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Lipidomic biomarkers of Parkinson's disease: protocol for a systematic review of diagnostic, clinical, and genetically associated alterations

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 August 2026 and was last updated on 18 August 2026.

INTRODUCTION

Review question / Objective This systematic review aims to identify, characterize, and critically appraise studies investigating lipidomic biomarkers of Parkinson's disease in blood and cerebrospinal fluid. The review will assess differences in individual lipid species or lipid classes between patients with Parkinson's disease and appropriate comparison groups, with particular attention to early-stage, de novo, and drug-naive patients. The review will also examine associations between lipid alterations and clinical characteristics, disease stage, genetic status, sex, and treatment status.

Rationale Parkinson's disease (PD) is one of the most common neurodegenerative disorders in the world. While established protein-based biomarkers of Parkinson's disease such as α-synuclein, neurofilament light chain, amyloid and tau markers, lysosomal enzymes, and neuroinflammation markers, provide valuable insight, there is a growing need for novel diagnostic and prognostic tools.

Lipids present as promising biomarkers for several reasons: 1) α-synuclein interacts with lipid membranes; 2) reduced breakdown of lipid substrates in lysosomes interferes with clearance of neurotoxic proteins; 3) abnormal lipid trafficking in various PD models has also been observed.

Biological fluids such as serum and plasma offer a promising alternative for large-scale screening, whereas cerebrospinal fluid may provide complementary information for diagnostic evaluation and disease characterization. Recent evidence suggests that metabolic shifts in PD patients are not confined to the brain but may also be reflected in altered lipid profiles in peripheral and central biological fluids. However, current findings remain heterogenous, with respect to patient populations, disease stage, medication status, biological matrices, analytical platforms, and lipidomic strategies. Therefore, a systematic review is essential to synthesize these findings, determine which lipid alterations are consistently associated with Parkinson's disease, whether they

differ according to disease stage or clinical subgroup, and which findings may have diagnostic and clinical relevance. Because substantial clinical and methodological heterogeneity is expected, this review will use a structured narrative synthesis according to biological matrix, lipid class, analytical method, disease stage, and clinical characteristics. Quantitative meta-analysis is outside the scope of the present review.

Condition being studied Parkinson's disease is a progressive neurodegenerative disorder characterized primarily by bradykinesia, resting tremor, rigidity, and other parkinsonian features, together with a broad range of non-motor manifestations. Its pathophysiology involves abnormalities in lipid metabolism, membrane composition, lysosomal function, mitochondrial pathways, inflammation, and oxidative processes. This review will focus on lipidomic alterations measured in blood and cerebrospinal fluid from individuals with clinically diagnosed Parkinson's disease.

METHODS

Search strategy A systematic literature search will be conducted in PubMed/MEDLINE. Additional searches will be performed in Cochrane Library, Google Scholar, eLIBRARY.RU. Reference lists of included studies and relevant systematic reviews will be screened for additional eligible articles. The search strategy will combine terms related to Parkinson's disease, lipidomics, lipid profiling, individual lipid species, and biological matrices. Example concepts include: ("Parkinson disease" OR "Parkinson's disease" OR parkinsonism) AND (lipidomics OR lipidomic OR "lipid profile" OR lipid* OR metabolomics OR ceramide* OR sphingolipid* OR phospholipid* OR fatty acid* OR cholesterol) AND (plasma OR serum OR blood OR cerebrospinal fluid OR CSF OR urine OR saliva OR sebum). Searches will not be restricted by publication date. Studies published in English and Russian will be included. Animal-only studies will be excluded during screening. The final search strategies will be adapted for each database and reported in the final review.

Participant or population The population will include adults with clinically diagnosed idiopathic Parkinson's disease, diagnosed according to recognized clinical diagnostic criteria, including the Movement Disorder Society Clinical Diagnostic Criteria, UK Parkinson's Disease Society Brain Bank criteria, or clearly described equivalent criteria. Studies involving early-stage, recently diagnosed, de novo, or drug-naive, and later disease stages patients will be considered.
Eligible studies must provide data from human participants and report the biological matrix, clinical characteristics, disease stage, and medication status of participants. Participants with genetically associated Parkinson's disease, including GBA- or LRRK2-associated disease, may be included and analyzed as prespecified subgroups.

Intervention Not applicable. This review will evaluate naturally occurring lipidomic profiles rather than therapeutic interventions.

Comparator Healthy controls, individuals without Parkinson's disease, or disease controls with other neurodegenerative or neurological disorders will be eligible as comparator groups. Studies without an appropriate comparator group will be excluded from the primary comparative synthesis but may be retained for descriptive evidence mapping if they provide relevant clinical or prognostic associations.

Study designs to be included Observational human studies, including case-control, cross-sectional, cohort, and diagnostic accuracy studies, will be included. Eligible studies must report original data on lipid species, lipid classes, or lipidomic profiles measured in human biological fluids. Genetic studies will be included only when they report lipid-related alterations relevant to Parkinson's disease. Reviews, meta-analyses, protocols, editorials, case reports, conference abstracts without sufficient data, and animal, cellular, or in vitro studies without separate human data will be excluded.

Eligibility criteria Studies will be included if they:
1. investigate adults with clinically diagnosed Parkinson's disease;
2. include a healthy, neurological, or disease-control group, where applicable;
3. measure individual lipid species, lipid classes, or lipidomic profiles in blood, plasma, serum, cerebrospinal fluid;
4. use a targeted or untargeted lipidomic approach, or a clearly defined metabolomics approach that reports individual lipid species or lipid classes
5. report quantitative or qualitative findings for lipid alterations; and
6. provide sufficient information about the participants, biological matrix, analytical method, and outcomes.

Studies will be excluded if they:

1. are animal, cellular, or in vitro studies without separate human data;
2. are reviews, meta-analyses, editorials, letters, protocols, or case reports;
3. assess only conventional serum lipids such as total cholesterol, HDL, LDL, or triglycerides without molecular lipidomic analysis;
4. measure only nonspecific oxidative-stress or lipid-peroxidation markers;
5. evaluate lipid changes induced by medication, dietary, exercise, or other therapeutic interventions without a relevant baseline comparison; or
6. do not provide sufficient data for interpretation.

Information sources The primary information sources will be PubMed/MEDLINE, eLIBRARY.RU, and Google Scholar. Reference lists of included studies and relevant systematic reviews will also be screened. Study authors may be contacted to clarify missing or ambiguous information. Duplicate records will be removed before screening.

Main outcome(s) The primary outcome will be reported differences in individual lipid species or lipid classes between participants with Parkinson's disease and comparator groups. Extracted outcomes will include lipid concentrations, fold changes, effect estimates, confidence intervals, p-values, diagnostic accuracy measures, and reported associations with disease status. Results will be analyzed separately by biological matrix, lipid class, analytical platform, disease stage, and medication status.

Additional outcome(s) Additional outcomes will include associations between lipid alterations and disease duration, Hoehn–Yahr stage, motor phenotype, cognitive status, age at onset, sex, genetic status, treatment status, and clinical severity. Where reported, prognostic associations with disease progression, change in clinical severity, cognitive decline, or other longitudinal outcomes will also be extracted. Methodological characteristics and potential confounding factors will be summarized.

Data management Search results will be imported into reference-management software for organization and duplicate removal. Screening will be performed using a systematic-review management platform. The first author conducted the screening of titles, abstracts, and full-text articles and will manage the extracted data. Data were recorded and stored in a structured electronic spreadsheet. The second author will assist with data verification, organization of extracted information, and preparation of the manuscript. Disagreements will be resolved through discussion and consensus. The extracted dataset will include study characteristics, participant characteristics, disease stage, medication status, biological matrix, analytical platform, lipid species, statistical results, clinical associations, and potential confounders.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of included studies will be assessed independently by two reviewers. The Newcastle–Ottawa Scale will be used for observational case-control and cohort studies. QUADAS-2 will be used for studies primarily designed to evaluate diagnostic accuracy. The assessment will consider participant selection, comparability of groups, exposure and outcome measurement, confounding, completeness of data, and selective reporting. Disagreements will be resolved through discussion and consensus.

Strategy of data synthesis Study characteristics and findings will first be summarized in structured tables, including study design, population, biological matrix, disease stage, medication status, analytical platform, lipid class or species, direction of change, effect estimates, and clinical associations. Because substantial heterogeneity is anticipated in populations, disease stages, biological matrices, analytical methods, and reported outcomes, the primary synthesis will be narrative. Findings will be organized by biological matrix and lipid class, including sphingolipids, glycerophospholipids, glycerolipids, sterols, fatty acids, and oxidized lipid species. The direction, consistency, methodological quality, and potential diagnostic or clinical relevance of reported associations will be assessed. No statistical meta-analysis will be conducted as part of the present review. Any future quantitative synthesis will be conducted as a separate research project.

Subgroup analysis Prespecified subgroup analyses will be performed narratively, where data permit, according to:
1. biological matrix: blood, cerebrospinal fluid,
2. disease stage: early-stage versus later-stage Parkinson's disease;
3. treatment status: drug-naive/de novo versus treated participants;
4. lipidomic strategy: targeted versus untargeted analysis;
5. analytical platform: mass spectrometry, nuclear magnetic resonance, or other methods;
6. clinical or genetic subtype, including GBA- or LRRK2-associated disease;
7. sex, age at onset, cognitive status, and motor phenotype, when adequately reported.

Sensitivity analysis The robustness of the narrative conclusions will be explored by examining the effect of excluding studies with high risk of bias, unclear diagnostic criteria, small sample sizes, inadequate comparator groups, or substantial unaddressed confounding. Findings from targeted and untargeted studies, different analytical platforms, mixed-stage populations, and treated versus drug-naive populations will be compared descriptively. No quantitative sensitivity analysis will be performed because statistical meta-analysis is outside the scope of the present review.

Language restriction English and Russian studies will be included.

Country(ies) involved Russia.

Other relevant information The review will be conducted and reported in accordance with relevant guidance for systematic reviews and protocol reporting. Any amendments to the registered protocol will be documented and reported in the final publication. The review will distinguish diagnostic lipid biomarkers from lipid alterations associated with disease severity, treatment, genetic subtype, or advanced disease stage.

Keywords Parkinson's disease; lipidomics; lipid biomarkers; metabolomics; sphingolipids; ceramides; phospholipids; fatty acids; lipid species; cerebrospinal fluid; plasma; serum; laboratory diagnostics; systematic.

Dissemination plans The findings will be submitted for publication in a peer-reviewed scientific journal and presented at relevant conferences in neurology, movement disorders, clinical biochemistry, laboratory diagnostics, and lipidomics. The results may also support the development of future studies evaluating minimally invasive lipid-based biomarkers for the diagnosis and stratification of Parkinson'sdisease.

Contributions of each author

Author 1 - Vera Kotina - Conceptualization and methodology; development of the search strategy; screening of all records and full-text articles; data extraction; risk-of-bias assessment; data synthesis; and drafting of the manuscript.
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Author 2 - Arseniy Berdnikov - Contribution to the interpretation of the results, drafting and critical revision of the manuscript, and approval of the final version.
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