Journal of Parkinson's Disease 10 (2020) 1315–1333
DOI 10.3233/JPD-202223
IOS Press

Review

The Effects of Respiratory Training in Parkinson's Disease: A Systematic Review

Veerle A. van de Wetering-van Dongen[a,*], Johanna G. Kalf[a], Philip J. van der Wees[b], Bastiaan R. Bloem[c] and Maarten J. Nijkrake[a]

[a]*Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Rehabilitation, Nijmegen, the Netherlands*

[b]*Radboud University Medical Center, Radboud Institute for Health Sciences, Department of Rehabilitation and IQ Healthcare, Nijmegen, The Netherlands*

[c]*Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Center of Expertise for Parkinson and Movement Disorders, Nijmegen, The Netherlands*

Accepted 31 August 2020

Abstract.

Background: Signs of respiratory dysfunction can be present already early in the course of Parkinson's disease (PD). Respiratory training could alleviate this, but its effectiveness is not well understood.

Objective: The purpose of this systematic review is to review the efficacy of different respiratory training interventions in PD.

Methods: A search strategy was performed in four databases: PubMed, Physiotherapy Evidence Database (PEDro), Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Methodological quality of original full-text articles was assessed using the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for the controlled trials (CTs). Levels of evidence were rated by the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach.

Results: Six papers reporting on four randomized controlled trials and another four controlled trials were included. Positive effects were reported for inspiratory muscle strength training (IMST), expiratory muscle strength training (EMST), air stacking, breath-stacking, incentive spirometry and postural training on respiratory muscle strength, swallowing safety, phonatory aspects and chest wall volumes. Best methodological quality was found for breath-stacking and incentive spirometry. Best levels of evidence were found for EMST, IMST and EMST plus air stacking.

Conclusion: Respiratory training shows positive effects and should be considered when people with PD experience respiratory dysfunction. Future studies should focus on standardizing both training devices, instruments to measure outcomes and intervention protocols to further increase the level of evidence.

Keywords: Respiratory training, breathing exercises, respiratory muscles, respiratory function tests, Parkinson's disease

INTRODUCTION

Respiratory dysfunction is a relatively unknown feature in Parkinson's disease (PD), even though inspiratory muscle weakness may be present already early in the course of the disease [1]. The rate of progression throughout the disease is unclear and,

*Correspondence to: Veerle van de Wetering-van Dongen, MSc, P.O. Box 9101 (internal code 898). 6500 HB, Nijmegen, the Netherlands. Tel.: 0031 243614892; Fax: 0031 243619839; E-mail: veerle.vandewetering-vandongen@radboudumc.nl.

ISSN 1877-7171/20/$35.00

importantly, there is uncertainty about the optimal management approach. In the more advanced stages, a limited lung expansion and chest compliance contributes to less effective coughing, which is especially relevant for those with dysphagia. The latter causes penetration or aspiration of saliva, liquid or food [2, 3]. This could lead to the occurrence of aspiration pneumonia [4], which is among the highest risks factors for mortality in the advanced stages of PD [5, 6].

Box 1 offers an oversight of commonly used outcome measurements of respiratory training as the respiratory function tests, swallowing outcomes and phonatory aspects measures. Compared to age-matched healthy controls, both obstructive and restrictive features can be found in persons with PD, as reflected by reduced values of the FVC, FEV_1, MVV, MIP and MEP [7]. Improving FVC, FEV_1, MVV, MIP and MEP using respiratory training is already an established intervention in patients with a range of neuromuscular disorders [8, 9], but is relatively new in neurodegenerative disorders. For example, lung volume-orientated training improves respiratory function tests such as FVC and peak cough expiratory flow in patients with amyotrophic lateral sclerosis [10]. Also, cut-off scores to determine when respiratory training is indicated are available for neuromuscular diseases, but are so far lacking for PD [11, 12]. What sets PD apart from neuromuscular disorders is the fact that, besides muscle weakness (which is present for both types of conditions) also muscle control seems to be even more affected in persons with PD due to bradykinesia and rigidity [2, 13, 14]. From this perspective, not only respiratory muscle strength training is an option in PD, but also muscle control training. With muscle control training we mean targeting bradykinesia and rigidity in terms of improving reduced chest compliance, amplitude and pulmonary expansion [15].

The number of respiratory training studies in PD is increasing and more different modalities of respiratory training interventions have become available in the last decade. Against this background, our purpose here is to perform a systematic review presenting the efficacy of different respiratory training interventions in PD. We will also discuss the clinical implication of respiratory training in PD.

Box 1. Outcome measurements of respiratory training

Respiratory function tests	
Abbreviation	
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
MV	Minute ventilation
MVV	Maximum voluntary ventilation
PDQ-39	Parkinson disease questionnaire 39
PEF	Peak expiratory flow
PmPeak	Inspiratory muscle endurance
POD	Perception of Dyspnea
QoL (SF-36)	Quality of Life (medical outcomes study 36-item short form health survey)
r-PCF	Reflex peak cough flow
SVC	Slow vital capacity
TV	Tidal volume
VFS	Videofluoroscopic studies
v-PCF	Voluntary peak cough flow
VT,rca	Abdominal ribcage tidal volume
VT,rcp	Pulmonary rib cage tidal volume
Swallowing outcomes	
Abbreviation	
PAS	Penetration-aspiration scale
SWAL-QoL	Swallowing Quality of Life Questionnaire
Phonatory capacity	
Abbreviation	
MPT	Maximum phonation time
Peak SGP	Peak subglottic pressure

MATERIALS AND METHODS

The process of this systematic review was reported according to the guidelines for PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [16].

Data sources and searches

A broad literature search was performed for four databases: PubMed, Physiotherapy Evidence Database (PEDro), Cochrane Library and Cumulative Index to Nursing and Allied Health Literature (CINAHL). From inception of the databases until December 31 2019, a search strategy was created using 'Parkinson's disease' as the patient, 'respiratory training' and related search terms as the intervention, and 'other training interventions or control group' as comparison. Because the pathophysiology of respiratory dysfunction is not fully understood, we decided to search without limitations with respect to the outcome measures, respiratory training interventions and control group. The PubMed search is presented in the Supplementary Material.

Table 1
Interpretation of domain-level and overall risk of bias judgements in ROBINS-I [18]

Judgement	Within each domain	Across domains	Criterion
Low risk of bias	The study is comparable to a well-performed randomized trial with regard to this domain	The study is comparable to a well-performed randomized trial	The study is judged to be at **low risk of bias for all domains.**
Moderate risk of bias	The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial	The study provides sound evidence for a nonrandomized study but cannot be considered comparable to a well-performed randomized trial	The study is judged to be at **low or moderate risk of bias for all domains.**
Serious risk of bias	the study has some important problems in this domain	The study has some important problems	The study is judged to be at **serious risk of bias** in at least one domain, but not at critical risk of bias in any domain.
Critical risk of bias	the study is too problematic in this domain to provide any useful evidence on the effects of intervention	The study is too problematic to provide any useful evidence and should not be included in any synthesis	The study is judged to be at **critical risk of bias in at least one domain**
No information	No information on which to base a judgement about risk of bias for this domain	No information on which to base a judgement about risk of bias	There is no clear indication that the study is at serious or critical risk of bias *and* there is a lack of information in one or more key domains of bias (*a judgement is required for this*).

Study selection

Two authors (VvdW, JK) independently screened the articles identified by the search strategy on title and abstract. Inclusion criteria were randomized controlled trials (RCTs) or controlled trials (CTs). Exclusion criteria were non-controlled studies, case reports, reviews and abstracts. In addition, the reference lists of each of the selected publications were screened for title and abstract for additional relevant articles. The included publications, relevant by domain and determinant, were read in full text.

Data extraction

The extracted data from the articles includes the following characteristics: study design, participants (number of participants, sex, age and Hoehn & Yahr stage), training protocol, outcome measures, summary of results and effect size. The data were extracted by the first author (VvdW) and checked by the second author (MN).

Methodological quality assessment

The methodological quality of the included articles was rated independently by two reviewers (VvdW, MN). To assess the risk of bias of the RCTs, the Cochrane Risk of Bias tool was used.[17] Risk of bias was assessed within seven domains: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, 7) other sources of bias. A summary of the methodological quality was given; a green plus symbol corresponds with a 'low risk of bias' (+), a red minus symbol corresponds with a 'high risk of bias' (–) and a yellow question mark symbol corresponds with an 'unclear risk of bias' (?).

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the risk of bias for the CTs [18]. The ROBINS-I tool evaluated the risk of bias for quantitative studies that compare the efficacy of an intervention in two or more groups of individuals. This tool includes seven domains: 1) bias due to confounding, 2) bias in selection of participants into the study, 3) bias in classification of interventions, 4) bias due to deviations from intended interventions, 5) bias due to missing data, 6) bias in measurement of outcomes, and 7) bias in selection of the reported results. Each of these domains could be rated as: 'low risk', 'moderate risk', 'serious risk', 'critical risk', or 'no information'. A rating of the overall risk of bias was given as described in Table 1 [18].

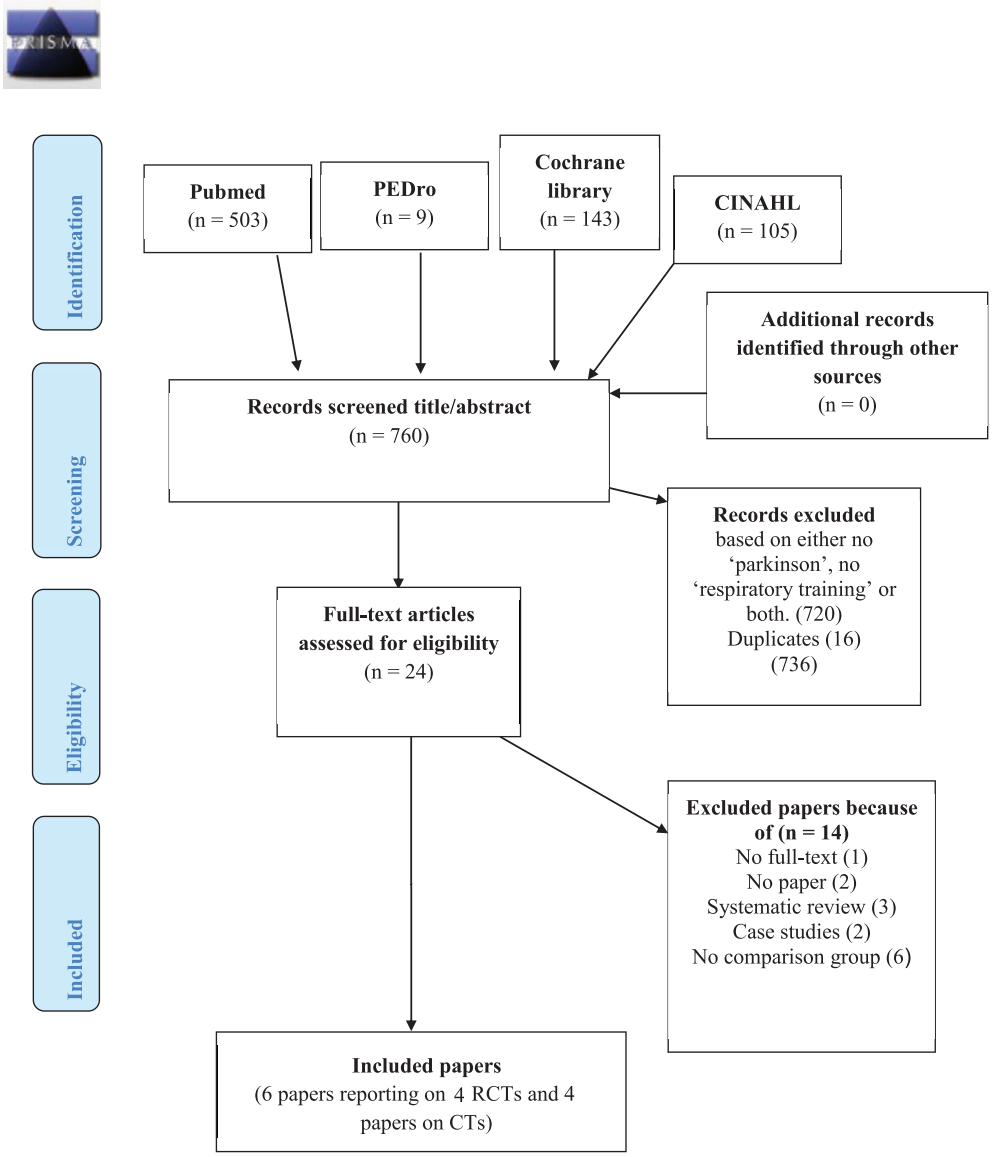

Fig. 1. Flow Diagram for article inclusion PRISMA.

Data synthesis and analysis

The heterogeneity of the interventions, training protocols as well as the wide variety of primary outcome measures made it impossible to pool the results in meta-analyses. Instead, we present a narrative synthesis organized by intervention and training protocols and outcome measures. The Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach was used to rate level of evidence into "high", "moderate", "low", or "very low" [19]. Detailed GRADE guidance was used to evaluate the risk of bias, imprecision, inconsistency, indirectness, and publication bias. These were all reasons to downgrade the level of evidence [20, 21]. Upgrading the level of evidence was possible in case of a large effect size, evidence of dose-response gradient, or all plausible confounding factors reducing an apparent effect.

RESULTS

Study inclusion

The process of article inclusion according to PRISMA is presented in Fig. 1. The search revealed

760 records. After screening titles and abstracts, 736 records were excluded, based on duplicates and either no 'Parkinson disease', no 'respiratory training' or both. The remaining eligible 24 articles were assessed based on their full text version, resulting in 10 papers that met the inclusion criteria for this review: six papers reporting on (four) RCTs, and four papers on CTs. These were published between 1997 and 2019 and were conducted worldwide including Chile (3), the United States of America (2), Brazil (2), Israel (1), Korea (1) and Taiwan (1). The study characteristics and outcomes are presented in Table 2.

Participants

The median sample size for all studies was 30.5 and ranged from nine to 60 participants, with mean ages ranging from 58.8 to 70.5 years within an overall woman-men ratio of 7:10.

Most studies included persons with PD in Hoehn & Yahr stage I to III. Information about disease duration in years or disease severity (as measured by the Unified Parkinson's Disease Rating Scale ((MDS-)UPDRS) scores) was given in only three studies.

Intervention and training protocols

Box 2 briefly summarizes the types of interventions and training devices that have been tested in persons with PD. The interventions in the RCTs were IMST only in one study, EMST only in two studies, both IMST and EMST in two studies, and breath-stacking and incentive spirometer techniques in one study. The interventions of the four CTs were EMST only in two studies, EMST complemented by postural techniques in one study, and EMST complemented by air stacking in one study. Three different devices were used for IMST and EMST: Threshold® (Philips Respironics, USA), POWERbreathe® (Southam, Warwickshire, UK), and EMST 150 (Aspire products LLC., USA). Training protocols and parameters were all different except for three EMST reports in which the same protocol was used consisting of 5 sets, 5 repetitions, 5 days per week for 4 weeks on 75% MEP [22–24].

Outcome measurement

Outcome measures used in the reviewed studies were several respiratory function tests (MEP was most frequently used), swallow function tests, quality of life scales and different optoelectronic plethysmography variables. All 10 studies showed a statistically significant positive effect of the intervention on the primary outcome compared to the control group (Table 2). Two different instruments were used to measure respiratory muscle strength: a pressure manometer (FLUKE 713–30 G [Fluke Corp., Everett, WA]) and the MICRO RPM respiratory pressure meter (MicroRPM; Micro Medical-Care Fusion, UK).

Expiratory muscle strength training

Three RCTs reported positive effects of EMST on the primary outcome compared to control group. Three RCTs, with different training protocols, showed a Cohen's d effect size between EMST and control group. A large effect was found for peak subglottic pressure ($d = 1.96$), MEP ($d = 1.4$), peak sound pressure level ($d = 1.10$) and voluntary PCF ($d = 0.89$). EMST and control showed a moderate effect on penetration aspiration score (PAS) ($d = 0.55$)and reflex PCF ($d = 0.27$) [22, 23, 25].

Four CTs reported positive effects of EMST compared to control group. The Cohen's d effect size between EMST and control group was large for MEP ($d = 1.07$) moderate for voluntary PCF ($d = 0.77$) and small for reflex PCF ($d = 0.32$) [26]. An 88% increase was found on MEP for EMST-5DE compared to the control group [24]. Compared to quiet breathing, EMST with different resistance settings (10, 15 or 20 cm H_2O) improved tidal volume and end-inspiratory chest wall volume ($p < 0.001$) [27]. Both EMST only and EMST combined with postural techniques enhanced the swallowing safety in persons with dysphagia caused by PD ($p < 0.05$) [28].

Inspiratory muscle strength training

Three RCTs performed IMST with significant positive effects on the primary outcome. In the first RCT, twelve weeks of IMST training significantly increased MIP by 25.8%, inspiratory muscle endurance by 45% and perception of dyspnea decreased by 27.8% compared to the control group ($n = 20$) [29]. The second RCT showed a moderate Cohen's d effect size between IMST and control group on MIP ($d = 0.76$) after two months of IMST training [25]. In the same RCT, two months of IMST (5 sets, 5 repetitions, 6 days/week on 50% MEP) showed large effect sizes for peak subglottic pressure ($d = 1.32$), peak sound pressure level ($d = 1.27$) and maximum phonation time ($d = 1.26$) when compared to the control group.[30]

Table 2
Overall characteristics of the included studies

Study	Participants	Training protocol	Outcome measures	Results and effect size
Inzelberg et al. 2005 [29]	**Intervention**: 10.	**Intervention:**	FVC	**IMST vs control:**
RCT	9 men	IMST	FEV_1	FVC and FEV_1: NS
	Age: 59.4 ± 4.9 years	30 min per session	Inspiratory muscle endurance	↑ inspiratory muscle endurance*
	Control:10.	6 d/wk	MIP	↑ MIP*
	9 men.	12 wk	POD	↓ POD*
				QoL (SF-36): NS
	Age: 65.2 ± 3.6 years	15% MIP first week.	QoL (SF-36)	
	H&Y stage: II - III	Increased 5%-10% each session to reach 60% MIP at end of first month.		Correlation between improvement in MIP and endurance and decrease in
		Monthly reset to 60% of the MIP.		POD in IMST group ($R^2 = 0.571$ and
		Control:		$R^2 = 0.423$, $p < 0.001$).
		Same protocol with fixed resistance of 7cm H_2O.		
Troche et al. 2010 [22]**	**Intervention:** 30.	**Intervention:**	**Primary outcome**	**EMST vs control:**
			PAS	↑ PAS (*d = 0.55)**
			Secondary outcomes	Duration of hyoid elevation: NS
			Duration of hyoid elevation Hyoid displacement	↑ hyoid displacement during swallowing*
				↑ SWAL-QoL*
RCT	25 men	EMST	SWAL-QoL	
	Age: 66.7 ± 8.9 years	5 sets		
	Control: 30.	5 repetitions		
	22 men	5 d/wk		
	Age: 68.5 ± 10.3 years	4 wk		
	H&Y stage: II - IV	75% MEP, adjusted weekly		
		Control:		
		Same protocol without load		
Sapienza et al. 2011 [23]**	**Intervention**: 30.	**Intervention:**	**Primary outcome:**	**EMST vs control**:
RCT	25 men	EMST	MEP	27% ↑ MEP*
	Age: 66.7 ± 8.9 years	5 sets	**Secondary outcomes:**	Secondary outcomes: NS
	Control: 30.	5 repetitions	FEV_1	
	22 men	5 d/wk 4 wk 75% MEP, adjusted weekly	FEV_1/FVC	
	Age: 68.5 ± 10.3 years	**Control:**	FVC	
	H&Y stage: II - III	Same protocol without load	PEF	

Reyes et al. 2018 [25]***	31 patients, 17 men	**Intervention**	FVC,	**EMST vs control:**
RCT	Age: 70.5 ± 8.2 years	-Home-based IMST	MEP,	MEP (*d = 1.40)*, v-PCF (*d = 0.89*), r-PCF (*d = 0.27)*, SVC (*d = 0.13)*, FVC (*d = 0.02)*
	H&Y stage: I - III	-Home-based EMST	MIP,	**IMST vs control:**
		Control: home-based EMST, fixed resistance	r-PCF,	MIP (*d = 0.76)*, v-PCF (*d = 0.08*)
		5 sets	SVC,	
		5 repetitions	v-PCF	
		6 d/wk		
		2 months		
		50% average MIP/MEP: adjusted until 75% last 2 wks.		
Ribeiro et al. 2018 [15]	14 patients, 9 men	**Intervention**	Volume variations of the chest wall before, immediately after, 15 min after and 30 min after intervention.	**BS and IS**: ↑ TV and MV*
RCT	Age: 65.6 ± 9.0 years	-Breath-Stacking (one-way valve, ventilometer)	Performed by optoelectronic plethysmography.	**IS**: ↑ VT,rcp and VT,rca*
	H&Y stage: I - III	-Incentive spirometer techniques (voldyne 5000).		
	All participants confirmed both interventions and participated in control protocol.	**Control:** no intervention.		
		3 sets		
		5 repetitions		
		35 sec interval between set.		
		4 non-consecutive days. Day1: general data. Day 2/3/4: BS/IS/control.		
Reyes et al. 2019 [30]***	31 patients, 17 men	**Intervention:**	**Primary outcome**	**IMST vs control**
RCT	Age: 70.5 ± 8.2 years	-Home-based IMST	MPT	MPT *(d = 1.26)*
	H&Y stage: I - III	-Home-based EMST	Peak SGP	Peak SGP (*d = 1.32)*
				Peak sound pressure level (*d = 1.27*)
				EMST vs control
				Peak SGP (*d = 1.96*)
				Peak sound pressure level (*d = 1.10*)

(*Continued*)

Table 2
(*Continued*)

Study	Participants	Training protocol	Outcome measures	Results and effect size
		Control: home-based EMST, fixed resistance 5 sets 5 repetitions 6 d/wk 2 months 50% average MIP/MEP: adjusted until 75% last 2 wks.	Peak sound pressure level	
Reyes et al. 2019 [26] CT	**Intervention**: Group EMST: 11, 7 men Age: 69.81 ± 6.75 years Group 2 EMST+AS: 11, 6 men Age: 65.81 ± 7.35 years **Control**: 11, 5 men Age: 70.45 ± 6.4 years H&Y stage: I-III	**Intervention**: EMST 5 sets 5 repetitions 6 d/wk 2 months 50% average MEP: adjusted until 75% last 2 wks. EMST+AS: Same protocol for EMST 10 sets 3-4 consecutive lung insufflations using a manual resuscitator bag **Control:** EMST with same protocol, fixed resistance on 9cm H_2O	**Primary outcome** r-PCF, v-PCF **Secondary outcome** SVC MIP MEP	**EMST vs control** v-PCF (*d = 0.77)* r-PCF (*d = 0.32)* MEP (*d = 1.07)* MIP (*d = 0.19)* **EMST+AS vs control** v-PCF (*d = 1.00)* r-PCF (*d = 1.34)* MEP (*d = 0.58)* MIP (*d = 0.57)* SVC showed small effects for both interventions
Frazao et al. 2014 [27] CT	**Intervention**: 15. 12 men Age: 59.1 ± 9.3 years H&Y stage: II-III **Control (healthy individuals)**: 15. 12 men Age: 58.8 ± 9.0 years	**Intervention:** EMST with 10, 15 or 20 cm H20. **Control:** Quiet breathing Measurements at baseline, during EMST, after EMST.	Spirometric assessment Respiratory muscle strength Chest wall volumes and long volume variables measured by optoelectronic plethysmography	**Intervention vs quiet breathing:** ↑ TV in all PEP levels* ↑ end-inspiratory and expiratory chest wall volume in all positive expiratory pressure levels*
Byeon 2016 [28] CT	33 patients. 31 men. EMST group: 18 Age: 63.8 ± 8.2 years	**Intervention:** EMST ($n = 18$) 8 repetitions	Functional Dysphagia Scale based on video fluoroscopic studies (VFS)	↓ in VFS for both groups.* Greater decrease in EMST+PT group than in the EMST-only group.*

	EMST+PT group: 15 Age: 65.1 ± 9.5 years H&Y stage: 0-V.	30 sec rest 20 min/d 5 d/wk 4 wk 75% MEP EMST+PT ($n = 15$): PT: chin tucking, head rotation, head tilting, bending head back, and lying down straight 30 minutes per session 5 d/wk 4 wk		
Kuo et al. 2017 [24] CT	**Intervention**: Group 1 5DE: 4. 2 men Age: 59.3 ± 3.8 years Group 2 3DE: 5 3 men Age: 58.4 ± 6.6 years **Control**: 4 2 men Age: 60.5 ± 6.1 years H&Y stage: I -III	**Intervention**: Group 1: EMST-5DE 5 sets 5 repetitions 5 d/wk 4 wk 75% MEP 75% average MEP: weekly reset. Group 2: EMST-3DE 5 sets 5 repetitions 3 d/wk 4 wk 75% MEP 75% average MEP: weekly reset. **Control:** Same protocol 3 d/wk EMST training without load	MEP PDQ-39	Bigger improvement in MEP EMST-5DE (88% increase of MEP) compared to EMST-3DE (61% increase in MEP)*. PDQ-39: only significant increase in mobility score*.

RCT, randomized controlled trial; CT, controlled trail; *Significant change; NS, no significant change; PD, Parkinson disease; NA, not applicable; H&Y stage, Hoehn and Yahr stage; IMST, inspiratory muscle strength training; EMST, expiratory muscle strength training; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; POD, Perception of Dyspnea; QoL, quality of life; SF-36, medical outcomes study 36-item short form health survey; PEF, peak expiratory flow; SGP, subglottic pressure, MPT, maximum phonation time; SWAL-QoL, Swallowing Quality of Life Questionnaire; TV, Tidal volume; MV, minute ventilation; VT,rcp, pulmonary rib cage tidal volume; VT,rca, abdominal ribcage tidal volume; MVV, maximum voluntary ventilation; SVC, slow vital capacity; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PAS, penetration-aspiration scale; PDQ-39 scale, Parkinson disease questionnaire 39; r-PCF, reflex peak cough flow; v-PCF, voluntary peak cough flow; PT, postural techniques. **Troche et al. [22] and Sapienza et al. [23] used the same population and intervention, but other outcome measurements. ***Two studies from Reyes et al. [25, 30] used the same population and intervention, but other outcome measurements.

Box 2. Types of respiratory training interventions and training devices

Abbreviation	Written in full	Aim intervention	Performance and devices
AS	Air stacking	Increase the inspiratory phase to improve cough effectiveness.	Stacking air behind the glottis by performing consecutive lung insufflations using a manual resuscitator bag.
BS	Breath-stacking	Increase long volumes, target lung expansion and prevent atelectasis.	Stacking air behind the glottis by performing successive breaths until no inspiratory volume was observed using a ventilometer (Ferraris Mark Wright ® 8, Middlesex, England).
EMST	Expiratory muscle strength training	Improve respiratory muscle strength, lung volumes, swallowing function and phonatory capacity.	Perform maximum expiratory muscle flows against resistance using a training device as EMST 150 (Aspire products LLC., USA), Threshold® (Philips Respironics, USA) or PEP valve (Vital Signs Inc., Totowa, NJ, United States)
IMST	Inspiratory muscle strength training	Improve respiratory muscle strength and phonatory capacity.	Perform maximum inspiratory muscle flows against resistance using a training device as POWERbreathe® (Southam, Warwickshire, UK) or Threshold® (Philips Respironics, USA). Aims to improve respiratory muscle strength.
IS	Incentive spirometer techniques	Increase lung volumes, target lung expansion and prevent atelectasis.	Performing a slow and deep breathing to total lung capacity has been reached, using an incentive spirometry (Voldyne 5000 ®; Sherwood Medical, St Louis, USA).
PT	Postural training	Conduct as swallowing intervention.	General postural compensation techniques were conducted being chin tuck, head rotation, head tilting, bending head back, and lying down.

Other interventions

Breath-stacking and incentive spirometer techniques were found to directly increase tidal volume and minute ventilation measured by optoelectronic plethysomography [15]. EMST complemented by air stacking showed a large Cohen's d effect size compared with the control group on r-PCF ($d = 1.34$) and v-PCF ($d = 1.00$) [26].

Quality assessment

Table 3 shows the quality assessments of the Cochrane risk of bias tool for the RCTs. Ribeiro et al. [15] showed a low risk of bias with a sample size of 14 persons with PD. Troche et al. [22] and Sapienza et al. [23] included 30 persons with PD and showed a low risk of bias except for unclear generation of a randomized sequence (selection bias). Inzelberg et al. [29] included 20 participants with an inadequate concealment of allocations prior to assignment (selection bias) and data from two persons from the training group with a low compliance to the training regime were left out of the analysis. Attempts were made to keep the participants blinded (by using sham devices) for at least the intervention. Blinding of outcome assessment was guaranteed in all studies, except for the two papers of Reyes et al. [25, 30]. Although in both papers of Reyes et al., the attempts to ascertain blinding of the personnel that provided instructions for training was unclear, we decided to rate all six RCTs for low risk of bias on the criterion 'blinding of participants and personnel'. We downgraded both papers of Reyes et al. for criteria 4 'blinding of outcome assessment' as the researchers were not blinded for group allocation. Both papers of Reyes et al. showed also a risk of bias because no information about the compliance of the training regime (home-based exercise program) was reported, and some participants were excluded from the analysis for unknown reasons.

Assessment of the methodological quality by both authors (VvdW, MN) showed an agreement for risk of bias assessment in five of the six RCTs. Disagreement for one study was caused by the lack of information about compliance to the training regime, but consensus was reached that this could lead to a high risk of performance bias.

Table 4 showed the results of the ROBIN-I checklist for the four included CTs. Both authors (VvdW, MN) indicated a serious risk of bias in three of the studies, and a critical risk of bias in one study. Frazao et al. showed a serious risk of bias because there was no blinding of outcome assessors.[27] Next to that, the aim and conclusion of this study suggested that PD patients were compared to healthy subjects. However, the methods and results section

Table 3
Cochrane Handbook for Systematic Reviews of Interventions quality assessment RCTs

Domain	Inzelberg et al. 2005	Troche et al. 2010	Sapienza et al. 2011	Reyes et al. 2018	Ribeiro et al. 2018	Reyes et al. 2019
Random sequence generation **(selection bias)**	?	?	?	+	+	+
Allocation concealment **(selection bias)**	?	?	?	+	+	+
Blinding of participants and personnel **(performance bias)**	+	+	+	+	+	+
Blinding of outcome assessment **(detection bias)**	+	+	+	-	+	-
Incomplete outcome data **(attrition bias)**	-	+	+	-	+	-
Selective reporting **(reporting bias)**	+	+	+	+	+	+
Other sources of bias **(other bias)**	+	+	+	-	+	-
Overall risk of bias	4/7	5/7	5/7	4/7	7/7	4/7

Low risk of bias = +, High risk of bias = -, unclear risk of bias = ?

Table 4
ROBINS-I tool quality assessment non-randomized controlled intervention studies (CTs)

Domain	Frazao et al. 2014	Byeon 2016	Kuo et al. 2017	Reyes et al. 2019
Bias due to confounding	Low	Low	Serious	Low
Bias in selection of participants into the study	Low	Low	Serious	Low
Bias in classification of interventions	Low	Serious	Low	Low
Bias due to deviations from intended interventions	Low	Low	Low	Low
Bias due to missing data	Low	Low	Critical	Low
Bias in measurement of outcomes	Serious	Low	Low	Serious
Bias in selection of the reported result	Low	Low	Low	Low
Overall risk of bias judgment	Serious	Serious	Critical	Serious

Low risk of bias, Moderate risk of bias, Serious risk of bias, critical risk of bias, no information (unknown)

showed a comparison between three different levels of expiratory resistance, compared to no resistance. The study of Haewon Byeon scored a serious risk of bias because the intervention protocol for the postural techniques and the measurement procedure of MEP were not described [28], limiting the reproducibility of this study. Reyes et al. showed a serious risk of bias because there was no blinding for outcome assessment as the researchers were not blinded for group allocation [26]. Kuo et al. showed a critical risk of bias because of a lack of randomization and reporting incomplete data of four of the thirteen participants [24].

Levels of evidence

Table 5 shows the levels of evidence per intervention and specified outcomes according to the GRADE approach. Out of 26 outcomes included in this study, 22 were measured in only one study. For these 22 outcomes, inconsistency in results could not be determined. Detecting risk of publication bias was complicated due to the limited number of studies for each outcome. This made it impossible to calculate funnel plots. However, nine out of the ten included studies presented both significant and non-significant results.

Table 5
GRADE evidence profile per outcome measurement

Intervention	Outcome	No. of participants (studies)	Results	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication Bias[e]	Large effect	Dose-response	Residual bias	Levels of evidence (GRADE)
EMST	MEP	115 (4)	**Reyes'18 (RCT):** ↑ MEP *(d = 1.4)* **Reyes'19 (CT):** ↑ MEP *(d = 1.07)* **Sapienza'11 (RCT):** ↑ MEP ($F = 3.214$, $P < 0.01$) **Kuo'17 (CT):** 88% ↑ of 5 days EMST vs 3 days EMST	Serious risk of bias	Serious inconsistency	Serious indirectness	Very serious imprecision	Not detected	Detected	Not detected	Not detected	(+)()()() Very low
	v-PCF	42 (2)	**Reyes'19 (CT):** ↑ v-PCF *(d = 0.77)* **Reyes'18 (RCT):** ↑ v-PCF *(d = 0.89)*	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)(+)()() Low
	r-PCF	42 (2)	**Reyes'19 (CT):** ↑ r-PCF *(d = 0.32)* **Reyes'18 (RCT):** ↑ r-PCF *(d = 0.27)*	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)(+)()() Low
	PAS	60 (1)	**Troche'10 (RCT):** ↑ PAS *(d = 0.55)*	No serious risk of bias	NA	Serious indirectness	No serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)(+)(+)() Moderate
	SVC	31 (1)	**Reyes'18 (RCT):** ↑ SVC *(d = 0.13)*	Serious risk of bias	NA	No serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
	FVC	31 (1)	**Reyes'18 (RCT):** ↑ FVC *(d = 0.02)*	Serious risk of bias	NA	No serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
	Peak SGP	31 (1)	**Reyes'19 (RCT):** ↑ Peak SGP *(d = 1.32)*	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Detected	Not detected	Not detected	(+)(+)(+)() Moderate
	Peak sound pressure level	31 (1)	**Reyes'19 (RCT):** ↑ Peak sound pressure level *(d = 1.27)*	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Detected	Not detected	Not detected	(+)(+)(+)() Moderate
	Chest wall volumes	30 (1)	**Frazao'14 (CT):** ↑ TV in all EMST levels* ↑ end-inspiratory and expiratory chest wall volume in all EMST levels*									

	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)(+)()() Low			
	Functional dysphagia scale by VFS	33 (1)	**Byeon'16 (CT):** ↓ in VFS for both groups.*	Serious risk of bias	NA	Very serious indirectness	Serious imprecision	Detected	Not detected	Not detected	Not detected	(+)()()() Very low
	PDQ-39	13 (1)	**Kuo'17 (CT):** Only significant increase in mobility score*.	Very serious risk of bias	NA	Very serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
EMST+AS	v-PCF	33 (1)	**Reyes'19 (CT):** ↑ v-PCF (*d = 1.00)*	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)(+)()() Low
	r-PCF	33 (1)	**Reyes'19 (CT):** ↑ r-PCF (*d = 1.34)*	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Detected	Not detected	Not detected	(+)(+)(+)() Moderate
	MEP	33 (1)	**Reyes'19 (CT):** ↑ MEP (*d = 0.58)*	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)(+)()() Low
	MIP	33 (1)	**Reyes'19 (CT):** ↑ MIP (*d = 0.57)*	Serious risk of bias	NA	Serious indirectness	Serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
IMST	MIP	41 (2)	**Reyes'18 (RCT):** ↑ MIP *(d = 0.76)* ↑ 2 cm H_2O for MIP after IMST. **Inzelberg'05 (RCT):** ↑ 16 cm H_2O in MIP	High risk of bias	Very serious inconsistency	Very serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
	v-PCF	31 (1)	**Reyes'18 (RCT):** ↑ v-PCF (*d = 0.08*)	Serious risk of bias	NA	No serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
	MPT	31 (1)	**Reyes'19 (RCT):** ↑ MPT *(d = 1.26*)	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Detected	Not detected	Not detected	(+)(+)(+)() Moderate
	Peak SGP	31 (1)	**Reyes'19 (RCT):** Peak SGP (*d = 1.32)*	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Detected	Not detected	Not detected	(+)(+)(+)() Moderate
	Peak sound pressure level	31 (1)	**Reyes'19 (RCT):** Peak sound pressure level (*d = 1.27*)	Serious risk of bias	NA	No serious indirectness	Serious imprecision	Not detected	Detected	Not detected	Not detected	(+)(+)(+)() Moderate
	FVC	20 (1)	**Inzelberg'05 (RCT):** FVC: NS	Serious risk of bias	NA	Very serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
	FEV_1	20 (1)	**Inzelberg'05 (RCT):** FEV_1: NS	Serious risk of bias	NA	Very serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low

(*Continued*)

Table 5
(*Continued*)

Intervention	Outcome	No. of participants (studies)	Results	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication Bias[e]	Large effect	Dose-response	Residual bias	Levels of evidence (GRADE)
	PmPeak	20 (1)	**Inzelberg'05 (RCT):** ↑ inspiratory muscle endurance*	Serious risk of bias	NA	Very serious indirectness	Serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
	POD	20 (1)	**Inzelberg'05 (RCT):** ↓ POD*	Serious risk of bias	NA	Very serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
	QoL (SF-36)	20 (1)	**Inzelberg'05 (RCT):** QoL (SF-36): NS	Serious risk of bias	NA	Very serious indirectness	Very serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)()()() Very low
BS + IS	Chest wall volume	14 (1)	**Ribeiro'18 (RCT):** **BS and IS**: ↑ TV and MV* **IS**: ↑ VT,rcp and VT,rca*	Low risk of bias	NA	Serious indirectness	Serious imprecision	Not detected	Not detected	Not detected	Not detected	(+)(+)()() Low

[a] issues related to inadequate allocation concealment, incomplete outcome data, blinding of outcome assessors and missing data; [b] issues related to differences in trainings protocol, follow-up time, intervention in control group, disease severity, outcome values, effect sizes; [c] issues related to indirect comparison of outcomes and use of control group, limit generalizability, only before-after measurements; [d] issues related to small sample sizes, different effect sizes and confidence intervals. [e] no funnel plots, because limit number of studies per outcome; No., number; GRADE, Grading of Recommendation Assessment, Development and Evaluation; NA, not applicable; EMST, expiratory muscle strength training; EMST + AS, expiratory muscle strength training + air stacking; IMST, inspiratory muscle strength training; BS + IS, breath stacking + Incentive spirometer techniques; MEP, maximal expiratory pressure; v-PCF, voluntary peak cough flow; r-PCF, reflex peak cough flow; PAS, penetration-aspiration scale; SVC, slow vital capacity; FVC, forced vital capacity; SGP, subglottic pressure; VFS, videofluoroscopic studies; PDQ-39 scale, Parkinson disease questionnaire 39; MIP, maximal inspiratory pressure; MPT, maximum phonation time; FEV_1, forced expiratory volume in 1 s; PmPeak, inspiratory muscle endurance; POD, Perception of Dyspnea; QoL, quality of life; SF-36, medical outcomes study 36-item short form health survey; TV, Tidal volume; MV, minute ventilation; VT,rcp, pulmonary rib cage tidal volume; VT,rca, abdominal ribcage tidal volume.

For EMST, 11 different outcomes were included in the studies. The MEP was measured in four studies and was scored as "very low". Reasons for downgrading were a serious risk of bias, inconsistency because of different outcome values and no comparison of outcomes between intervention and control group, indirectness by differences in follow-up time, a limited generalizability (severe PD was not included), and imprecision by small sample sizes. Despite an upgrade of evidence because of the large effect sizes in the four studies, the "very low" score remains. V-PCF and r-PCF were measured in two studies and scored as "low" due to serious risk of bias, small sample sizes and wide confidence intervals. All other outcomes were only measured in one study. The PAS, peak SGP and peak sound pressure level were scored as "moderate" as they only showed limitations in terms of small sample sizes and serious risk of bias caused by reporting incomplete outcome data and an unclear allocation concealment. Large effect sizes upgraded the level of evidence for peak SGP and peak sound pressure level. One study combined EMST with AS and scored "moderate" for r-PCF because of limitations due to a small sample size and an unclear recruitment of participants.

For IMST, ten different outcomes were included. The MIP was measured in two studies and was scored as "very low" due to high risk of bias, inconsistency because of different outcome values and effect sizes, indirectness caused by differences in the population for disease severity, differences in trainings protocols, the control group had a different intervention, and imprecision due to small sample sizes and unknown confidence intervals. All other IMST outcomes were measured in only one study. The MPT, Peak SGP and peak sound pressure level was scored as "moderate" showing limitations in terms of a serious risk of bias and small sample sizes. Large effect sizes upgraded the level of evidence for these outcomes.

One study combined BS with IS and was ranked as "low" due to the small sample size and serious indirectness and imprecision (the latter because the study only measured the effects directly after the intervention, without a follow-up).

All other outcomes scored "very low" or "low". The most important reasons for downgrading were: 1) a high risk of bias, 2) indirectness caused by heterogeneity in the population (disease severity), intervention, and treatment duration, and 3) imprecision because of small sample sizes ($n = 10$ per group). Overseeing all results of the included studies we had to much heterogeneities to do meta-analysis.

DISCUSSION

The overall conclusion of this systematic review is that all respiratory training interventions show positive effects in people with PD, underlining that respiratory training should be considered as a possible treatment option for people with PD. Our two main findings are: (1) EMST significantly improves swallowing safety (PAS score) and phonatory aspects (Peak SGP and peak sound pressure level) and, when EMST is combined with air stacking, improves coughing (r-PCF), with large effect sizes and a moderate level of evidence; and (2) IMST improves phonatory aspects (MPT, peak SGP and peak sound pressure) with large effect sizes and a moderate level of evidence.

This review provides good methodological quality scores for two different modalities of respiratory training: respiratory strength training (EMST more than IMST) and 'volume- orientated' training in which volume variations of the chest wall increase directly after breath-stacking combined with incentive spirometer techniques.[15] The methodological quality of the study about breath-stacking plus incentive spirometer techniques was superior followed by good to moderate quality for the five RCTs about IMST and EMST, and a serious risk of bias for the four CTs. Methodological limitations of all studies included an unclear randomization and allocation concealment, reporting of incomplete data, no blinding of outcome measurement, unclear intervention protocol and an unclear intervention for the control group.

The level of evidence measured by the GRADE approach showed different reasons for downgrading for most outcomes due to: 1) a serious risk of bias, 2) indirectness caused by heterogeneity in the population, intervention (for control group) and treatment duration and 3) imprecision because of small sample sizes ($n = 10$ per group).

Pre-post intervention studies (that had been excluded from the analyses) showed similar positive effects for either strength training (EMST and IMST) and other respiratory training techniques like air stacking, or deep breathing exercises (plus upper extremity exercises) and (global) postural training to improve respiratory function tests, swallowing safety and phonatory aspects.[24, 26–28, 31–37] This confirms that the positive results are robust, but also indicates that more high-quality studies for both respiratory strength training and volume-oriented training techniques remain needed. The included

studies all showed positive effects, but the magnitude of the effects was different. For example, Sapienza et al. [23] showed a 27% increase of MEP from pre- to post-EMST after four weeks of training. In contrast, Reyes et al. found an increase of MEP of only 8.5% after 8 weeks EMST [25]. There are several possible explanations for the differences in the magnitude of the effects in the included studies. First, differences might result from a lack of homogeneity of the training devices as two different devices were used for IMST [25, 29] and two different devices for EMST [22, 27]. Second, four out of the five included papers who used a respiratory function tests as outcome [24–26, 29] describe to measure according to the statement of the American Thoracic Society (ATS) and European Respiratory Society (ERS) [38]. This procedure included the performance of respiratory function tests. The ATS/ERS statement described the performance of MIP and MEP as: the maximum value of three inspiratory or expiratory maneuvers that vary by less than 10%. However, this procedure seems to attenuate the learning effect of repeated measurements insufficiently [39]. A 'warm up session' prior to measuring is recommended to improve the reliability, and this procedure should be incorporated in future studies having either MIP or MEP as primary outcome [40]. However, the number of repeating measurements differ in the five studies and the starting position and use of a nose clip while testing was different. The study of Sapienza et al. didn't describe to follow this statement and used another measurement device to capture the MEP [23]. Third, heterogeneity was found for the training protocol as training duration varied from 4 weeks to 12 weeks.[22, 29] For EMST, training frequency of 5 sets, 5 repetitions, 6 days a weeks within an intensity of 75% of MEP showed the greatest effects on MEP, PAS, and voice production.[22, 25, 30] Finally, in four studies, EMST was provided as a combined intervention with either IMST, air stacking and postural training.

Except improving respiratory (muscle) function tests, there are also indications that respiratory training improves coughing (PCF), swallowing safety (PAS score, VFS) and phonatory aspects (MPT, Peak SGP and peak sound pressure level). Having these positive outcomes the important question remains where, in the course of the disease, should respiratory training be considered? In almost all included studies, the disease severity ranged between H&Y I to III. Respiratory dysfunction measured with the MIP is already an early feature in PD. Also, notice that when treatment with levodopa is started in the early phase of PD, the MIP seems to improve, at least initially [1]. So, it can be questioned if respiratory training should be started that early in the disease. The lack of evidence for the effects of respiratory training in H&Y stages IV and V is clinically relevant, because coughing, speech and swallowing difficulties are more prevalent in advanced PD, and more often lead to serious complications such as aspiration pneumonia [5, 41]. In amyotrophic lateral sclerosis (ALS), patient also experience speech, swallowing and coughing problems [42]. We do know from ALS, that respiratory training in terms of lung volume-orientated training strongly enhances cough efficacy [10][43]. In ALS, lung volume-orientated training is indicated if the peak cough flow is less than 270 liters per minute [44]. For that reason, future respiratory intervention studies in PD should include more advanced PD patients and perhaps should consider to start training based on the criteria of ALS.

The impact of respiratory dysfunction on daily life is unknown, which makes it almost impossible to answer the question whether amelioration in MIP and MEP by respiratory training leads to meaningful improvements for the patient in daily life. A better understanding how experienced signs and symptoms relate to abnormal respiratory function tests is therefore needed. In addition, qualitative research enquiring the impact of respiratory training on daily functioning and respiratory symptoms could provide more information about the clinical impact of respiratory dysfunction in PD.

Despite the progressive and typically longstanding course of PD (which can extend to decades for some), the effects of respiratory training have not been investigated beyond a period of 3 months. Two studies included in this review only measured the effect of an intervention without a training period [15, 27]. Next to that, any possible changes resulting from discontinuation of training are not well established, so it remains unclear whether prolonged maintenance therapy (perhaps in the form of boost sessions) is needed to ascertain a long-term efficacy [45]. The suggested pathophysiology underlying respiratory dysfunction in PD is diffuse and still somewhat unclear [46]. Cardinal motor features of PD such as bradykinesia, hypokinesia, rigidity and dystonia can influence muscle control in the limbs, but can also influence muscle strength and control in the respiratory system [13, 14]. Although the motor control of respiratory muscles differs from that of skeletal muscles, the respiratory training effects found in our

review do show similarities with, e.g., the effects of gait interventions in PD [47]. These gait interventions in PD have been studied in more detail, yielding strong evidence that strength training of the skeletal leg muscles as well as amplitude-oriented training (by using compensatory strategies) can improve gait functions [48]. The rationale behind these finding is that a good strength in mainly the upper legs is a prerequisite to walk, and that stressing these muscles by training improves gait function [49]. Similar results are found for respiratory strength training in terms of IMST and EMST. However, solely strength training does not improve the decreased chest amplitudes due to bradykinesia, hypokinesia or akinesia [50]. For gait, compensatory cueing strategies which are applied consciously with the aim to improve step length improve gait function as well [47]. Volume-oriented respiratory training interventions like breath-stacking, air stacking or deep breathing exercises (which are performed consciously) seem to improve muscle control just as they do for gait. From this viewpoint, conscious and deep breathing exercises or existing techniques need to be considered and studied into more detail in future studies. These future studies should particularly examine how long the immediate effects found for volume-oriented techniques like incentive spirometry persist.

Another viewpoint is that intensive exercise stimulates a deeper ventilation [48]. The effects of aerobic exercise in PD have been studied extensively for outcomes related to balance, gait, functional mobility or motor function (UPDRS) but none of these studies looked at the impact of exercise on respiratory parameters such as FVC, MIP or MEP so far.

In summary, this review shows positive effects of respiratory training in PD. EMST significantly improves swallowing safety and phonatory aspects and IMST improves phonatory aspects. Volume-orientated respiratory training seems to improve chest amplitude, lung expansion and also the ability to produce an effective cough, the latter being a clinically important mechanism that can help to prevent pneumonia.

This review also reveals important research questions that need to be answered to better understand the implications for clinical practice. Future studies should: 1) standardize training devices, instruments to measure outcomes and protocols in respiratory training; 2) investigate volume oriented techniques and consciously performed breathing exercises; 3) explore the determinants of respiratory dysfunction, but also the impact of respiratory dysfunction on daily life functioning people with PD; and 4) include people with advanced PD as well. This is important to better understand the optimal timing of when to start respiratory training, with the overall aim of preventing respiratory complications such as aspiration pneumonia [6].

ACKNOWLEDGMENTS

This work was supported by funding from the Principal Clinician 2019 of Maarten, J. Nijkrake, Radboudumc Nijmegen. The Center of Expertise for Parkinson & Movement Disorders was supported by a center of excellence grant by the Parkinson Foundation.

CONFLICT OF INTEREST

The authors have no financial conflicts of interest related to this publication. Prof. Bloem currently serves as co-Editor in Chief for the Journal of Parkinson's disease, serves on the editorial of Practical Neurology and Digital Biomarkers, has received honoraria from serving on the scientific advisory board for Abbvie, Biogen and UCB, has received fees for speaking at conferences from AbbVie, Zambon, Roche, GE Healthcare and Bial, and has received research support from the Netherlands Organization for Scientific Research, the Michael J Fox Foundation, UCB, Abbvie, the Stichting Parkinson Fonds, the Hersenstichting Nederland, the Parkinson's Foundation, Verily Life Sciences, Horizon 2020 and the Parkinson Vereniging.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JPD-202223.

REFERENCES

[1] Baille G, Perez T, Devos D, Deken V, Defebvre L, Moreau C (2018) Early occurrence of inspiratory muscle weakness in Parkinson's disease. *PLoS One* **13**, e0190400.

[2] Gross RD, Atwood CW, Ross SB, Eichhorn KA, Olszewski JW, Doyle PJ (2008) The coordination of breathing and swallowing in Parkinson's disease. *Dysphagia* **23**, 136-145.

[3] Monteiro L, Souza-Machado A, Pinho P, Sampaio M, Nobrega AC, Melo A (2014) Swallowing impairment and pulmonary dysfunction in Parkinson's disease: The silent threats. *J Neurol Sci* **339**, 149-152.

[4] Pitts T, Bolser D, Rosenbek J, Troche M, Sapienza C (2008) Voluntary cough production and swallow

dysfunction in Parkinson's disease. *Dysphagia* **23**, 297-301.

[5] Fernandez HH, Lapane KL (2002) Predictors of mortality among nursing home residents with a diagnosis of Parkinson's disease. *Med Sci Monit* **8**, Cr241-246.

[6] Hegland KW, Okun MS, Troche MS (2014) Sequential voluntary cough and aspiration or aspiration risk in Parkinson's disease. *Lung* **192**, 601-608.

[7] Pal PK, Sathyaprabha TN, Tuhina P, Thennarasu K (2007) Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord* **22**, 420-424.

[8] Reyes A, Ziman M, Nosaka K (2013) Respiratory muscle training for respiratory deficits in neurodegenerative disorders: A systematic review. *Chest* **143**, 1386-1394.

[9] Pollock RD, Rafferty GF, Moxham J, Kalra L (2013) Respiratory muscle strength and training in stroke and neurology: A systematic review. *Int J Stroke* **8**, 124-130.

[10] Macpherson CE, Bassile CC (2016) Pulmonary physical therapy techniques to enhance survival in amyotrophic lateral sclerosis: A systematic review. *J Neurol Phys Ther* **40**, 165-175.

[11] Fromageot C, Lofaso F, Annane D, Falaize L, Lejaille M, Clair B, Gajdos P, Raphael JC (2001) Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. *Arch Phys Med Rehabil* **82**, 123-128.

[12] Mendoza M, Gelinas DF, Moore DH, Miller RG (2007) A comparison of maximal inspiratory pressure and forced vital capacity as potential criteria for initiating non-invasive ventilation in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* **8**, 106-111.

[13] Polatli M, Akyol A, Cildag O, Bayulkem K (2001) Pulmonary function tests in Parkinson's disease. *Eur J Neurol* **8**, 341-345.

[14] Sathyaprabha TN, Kapavarapu PK, Pall PK, Thennarasu K, Raju TR (2005) Pulmonary functions in Parkinson's disease. *Indian J Chest Dis Allied Sci* **47**, 251-257.

[15] Ribeiro R, Brandao D, Noronha J, Lima C, Fregonezi G, Resqueti V, Dornelas de Andrade A (2018) Breath-stacking and incentive spirometry in Parkinson's disease: Randomized crossover clinical trial. *Respir Physiol Neurobiol* **255**, 11-16.

[16] Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* **6**, e1000097.

[17] Higgins JPT, Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions*, The Cochrane Collaboration.

[18] Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hrobjartsson A, Kirkham J, Juni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schunemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP (2016) ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* **355**, i4919.

[19] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ (2008) GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924-926.

[20] Schünemann HJ, Mustafa RA, Brozek J, Steingart KR, Leeflang M, Murad MH, Bossuyt P, Glasziou P, Jaeschke R, Lange S, Meerpohl J, Langendam M, Hultcrantz M, Vist GE, Akl EA, Helfand M, Santesso N, Hooft L, Scholten R, Rosen M, Rutjes A, Crowther M, Muti P, Raatz H, Ansari MT, Williams J, Kunz R, Harris J, Rodriguez IA, Kohli M, Guyatt GH (2020) GRADE guidelines: 21 part 1. Study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. *J Clin Epidemiol* **122**, 129-141.

[21] Schunemann HJ, Mustafa RA, Brozek J, Steingart KR, Leeflang M, Murad MH, Bossuyt P, Glasziou P, Jaeschke R, Lange S, Meerpohl J, Langendam M, Hultcrantz M, Vist GE, Akl EA, Helfand M, Santesso N, Hooft L, Scholten R, Rosen M, Rutjes A, Crowther M, Muti P, Raatz H, Ansari MT, Williams J, Kunz R, Harris J, Rodriguez IA, Kohli M, Guyatt GH (2020) GRADE guidelines: 21 part 2. Test accuracy: Inconsistency, imprecision, publication bias, and other domains for rating the certainty of evidence and presenting it in evidence profiles and summary of findings tables. *J Clin Epidemiol* **122**, 142-152.

[22] Troche MS, Okun MS, Rosenbek JC, Musson N, Fernandez HH, Rodriguez R, Romrell J, Pitts T, Wheeler-Hegland KM, Sapienza CM (2010) Aspiration and swallowing in Parkinson disease and rehabilitation with EMST: A randomized trial. *Neurology* **75**, 1912-1919.

[23] Sapienza C, Troche M, Pitts T, Davenport P (2011) Respiratory strength training: Concept and intervention outcomes. *Semin Speech Lang* **32**, 21-30.

[24] Kuo YC, Chan J, Wu YP, Bernard JR, Liao YH (2017) Effect of expiratory muscle strength training intervention on the maximum expiratory pressure and quality of life of patients with Parkinson disease. *Neurorehabilitation* **41**, 219-226.

[25] Reyes A, Castillo A, Castillo J, Cornejo I (2018) The effects of respiratory muscle training on peak cough flow in patients with Parkinson's disease: A randomized controlled study. *Clin Rehabil* **32**, 1317-1327.

[26] Reyes A, Castillo A, Castillo J (2020) Effects of expiratory muscle training and air stacking on peak cough flow in individuals with Parkinson's disease. *Lung* **198**, 207-211.

[27] Frazao M, Cabral E, Lima I, Resqueti V, Florencio R, Aliverti A, Fregonezi G (2014) Assessment of the acute effects of different PEP levels on respiratory pattern and operational volumes in patients with Parkinson's disease. *Respir Physiol Neurobiol* **198**, 42-47.

[28] Haewon B (2016) Effect of simultaneous application of postural techniques and expiratory muscle strength training on the enhancement of the swallowing function of patients with dysphagia caused by parkinson's disease. *J Phys Ther Sci* **28**, 1840-1843.

[29] Inzelberg R, Peleg N, Nisipeanu P, Magadle R, Carasso RL, Weiner P (2005) Inspiratory muscle training and the perception of dyspnea in Parkinson's disease. *Can J Neurol Sci* **32**, 213-217.

[30] Reyes A, Castillo A, Castillo J, Cornejo I, Cruickshank T (2019) The effects of respiratory muscle training on phonatory measures in individuals with Parkinson's disease. *J Voice*, doi: 10.1016/j.jvoice.2019.05.001.

[31] Darling-White M, Huber JE (2017) The impact of expiratory muscle strength training on speech breathing in individuals with Parkinson's disease: A preliminary study. *Am J Speech Lang Pathol* **26**, 1159-1166.

[32] Montero Ferro A, P Basso-Vanelli R, Moreira Mello RL, Sanches Garcia-Araujo A, Gonçalves Mendes R, Costa D, Gianlorenço AC (2019) Effects of inspiratory muscle training on respiratory muscle strength, lung function, functional capacity and cardiac autonomic function in

Parkinson's disease: Randomized controlled clinical trial protocol. *Physiother Res Int* **24**, e1777.

[33] Genç A, Dönmez Çolakoğlu B, Kara B, çakmur R, Makalesi A (2012) Evaluation of the effects of home-based deep breathing exercises in Parkinson's disease patients. *Arch Neuropsychiatry* **49**, 59-62.

[34] Koseoglu F, Inan L, Ozel S, Deviren SD, Karabiyikoglu G, Yorgancioglu R, Atasoy T, Ozturk A (1997) The effects of a pulmonary rehabilitation program on pulmonary function tests and exercise tolerance in patients with Parkinson's disease. *Funct Neurol* **12**, 319-325.

[35] Pitts T, Bolser D, Rosenbek J, Troche M, Okun MS, Sapienza C (2009) Impact of expiratory muscle strength training on voluntary cough and swallow function in Parkinson disease. *Chest* **135**, 1301-1308.

[36] Clementino Salgado de Oliveira Rocha L, Natsumi Hosoda Mineshita L, Lobato Sobral L, Dias Magno L, Clementino de Souza Santos M, Santiago Barbosa Rocha R (2017) Influence of global postural reeducation method on respiratory muscle strength and parkinsonian quality of life. *Man Ther Posturol Rehabil J* **15**, 1-5.

[37] Silverman EP, Sapienza CM, Saleem A, Carmichael C, Davenport PW, Hoffman-Ruddy B, Okun MS (2006) Tutorial on maximum inspiratory and expiratory mouth pressures in individuals with idiopathic Parkinson disease (IPD) and the preliminary results of an expiratory muscle strength training program. *Neurorehabilitation* **21**, 71-79.

[38] (2002) ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* **166**, 518-624.

[39] Dimitriadis Z, Kapreli E, Konstantinidou I, Oldham J, Strimpakos N (2011) Test/retest reliability of maximum mouth pressure measurements with the microRPM in healthy volunteers. *Respiratory Care* **56**, 776-782.

[40] Volianitis S, McConnell AK, Jones DA (2001) Assessment of maximum inspiratory pressure. Prior submaximal respiratory muscle activity ('warm-up') enhances maximum inspiratory activity and attenuates the learning effect of repeated measurement. *Respiration* **68**, 22-27.

[41] Santos RBD, Fraga AS, Coriolano M, Tiburtino BF, Lins OG, Esteves ACF, Asano NMJ (2019) Respiratory muscle strength and lung function in the stages of Parkinson's disease. *J Bras Pneumol* **45**, e20180148.

[42] Plowman EK, Watts SA, Robison R, Tabor L, Dion C, Gaziano J, Vu T, Gooch C (2016) Voluntary cough airflow differentiates safe versus unsafe swallowing in amyotrophic lateral sclerosis. *Dysphagia* **31**, 383-390.

[43] Senent C, Golmard JL, Salachas F, Chiner E, Morelot-Panzini C, Meninger V, Lamouroux C, Similowski T, Gonzalez-Bermejo J (2011) A comparison of assisted cough techniques in stable patients with severe respiratory insufficiency due to amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* **12**, 26-32.

[44] Motor Neurone Disease: Assessment and Management. National Institue for Health and Care Excellence: Clinical Guidelines 2016.

[45] Troche MS, Rosenbek JC, Okun MS, Sapienza CM (2014) Detraining outcomes with expiratory muscle strength training in Parkinson disease. *J Rehabil Res Dev* **51**, 305-310.

[46] Torsney KM, Forsyth D (2017) Respiratory dysfunction in Parkinson's disease. *J R Coll Physicians Edinb* **47**, 35-39.

[47] Nonnekes J, Ruzicka E, Nieuwboer A, Hallett M, Fasano A, Bloem BR (2019) Compensation strategies for gait impairments in Parkinson disease: A review. *JAMA Neurol* **76**, 718-725.

[48] Uhrbrand A, Stenager E, Pedersen MS, Dalgas U (2015) Parkinson's disease and intensive exercise therapy – a systematic review and meta-analysis of randomized controlled trials. *J Neurol Sci* **353**, 9-19.

[49] Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR (2015) Freezing of gait: A practical approach to management. *Lancet Neurol* **14**, 768-778.

[50] Tamaki A, Matsuo Y, Yanagihara T, Abe K (2000) Influence of thoracoabdominal movement on pulmonary function in patients with Parkinson's disease: Comparison with healthy subjects. *Neurorehabil Neural Repair* **14**, 43-47.