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Specificity of non-motor symptoms of Parkinson's disease: A systematic review and meta-analysis

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Abstract

Background: Middle-aged and older adults (>55 years old) have a high risk of developing Parkinson's disease (PD); however, many non-motor symptoms (NMSs) indicative of PD are also common in middle-aged and older adults without a neurological disease diagnosis.

Objective: To identify symptoms specific to PD in comparison to controls without a neurological disease diagnosis.

Design: This is a systematic review and meta-analysis.

Data source and methods: We performed a meta-analysis, using Embase, SciSearch, MEDLINE, and BIOSIS from January 1, 2001, until April 1, 2025. We included observational studies reporting the prevalence of NMSs using the non-motor symptom questionnaire or non-motor symptom scale in the PD population versus controls. Using a random effects model, we generated a pooled estimate for the prevalence risk ratio (RR) for each symptom.

Results: The meta-analyses included 15 studies, involving 7393 PD patients and 2742 controls. It showed 28 out of 30 NMSs were more common in the PD population, with excessive drooling (RR = 7.30 (95% confidence interval; CI 5.05–10.57)), visual hallucinations (RR = 6.48 (95% CI 3.61–11.64)) and taste/smell issues (RR = 4.67 (95% CI 3.07–7.10)) being the most specific symptoms (having the largest RRs).

Conclusion: Planning screening campaigns to identify PD among middle-aged and older adults is difficult, due to the high numbers that are needed to screen using tools that are not specific enough. We showed that excessive drooling and taste/smell issues are highly specific NMSs of PD, as they have high RRs. More research is needed to assess their usefulness to be included as an enrichment factor in screening campaigns for PD patients in a middle-aged and older adult population.

Keywords

Parkinson's disease, non-motor symptoms, specific symptoms, systematic review, meta-analysis

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Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder affecting roughly 1%–2% of people aged over 60 years old.[1] Its incidence has risen drastically in the last 20 years, and is expected to continue to increase in the coming years, as the population continues to age.[2] It has been routinely diagnosed based on clinical symptoms: the presence of bradykinesia and at least one of resting tremor or rigidity. It is thought that these PD-defining motor symptoms are caused by the progressive nigrostriatal dopaminergic degeneration driven by underlying α-synucleinopathy.[3] However, as these clinical features are common in other neurological diseases, PD can be difficult to diagnose, and current tests and known biomarkers do not allow a definitive diagnosis during the early stages of the disease.[4] In fact, many clinical diagnoses will be reclassified after autopsy.[5] Although PD is still routinely diagnosed based on these clinical motor symptoms, there have been recent developments in the use of a biological diagnosis, particularly the use of the α-synuclein seeding amplification assays, to aid in the detection of PD.[2,3] These assays exploit the prion-like properties of misfolded α-synuclein to detect pathological aggregates in cerebrospinal fluid, skin, or other peripheral tissues, with the ability to distinguish PD from controls and other Parkinsonian syndromes with high sensitivity and specificity. Despite their promise as biomarkers of synucleinopathy, however, they remain research tools requiring prospective validation, cross-laboratory reproducibility, and testing in prodromal and early-stage disease before integration into diagnostic workflows.[6]

It is known that many people living with PD have already experienced neurodegeneration for years before motor symptoms occur and a diagnosis is made. Additionally, it has become clear that several non-motor symptoms (NMSs), such as autonomic dysfunction, sensory dysfunction, sleep-related disorders, neuropsychiatric symptoms, and cognitive dysfunction, often predate the detection of motor symptoms.[7]

Prodromal PD refers to the latent phase of PD, where people do not yet suffer from motor symptoms and hence, do not fulfill a clinical PD diagnosis, but do present certain symptoms of PD-related neurodegeneration. In addition, several studies have recently shown that imaging, biofluid, and tissue markers may play an important role in identifying people with prodromal PD.[8] Symptoms of prodromal PD include NMSs such as olfactory loss, autonomic dysfunction, depression and idiopathic rapid eye movement sleep behavior disorder (RBD).[9] We hypothesize that these early presenting NMSs, particularly those that present during the prodromal PD phase, could be included within a diagnostic tool to help identify PD earlier in its course. While previous reviews have examined selected non-motor symptoms in PD, comprehensive comparisons across the full spectrum of NMSs and their relative specificity to PD remain limited. This meta-analysis, therefore, aims to provide a broader and more detailed assessment of which symptoms most effectively distinguish PD from normal aging or other conditions.[10]

There have been several reviews recently that have investigated the prevalence of NMSs within the PD population. Many reviews have investigated how the prevalence of NMSs (such as cognitive function, sleep problems, and pain) changes based on specific treatment strategies, such as physical activity,[11] subthalamic deep brain stimulation,[12] non-drug interventions,[13] and acupuncture.[14] Xie et al.[15] looked at the difference in NMSs in PD patients with and without RBD, finding that depression symptoms and cognitive impairment were worse, and constipation and hallucinations were more common in PD patients with RBD. Paudel and Sah[16] looked at the prevalence of NMSs in PD patients in South East Asia, stating that nocturia, depression, and memory alteration were most common. However, it is believed that many of these prevalent NMSs are also common in middle-aged and older adults without a diagnosis of PD (or any other neurological disease),[17–19] and thus would not be specific enough to be included within a PD diagnostic tool.

The main purpose of this study was to assess the presence of NMSs in the prodromal PD population and in PD patients compared to adults without a neurological disease diagnosis to determine which NMSs best differentiate controls from the PD and prodromal PD populations. The NMSs which this study focused on included: excessive drooling, visual hallucinations, taste/smell issues, delusions, acting out dreams, loss of interest, difficulty swallowing, diplopia, anxiety, pains, constipation, feeling sad/down, falls, daytime sleepiness, sex difficulties, weight, sweating, difficulty concentrating, urgency, vivid dreams, bowel incomplete emptying, restless legs, dizziness, altered sex drive, insomnia, nocturia, difficulty remembering, swelling, bowel incontinence, and vomiting. Although there are more NMSs associated with PD not on this list, such as impulse control disorders,[20] heat sensitivity,[21] and osteoporosis[22] that have been recently investigated, we focused on the symptoms that were available in the multi-symptom surveys used in clinical practice, so as not to utilize many different surveys and keep the interpretation of results more streamlined across symptoms.

We aimed to undertake a meta-analysis of observational studies to compare the prevalence of NMSs between middle-aged and older adult controls (without a neurological disease diagnosis) versus prodromal PD participants and middle-aged and older adult controls (without a neurological disease diagnosis) versus PD patients. This review complements the current reviews available in the literature, investigating individual NMSs in populations of controls and PD patients.[10,23–26] Li et al.[23] indicated the loss of olfaction was more common in PD patients in comparison

to controls in 5/6 included studies. Trentin et al.,[24] similarly found worse olfactory function in PD patients across most of their included studies. In addition, Peeraully et al.[25] gathered 15 case-control studies that investigated sleep problems in PD patients in comparison to controls. Among their findings, the majority of studies showed that subjective sleepiness was greater in PD patients in comparison to controls. Zhang et al.,[26] similarly found RBD to be more common in PD patients across all eight included studies. To our knowledge, Chen et al.[10] is the only meta-analysis comparing the prevalence of multiple NMSs between participants living with PD and controls. However, the NMSs included in their review were restricted to only: hyposmia, constipation, RBD, excessive daytime sleepiness, depression, and anxiety. In addition, Chen et al.[10] were inconsistent in their methods to track the prevalence across each NMS, combining studies that used different methods and cutoff values to assess symptoms. They showed each symptom to be more prevalent in PD patients than controls, with hyposmia being the most prevalent in both populations and RBD being the most specific to PD.

To summarize, the current understanding of NMSs in the PD population is still incomplete, specifically lacking a precise, comparative analysis across the entire spectrum of symptoms. Our aim was to address this gap with a dual-focused investigation. First, we aimed to precisely identify which NMS are significantly more prevalent in individuals with diagnosed clinical PD compared to middle-aged and older adults without a neurological disease diagnosis. Second, we aimed to determine which NMSs are significantly more prevalent in the prodromal PD population (individuals at high risk of PD but without motor symptoms) when compared to controls without a neurological disease diagnosis.

Methods

Selection criteria

Types of participants. Participants of any age, recruited from any setting (general practitioner surgeries, hospitals, university teaching hospitals, etc.) who had been diagnosed with probable idiopathic PD by their doctor, using clinical diagnostic criteria, such as: MDS Clinical Diagnostic Criteria,[27] UK Parkinson's Disease Society Brain Bank, clinical diagnostic criteria,[28] or Gelb criteria.[29] We further included participants who had a diagnosis of prodromal PD. Any study with drug-induced PD patients or PD patients with a genetic variant known to be associated with PD, were removed.

Types of comparators. We included controls (participants without a neurological disease (including PD or prodromal PD) diagnosis) as our comparison population.

Types of outcome measures. We included studies that used a comprehensive tool, such as the non-motor symptom questionnaire (NMSQ),[30] the non-motor symptom scale (NMSS),[31] or the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS),[32] parts I and II, to record individual symptom prevalence for both PD patients and controls. Furthermore, we recorded or calculated the risk ratios (RR) and 95% confidence intervals to report the difference in prevalence of each symptom between PD patients and controls.

Types of studies. We included studies which fulfilled the following criteria:

- Observational studies (cross-sectional, cohort and case-control studies), *or*
- Randomized controlled trials (RCT) with NMS prevalence recorded at baseline, which included a control population.

We planned to only include RCTs if they recorded the NMS prevalence at baseline in both the PD population and control population, before participants were administered any intervention. We would only include these baseline NMS prevalences in our systematic review, as they would not be affected by the prescription of the novel treatment.

Electronic search strategy

A systematic literature search was performed in BIOSIS Previews, Embase, MEDLINE, and SciSearch for articles published in English and other languages from January 1, 2001, until April 1, 2025. Studies were identified and evaluated by the authors (H.J., R.A., and G.P.) using the major medical subject heading combined with the following text and keywords: "Parkinson's Disease," "Non Motor symptom questionnaire," "Non Motor symptom scale," "Movement Disorders Society-Unified Parkinson's Disease Rating Scale," and individual non-motor symptoms included within the NMSQ and/or NMSS. Further articles were identified from the reference lists of the selected articles as well as from previous review studies. We contacted the corresponding authors of identified studies for additional references and unpublished data. An example of our search strategy from MEDLINE is included in the Supplemental Material.

Selection of studies

Two authors (H.J. and R.A.) independently screened each identified title and abstract to discount any irrelevant reports. We conducted double screening (two independent reviewers) for the titles and abstracts of 50% of the initial search results. Given the high inter-reviewer agreement observed

in this initial phase, the remaining 50% of abstracts proceeded to single screening for efficiency. Any disagreement was resolved by discussion and consensus with a third investigator (G.P.), of which there were very few.

Any studies that included the same patients (or some of the same patients) were classified as duplicates and the smaller study was removed. Once duplicate results had been removed, two authors (H.J. and R.A.) independently reviewed full texts of the remaining studies to determine eligibility via single screening. Any dispute of study eligibility was resolved by discussion and consensus with the third investigator (G.P.).

The literature search found that the majority of studies did not investigate the prevalence of NMSs in prodromal PD, therefore, we focus only on the NMS prevalence in participants living with PD in comparison to controls. In addition, there was only one study that used the MDS-UPDRS parts I and II to record individual symptom prevalence, hence, we solely focus on the NMSS and NMSQ scales. Finally, we did not find any RCTs that recorded NMS prevalence at baseline in both a PD and control population; thus, all included studies were observational. Furthermore, we reached out to the corresponding authors of studies that did not list the prevalence of individual symptoms and asked them to share this information.

Data extraction

The data was extracted manually by a single author (H.J.) and all information was tabulated in a spreadsheet by study. For each study included in the analysis, we recorded the following information: trial characteristics (first author, publication year, type of study, and study location), total sample size of PD patients and controls, total number of PD patients and controls that had each symptom present, tool used to measure non-motor symptom prevalence (NMSQ or NMSS), demographics and baseline characteristics of the overall study population (PD patients and controls) (age, percent of male participants, disease duration, Hoehn and Yahr stage), percent of participants taking treatments (levodopa, monoamine oxidase-B inhibitors (MAOB-I) and use of dopamine agonist), motor features (MDS-UPDRS III) and cognitive function scores (the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). For all continuous variables, and the Hoehn and Yahr stage, we extracted the mean, or median if the mean was not available. For categorical variables, we extracted the percentages.

In the studies that compared multiple populations of participants living with PD (e.g., male PD patients vs female PD patients), we combined these subgroups into one PD population. If a study compared controls to different PD populations, we only included the comparison of interest, that is, controls and idiopathic PD patients. For studies reporting missing patients, we discounted these patients from the total population.

Quality assessment and bias

The Newcastle-Ottawa Scale (NOS)[33] was used to assess the quality of the studies included in our analysis, performed by a single author (H.J.). This scale investigates eight items split across three sections: selection, comparability, and exposure (for case-control studies) or outcome (for cohort studies). Each item can be awarded one star, with two stars available for comparability. The maximum score is 9 stars.

Non-reporting bias (publication bias and selective reporting bias) was investigated using cumulative meta-analysis and a funnel plot by two authors independently (H.J. and J.A.-C.). For the cumulative meta-analysis, we first ordered the studies by their weighting in the random effects model (from largest to smallest). Before performing an iterative meta-analysis, each study is added to the meta-analysis individually.[34] If publication bias is present, we would expect to see the cumulative prevalence risk ratio increasing as smaller trials are added to the meta-analysis. The presence of asymmetry in funnel plots was determined by eye.[35] If asymmetry was present, it indicated the potential presence of publication bias or selective reporting bias. Furthermore, if there was an empty space at the bottom left of the funnel plot, this indicated that smaller studies were more likely to show larger effects than larger studies or the potential presence of publication bias.

Assessment of heterogeneity

For each study, we summarized patient and study characteristics and the prevalence of each NMS with descriptive statistics. Heterogeneity was assessed by eyeballing the forest plots, the Chi-square test and the I^2 value.[36] Assessment of heterogeneity was based on the criteria suggested by Deeks et al.[37]:

- $0\% \leq I^2 \leq 40\%$ indicates heterogeneity might not be important,
- $30\% \leq I^2 \leq 60\%$ may represent moderate heterogeneity,
- $50\% \leq I^2 \leq 90\%$ may represent substantial heterogeneity,
- $75\% \leq I^2 \leq 100\%$ represents considerable heterogeneity.

For studies presenting some degree of heterogeneity (substantial or considerable), we determined if the heterogeneity was important by assessing the overlapping of confidence intervals and the direction of the effects (RR) of the individual studies.

Data synthesis and analysis

The prevalence of a particular NMS in the NMSQ was defined as the total number of patients who answered "Yes" to the related individual question divided by the total number of patients in which the symptom was assessed. The prevalence in the NMSS, was calculated as the number of patients who had a score of 1 or larger for a particular symptom divided by the total number of patients who responded to the question. The NMSQ and the NMSS are two different scales assessing similar symptoms. Table S1 shows the relationship between the individual symptom questions in each scale.

A random effects model was used for all meta-analyses to account for the distribution of effects across the included studies. Risk ratios, 95% confidence intervals, and 95% prediction intervals were used to report the difference in prevalence of each symptom between participants living with PD and controls.

For studies reporting zero participants with a particular symptom, the standard continuity correction of 0.5 was applied.[38] If neither population included a participant with the symptom present, the study was removed from the meta-analysis. All meta-analyses were performed using the "meta" package within the statistical program R.[39,40]

Meta-regression

A meta-regression analysis, using the log RR of the prevalence of each NMS, was performed to investigate the effect of the overall study patient characteristics (including both the PD and control populations) and the scale used (NMSQ or NMSS) on meta-analyses with high levels of heterogeneity. A random effects model was used for all meta-regression analyses. We used the *Z*-statistic to test the significance of the slope, where a *p*-value of <0.05 implied the true slope value was unlikely to be zero and hence, there was an association between the symptom prevalence RR and the baseline study characteristic.[41] We further note the variance of true effects about the regression line, τ^2 and the percentage of heterogeneity explained by the baseline study characteristic. As the number of studies is low, we carried out meta-regressions including only a single explanatory variable at a time. All meta-regressions were performed using the "meta" package (the DerSimonian–Laird method was used to estimate the between-study variance) within the statistical program R.[39,40]

Results

The search strategy (shown in Figure 1) identified a total of 2082 references (after de-duplication) from January 1, 2001, until April 1, 2025. We full-text screened 135 of these articles, which compared participants living with PD with controls. However, several of these articles only reported NMS domain prevalences such as Shalash et al.[42] and Yong et al.,[43] or only displayed the mean NMSS scores of symptoms such as Kim et al.,[44] but did not list the prevalences of individual symptoms. After reaching out to the authors of the articles that did not display the individual symptoms' prevalences, we finally had 15 articles to include in our meta-analysis, for which we had access to these prevalences for participants living with PD and controls.

Prevalence and study characteristics

This review includes 15 studies comprising a total of 7393 PD patients and 2742 controls. However, the Chaudhuri (2006) study had missing values in both the PD and control groups which varied across symptoms; these patients were removed from both the numerator and denominator when calculating the prevalence of each symptom, thus reducing the total PD and control participants for any one symptom. Ten studies used the NMSQ to compare the prevalence of each individual symptom and five used the NMSS.

The overall study characteristics are shown in Table 1.[30,45–58] The included studies were published between 2006 and 2021. The majority of studies were cross-sectional, one was a case-control and one was a longitudinal-prospective non-interventional study. However, we only use the baseline data collected from this longitudinal study within our analysis. The sample size range for PD patients was (23–5013), and for controls (20–1292). The mean age range was 58.5–68.0 years. The proportion of males ranged from 45.4% to 72.7%. The mean Hoehn and Yahr stage ranged from 0.5 to 1.7.

When the quality of evidence of each study was assessed,[59] two studies were considered of high quality with a NOS score of 9, eight studies were of medium quality with a NOS score ranging from 7 to 8 and five studies were of lower quality (having a NOS score ranging between 0–6). The NOS score for each study is displayed in Table 2.

Pooled RR (and 95% confidence intervals) from each of the meta-analyses for each individual NMS are reported in Figure 2. We also report the number of PD participants and controls presenting each symptom. In addition, for each group, we report the total number of participants included in the meta-analysis, 95% prediction intervals and heterogeneity, I^2. Forest plots depicting the meta-analysis for each individual symptom are shown in Figure S1.

Meta-analyses of individual NMSs

Higher prevalence in PD patients was shown for 28 of 30 symptoms. The symptoms with the highest pooled risk ratio included: excessive drooling, 7.30 (95% CI 5.05–10.57), visual hallucinations, 6.48 (95% CI 3.61–11.64), and taste/smell issues, 4.67 (95% CI 3.07–7.10). Of note,

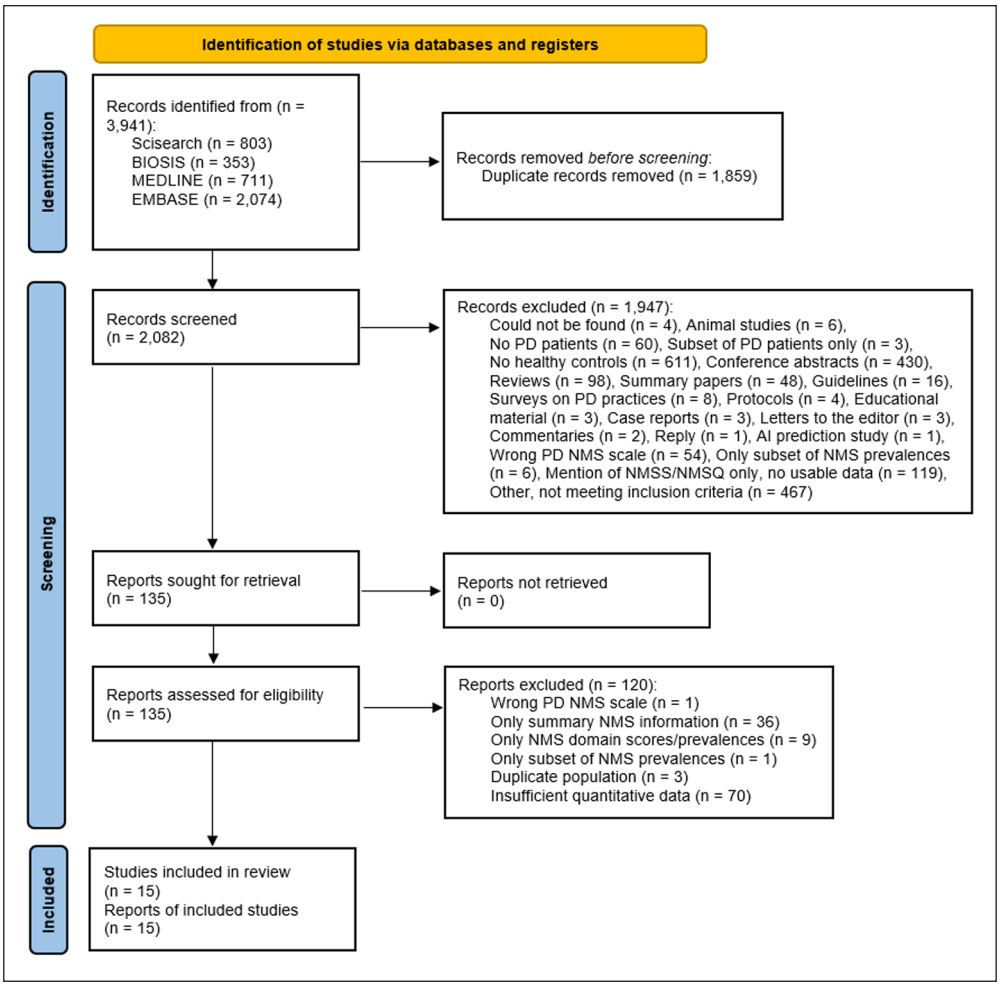

Figure 1. PRISMA flow diagram to select studies comparing the prevalence of individual non-motor symptoms between PD patients and controls.
PD: Parkinson's disease.

symptoms which are thought to be among the most common in participants living with PD such as: nocturia,[60] insomnia,[61] and urgency[1] had lower prevalence risk ratios (1.66 (95% CI 1.34–2.06), 1.65 (95% CI 1.25–2.18), and 2.05 (95% CI 1.70–2.48) respectively). The symptoms with the lowest pooled risk ratios were: leg swelling (RR = 1.54, (95% CI 1.01–2.35)), bowel incontinence (RR = 1.10, (95% CI 0.69–1.75)), and vomiting (RR = 1.09, (95% CI 0.68–1.75)).

Heterogeneity assessment

Visual hallucinations, acting out dreams, excessive drooling, difficulty swallowing, and falls had moderate heterogeneity (I^2=39.1%–55.2%); however, the direction of the effect from the individual studies indicated consistently higher prevalence in the PD group. Bowel incontinence also had moderate heterogeneity (I^2=35.1%), however, the RR 95% CIs were overlapping with the null value for 9 out of 10 studies. The remaining symptoms were classified as having substantial or considerable heterogeneity (Table S2).

To understand the heterogeneity present in the meta-analyses with an $I^2 > 50.00\%$, we performed meta-regression analyses including each of the following baseline characteristics one at a time: NOS score, NMS scale used (NMSS vs NMSQ), age, percentage of males, disease duration, and Hoehn and Yahr stage. These six characteristics were selected as they were the only ones that were available in at least 10 studies.[37]

Hoehn and Yahr stage explained between 24%–100% of the heterogeneity in the meta-regressions of the following symptoms: taste/smell issues, delusions, diplopia, excessive daytime sleepiness and nocturia. One point increase in the Hoehn and Yahr scale increases the risk ratio of these symptoms by 0.6–1.8 percent points.

The scale used in the analysis (NMSS or NMSQ) explained 34% of the heterogeneity for the urgency symptom. The NOS score and the proportion of males explained

Table 1. Baseline characteristics of studies included in the meta-analysis.

Study	Type of study	Location	Scale	Total PD patients	Total controls	Age	Male (%)	Disease duration (months)	Hoehn and Yahr stage	MDS-UPDRS part III	% on Levodopa	% drug Naive	% on Dopamine agonists	% on MAOB-I	MMSE	Total NMSS score	Total NMSQ score
Aldaz, 2019[a]	Cross-sectional	Spain	NMSQ	45	25	62.3	48.6	N/A	1.5	18.7	58.6%	N/A	34.3%	28.6%	N/A	N/A	5.4
Bo, 2010	Cross-sectional	China	NMSQ	90	270	62.0	58.3	N/A	0.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	8.3[b]
Bostantjopoulou, 2013[c]	Cross-sectional	Greece	NMSQ	166	66	58.6	62.7	60.9	1.7	N/A	N/A	34.1%	N/A	0.0%	N/A	N/A	6.4
Chaudhuri, 2006	Cross-sectional	Multi-country	NMSQ	123[d]	96[d]	66.9	54.4	43.1	1.4	N/A	47.2%	N/A	34.3%	N/A	N/A	N/A	6.8[e]
Khoo, 2013	Cross-sectional	United Kingdom	NMSQ	159	99	67.1	61.6	2.7[e]	1.2	16.8	18.6%	46.1%	22.5%	28.3%	28.8	N/A	6.3
Kim, HJ, 2009	Cross-sectional	South Korea	NMSS	23	23	64.8	47.8	4.8	0.8	11.8[f]	N/A	100%	N/A	N/A	N/A	26.6	6.9
Krishnan, 2011[c]	Case-control	India	NMSS	174	128	59.8	68.9	N/A	1.6	N/A	N/A	42.4%	N/A	N/A	N/A	33.9	N/A
Mao, 2014	Cross-sectional	China	NMSQ	142	80	68.0	58.1	45.1	1.3[e]	18.9[f]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Picillo, 2013	Cross-sectional	Italy	NMSQ	200	93	61.0	63.5	N/A	1.0[e]	16.5[f]	N/A	100%	N/A	N/A	N/A	N/A	3.6
Polo-Morales, 2021[c]	Cross-sectional	Mexico	NMSS	93	93	63.8	46.3	4.8	1.1	16.1	N/A	N/A	N/A	N/A	26.8[g]	38.5	8.4
Santos-Garcia, 2019[c]	Longitudinal-prospective	Spain	NMSS	690	206	62.2	57.8	50.8	1.5	22.9[f]	56.1%	N/A	53.3%	56.8%	29.3	38.3	N/A
Unluer, 2021[c]	Cross-sectional	Turkey	NMSQ	24	20	59.3	72.7	26.2[b]	1.1[b]	N/A	N/A	N/A	N/A	N/A	N/A	10.0[e]	N/A
Van der Heide, 2021[c]	Cross-sectional	multi-country	NMSQ	5013	1292	66.0	45.4	56.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wu, 2016	Cross-sectional	China	NMSS	301	101	58.5	52.7	18.9	1.4	21.9[f]	N/A	28.4	N/A	N/A	27.6	25.6	6.2
Sahu, 2021	Cross-sectional	India	NMSQ	150	150	58.6	71.7	37.8	1.2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6.4

PD: Parkinson's disease; NMS: non-motor symptom; NMSQ: non-motor symptom questionnaire; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MAOB-I, monoamine oxidase-B inhibitors; NMSS: non-motor symptom scale; N/A: Not available within the publication.
Unless otherwise stated continuous variables are reported as mean.
[a]Paper also includes Huntington's disease patients, which are not included within our analysis.
[b]Only median value found in paper, could be included in meta-regression as IQR was symmetric.
[c]Paper does not list individual symptom prevalence; information forwarded to us by the corresponding author.
[d]Paper had missing values for some symptoms.
[e]Only median found in the paper could not be included in the meta-regression as the IQR was not symmetric.
[f]Only UPDRS score found in paper, converted to MDS-UPDRS score.
[g]Only MoCA score found in the paper, converted to MMSE score.

Table 2. Quality of studies (Newcastle–Ottawa Scale).

Study	Selection of controls	Comparability	Ascertainment of exposure	Total score	Quality of evidence
Aldaz, 2019	0	0	1	5	Low
Bo, 2010	0	2	1	6	Low
Bostantjopoulou, 2013	0	2	1	7	Medium
Chaudhuri, 2006	1	2	1	7	Medium
Kim, HJ, 2009	0	2	1	7	Medium
Khoo, 2013	1	2	1	7	Medium
Krishnan, 2011	1	2	1	9	High
Mao, 2014	0	2	1	5	Low
Picillo, 2013	1	2	1	7	Medium
Polo-Morales, 2021	0	2	1	6	Low
Santos-Garcia, 2019	1	0	1	7	Medium
Unluer, 2021	0	2	1	7	Medium
Van der Heide, 2021	0	0	1	3	Low
Wu, 2016	1	2	1	9	High
Sahu, 2021	1	2	1	8	Medium

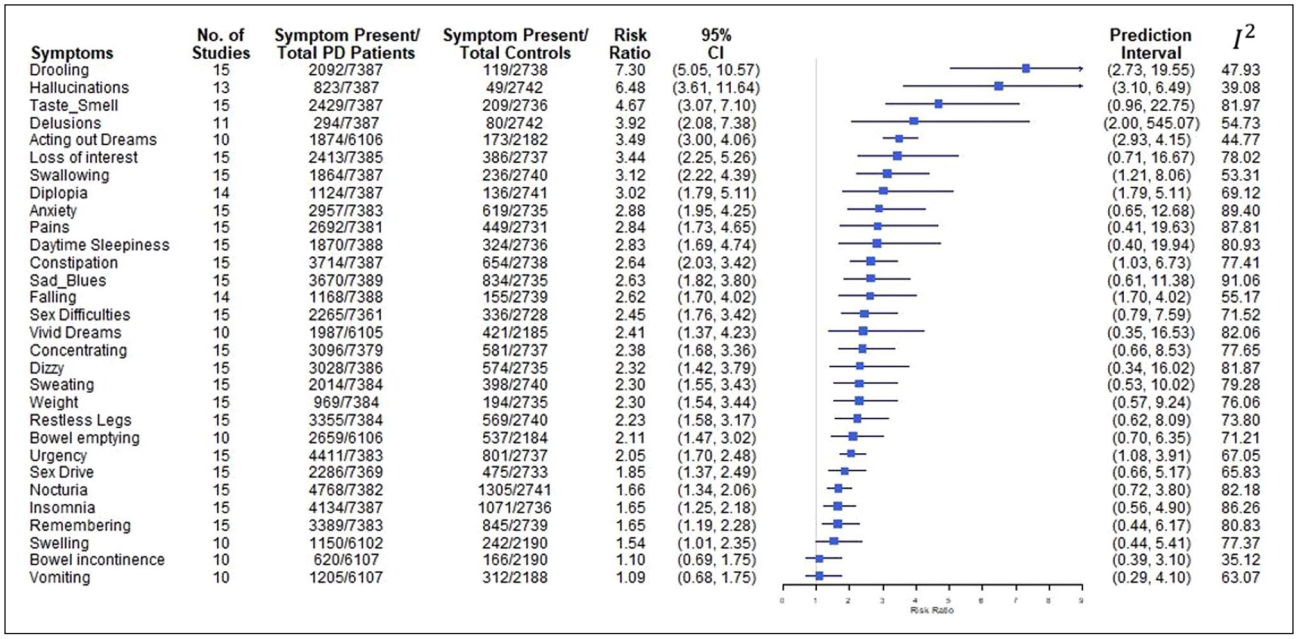

Figure 2. Pooled risk ratio from individual meta-analyses for the prevalence of each NMS in PD patients compared with controls.
PD: Parkinson's disease; NMS: non-motor symptom.

33% and 45%, respectively, of the heterogeneity present in the meta-analysis of feeling sad. See Table 3 for more details on the meta-regression for each symptom.

With the exception of taste/smell issues and bowel incontinence, all the funnel plots for the remaining symptoms were asymmetrical, indicating the possible presence of bias. Funnel plots are available on request.

The evidence presented in this paper demonstrates a degree of variability due to the potential for bias and heterogeneity in the results for many symptoms, as well as the inclusion of lower-quality studies. Nevertheless, it is important to note that the indirectness of evidence was minimal, and the precision across many symptoms was commendably high, as indicated by the relatively small confidence intervals.

Discussion

In this comprehensive study, we compared the prevalence of NMSs between controls (participants without a neurological diagnosis) and PD patients through the use of meta-analyses. Results from 15 observational studies were

Table 3. Meta-regression summary of the risk ratios of symptoms with high heterogeneity and their statistically significant relationships with the overall study baseline covariates.

Baseline characteristic	Explains heterogeneity for	No. of studies	Beta coefficient (95% CI)	τ^2	*p*-Value	% of heterogeneity explained
NOS	Loss of interest	15	0.266 (0.051, 0.481)	0.256	0.015	0.00
	Anxiety	15	0.274 (0.092, 0.457)	0.194	0.003	37.42
	Daytime sleepiness	15	0.271 (0.002, 0.540)	0.459	0.048	0.00
	Feeling sad	15	0.276 (0.103, 0.448)	0.198	0.002	32.75
	Difficulty concentrating	15	0.181 (0.000, 0.362)	0.195	0.049	0.00
	Dizziness	15	0.255 (0.025, 0.486)	0.335	0.030	0.00
NMSS/NMSQ scale	Urgency	15	0.348 (0.031, 0.665)	0.035	0.031	34.17
Age	Urgency	15	−0.055 (−0.103, −0.006)	0.043	0.028	18.63
	Nocturia	15	−0.062 (−0.116, −0.009)	0.067	0.023	0.00
	Insomnia	15	−0.075 (−0.147, −0.002)	0.150	0.043	0.00
	Difficulty remembering	15	−0.066 (−0.128, −0.003)	0.107	0.039	0.00
Disease duration	Anxiety	10	−0.021 (−0.042, −0.001)	0.169	0.044	41.02
	Pains	10	−0.024 (−0.048, 0.000)	0.351	0.047	0.00
% of males	Loss of interest	15	0.043 (0.007, 0.079)	0.204	0.020	15.97
	Anxiety	15	0.042 (0.007, 0.076)	0.191	0.018	38.36
	Feeling sad	15	0.045 (0.015, 0.075)	0.162	0.003	45.05
	Difficulty concentrating	15	0.035 (0.005, 0.066)	0.147	0.021	4.75
	Dizziness	15	0.049 (0.006, 0.093)	0.304	0.027	0.00
Hoehn and Yahr	Taste/Smell	12	1.466 (0.326, 2.607)	0.343	0.012	50.79
	Delusions	10	1.814 (0.936, 2.693)	0.000	<0.001	100.00
	Diplopia	11	1.636 (0.264, 3.008)	0.334	0.019	62.13
	Daytime sleepiness	12	1.279 (0.088, 2.470)	0.310	0.035	37.25
	Nocturia	12	0.629 (0.068, 1.190)	0.081	0.028	24.39

NOS: Newcastle–Ottawa Scale; NMSS: non-motor symptom scale; NMSQ: non-motor symptom questionnaire.

combined to suggest that 28 of the NMSs investigated are more prevalent in participants living with PD than in controls.

Excessive drooling, visual hallucinations and taste/smell issues were highly specific for PD, showing the largest risk ratios. Although nocturia, urgency, and insomnia were the symptoms most prevalent in the PD population, they turned out to be less specific symptoms for PD, with some of the smallest risk ratios (reflecting common occurrence in controls). Similarly, our group (Jackson et al.[62]) showed excessive drooling, swallowing difficulties and hallucinations to be specific NMSs of PD, while insomnia, pain, and urinary problems were the most prevalent NMSs among PD patients (and highly common in the control population), when analyzing the Parkinson's Progression Markers Initiative database. Chen et al.[10] also noted hyposmia, to be more specific of PD than daytime sleepiness, constipation, and anxiety, however, in contrast to our analysis, they found hyposmia to be the most prevalent NMS in PD patients, although Chen et al.[10] only investigated six NMSs. Several other studies have shown symptoms such as excessive drooling,[63] visual hallucinations,[64] and delusions[65] to be more common in PD patients than control patients without a neurological disease diagnosis. Bowel incontinence and vomiting did not show any difference in risks between PD patients and controls, as demonstrated by Serra et al.[66] and Edwards[67], respectively, and they could potentially be removed from a novel version of the non-motor symptom scale or questionnaire.

The higher specificity of certain NMSs- particularly excessive drooling, visual hallucinations, and taste/smell issues- likely reflects their close association with PD–specific neurodegenerative pathways. Consistent with Braak's staging hypothesis, α-synuclein pathology initially involves the olfactory bulb and dorsal motor nucleus of the vagus before extending to midbrain and cortical regions, producing early olfactory and autonomic dysfunction followed by cortical manifestations such as hallucinations.[68] Excessive drooling may result from degeneration of bulbar motor and autonomic nuclei, leading to impaired swallowing and salivary clearance.[69] Visual hallucinations are associated with cortical Lewy body pathology and cholinergic denervation of visual and attentional networks, while hyposmia and taste impairment correspond to early involvement of olfactory and limbic regions.[70] In contrast, highly prevalent symptoms such as nocturia and insomnia are influenced by aging and comorbidities, explaining their lower risk ratios and limited specificity despite frequent occurrence in the Parkinson's population.

In the past 20 years, since the NMSQ and NMSS were developed, many non-randomized studies have investigated the prevalence of NMSs in participants living with

PD, several of which include a comparison with age-matched controls. However, for most symptoms investigated, meta-analyses showed the presence of heterogeneity. For some symptoms, heterogeneity was moderate (excessive drooling and visual hallucinations). For other symptoms, heterogeneity could be explained by a baseline covariate (taste/smell issues). However, for symptoms with high heterogeneity ($I^2 > 70\%$), meta-regression analyses were unable to find baseline characteristics that could explain such heterogeneity. Unsurprisingly, many funnel plots were asymmetric, reflecting the high levels of heterogeneity in the meta-analyses. Due to this heterogeneity, these findings should be interpreted cautiously.

As many NMSs tend to occur earlier in the course of the disease than motor symptoms,[71] these could be used to help identify PD earlier. Although, the current results of our study could not be used to predict PD in a middle-aged or older adult population in isolation, we hypothesize that in large screening campaigns, the most specific symptoms of PD (e.g., excessive drooling, hallucinations and taste/smell issues), could be more useful to help identify PD in the population, than symptoms that are most common in PD participants but are also common in middle-aged and older adults without PD (e.g., nocturia and insomnia). In this context, a two-step screening strategy could be envisioned, in which self-reported or questionnaire-based assessment of these highly specific symptoms serves as an initial enrichment step, followed by confirmatory testing using objective biomarkers or neuroimaging tools. Additional investigations are needed to determine which combinations of NMSs would be most predictive of PD in the population, and hence could be most relevant to include in a screening campaign. Integrating such weighted combinations of symptoms into multimodal diagnostic algorithms may enhance early differentiation of PD from other neurodegenerative and age-related disorders. This approach could also inform personalized treatment planning, allowing clinicians to identify and manage burdensome NMSs earlier in the disease course and to enroll suitable individuals into neuroprotective or disease-modifying trials.

The main strengths of this work are the inclusion of all 30 symptoms in the NMSQ and the comparison of these symptoms in participants living with PD and controls. The addition of this comparison allows us to consider the specificity of a symptom, instead of only looking at its prevalence in PD patients alone. Those symptoms that are not specific to PD are unlikely to be good tools to aid in the detection of PD, at least in isolation.

This study has several limitations. One limitation of this work is the small number of studies that included all the baseline characteristics. This meant we could not explore the symptom RR meta-regressions for as many of the baseline characteristics as we would have liked. In addition, several included studies lacked detailed reporting on medication status and disease duration, both of which may influence the prevalence and severity of NMSs.[72,73] The use of differing treatment regimens across studies could have introduced variability, as dopaminergic and anticholinergic medications are known to modulate the presence of symptoms such as hallucinations, drooling, and sleep disturbances. A further limitation of these meta-analyses is the potential bias included, 16 symptoms had a high risk of bias, and this could make our RR estimations an exaggeration of the true value. Also, when comparing the PD populations to their respective control population, they were not always similar. The studies by Aldaz et al.[45] and van der Heide et al.[56] included PD patients who were statistically significantly older than their comparative control population. Furthermore, we cannot be sure how well each control population within our included studies represents the non-PD control population in practice. While they were all described as not having a PD diagnosis, they were recruited in very different ways across the studies. Bo et al.[46] included inpatients with diabetes mellitus, stroke and heart disease from their hospital, similarly Mao et al.[51] recruited "healthy" controls subjects from their medical center and Polo-Morales et al.[53] also recruited "healthy" participants from their institute's waiting room. Krishnan et al.,[50] Picillo et al.,[52] Santos-Garcia et al.,[54] van der Heide et al.,[56] Wu et al.,[57] and Sahu et al.[58] all included controls who were relatives, friends or carers of people suffering from PD and thus, were not the best population to recruit as an unbiased control group. Furthermore, both the NMSQ and NMSS rely on self-reported symptoms, which may be influenced by participant recall bias or cognitive impairment, particularly in older PD cohorts.[74] There have been a number of publications highlighting the potential challenges of this approach.[75] Future studies should incorporate objective or clinician-rated assessments to validate self-reported measures and reduce reporting bias. Another limitation is the large proportion of observed heterogeneity in the studies which are not down to random chance. This heterogeneity could be due to the difference in the study participants' baseline characteristics, however, this needs investigating further due to the small number of baseline characteristics which we could include in our meta-regressions.

Conclusion

These meta-analyses demonstrate 28 NMSs of the 30 investigated were more prevalent in PD patients than controls. The use of these symptoms, particularly the ones which have a high RR and therefore, higher specificity for PD, should be explored in large screening campaigns to identify PD patients in older adults. As this work has only looked at the prevalence of these symptoms in participants with prevalent PD, more work needs to be done in the prodromal PD population, to help understand the prevalence and time course of these symptoms. Future work would

also include investigating the biological evidence of why some symptoms are more specific to PD.

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Ethical considerations

Our study did not require an ethical board approval because it is a systemic review and meta-analysis of studies identified through literature search.

Consent for participate

Our study did not require consent for participation because it is a systemic review and meta-analysis of studies identified through literature search.

Consent for publication

Our study did not require a consent for publication because it is a systemic review and meta-analysis of studies identified through literature search.

Author contributions

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Judith Anzures-Cabrera: Conceptualization; Formal analysis; Methodology; Supervision; Writing – original draft; Writing – review & editing.
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Supplemental material

The Supplemental Material is available in the electronic version of this article.

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