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REVIEW

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Laryngeal symptoms related to motor phenotypes in Parkinson's disease: A systematic review

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Abstract

Objective: This study aimed to systematically review the associations between motor clinical phenotypes in Parkinson's disease (PD) and laryngeal disease symptoms. Laryngeal dysfunctions such as dysphonia and dysphagia are ubiquitous in people with Parkinson's disease (PwPD). Similar to other disease symptoms, they manifest variably across PwPD. Some of the variability within PD has been explained by clinical phenotypes. However, it is unclear how laryngeal symptoms of PD express themselves across these phenotypes.

Methods: Five databases were searched (MEDLINE, CINAHL, Web of Science, Embase, Scopus) in May 2022. After the removal of duplicates, all retrieved records were screened. Cohort, case–control, and cross-sectional studies in English discussing laryngeal symptoms and clinical PD phenotypes were included. Data were extracted, tabulated, and assessed using Moola et al.'s (2021) appraisal tool for systematic reviews of risk and etiology.

Results: The search retrieved 2370 records, representing 540 PwPD. After the removal of duplicates and screening, eight articles were included for review. The most common phenotype categories were tremor-dominant and postural-instability gait disordered (PIGD). Five studies addressed vocal characteristics, while four considered swallowing. Differences and lack of rigor in methodology across studies complicated conclusions, but a tendency for tremor-dominant phenotypes to present with less severe laryngeal symptoms was found.

Conclusion: Some minor differences in laryngeal function were found between tremor-dominant and PIGD phenotypes in PD. However, there is a need for more standardized and high-quality studies when comparing motor phenotypes for laryngeal function.

KEYWORDS

dysphagia, hypokinetic dysarthria, larynx, Parkinson's disease, phenotypes, voice

Work was performed at both institutions.

1 | INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease affecting up to 1% of the population older than 60 and increasing prevalence in older age groups.[1,2] The hallmark symptoms of the disease are tremor, rigidity, bradykinesia, and postural imbalance.[3,4] While these motor symptoms are the most salient, people with Parkinson's disease (PwPD) present with additional non-motor symptoms, sometimes years before the presence of the hallmark motor symptoms.[3] Examples of non-motor symptoms include gastrointestinal dysfunction, sleeping disorders, and neuropsychiatric disorders.[3] Similarly, while often overlooked until later stages, PwPD often display laryngeal related dysfunction, leading to dysphagia and dysphonia.[1,3,5]

The majority of people diagnosed with PD are expected to experience dysphagia at some point in the disease process,[6] though not all of them are aware of their symptoms.[5,7] Dysphagia caused by PD may be due to disturbances in the oral, pharyngeal, and esophageal stages of swallowing.[7] However, established literature indicates that impaired laryngeal function and movement are significant contributors to post-swallow residue and impaired laryngeal vestibule closure (LVC), and the most prominent manifestations of dysphagia in PwPD include high frequencies of pharyngeal residue, prolonged time-to-LVC, and reduced laryngeal elevation.[8] This evidence suggests that the function (e.g., LVC) and movement (e.g., elevation) of the larynx are primary contributors to dysphagia in PwPD. Understanding dysphagia in PD is critical as it can reduce quality of life, contribute to malnutrition and dehydration, and increase mortality risk due to aspiration pneumonia.[7,9]

Laryngeal dysfunction in PwPD may also manifest in less efficient vocal behaviors. This hypophonia is a subpart of the typically presenting hypokinetic dysarthria associated with PD.[10] Hypophonia is characterized by soft, breathy, and hoarse voice quality.[10,11] Acoustically, this reflects itself in higher, more disordered values for perturbation

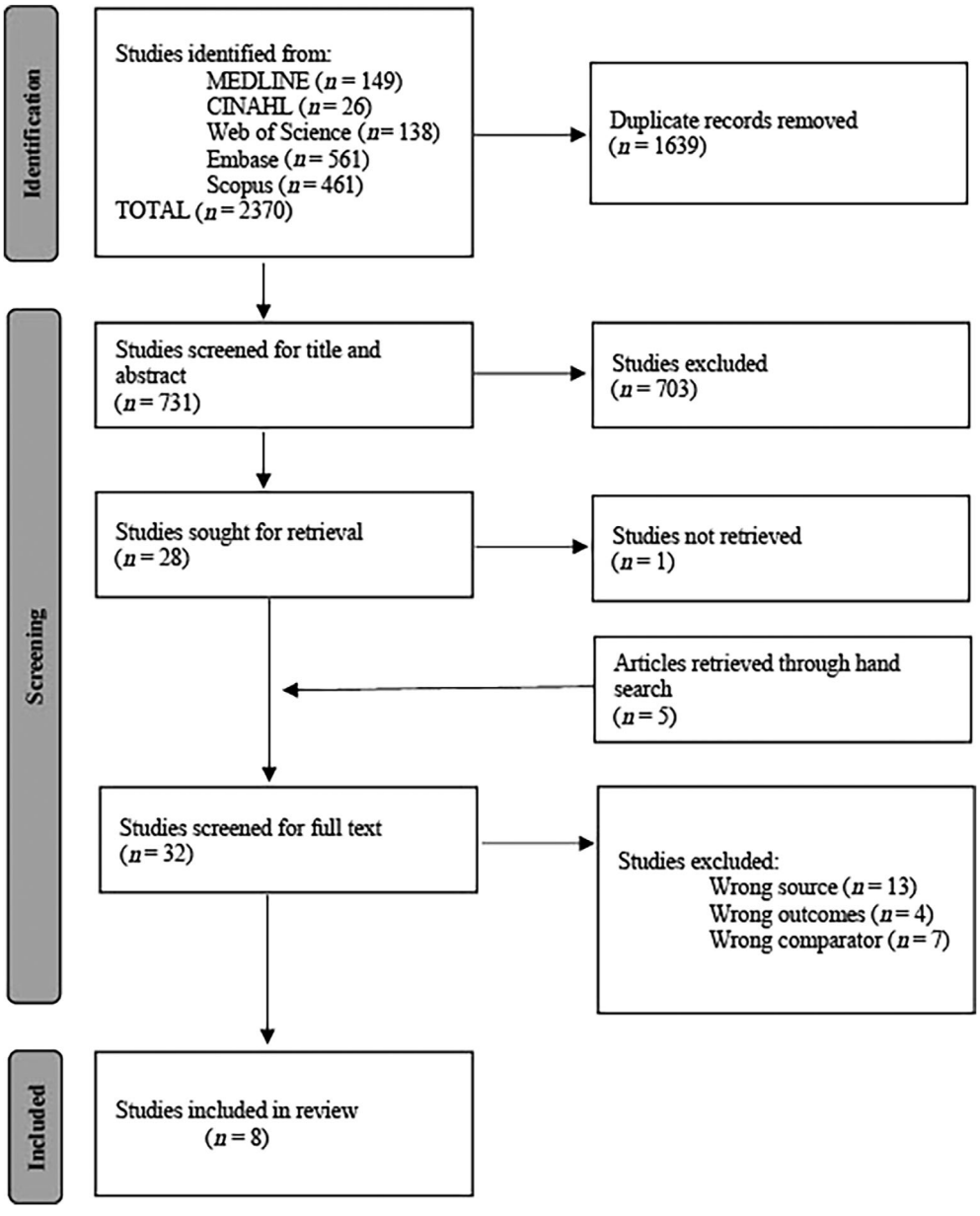

FIGURE 1 Overview of the screening, in- and exclusion process of the different articles.

measures. Visually, the vocal folds may present with bowing and incomplete closure during phonation,[10] further contributing to measures of perturbation. These vocal changes can impact communication and lead to decreases in quality of life and participation for PwPD.[12]

An ongoing challenge related to the assessment and management of PD is the disease's variable and often individualistic expression.[13] Consequently, multiple phenotypes have been proposed in the literature[14,15] as a means to describe and categorize a broad sample of PwPD according to their most salient symptoms and presentation. The most commonly used system for phenotyping PD divides up PwPD into tremor-dominant (TD) and postural-instability gait disorder (PIGD), also called non-tremor dominant (NTD) or akinetic-rigid.[14–16] Additionally, some sources also include a bradykinetic subtype[17] and a mixed or indeterminate subtype.[14–16] Classification of patients into subtypes can be obtained through clinical data such as the use of the Unified Parkinson's Disease Rating Scale score.[14,16] Each phenotype has its own clinical presentation based on the primary symptomatology. For example, PwPD categorized as PIGD often present with primary complaints of bradykinesia and rigidity, and are more likely to present with dementia and depression. This subtype overall is associated with a worse prognosis and progresses more rapidly.[14,15] On the other hand, TD subtypes present with mainly tremor, and have a better prognosis with slower disease progression.[15] Moreover, these TD and PIGD phenotypes present with atrophy and reduced brain activation in different brain areas.[14,15]

It has also been suggested that TD and PIGD phenotypes differ based on characteristics of their laryngeal dysfunction such as voice[18–20] and swallowing.[8,20,21] A comprehensive summary of the effects of PD phenotype related to laryngeal function for voice and swallowing is lacking. Consequently, this study aims to critically review the available evidence on how different PD phenotypes are associated with the laryngeal disorders in PD, namely dysphagia and dysphonia. We hypothesized that there would be an association between non-tremor PD phenotypes (i.e., PIGD) and more frequent occurrences of laryngeal dysfunction.

2 | METHODS

Using the PICO model for etiology and risk, the research question for this systematic review was the following: Are PwPD (population) with the TD phenotype (intervention) compared to those with other phenotypes (comparison) at increased risk for laryngeal dysfunctions (outcome)? This systematic review was not registered, and consequently the a priori developed protocol is not publicly available.

In May 2022, a literature search was performed in the following databases: MEDLINE (via PubMed), CINAHL, Web of Science, Embase, and Scopus. The search was limited to articles written in English published in the aforementioned databases before the date of the search.

TABLE 1 Extracted demographic data for the articles included in this systematic review.

Article	Population	Phenotypes	Age (years)	Disease duration (years)	Disease severity[a]
Brown and Spencer[18]	27 (18♂; 9♀) with IPD	TD (9 men; 6 women) and NTD (9 men; 3 women)	TD: 69.60 (±5.66) NTD: 72.67 (±6.05)	TD: 9.57 (±5.65) NTD: 8.67 (±3.98)	Not reported
Burk and Watts[19]	32 (22♂; 12♀) with IPD and 11 HC (4♂; 7♀)	TD ($n = 16$) and NTD ($n = 16$)	TD: 70.35; NTD: 69.23	TD: 6.23 (±4.5) NTD: 4.04 (±2.78)	H&Y Staging TD: 3 NTD: 3
Claus et al.[23]	200 (137♂; 67♀) with PD	BK ($n = 121$); TD ($n = 57$): PIGD ($n = 22$)	Total: 68.2 (±9.6)	Total: 7.6 (±5)	Mean H&Y: 2.8 (±0.8)
Dumican and Watts[21]	31 with IPD (TD 8♂, 6♀; NTD 15♂, 9♀)	TD ($n = 14$); NTD ($n = 24$)	TD: 68.3 (±9.1) NTD: 70.9 (±6.5)	TD: 3.9 (±2.5) NTD: 3.8 (±3.1)	TD: 2.5 NTD: 3
Mohamed et al.[20]	54 (38♂; 16♀) with PD	TD ($n = 46$); PIGD ($n = 8$)	Total: 62.30 (±5.64)	Total: 4.7 (±2.2)	Mean UPDRS Part II: 15.5 (±8.9); Mean UPDRS Part III: 37.5 (±16.3); Mean modified H&Y: 2.1 (±0.6)
Sung et al.[24]	54 (22♂; 32♀) de novo PD	TD ($n = 25$); PIGD ($n = 26$); Intermediate ($n = 3$)	Total: 67.1 (±10.3)	Total: 11.5 (±8.8) months	Mean UPDRS 25.1 (±18.6); Mean H&Y: 1.6 (±0.4)
Suphinnapong et al.[25]	100 (53♂; 47♀) with PD; 101 HC (46♂; 55♀)	NA	Total: 66.56 (±7.52)	Total: 7.90 (±5.90)	Mean UPDRS: 21.81 (±14.31) Mean H&Y: 2.70 (±1.08)
Tykalova et al.[26]	42 with IPD (TD 14♂, 7♀; PGID 13♂, 8♀) 21 HC (12♂; 9♀)	TD ($n = 21$), PGID ($n = 21$)	TD: 65.5 (±9.8); PGID: 63.4 (±7.6)	TD: 4.7 (±2.2); PGID: 5.8 (±3.1)	UPDRS III Motor score, TD: 16.8 (±7.3), PGID: 19.2 (±8.1)

Abbreviations: BK, bradykinesia; H&Y, Hoehn and Yahr; HC, healthy control; IPD, idiopathic Parkinson's disease; NTD, non-tremor dominant; PIGD, postural instability and gait difficulty; TD, tremor dominant; UPDRS, Unified Parkinson's Disease Rating Scale.

[a]Disease severity: Hoehn and Yahr reported as Median, if available, unless otherwise noted.

TABLE 2 Extracted data on laryngeal function for the articles included in this systematic review.

Article	Voice measures	Swallowing measures	Phenotypical differences	Effect sizes reported
Brown and Spencer[18]	F0 range during connected speech; CPPS	NA	No sig. differences	NA
Burk and Watts[19]	CPP vowel; CPP in speech; TAF vowel; TAF speech	NA	No sig. differences in CPP speech, or TAF speech; Lower CPP vowel in NTD vs TD ($p = .04$); lower TAF vowel in TD vs NTD ($p = .01$)	CPP vowel ($d = 0.65$); TAF vowel ($d = 0.88$)
Claus et al.[23]	NA	Delayed swallowing reflex, pharyngeal residue, penetration/aspiration	More frequent delayed swallow reflex ($p = .006$) in PIGD; lower penetration/aspiration ($p = .001$) in BK compared to PIGD	NA
Dumican and Watts[21]	V-RQOL, custom questionnaire	DHI, custom questionnaire	Worse speech/voice rating ($p < .001$), swallow rating ($p = .02$) and V-RQOL ($p = .02$) in NTD	Speech/voice rating: $\omega^2 = 0.07$; swallow rating: $\omega^2 = 0.04$; V-RQOL: $\omega^2 = 0.07$)
Mohamed et al.[20]	NA	SDQ; Sialorrhea; Normal or Dysphagic	No sig. differences in SDQ; higher frequency of sialorrhea ($p = .04$) and presence of dysphagia ($p = .033$) in PIGD; Phenotype sig. predictor of dysphagia in PD ($p = .033$).	Phenotype predictor of dysphagia in PD (OR = 7.01; CI = 1.17–41.97)
Sung et al.[24]	NA	Dysphagia questionnaire; Manometric parameters	Manometric abnormalities more present on viscous bolus consistencies ($p = .02$) in PIGD	NA
Suphinnapong et al.[25]	Fundamental frequency parameters (F0 SD in semitones, jitter, RAP, PPQ, sPPQ, F0 variation); amplitude parameters (shimmer, APQ, sAPQ, peak-to-peak amplitude variation), voice irregularity (degree of unvoiced segments), noise parameter (NHR, VTI, SPI), duration (Tsam)	NA	UPDRS Bradykinesia scores correlated with F0 SD, jitter, RAP, PPQ, sPPQ, F0 variation, NHR. UPDRS Rigidity scores correlate with F0 SD, F0 variation. UPDRS Tremor scores correlated with F0 SD, sPPQ, F0 variation. UPDRS Gait and Postural Instability scores correlated with F0 SD, jitter, RAP, PPQ, sPPQ, F0 variation, NHR.	NA
Tykalova et al.[26]	HNR, PSI, MDFT, MDAT, intensity SD, F0 SD	NA	No singular parameter could distinguish phenotypes	NA

Abbreviations: APQ, Amplitude Perturbation Quotient; CI, confidence interval; CPP, cepstral peak prominence; DHI, Dysphagia Handicap Index; F_0, fundamental frequency; MDAT, modulation depth of amplitude tremor; MDFT, modulation depth of frequency tremor; NHR, Noise to Harmonics Ratio; OR, odds ratio; PPQ, Pitch Perturbation Quotient; PSI, proportion of subharmonic intervals; RAP, Relative Average Perturbation; sAPQ, Smooth Amplitude Perturbation Quotient; SDQ, Swallowing Disturbance Questionnaire; SPI, Soft Phonation Index; sPPQ, Smooth Pitch Perturbation Quotient; TAF, transglottal airflow; UPDRS, Unified Parkinson's Disease Rating Scale; V-RQOL, Voice Related Quality of Life; VTI, Voice Turbulence Index.

The search string used consisted of three separate elements connected with a Boolean operator (AND). The search string included search terms on laryngeal symptoms (dysphonia and dysphagia), verbiage on PD and its symptoms, and search terms considering its phenotypes. Synonyms for each of those terms were also included. The search string was adapted to the characteristics of each database, making use of the database's organized vocabulary (e.g., MeSH terms for MEDLINE, Emtree for EmBase, etc.). All search strings were partially or completely test-run. The full string (undifferentiated to any database) can be found in Appendix S1.

A total of 2370 records were retrieved after running the search in all databases on May 4, 2022. The breakdown of the records in the different databases can be found in Figure 1. Inclusion criteria were: publication date before May 2022, appropriate study design (cohort, case–control, cross-sectional studies, clinical trials if enough data prior to the trial), appropriate population (PwPD), discussion of PD's clinical phenotype, inclusion of assessment of phonation and/or swallowing. Exclusion criteria consisted of inappropriate study design (case study, poster presentations

TABLE 3 Quality assessment and risk of bias of the included articles.

Article	(1) Inclusion criteria	(2) Subjects and setting	(3) Phenotype valid and reliable	(4) Objective, standard criteria for PD	(5) Confounding factors	(6) Strategies to deal with confounding factors	(7) Outcomes valid and reliable	(8) Appropriate statistical analysis	Overall judgment
Brown and Spencer[18]	Y	Y	Y	N	Y	Y	Y	Y	Y
Burk and Watts[19]	Y	N	N	N	Y	Y	Y	Y	N
Claus et al.[23]	Y	Y	U	Y	N	N	Y	Y	N
Dumican and Watts[21]	Y	N	N	N	N	N	Y	Y	N
Mohamed et al.[20]	Y	Y	Y	Y	N	N	Y	Y	Y
Sung et al.[24]	Y	N	Y	Y	Y	Y	Y	Y	Y
Suphinnapong et al.[25]	N	N	N	Y	N	N	Y	Y	N
Tykalova et al.[26]	N	N	Y	N	Y	Y	Y	Y	N

Note: Quality assessment was performed using the Checklist for Analytical Cross-Sectional Studies by the Joanna Briggs Institute (Moola et al., 2020).
Abbreviations: N, no; NA, not applicable; U, unclear; Y, yes.

with only abstract) and lack of relating phenotyping with laryngeal function.

Study titles and abstracts were screened for eligibility using the above-mentioned inclusion and exclusion criteria. The first and second authors (Z.T., M.D.) each screened all records individually, seeking consensus in case of disagreement. After title and abstract screening, an additional five articles found through hand-searching were added to the pool of articles. Next, the full texts for all remaining articles were retrieved and similarly screened. This process resulted in the inclusion of 8 articles, the details of which can be found in Tables 1 and 2.

The final group of articles was examined for methodological quality first independently and then in consensus. The Checklist for Analytical Cross-Sectional Studies by the Joanna Briggs Institute was used for quality assessment.[22] This tool assesses study quality across eight domains, allowing four different answers to each domain and an overall appraisal decision option. An overview of the quality assessment can be found in Table 3.

After quality assessment, both authors extracted the following information in collaboration: first author and year of publication, mean age and standard deviations of the study sample, phenotype categorization, disease duration, disease staging & severity, and measurement of laryngeal function, broken down into either voice or swallowing parameters. For laryngeal function, where available, results from statistical hypothesis testing were extracted. Information on laryngeal function was reported in two categories: voice and swallowing outcomes. If included in the study, effect sizes to estimate clinical relevance were also extracted. The extracted data can be found in Tables 1 and 2, indicating any missing data.

Statistical analysis could not be performed due to the large amount of variability in methodology of the included studies. Therefore, no meta-analysis was conducted. The data were analyzed descriptively, as can be found in Tables 1 and 2 and Section 3.

3 | RESULTS

Figure 1 outlines the step-by-step yield of the literature search including reasons for exclusion. A final total of eight articles, representing 540 PwPD, met eligibility criteria. Tables 1 and 2 represent the extracted data for each of the articles.

A critical appraisal of every reviewed manuscript is provided in Table 3. All reviewed manuscripts displayed a risk of bias in at least one category. The most common risks of bias included inadequate or missing information regarding the subject populations & settings (63% of studies) and inadequate or missing strategies to deal with confounding variables in the methodology (50% of studies). Another common risk of bias was the lack of a standardized phenotyping procedure across four of the nine (50%) studies.

Statistical hypothesis testing was used in every study collected with no qualitative work included for final extraction. Relevant outcome measures and their statistical significance are also included in Table 2. Where they did not detect or report statistically significant

results, this is also provided in Table 2. If reported, effect sizes were also extracted from the manuscripts.

3.1 | Participant demographics

Over the eight included studies, the data from 540 PwPD were included. All studies compared the TD phenotype with PIGD phenotype, sometimes called NTD (100% of studies). Two studies[23–25] examined a third phenotypic category, with one[24] including a bradykinetic category and another[23,25] including an intermediate category. In most studies, the TD phenotype was most commonly reported. In Claus et al.,[24] bradykinetic type PD was more common than either TD or PIGD. All but one study (88%)[25] included more biological male than biological female participants. Importantly, no effects of gender were assessed or analyzed in any studies included (0/8). Most study participants were in non-advanced stages of PD. As an example, all H&Y staging (whether reported as mean or median) was 3 or lower on a scale of 1 through 5. One study did not report any disease severity measures.[18]

3.2 | Laryngeal function measures and outcomes: Voice

Five (63%) out of eight included studies reported on vocal function across the different phenotypes. Interestingly, none of the included studies included identical vocal measures. The most reported measures related to the voice's fundamental frequency: three studies (60%) included measures such as the fundamental frequency range, standard deviation of the fundamental frequency, or jitter (i.e., fundamental frequency perturbation).[18,26,27] Both Brown and Spencer[18] and Tykalova et al.[27] found no differences between the TD and NTD/PGID phenotypes for these parameters. On the other hand, Suphinnapong et al.[26] found that the UPDRS bradykinesia and UPDRS gait and postural instability scores correlated with most of the fundamental frequency measures. The UPDRS rigidity and UPDRS tremor scores also correlated with fundamental frequency variation, but not with other related measures.

Two studies (40%) included measures of intensity and its perturbation,[26,27] though neither study found any differences or correlations between the different phenotypes for these measures. Cepstral peak prominence was also included in two studies (40%).[18,19] Brown and Spencer[18] found no differences between phenotypes, while Burk and Watts[19] found lower cepstral peak prominence in the PIGD phenotype. Finally, one study (20%) included self-assessment of vocal symptoms.[21,23] Dumican and Watts[21] found worse voice quality, as assessed by the Voice-Related Quality of Life and a custom questionnaire, in the PIGD-phenotype.

All other measures were reported sporadically. Vocal tremor was considered by Tykalova et al.[27] and was not able to distinguish the different phenotypes. Aerodynamic measures of voice were reported on by Burk and Watts.[19] They found lower transglottal airflow in the TD phenotype.

3.3 | Laryngeal function measures and outcomes: Swallowing

Four studies (50%)[20,21,23–25] reported one or more measures of swallowing function. However, inconsistencies in metrics are especially prevalent in these outcomes. No studies examining dysphagia used the same measures. Only one study[24] examined physiological swallowing function using imaging (fiberoptic endoscopic evaluation of swallowing [FEES]) and reported specific swallowing physiology parameters. They found higher rates of penetration or aspiration of material into the airway in PIGD compared to BK. Although not inherently a symptom of laryngeal function, the authors reported more frequently delayed swallow reflex times in PIGD.

Mohamed and colleagues[20] utilized FEES to examine dysphagia but provided no swallowing parameters and dichotomized swallowing function into "normal" or "dysphagic." The PIGD phenotype in this study was significantly more likely to be "dysphagic," though the physiological breakdowns and severity of dysphagia were not provided. This was the only study that examined swallowing physiology via imaging that reported standardized effect sizes. In using phenotype to predict if PwPD would present with dysphagia, the PIGD phenotype was 7x more likely to present with dysphagia than TD (OR = 7.01), though with large confidence intervals (CI = 1.17–41.97), suggesting uncertainty in the magnitude of this effect. Finally, Sung et al.[25] utilized manometry to assess pharyngeal and esophageal motility. The authors reported a more frequent presence of manometric abnormalities in the PIGD phenotype, particularly with thicker consistency liquids. However, the specific abnormalities, or their locations along the oropharynx or esophagus, are not provided.

Of the four studies examining swallow function, three included perceptual ratings of swallowing function, such as questionnaires.[20,21,23,25] Two of the three studies (66.6%) utilized standardized questionnaires that are commonly used for PwPD including the Dysphagia Handicap Index (DHI) and the Swallowing Disturbance Questionnaire (SDQ).[20,21,23] None of these established questionnaires displayed significant differences between phenotypes in any study. Dumican and Watts[21] and Sung et al.[25] implemented custom dysphagia questionnaires to measure patient perceptions of swallowing dysfunction. Only Dumican and Watts[21] found significant differences in swallowing function through a custom questionnaire, with PIGD phenotype reporting significantly worse swallowing severity (reporting more severe dysphagia symptoms) compared to TD. In examining the magnitude of effect of swallow severity ratings, the authors reported an omega-squared (ω^2) value of $\omega^2 = 0.04$. This suggests a small-to-medium effect of the differences seen between phenotypes.

4 | DISCUSSION

The current study aimed to systematically review the available evidence for a potential association between motor phenotypes in PwPD and their experienced laryngeal symptoms (i.e., dysphonia and/or dysphagia). Eight articles discussing laryngeal function were identified in

the literature search. The majority of studies[19–21,24–26] reported at least some differences in either voice or swallowing in different phenotypes of PwPD. These differences highlighted that TD phenotypes in PD tend to experience less severe voice or swallowing symptomology than other phenotypes, such as NTD/PIGD. This conclusion is preliminary as several substantial limitations exist. Most notably, there is a lack of consistency in the measures reported in both voice and swallowing domains of this literature.

Additionally, the methodological goals and subsequent quality of these studies are mixed. This inherently makes broad comparisons, and therefore generalizations, difficult. As an example, despite there being five studies that examined dysphagia as it pertains to laryngeal function in some capacity, all underlying subdomains being investigated were different for each study. These discrepancies are present in reported vocal outcomes as well. As an example, while Burk and Watts[19] investigated transglottal airflow, no other articles included this as a measure. This is despite the knowledge that transglottal airflow is highly relevant to phonatory function and laryngeal function, aspects of voicing that are expected to be decreased in PD-related hypokinetic dysarthria.[28]

Finally, the overall body of literature that met the criteria for this review was small. The limited available literature comparing TD and variations of PIGD, or other motor phenotypes of PD, combined with substantial methodological differences and quality, does not allow for the identification of clear differences between various phenotypic presentations of PD at the time of this review. These findings are discussed below.

4.1 | Phenotyping considerations

A common finding throughout the articles reviewed that impacts clinical relevance is the lack of a standardized method to determine the participants' phenotype. A significant limitation not just to the studies included in this review but to the broader PD phenotype literature is a lack of consensus on how best to phenotype, or replicate phenotypes, in PwPD.[29] While there are several accepted variations of phenotyping PwPD in the literature, particularly into motor or non-motor classifications, many of these rely on patient reports (i.e., patient perceptions of tremor) in at least some capacity.

The reliance on patient perception and reporting in all of these phenotyping strategies may inherently bias the categorization of a patient into one phenotype based on potentially inaccurate information, especially since a lack of symptom awareness has been found in PwPD for both motor and laryngeal symptoms.[30] Importantly, the discrepancies in phenotyping procedures likely limit the accuracy and generalizability across studies. Alternative approaches have been used to stratify PwPD into clinical phenotypes using data-driven, rather than hypothesis-driven, studies. The purpose of this review was to examine studies that pre-defined the phenotypes of PD to be examined and measure the differences in specific pre-defined measures of laryngeal function. However, other studies have attempted to classify PwPD utilizing physiological data collected, rather than examining differences between pre-determined or expected phenotypes. This is often seen as a preferred method, as it reduces a large amount of bias in how phenotyping is performed.[29,31]

Another consideration regarding phenotyping is the multitude of different approaches to phenotyping that are currently examined or used. In a review on current phenotypes, Mestre et al.[31] found that while motor phenotyping (i.e., tremor vs. non-tremor) was the most common, several different phenotyping approaches including using cognitive, autonomic, or treatment phenotypes have been explored. The number of possible methods for phenotyping PD, and with this, the innumerable potential approaches to conducting and evaluating these phenotyping procedures, may therefore limit their clinical utility. Moreover, in the context of this review, motor phenotypes are rarely stable in PwPD,[31] and the differences between TD and NTD/PIGD phenotypes decrease over time.[32] All studies included in this review were observational, cross-sectional studies, suggesting that even though differences were present at those time points, the magnitude of change in these differences over time is unknown. Though excluded from this review because of its longitudinal approach, Watts and Zhang[23] examined progression of voice and swallowing severity in their identified phenotypes but tracked these groups as the same phenotype across all time points. While this is a novel approach in our field to examine longitudinal changes in voice and swallowing in PD, their null findings of differences in progression comparing TD and PIGD phenotypes may be due to the shifting of patients between phenotypic groupings.

Despite the potential difficulties of using, implementing, or translating phenotypic differences as useful markers to the clinic, there is an understanding that PwPD who present at disease onset with clusters of symptoms may progress through the disease faster and experience more severe disease symptomology.[33] This suggests that clinical motor phenotyping of PwPD for voice and swallowing prognosis and longitudinal tracking is likely useful, as both self-perceived[34] and physiological[35] voice and swallow function decline with longer disease duration. Nevertheless, based on substantial differences and approaches, all phenotypic categorizations reported in this review should be interpreted with caution.

4.2 | Voice measures

The most commonly included measures of vocal function were acoustic measures relating to fundamental frequency. However, these analyses did not differentiate between male and female voices, despite the difference between male and female voices for fundamental frequency being well described. For example, converting fundamental frequency standard deviations to semitones, as in Suphinnapong et al.,[26] is needed to compare across biological sex validly.[36]

Interestingly, only two of the studies included intensity measures.[26,27] Reduced intensity has been purported as one of the most salient characteristics of PwPD's hypokinetic dysarthria and has been used as a primary outcome measure in most studies considering voice therapy effectiveness.[11,37,38] A possible explanation could be that the measurement of intensity requires additional methodological rigor

(i.e., stable mouth-to-mic distance, calibration of the system)[36] which might not have been feasible in all studies.

Overall, the assessment of voice and voice quality in the included studies was limited and did not constitute a comprehensive voice evaluation. It is understood that to describe voice and voice disorders completely, several aspects need to be assessed: auditory-perceptual evaluation, acoustic analysis, aerodynamic measures, laryngeal visualization, and patient self-perception.[39–41] Given that the majority of studies included only limited voice measures, the current review highlights the need to include comprehensive voice assessments across the parkinsonian phenotypes. While a full voice evaluation may not be feasible or even desirable within one research project, measures other than acoustic voice measures need to be considered.

4.3 | Swallowing function measures

Swallowing measures as they relate to laryngeal function used by the studies included in this review were subject to substantial methodological variability and differences in rigor. The lack of uniform measures, whether physiological or perceptual, significantly hinders generalizability and the ability to form a conclusion.

In the context of existing literature on swallow function in PD using FEES, there were only two studies to examine phenotypic effects, with no studies examining phenotypic swallowing physiology via videofluoroscopic swallow study (VFSS). However, several recent and comprehensive studies examining swallow function in PD via FEES present comparison data regarding prevalence rates and sample characteristics. Niendstedt et al.[42] and Pflug et al.,[43] found frequent, atypical occurrences of penetration and aspiration, as well as residues, across consistencies in a broad sample of PD. Results from Claus et al.[24] are consistent with these findings, while Mohamed et al.[20] found no airway invasion differences. However, this is likely due to methodological discrepancies.

Questionnaire and perceptual use of dysphagia identification between phenotypes suggest that perceptual measures may be able to identify differential changes in swallowing function. The majority of studies utilized established questionnaires that have been validated for use either in PwPD, such as the Swallow Disturbance Questionnaire (SDQ), or have been validated in broad neurogenic swallowing etiologies like the DHI.[44] Interestingly, none of these established questionnaires detected phenotypic differences in perceptual swallowing function. It is possible that tools like the DHI are too broad and do not ask specific enough questions to identify physiological manifestations of dysphagia for a population such as PD. While severely unbalanced groups in Mohamed and colleagues[20] study may have reduced the SDQ's ability to detect differences, it may have more merit in identifying the physiological presence of dysphagia, particularly as it relates to laryngeal manifestations, as it asks specifically about coughing with solids or liquids, respiratory conditions, and food feeling stuck (i.e., residue). This gives further support to the use, and sorely needed development, of perceptual dysphagia questionnaires that are clinically applicable and ask about specific physiological manifestations. This may be an underlying reason Dumican and Watts[21] found differences between phenotypes with a custom questionnaire, compared to validated ones.

4.4 | Limitations and directions for future research

Like all studies, the current review presented some limitations. Firstly, the conclusions drawn in this review are only as strong as the evidence included. The review only included studies in English that were published in peer-reviewed journals. Potentially more relevant literature was published in other languages. Publication bias may also have been introduced in the results. More extensive evaluation of gray, non-published literature could be considered for future reviews.

This systematic review underscored the paucity of methodologically rigorous studies comparing laryngeal symptomatology in the different parkinsonian motor phenotypes. There is a need to establish more standardized phenotyping of the different disease forms in PD. While this may be challenging, per the above discussion, there is a clear clinical relevance and use of (motor) phenotypes in PD. The assessment of laryngeal characteristics needs to be more comprehensive and standardized. Clinicians are encouraged to perform comprehensive assessments of their patients, and consequently, research should provide evidence for all measures they are likely to use. Secondly, standardizing measures and/or protocols will enable researchers to compare and generalize results more easily across different populations.

5 | CONCLUSION

This systematic review considered the different motor phenotypes in PD and their potentially associated laryngeal characteristics. Nine studies were identified and considered. A slight pattern was discovered for TD phenotypes to present with less severe laryngeal symptoms compared to other phenotypes (PIGD, NTD). However, these results should be interpreted with caution due to the paucity of studies included and the substantial methodological variability within the studies. More research is needed to determine the exact differences in laryngeal symptomatology across the different PD phenotypes.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primer*. 2017;3(1):1-21. doi:10.1038/nrdp.2017.13

2. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm*. 2017;124(8):901-905. doi:10.1007/s00702-017-1686-y
3. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem*. 2016;139:318-324. doi:10.1111/jnc.13691
4. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-376. doi:10.1136/jnnp.2007.131045
5. Sapir S, Ramig LO, Fox C. Speech and swallowing disorders in Parkinson disease. *Curr Opin Otolaryngol Head Neck Surg*. 2008;16(3):205-210. doi:10.1097/MOO.0b013e3282febd3a
6. Simons JA. Chapter Forty-Three – swallowing dysfunctions in Parkinson's disease. In: Chaudhuri KR, Titova N, eds. *International Review of Neurobiology*. Vol 134. Nonmotor Parkinson's: The hidden face. Academic Press; 2017:1207-1238. doi:10.1016/bs.irn.2017.05.026
7. Suttrup I, Warnecke T. Dysphagia in Parkinson's disease. *Dysphagia*. 2016;31(1):24-32. doi:10.1007/s00455-015-9671-9
8. Dumican M, Watts C, Drulia T, Zhang Y. Dysphagia presentation, airway invasion, and gender differences in a clinically based sample of people with Parkinson's disease. *Dysphagia*. 2023;38:353-366. doi:10.1007/s00455-022-10472-y
9. Kwon M, Lee JH. Oro-pharyngeal dysphagia in Parkinson's disease and related movement disorders. *J Mov Disord*. 2019;12(3):152-160. doi:10.14802/jmd.19048
10. Ma A, Lau KK, Thyagarajan D. Voice changes in Parkinson's disease: what are they telling us? *J Clin Neurosci*. 2020;72:1-7. doi:10.1016/j.jocn.2019.12.029
11. Ramig LO, Fox C, Sapir S. Parkinson's disease: speech and voice disorders and their treatment with the Lee Silverman Voice Treatment. *Semin Speech Lang*. 2004;25(2):169-180. doi:10.1055/s-2004-825653
12. Miller N, Noble E, Jones D, Allcock L, Burn DJ. How do I sound to me? Perceived changes in communication in Parkinson's disease. *Clin Rehabil*. 2008;22(1):14-22. doi:10.1177/0269215507079096
13. Politis M, Wu K, Molloy S, G Bain P, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. *Mov Disord*. 2010;25(11):1646-1651. doi:10.1002/mds.23135
14. Marras C. Subtypes of Parkinson's disease: state of the field and future directions. *Curr Opin Neurol*. 2015;28(4):382-386. doi:10.1097/WCO.0000000000000219
15. Thenganatt MA, Jankovic J. Parkinson disease subtypes. *JAMA Neurol*. 2014;71(4):499-504. doi:10.1001/jamaneurol.2013.6233
16. von Coelln R, Shulman LM. Clinical subtypes and genetic heterogeneity: of lumping and splitting in Parkinson disease. *Curr Opin Neurol*. 2016;29(6):727-734. doi:10.1097/WCO.0000000000000384
17. Tinazzi M, Gandolfi M, Ceravolo R, et al. Postural abnormalities in Parkinson's disease: an epidemiological and clinical multicenter study. *Mov Disord Clin Pract*. 2019;6(7):576-585. doi:10.1002/mdc3.12810
18. Brown KA, Spencer KA. The relationship between speech characteristics and motor subtypes of Parkinson's disease. *Am J Speech Lang Pathol*. 2020;29(4):2145-2154. doi:10.1044/2020_AJSLP-20-00058
19. Burk BR, Watts CR. The effect of Parkinson disease tremor phenotype on cepstral peak prominence and transglottal airflow in vowels and speech. *J Voice*. 2018;33(4):580.e11-580.e19. doi:10.1016/j.jvoice.2018.01.016
20. Mohamed AAB, Mohamed GF, Elnady HM, et al. Evaluation of dysphagia in different phenotypes of early and idiopathic parkinsonism. *Egypt J Neurol Psychiatry Neurosurg*. 2018;54(1):28. doi:10.1186/s41983-018-0031-1
21. Dumican M, Watts C. Self-perceptions of speech, voice, and swallowing in motor phenotypes of Parkinson's disease. *Clin Park Relat Disord*. 2020;3:100074. doi:10.1016/j.prdoa.2020.100074
22. Moola S, Munn Z, Aromataris E, et al. Chapter 7: Systematic reviews of etiology and risk. *JBI Manual for Evidence Synthesis*. JBI; 2020. 10.46658/JBIMES-20-08
23. Watts CR, Zhang Y. Progression of self-perceived speech and swallowing impairment in early stage Parkinson's disease: longitudinal analysis of the unified Parkinson's disease rating scale. *J Speech Lang Hear Res*. 2022;65(1):146-158. doi:10.1044/2021_JSLHR-21-00216
24. Claus I, Muhle P, Suttrup J, et al. Predictors of pharyngeal dysphagia in patients with Parkinson's disease. *J Parkinsons Dis*. 2020;10(4):1727-1735. doi:10.3233/JPD-202081
25. Sung HY, Choi MG, Kim JS. The prevalence and patterns of oesophageal dysmotility in patients with Parkinson's disease. *Eur J Neurol*. 2009;16(S3):555-624. doi:10.1111/j.1468-1331.2009.02822.x
26. Suphinnapong P, Phokaewvarangkul O, Thubthong N, et al. Objective vowel sound characteristics and their relationship with motor dysfunction in Asian Parkinson's disease patients. *J Neurol Sci*. 2021;426:117487. doi:10.1016/j.jns.2021.117487
27. Tykalová T, Rusz J, Švihlík J, Bancone S, Spezia A, Pellecchia MT. Speech disorder and vocal tremor in postural instability/gait difficulty and tremor dominant subtypes of Parkinson's disease. *J Neural Transm*. 2020;127(9):1295-1304. doi:10.1007/s00702-020-02229-4
28. Panzone L, Watts CR. Regulation of transglottal airflow in speakers with Parkinson's disease. *J Voice*. 2020;34(6):961.e1-961.e7. doi:10.1016/j.jvoice.2019.06.021
29. Qian E, Huang Y. Subtyping of Parkinson's disease – where are we up to? *Aging Dis*. 2019;10(5):1130-1139. doi:10.14336/AD.2019.0112
30. Friedman JH. Misperceptions and Parkinson's disease. *J Neurol Sci*. 2017;374:42-46. doi:10.1016/j.jns.2016.12.059
31. Mestre TA, Fereshtehnejad SM, Berg D, et al. Parkinson's disease subtypes: critical appraisal and recommendations. *J Parkinsons Dis*. 2021;11(2):395-404. doi:10.3233/JPD-202472
32. Luo L, Andrews H, Alcalay RN, et al. Motor phenotype classification in moderate to advanced PD in BioFIND study. *Parkinsonism Relat Disord*. 2019;65:178-183. doi:10.1016/j.parkreldis.2019.06.017
33. De Pablo-Fernández E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of Parkinson disease. *JAMA Neurol*. 2019;76(4):470-479. doi:10.1001/jamaneurol.2018.4377
34. Silbergleit AK, Schultz L, Hamilton K, LeWitt PA, Sidiropoulos C. Self-perception of voice and swallowing handicap in Parkinson's disease. *J Parkinsons Dis*. 2021;11(4):2027-2034. doi:10.3233/JPD-212621
35. Troche MS, Schumann B, Brandimore AE, Okun MS, Hegland KW. Reflex cough and disease duration as predictors of swallowing dysfunction in Parkinson's disease. *Dysphagia*. 2016;31(6):757-764. doi:10.1007/s00455-016-9734-6
36. Watts CR, Awan SN. *Laryngeal Function and Voice Disorders: Basic Science to Clinical Practice*. Thieme Medical Publishers; 2019.
37. Ramig LO, Halpern A, Spielman J, Fox C, Freeman K. Speech treatment in Parkinson's disease: randomized controlled trial (RCT). *Mov Disord*. 2018;33(11):1777-1791. doi:10.1002/mds.27460
38. Yuan F, Guo X, Wei X, et al. Lee Silverman voice treatment for dysarthria in patients with Parkinson's disease: a systematic review and meta-analysis. *Eur J Neurol*. 2020;27(10):1957-1970. doi:10.1111/ene.14399
39. Barsties B, De Bodt M. Assessment of voice quality: current state-of-the-art. *Auris Nasus Larynx*. 2015;42(3):183-188. doi:10.1016/j.anl.2014.11.001
40. Dejonckere PH. Assessment of voice and respiratory function. In: Remacle M, Eckel HE, eds. *Surgery of Larynx and Trachea*. Springer-Verlag; 2010:11-26. doi:10.1007/978-3-540-79136-2

41. LeBorgne WDL, Donahue EN. Voice therapy as primary treatment of vocal fold pathology. *Otolaryngol Clin North Am*. 2019;52(4):649-656. doi:10.1016/j.otc.2019.03.009
42. Nienstedt JC, Bihler M, Niessen A, et al. Predictive clinical factors for penetration and aspiration in Parkinson's disease. *Neurogastroenterol Motil*. 2019;31(3):e13524. doi:10.1111/nmo.13524
43. Pflug C, Bihler M, Emich K, et al. Critical dysphagia is common in Parkinson disease and occurs even in early stages: a prospective cohort study. *Dysphagia*. 2018;33(1):41-50. doi:10.1007/s00455-017-9831-1
44. Silbergleit AK, Schultz L, Jacobson BH, Beardsley T, Johnson AF. The dysphagia handicap index: development and validation. *Dysphagia*. 2012;27(1):46-52. doi:10.1007/s00455-011-9336-2

SUPPORTING INFORMATION

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

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