Received: 21 September 2023 | Revised: 12 January 2024 | Accepted: 16 April 2024

DOI: 10.1002/hsr2.2092

STUDY PROTOCOLS

Health Science Reports Open Access WILEY

Cognitive function in different motor subtypes of Parkinson's disease: A systematic review protocol

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Funding information
James and Diana Ramsay Foundation

Abstract

Background and Aims: As the fastest-growing neurological disorder globally, a better understanding of Parkinson's disease (PD) is needed to improve patient outcomes and reduce the increasing economic and healthcare burden associated with the disease. Whilst classified as a movement disorder, this disease is highly heterogeneous, encompassing a broad range of both motor and non-motor symptoms (NMS). Cognitive impairment, presenting as either mild cognitive impairment or PD-dementia, is one of the most prevalent and disabling NMS. To better understand heterogeneity in PD, researchers have sought to identify subtypes of individuals who share similar symptom profiles. To date, this research has predominantly focused on motor subtyping, with many studies comparing these motor subtypes on non-motor outcomes, such as cognitive impairment. However, despite evidence of a motor-cognitive relationship in healthy aging, findings regarding the presence of a motor-cognitive relationship in PD are inconsistent. In our proposed systematic review, we will investigate motor subtyping studies that have evaluated the relationship between motor and cognitive function in PD. We aim to examine what is currently known about the relationship between motor and cognitive impairment in PD and evaluate the state of the field with respect to the subtyping methods and quality of cognitive assessment tools used.

Methods: Systematic literature searches will be conducted in PubMed, PsycINFO, CINAHL, Scopus, and Web of Science.

Results: Results will be synthesized using meta-analysis and, where meta-analysis is not feasible, narrative synthesis.

Conclusion: Despite the preponderance of motor subtyping research in PD, our study will be the first to systematically review evidence regarding the association between motor subtypes and cognitive impairment. Understanding the nature of the motor-cognitive relationship in PD may lead to important insights regarding shared underlying disease pathology, which would have significant implications for early diagnosis, prognosis, and treatment of cognitive impairment in PD.

KEYWORDS

aging, classification, cognition, motor activity, motor disorders, Parkinson disease

1 | INTRODUCTION

The proportion of older adults in our population is increasing rapidly; by 2050, more than 16% of the world's population will be aged over 65 years, compared to 9.3% in 2020.[1] As our population ages, age-related health conditions such as arthritis, dementia, and Parkinson's disease (PD) are becoming increasingly prevalent.[2] Currently, PD is the fastest growing neurological disorder worldwide,[3] with its prevalence expected to double between 2014 and 2040.[4] As such, PD is anticipated to place a considerable, increasing burden on healthcare systems, and focusing efforts on its prevention and treatment could have substantial long-term social and economic benefits.

PD is a movement disorder characterized by several cardinal motor symptoms, including tremors, bradykinesia (slowness of movement), muscle rigidity, gait problems, and postural instability.[5] There is, however, increasing recognition of the vast array of non-motor symptoms (NMS) experienced by people with PD (PwPD), including olfactory, sleep, and cognitive impairments.[6] PD is highly heterogeneous in its presentation and progression; individuals can vary dramatically in symptom profile, symptom severity, and rate of decline. This makes it difficult for clinicians to provide accurate prognoses regarding disease trajectory and personalized treatment tailored to an individual's unique symptom profile.[7]

In response, an active field of subtyping research has emerged, which seeks to identify demographic and disease features that co-occur, resulting in distinct clusters—or subtypes—of PwPD with similar symptom profiles.[8] It is assumed that any disease features that cluster together may be indicative of some shared underlying pathophysiology and that PwPD belonging to the same subtype will have similar treatment responses distinct from those of PwPD that do not share these features.[8,9] Moreover, the assignment of individual patients to a known subtype based on current symptoms may provide insights into the likelihood of other emerging symptoms over the course of the disease (e.g., sleep problems, medication-induced impulsivity), thereby providing opportunities for early intervention and prevention.[10]

To date, subtyping research has predominantly focused on identifying subtypes derived from an individual's motor symptoms alone. Of these motor subtyping frameworks, the most widely used classifies patients as belonging to either a “tremor-dominant” (TD) or “postural instability gait disturbance” (PIGD) subtype.[11–13] Using similar models, others have grouped patients according to whether they present as TD or “akinetic-rigid” (AR).[14–17] These subtyping frameworks are hypothesis-driven, derived from clinicians' observations that patients with strong tremors often do not present with severe axial symptoms (e.g., postural instability, gait impairment).[9] These subtyping frameworks have demonstrated utility in differentiating PwPD with respect to other disease characteristics and outcomes; relative to TD patients, AR/PIGD patients are older,[18] have a longer disease duration,[19] and shorter survival.[17]

In addition, researchers have investigated motor subtype differences in NMS, such as cognitive impairment, one of the most important yet under-researched NMS in PD. Cognitive impairment is common, with approximately half of PwPD developing some degree of cognitive impairment within 5–6 years of diagnosis[20,21]; but it is highly heterogenous, ranging from subjective cognitive impairment to formally diagnosed mild cognitive impairment (PD-MCI) and dementia (PDD)[22,23]; and known to have a significant impact on quality of life for patients[24] and their carers.[25] There is already clear evidence of a motor-cognitive relationship in healthy ageing[26]; multiple longitudinal studies have, for example, demonstrated an association between declining cognition and impaired gait.[27–30] Consistent with this, when comparing motor subtypes in PD, findings support a motor-cognitive relationship; several studies have found the AR/PIGD subtype to be associated with a higher incidence of PD-MCI (e.g., Poletti et al.[31]) and PDD (e.g., Alves et al.[32]) compared to the TD subtype. Other studies, however, have found no differences in cognitive performance between motor subtypes (e.g., Ren et al.,[33] Urso et al.[34]).

There is considerable methodological heterogeneity in PD subtyping research, which may account for these inconsistent findings (for discussion, see van Rooden et al.,[10] Qian et al.,[35] Mestre et al.[36]). Multiple procedures have been proposed for classifying PwPD into the aforementioned motor subtypes, depending on the measure(s) used to assess motor function. There is also variation in the subtyping methods used, with alternative motor subtyping frameworks proposed. In particular, there has been a proliferation of recent data-driven approaches, wherein statistical methods (e.g., *k*-means clustering) are used to determine which feature, or combination of features, gives rise to distinct clusters of patients.[9] Whilst the relationship between axial symptoms (i.e., PIGD) and poor cognitive outcomes is well established in studies using a hypothesis-driven approach, it is unclear whether this relationship between axial motor symptoms and cognitive impairment is reliably replicated using data-driven methods.

Our proposed review will summarize motor subtyping studies that have investigated the relationship between motor function and cognitive impairment in PD. In doing so, we will aim to resolve inconsistent findings regarding the motor-cognitive relationship by synthesizing the results of multiple studies whilst accounting for their methodological quality. Our review will seek to determine whether the motor-cognitive relationship differs depending on the measures used to assess motor and cognitive function (e.g., objective vs. clinician-rated assessments) and the type of subtyping procedure (e.g., hypothesis- or data-driven) applied. Whilst there have been several recent reviews on subtyping in PD,[8–10,35,37,38] many of these are expert reviews not performed systematically,[8,9,37] and none have specifically sought to investigate the relationship between motor subtype and cognition. Critically, the most recent PD subtyping review[38] only included studies where a novel subtyping framework was reported for the first time. This resulted in the exclusion of many studies and precluded evaluation of each subtype method's reproducibility. The reproducibility of a subtyping procedure is essential to its clinical utility, yet has been difficult to achieve for many proposed PD subtyping procedures.[36] By including studies applying the same

subtyping procedure to new datasets, we will be well-positioned to evaluate the reproducibility of these different frameworks.

Our research questions are as follows:

1. Which subtyping methods are most commonly used?
2. What is the nature of the relationship observed between motor and cognitive function in PD, as investigated by studies using motor subtyping methods?
3. Does the subtyping method used influence the motor-cognitive relationship observed?
4. Does the type of motor and/or cognitive assessment(s) used influence the motor-cognitive relationship observed?

2 | METHODS

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic review protocols[39] (PRISMA-P; for checklist, see Supporting Information 1) and is registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42022362290).

2.1 | Inclusion and exclusion criteria

2.1.1 | Participants

We will include studies with adult participants with a formal PD diagnosis made by a neurologist using established diagnostic criteria, including, but not limited to, the UK Brain Bank Criteria[40] and Movement Disorder Society (MDS) Clinical Diagnostic Criteria.[41] For studies that include healthy controls and/or participants with suspected PD, a diagnosis of parkinsonism, or a diagnosis of a related movement disorder or neurological condition (e.g., essential tremor), we will include these studies only if data for participants with a formal PD diagnosis are reported separately.

No limits will be placed on participants' sex, gender, or ethnicity. In addition, there will be no restrictions on disease severity, duration, or age at disease onset. We will include studies where participants are reported as having one or more mood disorder comorbidities (e.g., depression), but, given the documented relationship between mood and cognition,[42,43] will take this into consideration during data synthesis (see "Data Synthesis and Analysis" section for details).

2.1.2 | Assessments

Motor function

All included studies must include at least one motor assessment validated for use with PwPD. This assessment must comprise one or several measures that evaluate the presence or severity of one or more cardinal symptoms of PD: tremor, bradykinesia, muscle rigidity, gait problems, and postural instability. We will include studies that use objective and/or clinician-rated motor assessment tools (see Table 1 for examples). Any study that only reports on motor symptoms assessed via patient self-report will be excluded. Studies that only report on motor symptom asymmetry or side of motor symptom onset will be excluded.

Cognitive function

All included studies must use at least one objective or clinician-completed assessment of cognition. We will include both objective and clinician-rated cognitive assessments, regardless of whether they are domain-specific or general (i.e., global, multi-domain) assessments. We will also include studies that have categorized participants according to their cognitive status (e.g., normal cognition, PD-MCI, PDD) using cut-off scores and/or diagnostic criteria validated for use with PwPD (see Table 2 for examples). Studies that only report on cognition using patient self-report (e.g., memory or attention items on the Non-Motor Symptoms Questionnaire)[56] will be excluded.

2.1.3 | Study design

Subtyping methods

All included studies must have applied one or more subtyping methods to their PD sample. We will adopt the definition used by Mestre et al.,[38] who described a PD subtyping study as "any research study conducted with the purpose of dividing PD patients into subtypes, as stated by its authors, or identified by distinct groups of PD patients that were discussed as possible subtypes" (p. 397). We are only interested in studies that separate PwPD into two or more groups to better characterize heterogeneity within this population. We will, therefore, exclude studies solely concerned with applying a subtyping approach to differentiate PwPD—considered as a single group—from other groups (e.g., healthy controls).

Given that our review is focused on the use of subtyping methods to investigate the differences in cognition between motor subtypes specifically, included studies must make use of motor

TABLE 1 Some examples of motor assessment tools eligible for inclusion in our systematic review.

Clinician-rated (subjective) measures	Objective measures
- Part III of the Unified Parkinson's Disease Rating scale (UPDRS; any version)[44,45]	- Digital tapping test for bradykinesia assessment - Accelerometer data for tremor measurement - Electronic sensors for gait assessment

TABLE 2 Some examples of cognitive assessment tools eligible for inclusion in our systematic review.

Domain-specific measures	General cognition measures	Diagnostic criteria
- Digit span (working memory)[46] - Inspection time (processing speed)[47] - Stop-signal task (response inhibition)[48] - Probabilistic selection task (reinforcement learning)[49]	- MMSE[50] - MoCA[51] - Dementia Rating Scale[52]	- MDS diagnostic criteria for PD-MCI[53] - MDS diagnostic criteria for PDD[54] - DSM-5 criteria for dementia[55]

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; MCI, mild cognitive impairment; MDS, Movement Disorder Society; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; PD, Parkinson's disease; PDD, Parkinson's disease dementia

assessments in the derivation of their subtypes. Specifically, included studies must use at least one motor assessment to derive their subtypes and then report subtype differences on at least one cognitive assessment post hoc. While studies may use more than one motor assessment in their subtype derivation, they cannot use any non-motor variables, as this would confound the motor-cognitive relationship being investigated.

Both hypothesis- and data-driven approaches will be eligible for inclusion. In hypothesis-driven studies, subtypes are derived based on disease features that have been clinically observed to co-occur.[57] In contrast, data-driven approaches tend to be more exploratory, as they rely on statistical or machine learning methods (e.g., *k*-means clustering) to discover which feature(s) give rise to distinct subgroups of patients.[57]

We will include studies that report on a novel or previously used subtyping system, provided that any previously used subtyping systems are being applied to new data. We will also include any studies that report on novel, follow-up data for a sample for whom earlier data has already been published.

2.1.4 | Miscellaneous

All types of study designs (e.g., cohort, cross-sectional, longitudinal) will be included. Only peer-reviewed original research studies published in English will be eligible for inclusion. The following publication types will be excluded: books, opinions/editorials, replies/commentaries, conference abstracts, posters, reviews, protocols, case studies, theses/dissertations, and unpublished/gray literature. We will place no lower limit on the publication year and include all studies published up until the time our search is performed.

2.2 | Search strategy

We will search the following online databases from inception: PubMed, PsycINFO (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost), Scopus, and Web of Science. Our search terms are relatively broad to increase the likelihood of capturing eligible studies. We developed our search strategy for each database in consultation with a research librarian who has expertise in medicine and psychology. Key search terms were variations on PD, subtyping, motor function, and cognition, as well as names of specific assessment tools, such as the UPDRS and MMSE. We have customized our search strategy for each database to include relevant subject headings and MeSH terms. Consistent with our eligibility criteria, we have included search terms and/or applied search filters to exclude animal-only studies and non-English studies. The proposed search strategies for all chosen databases are provided in Supporting Information 2. Any amendments made to searches will be documented on PROSPERO. We will rerun our searches before commencing data synthesis to ensure that any eligible studies published between this date and the initial search date are captured. We will also hand-search the reference lists of included studies and key reviews in the field[8–10,35,37,38,58] to identify other relevant studies not found by our database searches. In addition, studies that cited included studies will be screened for eligibility.

2.3 | Data management

We will use Covidence (Veritas Health Innovation) to manage records. All search results will be exported as .ris or .txt files, which will then be imported into and deduplicated in Covidence. Following this, title and abstract screening, full-text screening, data extraction, and quality assessment will be completed in Covidence.

2.4 | Study selection

At both title and abstract screening and full-text screening, two independent reviewers will screen each study for eligibility. When studies are excluded at the full-text stage, each reviewer will be required to specify a reason for exclusion based on a list of prespecified reasons. Conflicts where reviewers disagree on the decision or disagree on the reason for exclusion will be resolved through discussion between the two reviewers and, where necessary, arbitration by a third reviewer. At both stages of screening, interrater reliability will be quantified using Cohen's kappa.[59] No threshold values will be set, however these values will be monitored throughout screening and reported in the final review.

2.5 | Data extraction

We have developed a review-specific data extraction form comprising 125 items (Supporting Information 3). We will extract critical study information relating to sample size and characteristics, motor

and cognitive measures, subtyping methods, and results. One reviewer will extract data for all studies and a second reviewer will independently extract data for at least 20% of included studies, selected randomly. After both reviewers have completed data extraction on this subsample of studies, the extracted data will be compared. If raw agreement is less than satisfactory (<85% of critical fields, denoted by an asterisk in Supporting Information 3), discussion between the reviewers will take place, and the second reviewer will independently extract data for an additional 10% of included studies. This process will be repeated, if necessary, until a satisfactory level of agreement (≥85% of critical fields) is reached. Any inconsistencies will be resolved by discussion between the reviewers and, where necessary, arbitration by a third reviewer.

In instances where a single study reports on the results of multiple subtyping approaches that meet our inclusion criteria, the methods and results for each approach will be extracted separately. When data cannot be found in the main text or supplementary materials, it will be requested from corresponding authors via email. Up to three attempts at contact will be made; if the author does not respond within a 2-week period from the date of the third email being sent, or the requested data cannot be provided, the study will be excluded.

2.6 | Quality assessment

Study quality will be appraised using a quality assessment tool (Supporting Information 4) developed specifically for this review. This tool is adapted from Hayden et al.'s[60] Quality in Prognosis Studies (QUIPS) tool, which was designed to evaluate validity and bias in studies of prognostic factors. We modified the QUIPS' prognostic factor and outcome measurement domains to appraise the quality of motor and cognitive measures in our included studies. We also renamed the QUIPS' attrition domain to "use of follow-up data" and replaced the QUIPS' study confounding domain with a single item. Our revised quality assessment tool comprises five domains: participant recruitment and characteristics, motor function measurement, cognitive function measurement, statistical analysis and reporting, and use of follow-up data. Throughout, we have modified items to be specific to our review and integrated several items adapted from Mestre et al.'s[38] methodological quality tool, which was specifically developed for appraising PD subtyping studies. Finally, we have adopted a numeric scoring approach to increase sensitivity and allow greater weight to be given to items considered more important. We have identified cut-off scores for classifying a study's risk of bias as low, moderate, or high for each domain and overall (see Supporting Information 4).

One reviewer will appraise the quality of all included studies, and a second reviewer will independently complete a quality assessment for 20% of included studies, selected randomly. Any inconsistencies will be resolved via discussion and, where necessary, arbitration by a third reviewer. Intraclass correlations (ICC) will be used to assess interrater agreement, with ICCs calculated for each domain and for the overall risk of bias. Where the ICC is less than 0.75, a discussion between reviewers will take place, and the second reviewer will independently complete a quality assessment for an additional 10% of the included studies. This process will be repeated, if necessary, until a satisfactory level of agreement (≥0.75) is reached. This threshold has been selected based on Koo and Li's[61] guidelines, according to which values above 0.75 indicate good-to-excellent agreement.

2.7 | Data synthesis and analysis

Although high methodological heterogeneity will likely prevent the use of meta-analysis to synthesize the results of data-driven studies, it will be feasible to perform meta-analyses on hypothesis-driven studies that have adopted the same subtyping framework. In these cases, we intend to extract or calculate Hedges' *g* as an effect size measure of the difference between subtypes on one or more cognitive measures and perform a random-effects meta-analysis using the dmetar package in R.[62] In instances where multiple studies have used the same data set (or a single study reports on multiple subtyping methods applied to the same data set), we will select the study (or method) with the highest quality rating, as determined by our quality assessment tool, for inclusion in any meta-analyses. Results of meta-analyses will be presented visually using forest plots, and study heterogeneity will be assessed using I^2.[63] To evaluate publication bias, we will generate funnel plots and perform Egger's test.[64] Where feasible (≥10 studies[65]), we will run subgroup analyses to compare the results of studies that have used clinician-rated versus objective assessments, and studies that have used domain-specific versus global measures of cognition. Where data are available, meta-regression will be used to investigate the effect of comorbid mood disorders on the association between motor subtype and cognitive function. To achieve this, the proportion of participants in each motor subtype group with a diagnosed mood disorder (e.g., depression, anxiety) will be extracted for each study. If there is a sufficient number of studies (≥10 studies), separate meta-regression analyses will be conducted for each class of mood disorder (e.g., depressive disorders, anxiety disorders).

For data-driven subtyping studies and other studies that are not suitable for inclusion in our meta-analyses, it is our primary intention to analyze data using a narrative synthesis approach.[66] We plan to synthesize data (in both tables and text) according to the broad subtyping approach used, grouping studies based on whether they adopted a hypothesis- or data-driven approach. In addition, we will consider how the quality of assessment tools used to measure motor and cognitive function influences results, with a focus on comparing clinician-rated versus objective assessments, as well as single- versus multi-domain assessments.

2.8 | Outcome prioritization

With respect to cognitive assessments, domain-specific measures will be prioritized over general measures of cognitive function. For example, if a study compares motor subtypes on both general (e.g., MMSE) and domain-specific (e.g., working memory task) measures of cognition, then only the domain-specific measure(s) will be included

in our meta-analyses. Our prioritization of domain-specific measures is warranted, given that general measures of cognition have been shown to suffer from ceiling and floor effects.[67] Prioritizing domain-specific measures will also allow us to examine which specific aspects of cognitive function co-vary with motor subtype.

Another important consideration concerns the prioritization of objective assessments (e.g., stop-signal task) over clinician-rated assessments (e.g., MoCA). Clinician-rated assessments may be affected by rater bias and expertise,[68] leading to unwanted variability between raters. Given this, where a study compares motor subtypes on both objective and clinician-rated cognitive assessments, only the objective assessment(s) will be included in our meta-analyses. Finally, due to the increased sensitivity of continuous measures, cognitive assessments measured and analyzed continuously will be prioritized over assessments analyzed discretely. For example, continuous scores taken from the MoCA will be preferred to categorical data capturing participants' cognitive status (e.g., PD-MCI, PDD) derived from cut-off scores or diagnostic criteria. Where no continuous data are available, categorical data will be meta-analyzed using Cramer's *V* as the effect size measure. Alternatively, if too few studies are available for meta-analysis, categorical data will be synthesized narratively.

2.9 | Confidence in cumulative evidence

We will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines[69] to determine confidence in evidence. Overall GRADE for all studies will be rated by a single reviewer as high, moderate, low, or very low, depending on the risk of bias, consistency, directness, precision, and publication bias. The risk of bias will be determined using our quality assessment tool. Where meta-analysis is appropriate, consistency will be judged using I^2 values, and publication bias will be graded using Egger's test. Where required, we will follow Murad et al.'s[70] recommendations for applying GRADE guidelines when a meta-analysis has not been performed.

2.10 | Amendments

Any protocol amendments will be recorded on PROPSERO (registration number CRD42022362290).

3 | DISCUSSION

To our knowledge, our proposed systematic review will be the first to investigate the relationship between motor function and cognition in PD subtyping studies. Currently, symptom heterogeneity in PD restricts clinicians' capacity to provide accurate and detailed prognoses and to offer treatment plans customized to an individual's distinct symptom profile. Understanding the relationship between motor subtypes and cognitive impairment in PD may help to address these challenges; knowledge of impairment in one domain (e.g., gait problems) could be leveraged to inform early diagnosis, improve prognostic accuracy, and allow for early interventions that prevent or slow impairment in another domain (e.g., executive function).[71] As our population ages and PD becomes more prevalent, improving the management and treatment of this disease will be important for maximizing individuals' quality of life and reducing demands on our healthcare systems. Moreover, any motor-cognitive relationship observed in PD may be generalizable to other neurodegenerative diseases that affect our aging population, such as Alzheimer's disease and Huntington's disease, and could therefore lead to improvements in health outcomes for our aging population more broadly.

AUTHOR CONTRIBUTIONS

Brittany Child: Conceptualization; writing—original draft; writing—review and editing; methodology. **Isaac Saywell**: Methodology; writing—review and editing. **Robyn da Silva**: Methodology; writing—review and editing. **Lyndsey Collins-Praino**: Conceptualization; methodology; supervision; writing—review and editing; funding acquisition. **Irina Baetu**: Conceptualization; funding acquisition; writing—review and editing; methodology; supervision.

ACKNOWLEDGMENTS

The authors would like to thank Vikki Langton, Liaison Librarian at The University of Adelaide, for assistance with developing the search strategy. This project is not directly sponsored but has been developed from a larger project receiving funding from the James and Diana Ramsay Foundation (Evolution of decision-making in Parkinson's disease, 18th March 2019). B. C. is supported by an Australian Government Research Training Program Scholarship. Neither funding body will be involved in the study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit the report for publication. Open access publishing facilitated by The University of Adelaide, as part of the Wiley - The University of Adelaide agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data availability is not applicable to this article as no new data were created or analyzed for this study protocol paper.

TRANSPARENCY STATEMENT

The lead author, Brittany Child, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Child B, Saywell I, da Silva R, Collins-Praino L, Baetu I. Cognitive function in different motor subtypes of Parkinson's disease: a systematic review protocol. *Health Sci Rep*. 2024;7:e2092. doi:10.1002/hsr2.2092