms denoting Parkinson's disease, psychiatric conditions, prognosis and longitudinal observational studies. The full search strategy is presented in Supplementary Methods 1. Additional papers were sought by approaching experts in the field and searching the reference lists of included studies. Automatic deduplication was conducted in EndNote, then further manual deduplication was conducted by comparing similar citations. Where more than one study reported data from the same cohort with the same combination of exposure and outcome, only the study with the longest follow-up period was used; where two studies had the same follow-up period, the study reporting the largest sample size was used.

Eligibility was ascertained for titles and abstracts independently by two authors using the Rayyan software

Criterion	Inclusion	Exclusion
Population	Adults with a diagnosis of idiopathic Parkinson's disease.	• Animal studies • Other parkinsonian conditions (e.g. drug-induced parkinsonism, dementia with Lewy bodies)
Exposure	Any psychiatric condition, whether standard ICD-11 psychiatric disorders (e.g. depressive disorders) or Parkinson's-specific psychiatric syndromes (e.g. apathy, impulse control disorders)	• Dementia or other neurocognitive disorders • Sleep disorders
Comparison	Adults with a diagnosis of Parkinson's disease without a diagnosis of psychiatric comorbidities	
Outcome	Any outcomes denoting disease prognosis, disease progression, cognitive impairment, medical complications, disability, care home admission or death	• Sleep disorders • Suicide attempts • Quality of life • Treatment with particular therapy • Measurement of a single cognitive domain • Prognostic measures that are highly contaminated by psychiatric disorders or symptoms (such as Non-Motor Symptom Scale and 36-Item Short Form Health Survey)
Study type	Peer-reviewed articles without date restriction reporting the results of longitudinal observational studies (i.e. cohort studies or case–control studies) with a total sample size of at least 20.	• Review articles, cross-sectional studies, interventional studies, case reports and case series • Conference abstracts

Table 1: **Selection criteria.**

(https://www.rayyan.ai/). Where there was disagreement about a study's inclusion, the full text was examined. Full texts were also assessed for eligibility independently by two authors. Where there were disagreements, a third author arbitrated. Where studies measured relevant exposures and outcomes but did not report the required results, attempts were made to calculate effect sizes based on the available data and, failing this, to contact the study authors; if these options were not successful, the study was excluded. Articles published in English were considered by the authors. Articles that were published in French, German, Polish or Chinese were assessed for eligibility in collaboration with a co-author who spoke the language; the same process was used for data extraction from these studies.

Data extraction

Data were extracted by two authors in parallel with blinding. Where there were disagreements, a third author arbitrated. Throughout this process, one author ensured consistency of format for data extraction items. Where data were available only in graphical form, PlotDigitizer was used to extract from graphs.[13] Only between-person (not within-person) effects were extracted. Where data from multiple time-points were available, we extracted data for the longest follow-up time.

The exposures were grouped as psychosis, depression, apathy, anxiety, impulse control behaviours and bipolar affective disorder. The outcomes were grouped as cognitive impairment, death, disability, disease (motor) progression, falls or fractures and care home admission. Full definitions of all extracted variables are provided in Supplementary Table S2. Where a study reported an outcome combining more than one of these outcome groups, this outcome was not used. Where a study reported on more than one outcome that was categorised as belonging to the same group (for example, diagnosis of dementia, Montreal Cognitive Assessment (MoCA) score and MoCA subscale scores), aggregate scores were preferred to subscale scores, continuous outcomes were preferred to discrete outcomes, measures without zero cells were preferred to measures with zero cells, adjusted estimates were preferred to unadjusted estimates, diagnostic thresholds of scales were preferred to sub-diagnostic thresholds and off-medication states were preferred to on-medication states. When studies reported more than one continuous aggregate outcome in a particular group where these criteria did not distinguish a preferred measure, the authors prioritised outcomes with a coverage of a greater number of relevant subdomains, for instance, choosing the Unified Parkinson's Disease Rating Scale (UPDRS) over the Hoehn and Yahr Scale, and the MoCA over the Mini-Mental State Examination (MMSE). Where no overall aggregate outcome was provided for a group but outcomes for more than one domain within the group were available, a consensus was agreed as to the more clinically relevant Parkinson's disease outcome.

Risk of bias was assessed using the Newcastle–Ottawa Scale (NOS) for cohort and case–control studies.[14] This assesses selection, comparability, exposure assessment and outcome assessment. In order to enhance reproducibility, we defined the items of the NOS according to how they would be represented in studies eligible for our review, as shown in Supplementary Tables S3 and S4. The NOS is scored out of a maximum of 9 points and we considered 0–3 points to be low quality, 4–6 to be moderate and 7–9 to be high. The NOS was performed by two authors and, where the overall rating differed between reviewers, a third author arbitrated.

Data analysis

All studies meeting the eligibility criteria were tabulated with their demographics, selection criteria, design and results. Given the heterogeneity in exposures and outcomes, each exposure-outcome pair was meta-analysed separately. Only exposure-outcome pairs where there were a minimum of two studies were included in the meta-analysis.

For each exposure-outcome pair in a study, the standardised mean difference (SMD) was calculated. Where another effect size measure was used (odds ratio, risk ratio, incidence rate ratio, hazard ratio or unstandardised regression coefficient), these were converted to equivalent SMDs using the procedures described in Supplementary Table S5. We have supplied a summary of all included studies in Supplementary Table S8, with all original effect sizes reported by individual studies found in Supplementary Table S9. Where effect sizes were not calculated but data were available that enabled calculation of an SMD (either directly, or indirectly via one of the procedures in Supplementary Table S5). For consistency, we considered that a positive SMD indicated poorer outcomes in the exposed group and a negative SMD poorer outcomes in the unexposed group. We considered an SMD of 0.15 to be a small effect size, 0.40 medium and 0.75 large, as these thresholds have previously been established as the 25th, 50th and 75th percentile ranks for research summarised in gerontology meta-analyses.[15]

The meta-analysis was conducted using *R* version 4.3.1 with the metafor package version 4.2.0 and the esc package version 0.5.1 for conversion of effect sizes. The threshold for statistical significance was set to $p < 0.05$. A generic inverse variance approach was chosen to accommodate the range of effect size measures, while a random-effects model was used, as we considered *a priori* that there would be substantial variability in study design, resulting in heterogeneity in effect sizes. Between-study variance was estimated using the restricted maximum likelihood estimator method[16,17]

and confidence intervals were calculated based on a standard normal distribution. The proportion of the variation in effect sizes that is due to between-study variability was quantified using the I^2 statistic.

A forest plot was produced for each exposure-outcome pair with 95% confidence intervals, showing the overall estimate and–as a sensitivity analysis–the estimate for only the adjusted effect sizes. Within each forest plot, studies were ordered in ascending order by year with summary polygons provided for all studies (adjusted used as preference), and then adjusted alone. A heat map was generated to summarise the effect sizes and statistical significance across all exposure-outcome pairs. Assessment of reporting bias was conducted using a funnel plot for each exposure-outcome pair.

Certainty of the overall evidence was ascertained by considering the magnitude of the effect sizes, whether adjusted effect sizes were different from unadjusted effect sizes, the risk of bias of the studies for a particular outcome and the likely impact of reporting bias.

Role of the funding source

The funders played no role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit it for publication.

Results

Searching databases identified 30,753 records, supplemented by 11 records from reference lists, as illustrated in Fig. 1. Ultimately, 55 eligible studies were included, representing 94 exposure-outcome pairs. Articles potentially meeting the inclusion criteria but which were ultimately excluded are listed with an explanation in Supplementary Table S7. Demographic characteristics of the included studies are summarised in Table 2, with full details of all included studies reported in Supplementary Tables S8 and S9.

Exposures included in the studies were psychosis, depression, apathy, anxiety, impulse control behaviours and bipolar affective disorder. Included outcomes were cognitive impairment, death, disability, disease progression, falls or fractures and residential home admission. A full list of all eligible studies that were included is shown in Supplementary Tables S8 and S9.

Psychosis

The association of psychosis with cognitive impairment, death, disease progression, falls or fractures and residential home admission was tested across 21 studies in 159,438 patients.[18–40] Psychosis was significantly associated with cognitive impairment (SMD 0.44, [95% CI 0.23–0.66], p < 0.0001, I^2 30.9 [I^2 95% CI 0–48.6]) and disease progression (SMD 0.46, [95% CI 0.12–0.80], p = 0.0078, I^2 70.3% [I^2 95% CI 13.4–96.9]). There was no significant association with residential home admission (SMD 0.38, [95% CI –1.27 to 2.03], p = 0.65, I^2 0% [I^2 95% CI 0–95.1]), death (SMD 0.59 [95% CI –0.78 to 1.96], p = 0.40, I^2 0%, [I^2 95% CI 0–97.7]), or falls/fractures (SMD 0.39 [95% CI –0.77 to 1.56], p = 0.51, I^2 0% [I^2 95% CI 0–98.7]).

The results of the meta-analysis are summarised in Fig. 2. Funnel plots are available in Supplementary

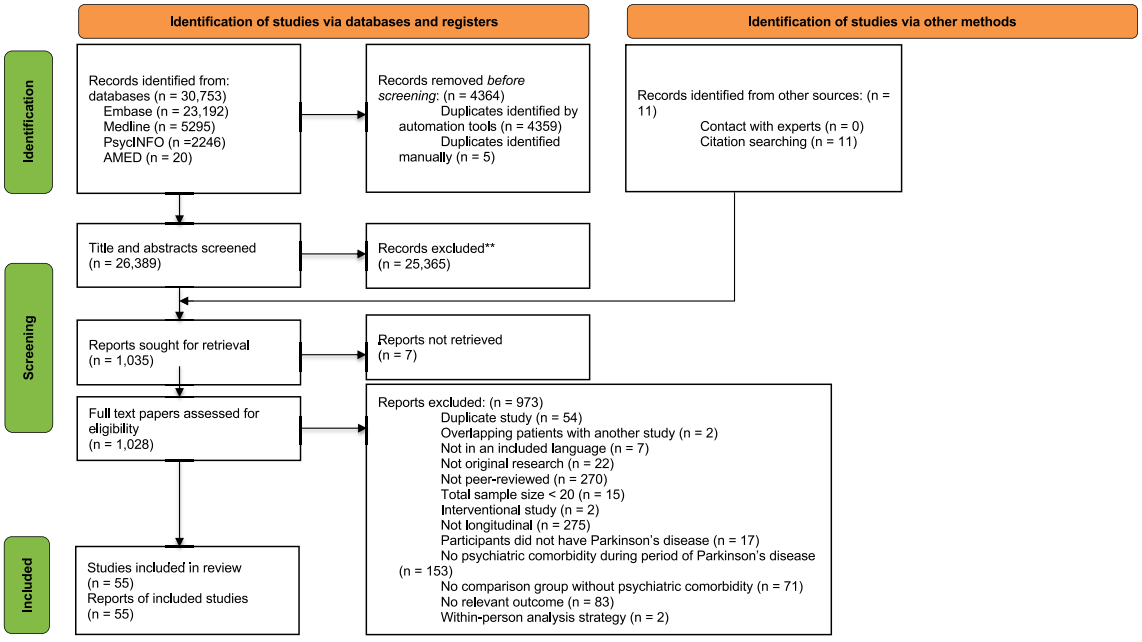

Fig. 1: **PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.**

N of patients per study (k)	165,828
Funding (k)	
No funding	3
Non-commercial	28
Commercial	8
Funding statement not provided	16
Country of study (k)	
USA	14
Norway	6
Italy	5
Spain	5
UK	4
Korea	4
France	2
Germany	2
Japan	2
Israel	2
Singapore	2
Multi-country	2
Other	5
Study design (k)	
Case-control	3
Cohort	52
Prospective	45
Retrospective	10
Single-centre	32
Multi-centre	23
Follow-up duration (k)	
Range (years)	1–11
Sex	
49 studies, n studied = 164,514	
Male (n, %)	99,182 (60.3%)
Female (n, %)	65,460 (39.7%)
Age of participants	
Weighted means (SD)	71.8 (11.4)

Table 2: **Characteristics of included subjects (n) and studies (k).**

Figure S1, showing a largely symmetrical distribution across all outcomes.

Depression

The association of depression with subsequent cognitive impairment, disease progression, death, disability, falls or fractures and residential home admission was tested across 6324 participants in 29 studies.[18–21,40–64] Depression was significantly associated with cognitive impairment (SMD 0.37 [95% CI 0.10–0.65], p = 0.0085, I^2 27.1%, [I^2 95% CI 0–35.0]), disease progression (SMD 0.46 [95% CI 0.18–0.74], p = 0.0011, I^2 52.2 [I^2 95% CI 0–81.1]), and disability (SMD 0.42 [95% CI 0.25–0.60], p = <0.0001, I^2 7.9%, [I^2 95% CI 0–91.2]). There was no significant association for falls or fractures (SMD –0.28 [95% CI –0.90 to 0.34], p = 0.37, I^2 0%, [I^2 95% CI 0–99.5]) and death (SMD 0.32 [95% CI –0.56 to 1.20], p = 0.47, I^2 0% [I^2 95% CI 0–37.0]).

The results of the meta-analysis are summarised in Fig. 3.

The association between residential home admission and depression was not eligible for meta-analysis due to there being only one study with results for this outcome[18] which did not find evidence of such an association (relative risk 1.4 [95% CI 0.6–3.6]).

Funnel plots are available in Supplementary Figure S2, showing a largely symmetrical distribution across all outcomes.

Apathy

The association of apathy with subsequent cognitive impairment and disease progression was tested across 1332 participants in seven studies.[39–41,43,65–67] Apathy was significantly associated with cognitive impairment (SMD 0.60 [95% CI 0.02–1.19], p = 0.04, I^2 27.9%, [I^2 95% CI 0–73.9]). The association between apathy and disease progression was not statistically significant (SMD 0.35 [95% CI –0.16 to 0.85], p = 0.18, I^2 5.7% [I^2 95% CI 0–95.2]).

The results of the meta-analysis are summarised in Fig. 4.

Funnel plots are available in Supplementary Figure S3. This shows an asymmetrical distribution for apathy and cognitive impairment, where we also observed a high heterogeneity between studies.

Anxiety

The association of anxiety with subsequent cognitive impairment, disease progression and falls or fractures were tested across 1761 participants in eight studies.[39–46] There was no significant association found for anxiety with cognitive impairment (SMD 0.41 [95% CI –0.19 to 1.01], p = 0.18, I^2 0%, [I^2 95% CI 0–77.8]]), there was also no significant association for anxiety and disease progression (SMD –0.27 [95% CI –0.84 to 0.29], p = 0.34, I^2 35.9% [I^2 95% CI 0–91.4]). The results of the meta-analysis are summarised in Fig. 5.

Falls or fractures risk was not eligible for meta-analysis because there was only one study with results which did not find evidence of such an association after adjustment for potentially confounding variables: unadjusted odds ratio of 1.13 (95% CI 1.04–1.22, p = 0.003); adjusted odds ratio of 1.06 (95% CI 0.91–1.24, p = 0.46).[42]

Visual inspection of the funnel plots in Supplementary Figure S4 showed no convincing evidence for publication bias.

Impulse control behaviours

The association of impulse control behaviours with cognitive impairment and disease progression was tested across four studies in 394 patients.[68–71] Neither of these associations was statistically significant: the association with cognitive impairment had an SMD of 0.26 ([95% CI –0.60 to 1.11], p = 0.56, I^2 79.7%, [I^2 95% CI

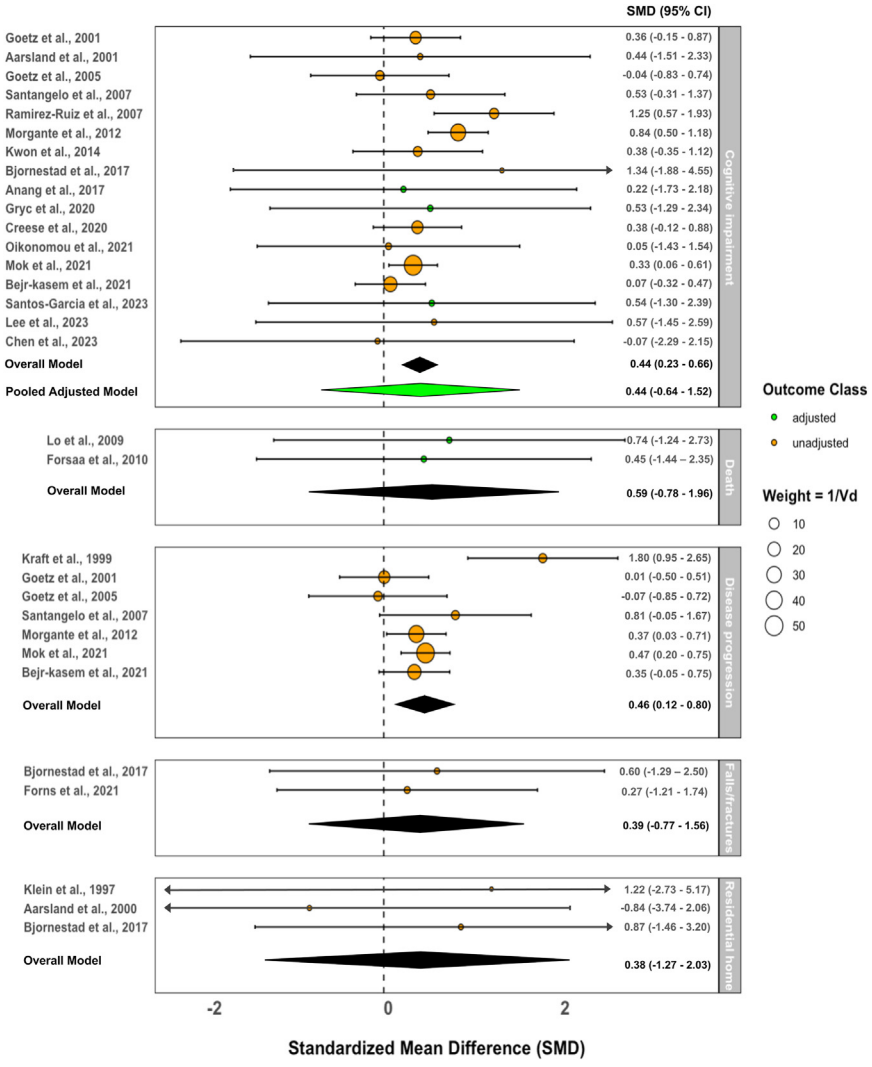

Fig. 2: **The association of psychosis with Parkinson's disease outcomes.**

21.5–99.3]) and the association with disease progression had an SMD of 0.18 ([95% CI –0.12 to 0.47], p = 0.24, I^2 = 0% [I^2 95% CI 0–99.5]).

The results of the meta-analysis are summarised in Fig. 6. Funnel plots are available in Supplementary Figure S5; visual inspection of these suggests a minimally asymmetrical distribution between ICBs and cognitive impairment.

Bipolar affective disorder

The association of bipolar affective disorder with subsequent cognitive impairment, disease progression and death was tested across one study with 639 participants.[72] This study showed an association with cognitive impairment (measured as MMSE score) with a hazard ratio (HR) of 1.43 (95% CI 1.16–1.75), association with earlier mortality (defined as death before 75 years of age) with a HR 1.48 (1.11–1.97) and association with disease progression (measured with UPDRS) with an SMD of –0.0759 (variance 0.007). Since there was only one study reporting on these outcomes, these results were not eligible for meta-analysis.

In Fig. 7, we present an effect size heatmap, summarising the meta-analytic results.

Quality assessment

Based on the Newcastle–Ottawa Scale, 46 (84%) studies were considered of high quality, 9 (16%) of moderate quality and none (0%) of low quality. Those studies that were deemed moderate quality lost points due to case representativeness (e.g. all patients were from a selected group, such as a nursing home, and therefore not wholly representative of the Parkinson's disease population as a whole) and a lack of reported follow-up, with

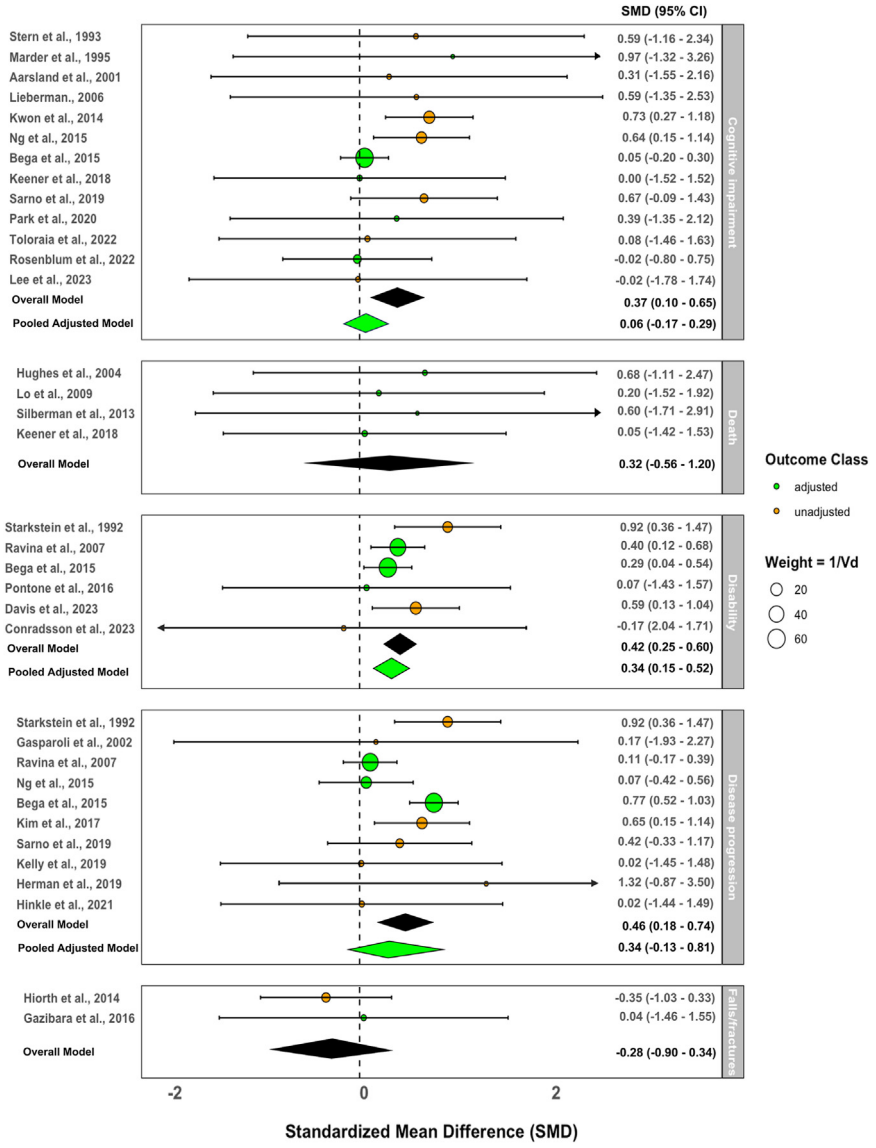

Fig. 3: **The association of depression with Parkinson's disease outcomes.**

no description or explanation of those lost. Nonetheless, the overwhelming majority of the included studies were of high quality.

As per our study protocol (see Prospero), we originally intended to perform prespecified group analyses and meta-regressions. However, these analyses were subsequently not performed for the following reasons. With study design, 52 of 55 included studies were cohort design, meaning insufficient variability for comparison. The follow-up period varied extensively within studies, risking study variability dwarfing between-study variability, in addition to the issue of missing data from original studies. With age, again we noted large variability within studies.

Discussion

This study reports, to our knowledge, the largest and most comprehensive systematic review of the impact of psychiatric comorbidities in Parkinson's disease, quantifying the high relevance of these psychiatric conditions to clinical outcomes. We identified 55 eligible studies, published from 1992 to 2023, with a total population of 165,828. We report that psychosis, depression and apathy in Parkinson's disease are associated with subsequent cognitive impairment; psychosis and depression are associated with worse disease progression, and depression is also associated with disability.

Hallucinations are known to be common in Parkinson's disease, with psychotic experiences occurring in

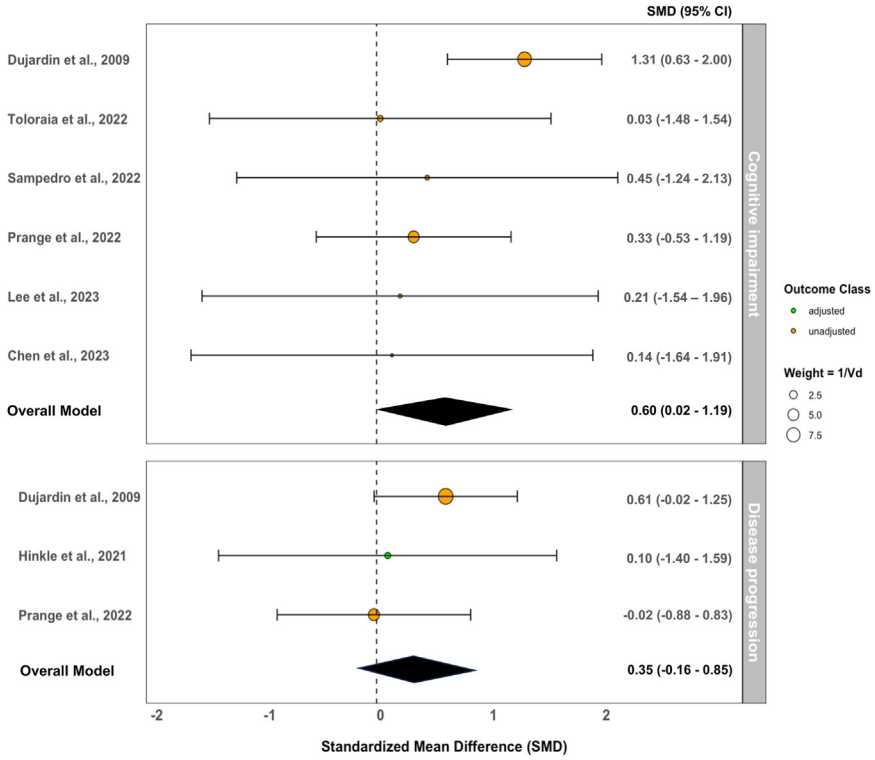

Fig. 4: The association of apathy with Parkinson's disease outcomes.

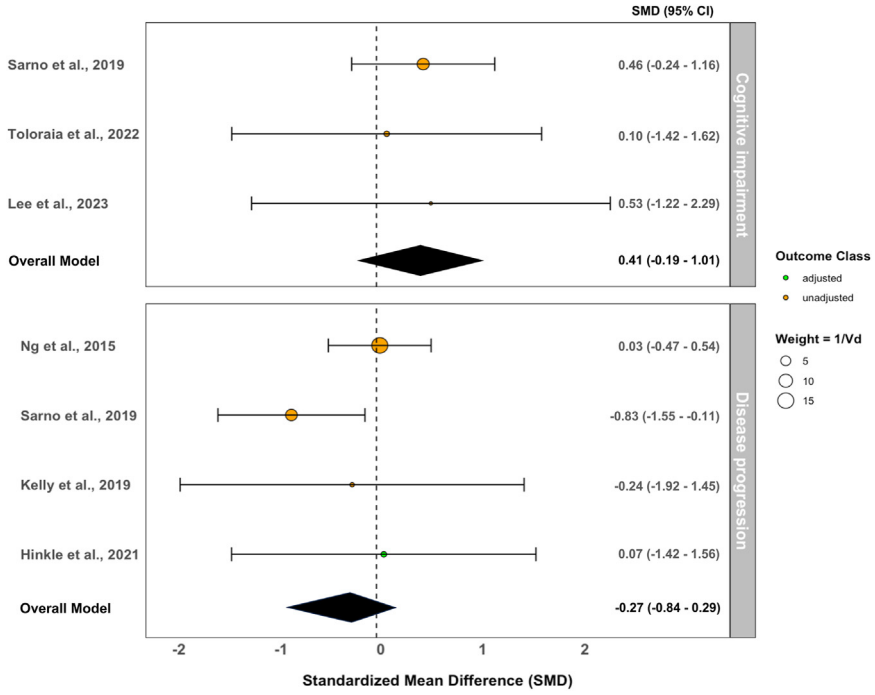

Fig. 5: The association of anxiety with Parkinson's disease outcomes.

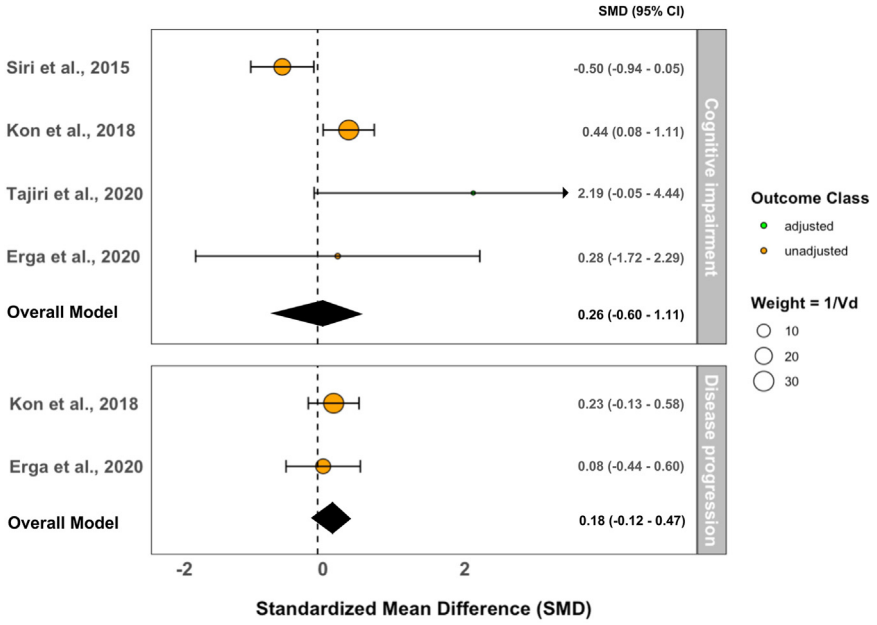

Fig. 6: **The association of ICBs with Parkinson's disease outcomes**.

25–40% of patients, visual hallucinations in 15–30%, non-visual hallucinations in 35% and delusions in 4% (point prevalence), which is significantly higher compared to the general population.[73,74] We found psychosis to be significantly associated with cognitive impairment (medium effect size) and disease progression (medium effect size). This is consistent with psychosis being more common in advanced disease, with a cumulative prevalence up to 60%[75] and, previous work which has found significant correlations between delusions and hallucinations with akinesia and rigidity scales.[76] Surprisingly, we did not find a significant association between psychosis and residential home admission or mortality, as previous work has suggested psychosis is a key determining factor leading to care home placement and is also linked to increased mortality.[22] This may be due to limited numbers of eligible studies focusing on these outcomes and small numbers

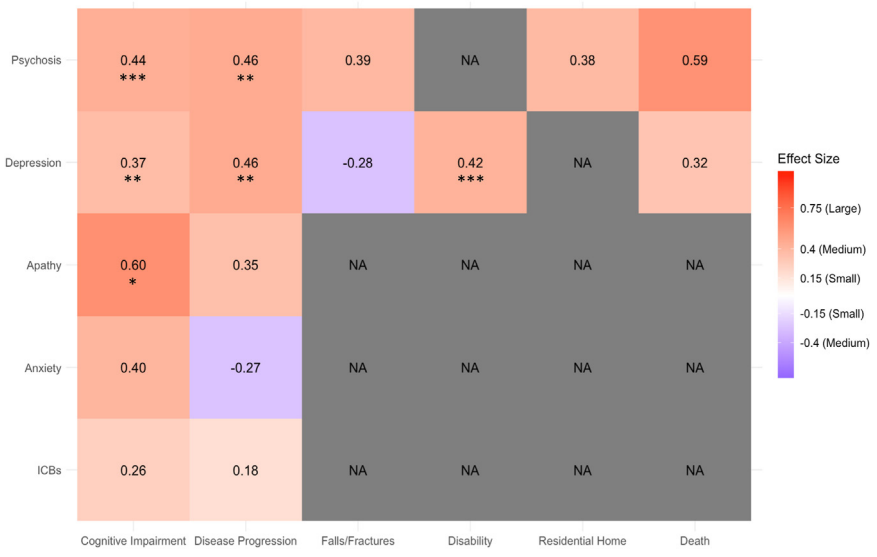

Fig. 7: **A heatmap of the association of psychiatric exposures with Parkinson's disease outcomes**.

of participants in these studies. We also found no evidence of association between psychosis and falls or fractures risk. This finding is perhaps surprising, conflicting with existing literature on this topic, and warrants further investigation due to the small numbers of patients in the studies included.[32]

Depression is very common in Parkinson's disease, with a 35% point prevalence, higher than in the general population (17.2% point prevalence).[77,78] We found significant associations between depression and cognitive impairment (small effect size), disease progression (small effect size) and disability (large effect size). This is consistent with the notion that depression contributes to disease burden and is thought to be the most important predictor of quality of life.[11] Indeed, a large recent cohort study found increased neuropsychiatric symptoms, particularly depression, were associated with worsening motor severity and contributed to poorer quality of life.[5]

We did not find associations between depression and falls or fractures risk and death. This non-significant result for death is consistent with a large recent cohort study of Parkinson's disease patients, which found depression to be a possible confounding factor for mortality but not predictive of the outcome itself.[6] Furthermore, one study (not eligible for meta-analysis) supports an association between depression and residential home admission,[18] possibly due to the links between depression with cognitive and functional impairment and overall disease progression.

Apathy is an established distinct symptom of Parkinson's disease, independent of depression or fatigue.[11] Patients with Parkinson's disease have higher levels of apathy than equally disabled people with other chronic conditions such as osteoarthritis, suggesting a neurodegenerative component.[79] In our review, we found apathy to be significantly associated with cognitive impairment, with a medium effect size. This is consistent with longitudinal cohort studies, which have demonstrated apathy to be a behavioural indicator predictive of future cognitive impairment and dementia.[65,80] We did not find a significant association between apathy and disease progression. Our findings are also possibly limited due to high clinical heterogeneity between studies. Further work is needed to better understand the relationship between apathy and motor impairment (and disease progression), as earlier studies have suggested worse motor symptoms are correlated with apathy.[81]

Anxiety is common in patients with Parkinson's disease, with a 30% point prevalence, higher than in the average general population (14.7% point prevalence).[78,82] Anxiety, often in association with depression, can occur before the onset of motor symptoms, suggesting a prodromal stage of the disease.[83,84] We did not find anxiety to be significantly associated with subsequent cognitive impairment nor with disease progression, perhaps surprisingly. One study (not eligible for meta-analysis) also suggests anxiety is linked to greater fall or fracture risk. This warrants further investigation as previous work has suggested anxiety is linked to motor complications and fluctuations, suggesting a dopaminergic component.[85]

No significant associations were found between impulse control behaviours and cognitive impairment and disease progression. Again, this may be a result of high heterogeneity between studies and small sample size. Impulse control behaviours have previously been associated with poorer quality of life and greater caregiver burden[86,87]; therefore further work is warranted to elicit if there is a true association with poorer neurological outcomes.

Conclusions about bipolar affective disorder are limited by the lack of available evidence as we found only one eligible study. This reflects bipolar affective disorder being relatively uncommon in Parkinson's disease, compared to other psychiatric comorbidities. However, the results of this study are meaningful, suggesting associations between bipolar affective disorder and cognitive impairment, earlier mortality, and disease progression. Bipolar affective disorder is relatively understudied in Parkinson's disease, but a recent systematic review suggests that patients with bipolar disorder have a significantly increased likelihood of later developing Parkinson's disease, compared to the general population.[88]

The strengths of the study include the large overall population of Parkinson's disease patients and the robust quality of evidence included in this review. The majority (84%) of studies included were of high quality. Further requirements such as the minimum sample size threshold ($n > 20$) reduce the risk of reporting bias and chance findings. Requiring a control group strengthens our conclusions of the specific contribution of psychiatric comorbidity to neurological outcomes, suggesting differences found are due to the presence of psychiatric comorbidity and not merely the presence of Parkinson's disease. This highlights this review's novel approach and substantially adds to the existing literature—allowing us to make firmer conclusions on the role of psychiatric comorbidity in association with adverse outcomes in Parkinson's disease.

There are several limitations of this work, relating to the limitations of the underlying evidence and to the data synthesis itself. Among the included studies, there is a possibility that differences were found between groups due to chance, since multiple hypotheses were tested, and psychiatric comorbidity was sometimes only included as a secondary analysis. Furthermore, it is known that psychiatric comorbidities in Parkinson's disease often co-occur with each other.[3] It is possible that included studies did not adequately account for this, by either exclusively focussing on one psychiatric condition, or by recording a combination of symptoms the

impact of individual comorbidities may be difficult to delineate. Where possible, we accounted for all measured psychiatric comorbidities reported in individual studies, by separately delineating all exposure-outcome pairs accordingly, and then including these in separate meta-analyses. This relies on studies reporting psychiatric comorbidity or diagnosis, and regrettably does not account for unmeasured and hence unrecorded psychiatric symptoms. Due to inconsistencies with individual studies reporting on one versus multiple psychiatric comorbidities, we were unable to analyse the role of the number of psychiatric symptoms and impact on the outcome of interest. There is potential for residual confounding in studies, including the possibility for individuals with psychiatric comorbidity to be older, more advanced in their disease or more frail at study initiation; most studies did not present estimates adjusted for these variables. Missing data, particularly where this is due to differential loss to follow-up between groups, is also a concern in some studies. Some studies had very narrow inclusion criteria, which may not be representative of the wider Parkinson's disease population, limiting the generalisability of conclusions.

The methodological analysis approach of converting all outcome measurements reported by individual included studies to SMDs also warrants consideration—it is well-established that SMDs are most appropriate for continuous outcomes, which we note includes the vast majority of outcomes reported in this study. However, there are limitations to using SMDs for dichotomous outcomes, which we acknowledge, and we report all original effect sizes in Supplementary Material.

We observed a large range of follow-up intervals, which reflects the heterogeneity in our included studies. We attempted to minimise the impact of this large range by only including studies with a control (non-psychiatric) group, and we assume the differences between exposed and unexposed (psychiatric versus no psychiatric comorbidity) remain stable over time.

We found significant heterogeneity between studies, particularly with certain outcomes (psychosis and disease progression, impulse control behaviours and cognitive impairment). This suggests that variation in Parkinson's disease populations, outcomes and measurement techniques may account for some of the differences between studies. Variation in follow-up duration between studies may have obscured a differential impact of a psychiatric comorbidity representing a prodrome versus a risk factor. Differences in baseline demographic, socioeconomic and clinical variables may also be relevant moderators of effect size and could be the subject of a future individual patient data meta-analysis. Visual inspection of the funnel plots suggested a low risk of publication bias for most exposure-outcome pairs.

Our findings highlight areas for future research. Further studies are needed which examine mortality, disease progression, cognitive impairment, residential home admission and disability in the context of psychiatric comorbidity, with representative community-based samples in addition to hospitalised or institutionalised populations, with longer term follow-up. While our findings show that there is an association of various psychiatric comorbidities with poorer outcomes, in order to provide compelling evidence for a predictive or causal effect, more robust methods are needed for dealing with confounding, such as matching, adjustment or use of propensity scores. If this relationship is found to be causal, there could be additional benefits to aggressively managing psychiatric comorbidities in Parkinson's disease. Studies that assess the temporality of symptoms with longer follow-up and repeated measurement of symptoms are also necessary, as a combination of non-motor and psychiatric symptoms may identify a prodromal pre-motor psychiatric Parkinson's disease phenotype. One trend emerging from the pattern of our results is the frequency with which cognitive impairment was linked significantly to psychiatric morbidities. This may be because it is more readily quantifiable than the other outcomes but also because it may lie on a final common path towards adverse outcomes. It is interesting to consider this work from a pharmacological perspective: whilst some of the neuropsychiatric comorbidities in Parkinson's disease have been linked to dopaminergic medication (notably ICBs and psychosis),[89,90] there is evidence that initiation of dopaminergic medication is actually associated with an improvement in mortality.[91]

Studies included in our meta-analysis did not consistently report on dopaminergic medication, however where a study reports an outcome in both "off and on" medication states, the "off medication" assessment is used due to the removal of medication confounders. The paucity of data in the original studies is an inevitable limitation of this review in terms of interpreting the results.

This work has several clinical implications. Firstly, clinicians should be aware that in addition to motor manifestations of the disease, neuropsychiatric symptoms are common and potentially harmful in people with Parkinson's disease. Often, the presence of these symptoms constitutes a major source of disease burden for patients and carers, severely affecting quality of life and overall wellbeing. We have shown in addition that neuropsychiatric symptoms are associated with poorer overall disease outcomes in Parkinson's disease, in particular significantly affecting cognitive impairment and disease progression.

Hence, increased awareness of the role of psychiatric comorbidity in Parkinson's disease, early detection of symptoms and identification of risk factors is essential if

we are to modify and prevent these symptoms and to identify those with a poor prognosis who may require more intensive clinical management. Current dopaminergic treatments for Parkinson's disease are limited in their efficacy for neuropsychiatric deficits and may in part contribute to them. We therefore need a range of efficacious treatment options with the potential to improve overall disease outcomes. A better understanding of the neurobiological mechanisms underlying these psychiatric comorbidities in Parkinson's disease is critical. Identifying, assessing, and managing neuropsychiatric comorbidities in Parkinson's disease will require a comprehensive patient-tailored, multidisciplinary approach.

Contributors

EB and JPR conceived the study. EB and JPR led and coordinated the study. JPR ran the literature search. Screening for eligibility at a title and abstract level was conducted by EB, JBF, MAS, JBB, ER, GM, CH, IC, EK, DG, A Lahmar, RMFG, CJW and B Cross, and at a full-text level by A Lahmar, A Saini, B Cross, CH, CJW, DAG, EB, EK, ER, IC, JBB, JBF, JPR, JS, JW, AN. Where there was disagreement, a third author (B Cross, JBB, JBF, JPR) arbitrated.

A Lahmar, A Saini, DAG, EB, ER, GM, IC, JBF, JS, JW, MAS, RMFG, AN, B Cross, CH extracted the data. Where there were disagreements, a third author (CJW, DAG, ER, IC, JBB, JBF) arbitrated. Throughout this process, one author (CJW) ensured consistency of format for data extraction items. A Lahmar, AN, A Saini, B Cross, CH, EB, ER, GM, IC, JBF, JPR, JS, MS and RMFG conducted quality assessment. A Lahmar, A Saini, B Cross, ER and JBB arbitrated quality assessment if overall rating differed between reviewers. CJW calculated descriptive statistics. CJW conducted the meta-analysis, supported by JPR, EB and B Carter. CJW created figures. JPR made the PRISMA flow chart. EB sorted references. EB checked adherence to PRISMA guidelines. EB and JPR drafted the original manuscript. EB checked the completed manuscript. EB created tables. EB sorted funding statements. EB formatted the manuscript. AD, GL, B Carter, A Lees, MSZ and A Sommerlad advised on the interpretation of the findings and the final manuscript. EB and JPR are responsible for the overall content of the study. All authors had full access to all the data included in this study and included data was verified by EB and CW. All authors had final responsibility for the decision to submit for publication.

Data sharing statement

Data for each included study and a data dictionary are available in the Supplementary Material. The protocol is available from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=373072.

Data analysis code can be found at the following link–https://github.com/CameronWatson2020/pd_neuropsychiatry.

Declaration of interests

JPR reports research funding from the Wellcome Trust, royalties from Taylor & Francis, payment for reviewing from Johns Hopkins University Press and speaker fees from the Alberta Psychiatric Association and Infomed Research & Training Ltd. A Lees reports consultancies from Britannia Pharmaceuticals and BIAL Portela. He also reports grants and/or research support from the Frances and Renee Hock Fund, and honoraria from Britannia Pharmaceuticals, BIAL and Convatec. MSZ declares honoraria for one lecture each for each of the three mentioned in the last 3 years: Norwegian Neurological Society; Copenhagen Neuropsychological Society, Rigshospitalet; and Cygnet Healthcare. A Sommerlad reports research grants from the Wellcome Trust, Alzheimer's Association and Brain Canada. CW reports grant funding, including support for attending meetings and travel, from the NIHR Academic Clinical Fellowship. GL reports funding from the Wellcome Trust, NIHR, UK Research Institute (UKRI). He also reports funding support for attending meetings and/or travel from ECNP 2023, participation on NIHR trial TSC and holds a leadership role on the NIHR doctoral training fellowship panel.

All other authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100870.

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