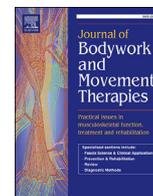




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The motor and the non-motor outcomes of Nordic Walking in Parkinson's disease: A systematic review

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ABSTRACT

Background: The current study investigated the motor and the non-motor outcomes of Nordic Walking (NW) in Parkinson's disease (PD) using a systematic review of studies with any design.

Methods: The search of PubMed, PsycInfo, Medline and SCOPUS until November 2018 identified $k = 13$ relevant studies: five randomised controlled-trials (RCTs) and eight observational studies. Study designs, intervention, patient and outcome details were coded. Study quality was assessed with the Physiotherapy Evidence Database scale.

Results: All studies reported either benefits or no effects of NW in 318 patients at the early stages of PD with low to moderate severity. NW was well accepted and relatively safe. Symptom severity, walking speed and gait pattern consistently improved after 4 – 24 weeks of NW relative to baseline or any control condition during the ON-phases of pharmacotherapy. The NW benefits were less consistent during the OFF-phases and at the follow-up in the absence of regular training.

Conclusions: NW may contribute to the maintenance of the overall mobility in addition to pharmacotherapy. Since the quality of studies was poor to moderate, future single-blind RCTs should investigate the clinical relevance of the NW outcomes and the training parameters necessary to optimise the benefits of NW in PD.

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1. Background

Parkinson's disease (PD) is a chronic, neurodegenerative disorder characterised by progressive worsening in motor functioning leading to reduced quality of life. PD is typically managed with pharmacotherapy and complementary physical exercise therapies. The physical exercise therapies aim to prevent the sedentary lifestyle associated with PD and to prolong mobility (Cugusi et al., 2017). One example of the physical exercise therapy is walking with poles, known as Nordic Walking (NW) or pole striding. NW may be useful as a long-term complementary therapy for PD because it can be conducted all-year-round either individually or in group-settings and the poles provide additional walking assistance.

Two recent systematic reviews addressed the outcomes of NW in PD using data from randomised controlled trials (RCTs) and observational studies published in English until 2017 (Bombieri et al., 2017; Cugusi et al., 2017). Both reviews concluded that NW

has some beneficial effects on the motor functioning in PD. However, this conclusion was based on data from up to $k = 8$ primary studies, including only $k = 4$ single-blind RCTs with low to moderate quality on the Physiotherapy Evidence Database scale (PEDro). Thus, the clinical relevance of NW remains unclear in PD.

The current study aimed to investigate the motor and the non-motor outcomes of NW in PD using a systematic review of studies with any design published in academic journals. We also aimed to quantify the outcomes of NW using a meta-analysis depending on the volume and the quality of available data. Our decision to include studies with any design was based on the following reasons. First, based on the small number of RCTs located in the recent systematic reviews (Bombieri et al., 2017; Cugusi et al., 2017) we expected that the outcomes of NW in PD would be mainly reported in observational studies, with or without control conditions. Second, our aim was to systematically inspect the trends in the available data based on the type of study design. Third, our approach was designed to reduce the redundancy in the current review because we did not expect to find a large number of new RCTs published in this field after 2017.

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2. Methods

The current study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and A Measurement Tool to Assess Systematic Reviews, version 2 (AMSTAR2) (Shea et al., 2017). The protocol was preregistered prior to commencement of this review (PROSPERO CRD42018112247, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018112247). The methodological details are reported in the Supplementary Information File.

Eligibility criteria. Primary studies with any design, published in peer-reviewed journals were eligible for inclusion in this review. The studies had to fulfill the following PICO characteristics (Supplementary Information File, Table S1): 1) **Population:** primary diagnosis of idiopathic PD; 2) **Intervention:** NW program of any length or intensity; 3) **Control group:** other physical exercise, any other intervention (standard medical care) or own baseline in studies with one group only; 4) **Outcome:** any motor or non-motor outcome assessed at baseline and after the intervention and measured using any standardised scale. The exclusion criteria were: 1) no primary data (review, comment), 2) NW outcomes not assessed (for example, NW poles used as walking aid).

Search strategy and study selection. The electronic literature search conducted in PubMed, PsycInfo, Medline and Scopus (any date to 01.11.2018) identified $k = 29$ studies with terms 'NW AND PD' in title or abstract (Supplementary Information File, Table S2). The study selection was done by both authors independently and any inconsistencies were resolved by consensus during discussion. Following the study assessment (Supplementary Information File, Figure S1 and Table S3), $k = 13$ studies reported in 15 articles in English fulfilled the inclusion criteria for the current review (Baatile et al., 2000; Bang and Shin, 2017; Cugusi et al., 2015; Ebersbach et al., 2010, 2014; Franzoni et al., 2018; Fritz et al., 2011; Gougeon et al., 2017; Herfurth et al., 2015; Krishnamurthi et al., 2017; Monteiro et al., 2017; Reuter et al., 2011; van Eijkeren et al., 2008; Warlop et al., 2017; Zhou et al., 2018). In a minor diversion from our protocol we also included studies that measured the outcomes of NW with biomechanical methods and gait assessments rather than the standardised scales. The reason for this decision was to include more studies in the current review.

Data coding. Data coding was done by both authors independently using self-developed tables and any inconsistencies were resolved during discussion. Overall, there were only minor disagreements between both authors. All disagreements were checked in detail against the original studies and resolved by consensus. The data coded included study designs, participant characteristics, intervention details and the outcome measures (assessment methods and results).

Study quality. The quality of the primary studies was assessed using the PEDro scale (Sherrington et al., 2000). The scale consists of 11 items regarding randomisation, blinding and reporting of outcome measures. A total score is computed based on items 2 to 11 and ranges between 0 and 10 points, indicating minimum to maximum quality, respectively.

Data synthesis. The outcomes of NW were synthesised qualitatively based on descriptive statistics and/or the results of statistical analyses reported in the primary studies. The inspection of all studies revealed that insufficient quantitative data were reported for a meta-analysis. However, we performed an exploratory meta-analysis (not controlled for the placebo effect) to quantify the most commonly reported outcome of NW (the change in the motor symptom severity) based on data from $k = 5$ studies (more details are reported in the Results section).

3. Results

Study designs. The current review includes the results of $k = 13$ primary studies reported in 15 articles published in peer-reviewed academic journals in English between 2000 and 2018. There were $k = 7$ (54%) studies from Europe, $k = 4$ (31%) studies from North America and $k = 1$ (8%) study each from Asia and South America (Table 1).

Of the $k = 13$ studies, $k = 5$ (38%) were RCTs, including $k = 4$ single-blind RCTs with control conditions involving various forms of physical exercise (free walking without poles, structured physiotherapy program BIG, unsupervised home exercises, flexibility and relaxation training) and $k = 1$ non-blinded RCT with a control condition not involving any physical exercise (standard medical care). Further $k = 5$ (38%) studies were observational (open-label) studies either without control conditions ($k = 4$) or with a healthy control group ($k = 1$). Finally, $k = 3$ (23%) observational studies with cross-over designs compared gait during NW vs. free walking in the same PD patients.

Patient characteristics. The $k = 13$ studies included 318 patients with idiopathic PD: 182 in NW groups and 136 in control groups. The PD patients were on average in the late 50s to early 70s, with low to moderate illness severity (1–3 on the Hoehn-Yahr scale), at the early stages of PD (illness length of 1.5–8 years) and the Body Mass Index (BMI) of 25–29 per study. All PD patients received various types and doses of the antiparkinsonian medications. Evaluations were conducted during either the ON- or the OFF-phases of such medications.

Intervention details. Following professional instruction NW was conducted outdoors in groups ($k = 7$ studies), outdoors individually ($k = 4$ studies) or indoors on treadmills ($k = 2$ studies). The NW protocol consisted of 60 min sessions, 2–3 times per week for 6–12 weeks in $k = 10$ studies. The remaining studies used NW protocols with either a longer duration (24 weeks in $k = 1$ study), a shorter duration (1 week in $k = 1$ study) or a high intensity (5 times per week for 4 weeks in $k = 1$ study). Compliance with the NW training was high although drop-outs for reasons unrelated to training were reported in $k = 6$ studies.

Study quality and potential biases. The overall quality of $k = 13$ studies was 2–8 out of 10 points according to the PEDro scale (Supplementary Information File, Table S4; Figure S2). The study quality tended to be higher in the $k = 5$ RCTs (5–8 out of 10 points) relative to the $k = 8$ observational studies (2–6 out of 10 points). The sources of potential bias in most studies were the lack of: randomisation (PEDro item 2), concealed allocation into groups (item 3), blinding of participants (item 5), therapists (item 6) and assessors (item 7). The sources of funding were reported in $k = 11$ studies and the risk of any conflict of interest was low in all studies.

Outcome assessment. The outcomes of NW were assessed immediately after the last NW session in $k = 9$ studies, at follow-up (16–24 weeks after baseline) in $k = 3$ studies and during NW in $k = 3$ studies. The outcomes were assessed using standardised scales in $k = 6$ studies, biomechanical measures in $k = 4$ studies or both in $k = 3$ studies.

All studies reported either benefits or no effects of NW relative to the pre-training baseline and/or the control conditions (Table 1). Negative effects of NW were not reported.

Outcomes post NW vs. baseline ($k = 9$ studies). Of the $k = 9$ studies, the immediate outcomes of 4–24 weeks of NW were assessed relative to baseline during the ON-phases in $k = 6$ studies or during the OFF-phases in $k = 3$ studies. During the ON-phases all $k = 6$ studies showed the following consistent motor and non-motor benefits of NW relative to baseline:

Table 1
Study designs and outcomes of NW in $k = 13$ primary studies.

Study	Intervention (NW) ^a ; control	n (% female)	Aage (years)	BMI	H–Y score	PD duration (years)	Dropouts	Study quality (PEDro score)	Funding reported	Motor outcomes	Non-motor outcomes	Post NW vs. baseline ^a	NW vs. control conditions
OBSERVATIONAL STUDIES WITHOUT CONTROL CONDITIONS OR WITH HEALTHY CONTROLS													
Baatile et al. (2000); USA	NW (individual): 8w, 3x/week, 60 min	6 (0%)	73	28	2–3	4	2/8	2	Yes	UPDRS	PDQ-39	↑ UPDRS total, PDQ-39	
van Eijkeren et al. (2008); The Netherlands	NW: 6w, 2x/week, 60 min	19 (26%)	67	–	1–3	5	0	4	Yes	TUG, 10MWT, 6MWT	PDQ-39	↑ 10MWT, 6MWT, TUG, PDQ-39; Follow-up 20w: ↑ all outcomes	
Fritz et al. (2011); Germany	NW: 12w, 3x/week, 60 min C (healthy); NW: 12w, 3x/week, 60 min	11 (27%) 11 (27%)	66 67	28 28	2–3 –	– –	11/22 6/18	3	Yes	Sit-to-stand transfer	–	↔ sit-to-stand transfer (total duration, individual aspects of movement); ↓ total duration, horizontal/vertical velocity in more severe PD (OFF) ↔ UPDRS III (OFF)	PD vs. healthy: ↓ total duration, horizontal/vertical velocity in more severe PD
Herfurth et al. (2015); Germany	NW: 12w, 3x/week, 60 min	18 (–)	63 ^b	–	2–2.5	3 ^b	4/22	2	Yes	UPDRS	–	↔ UPDRS III (OFF)	
Krishnamurthi et al. (2017); USA	NW: 12w, 3x/week, 60 min	17 (53%)	64	29	2.5–3	–	1/17	6	Yes	UPDRS, gait	PDQ-39	↑ UPDRS III, stride length, speed, variability; ↔ UPDRS total, PDQ-39, cadence (steps/min), leg support, swing power (OFF); Follow-up 24w: ↔ all outcomes (OFF)	
RCTs													
Ebersbach et al. (2010) and Ebersbach et al. (2014); Germany (single-blind)	NW: 8w, 2x/week, 60 min C1: physiotherapy BIG program: 4w, 4x/week, 60 min C2: unsupervised home training: 4w, individual intensity	19 (63%) 20 (65%) 19 (58%)	66 67 69	– – –	1–3 1–3 1–3	8 6 7	1 0 1	6	Yes	UPDRS, TUG, 10MWT, reaction times	PDQ-39	Follow-up 16w: ↔ UPDRS III, TUG, 10MWT; ↑ or trend PDQ-39, cued RT, non-cued RT	Follow-up 16w: NW vs. BIG: ↓ UPDRS III, TUG, ↔ 10MWT, cued RT, non-cued RT, ↑ trend PDQ-39; NW vs. home training: ↔ UPDRS III, TUG, 10MWT, non-cued RT, ↑ or trend PDQ-39, cued RT
Reuter et al. (2011); Germany (single-blind)	NW: 24w, 3x/week, 70 min C1: free walking: 24w, 3x/week, 70 min C2: flexibility and relaxation training: 24w, 3x/week, 70 min	30 (–) 30 (–) 30 (–)	62 63 62	26 27 27	2–3 2–3 2–3	5 6 5	0 0 0	7	No	UPDRS, BBS, 12MWT, 24MWT, gait	PDQ-39	↑ UPDRS total, UPDRS III (83% NW group improved >5 points), BBS, 12MWT, 24MWT, stride length, variability, time, double-stance phase, PDQ-39	NW vs. free walking: ↑ trend UPDRS total, UPDRS III; ↑ 12MWT, stride length, variability, time; ↔ BBS, 24MWT, double-stance phase, PDQ-39; NW vs. flexibility and relaxation training: ↑ trend UPDRS total, UPDRS III; ↑ 12MWT, 24 MWT, stride length,

Cugusi et al. (2015); Italy (non-blinded)	NW: 12w, 2x/week, 60 min	10 (20%)	68	26	1–3	7	0	6	No	UPDRS, TUG, BBS, 6MWT, FTSST, HGT, SRT, BST	BDI II, PFS-16, SAS, NMSS	↑ UPDRS III, 6MWT, FTSSS, BBS, TUG, SRT, BDI II, PFS-16, SAS, NMSS; ↔ HGT, BST	variability, time, double-stance phase; ↔ BBS, PDQ-39	
	C: standard medical care	10 (20%)	67	27	1–3	7	0						NW vs. conventional care: ↑ UPDRS III, 6MWT, FTSSS, BBS, TUG, SRT, BDI II, PFS-16, SAS, NMSS; ↔ HGT, BST	
Bang and Shin (2017); Republic of Korea (single-blind)	NW (treadmill/individual): 4w, 5x/week, 60 min	10 (50%)	58	25	1–3	1.5	0	8	Yes	UPDRS, TUG, BBS, 10MWT, 6MWT	-	↑ UPDRS III, TUG, BBS, 10MWT, 6MWT	NW vs. free walking: ↑ all outcomes	
	C: free walking (treadmill/individual): 4w, 5x/week, 60 min	10 (60%)	61	25	1–3	1.5	0							
Monteiro et al. (2017) and Franzoni et al. (2018); Brazil (single-blind)	NW (treadmill/individual): 9w, 2x/week, 60 min	16 (19%)	65	28	1–3	6	2/16	5	Yes	UPDRS, BBS, SSW, TUGSS, TUGFS, LRI, COP	-	↑ UPDRS III, BBS, TUGSS, TUGFS, SSW, LRI, COP	NW vs. free walking: ↑ UPDRS III, TUGFS, SSW, LRI; ↔ BBS, TUGSS, COP	
	C: free walking (treadmill/individual): 9w, 2x/week, 60 min	17 (59%)	71	27	1–3	5	3/17							
OBSERVATIONAL STUDIES WITH CROSS-OVER DESIGNS														
Gougeon et al. (2017); Canada ^c	NW (individual): 6w, 2-3x/week, 30–45 min	12 (25%)	62	-	1–3	7	0	5	Yes	Trunk stability, gait	-		During NW vs. free walking: ↑ gait cycle time and trunk stability; ↔ cognitive load of NW, stride length, gait speed, cadence (steps/min)	
Warlop et al. (2017); Belgium	NW (individual): 1w, 3x/week, 60 min	14 (36%)	62	25	1–3	4	0	5	Yes	Gait	-		During NW vs. free walking: ↑ temporal organisation of stride, step length, gait cadence (steps/min); ↔ gait speed	
	C (healthy): NW (individual): 1w, 3x/week, 60 min	10 (70%)	60	23	-	-	0						PD vs. healthy during NW: ↓ (trend) temporal organisation of stride, step length, gait speed, gait cadence	
Zhou et al. (2018); Canada ^c	NW (individual): 6w, 3-4x/week, 60 min	12 (25%)	62	-	1–3	7	0	5	Yes	Power profile in hip, knee, ankle; gait	-		During NW vs. free walking: ↑ knee power absorption on less affected side, stride length, cadence; ↔ ankle, hip power profile, gait velocity	
	C (healthy): NW (individual): 6w, 3-4x/week, 60 min	12 (67%)	68	-	-	-	0						PD vs. healthy during NW: ↔ or ↓ power profile hip, knee, ankle	

Notes. Arrows indicate statistically significant improvement ↑, worsening ↓, or no effect ↔ of NW on the motor or the non-motor outcomes. ^aUnless stated otherwise, it was assumed that all patients received instruction from professional trainers, completed the NW training outdoors in groups, and were evaluated during the ON-phases of the antiparkinsonian medications; ^bMedian; ^cBoth studies include the same PD group.

Abbreviations: BBS, Berg Balance Scale (functional balance); BDI, Beck Depression Inventory; BMI, Body Mass Index; BST, Back Scratch Test (lower back flexibility); C, control condition; COP, Centre of Pressure (static postural control); FTSST, Five-Times Sit-To-Stand Test (sit-to-stand ability); HGT, Hand-Grip Test (grip strength); H-Y, Hoehn and Yahr Staging (PD severity); k, number of studies; LRI, Locomotor Rehabilitation Index (functional mobility); 6MWT, Six-Minute Walk Test (walking endurance); 10, 12, 24MWT, 10-, 12-, 24-Meter Walk Test (walking speed); n, sample size; NMSS, Non-Motor Symptoms Scale; NW, Nordic Walking; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Questionnaire (quality of life); PFS-16, Parkinson's Fatigue Scale; RCT, randomised-controlled trial; RT, reaction times to visual stimuli (alertness without or with acoustic, preparatory cues); SAS, Starkstein Apathy Scale; SRT, Sit and Reach Test (hamstring flexibility); SSW, Self-Selected Walking Speed; TUG, Timed Up and Go Test (dynamic balance); TUGFS, TUG at Forced Speed; TUGSS, TUG at Self-Selected Speed; UPDRS, Unified Parkinson's Disease Rating Scale total (overall symptom severity) or part III (motor symptom severity); w, weeks.

1. reduction in the overall or the motor symptom severity on the Unified Parkinson's Disease Rating Scale (UPDRS total or part III),
2. improvement in balance, mobility and flexibility on the Timed Up and Go Test (TUG), the Berg Balance Scale (BBS), the Locomotor Rehabilitation Index (LRI), the Centre of Pressure (COP), the Five-Times Sit-To-Stand Test (FTSST), the Sit and Reach Test (SRT),
3. improvement in walking endurance and speed on the Six-Minute Walk Test (6MWT), the 10-, 12- or 24-Meter Walk Test (10MWT, 12MWT, 24MWT), the Self-Selected Walking Speed test (SSW),
4. improvement in the gait pattern (stride length, variability, time and double-stance phase),
5. improvement in the quality of life on the Parkinson's Disease Questionnaire (PDQ-39),
6. reductions in the non-motor symptoms on the Non-Motor Symptoms Scale (NMSS), depression severity on the Beck Depression Inventory (BDI II), fatigue on the Parkinson's Fatigue Scale (PFS-16) and apathy on the Starkstein Apathy Scale (SAS).

Two motor functions did not change after NW relative to baseline: the grip strength on the Hand-Grip Test (HGT) and the lower back flexibility on the Back Scratch Test (BST).

The NW outcomes were less consistent when evaluated during the OFF-phases in $k = 3$ studies. There were no effects of NW on the overall symptom severity, the sit-to-stand transfer, the gait pattern (cadence, leg support, swing power) and the quality of life while the motor symptom severity was reduced and other aspects of the gait pattern (stride length, speed, variability) improved in only 1/3 studies.

Outcomes post NW at follow-up vs. baseline ($k = 3$ studies). Of the $k = 3$ studies, the motor and the non-motor outcomes were assessed at the follow-up in the absence of training during the ON-phases in $k = 2$ studies and during the OFF-phases in $k = 1$ study. During the ON-phases all motor benefits (motor symptom severity, balance, walking speed) declined back to baseline in 1/2 studies while the improvements in the quality of life and alertness were maintained 16 – 20 weeks after baseline in $k = 2$ studies. However, during the OFF-phases any motor or non-motor benefits of NW were not maintained 24 weeks after baseline in $k = 1$ study.

Outcomes of NW vs. control conditions ($k = 5$ RCTs). All $k = 5$ RCTs evaluated the motor and the non-motor outcomes during the ON-phases either immediately after NW (in $k = 4$ RCTs) or at the follow-up (in $k = 1$ RCT). Relative to any control condition (standard medical care, flexibility and relaxation training, free walking), NW for 4 – 24 weeks consistently reduced the motor symptom severity, improved the walking speed and improved the gait pattern in $k = 4$ RCTs while balance and the non-motor outcomes improved less consistently (in 2/4 and in 1/2 RCTs, respectively).

Any motor benefits of NW were not maintained relative to a structured physiotherapy program BIG or unsupervised home training 16 weeks after baseline in the absence of training in $k = 1$ RCT. However, the NW group tended to have a higher quality of life and a better alertness relative to both control conditions in the same RCT.

Outcomes during NW vs. free walking ($k = 3$ studies). Biomechanical assessments of gait were conducted during NW or free walking in $k = 3$ studies (all during the ON-phases). There were some improvements in the motor outcomes (temporal organisation of gait, trunk stability, power absorption in knee on the less affected side) during NW relative to free walking in all $k = 3$ studies. Other outcomes, including walking speed, ankle and hip power profiles and the cognitive load were comparable during NW and free walking in all $k = 3$ studies.

Outcomes of NW in PD vs. healthy controls ($k = 3$ studies).

Regardless of any motor benefits of NW in PD, the motor functioning was deficient in PD patients relative to healthy controls in $k = 3$ studies. PD patients were slower at the sit-to-stand transfer after 12 weeks of NW and had worse temporal organisation of gait and power absorption during NW in all $k = 3$ studies.

Exploratory meta-analysis: outcomes post NW vs. baseline ($k = 5$ studies). The quantitative data for the most commonly assessed outcome (the motor symptom severity on UPDRS III) were reported in $k = 5$ studies while the quantitative data for all other motor or non-motor outcomes were reported in less than $k = 4$ studies. Due to such a low volume of quantitative data we conducted an exploratory meta-analysis (not controlled for the placebo effect) to quantify the change in the UPDRS III scores post vs. pre NW based on data from $k = 5$ studies (Bang and Shin, 2017; Cugusi et al., 2015; Herfurth et al., 2015; Krishnamurthi et al., 2017; Reuter et al., 2011). The approach to meta-analysis is described in the Supplementary Information File and the data included in the meta-analysis are reported in the Supplementary Information File, Table S5.

According to the random-effects meta-analysis with inverse-variance weights (Borenstein et al., 2009), there was a large reduction in the motor symptom severity after 4 – 24 weeks of NW relative to baseline in $k = 5$ studies with 84 PD patients (pooled standardised effect size: Cohen's $d = 0.89$, 95% confidence interval: 0.21 – 1.58, $p = 0.011$; Supplementary Information File, Figure S3). The inspection of the individual studies revealed that $k = 2$ out of five studies (Bang and Shin, 2017; Reuter et al., 2011) reported statistically significant reductions in the motor symptom severity with high effect sizes. Both studies were single-blind RCTs with higher study quality, evaluations during the ON-phases and either intensive (five times per week) or long (24 weeks) NW protocols. Such reductions were not observed in $k = 3$ studies without blinding, with lower study quality and/or with evaluations during the OFF-phases (Cugusi et al., 2015; Herfurth et al., 2015; Krishnamurthi et al., 2017).

4. Discussion

Our systematic review shows some benefits of NW based on data from $k = 13$ studies with 318 patients at the early stages of PD with low to moderate severity. Various motor outcomes, including the motor symptom severity, the walking speed and the gait pattern consistently improved after 4 – 24 weeks of NW relative to baseline or any control condition during the ON-phases of pharmacotherapy. There is also limited evidence that balance and the non-motor outcomes, including the quality of life, improve after NW in PD during the ON-phases. However, these immediate motor and non-motor benefits of NW were mostly absent when evaluated either during the OFF-phases or in the absence of training at the follow-up (16 – 24 weeks after baseline). While NW was well accepted and relatively safe in all studies, the clinical relevance of any benefits of NW remains unclear.

The improvement in the motor outcomes following NW is not surprising considering that NW is an aerobic exercise that aims to reduce sedentary lifestyle in people with PD. Indeed, participants reported being more physically active after participating in the studies than at baseline (Baatile et al., 2000; van Eijkeren et al., 2008). The improved mobility was also carried over to the other activities of daily life, including housework and other leisure activities (Baatile et al., 2000; Reuter et al., 2011).

The motor benefits of NW likely depend on a number of factors. First, the most consistent motor improvements were observed during the ON-phases of various antiparkinsonian medications suggesting that NW can enhance the effects of pharmacological treatment. Interestingly, one study reported that during the 12-

week protocol, 11/16 patients either maintained or reduced their stable medication doses (Krishnamurthi et al., 2017). Thus, although NW may not improve the motor functioning back to the healthy level nor replace the pharmacological treatment, the regular training may counterbalance the progression of PD and prolong the beneficial effects of the antiparkinsonian medication. Second, the demographic and the clinical characteristics of patients suggest that NW may particularly benefit people with PD who are more mobile (Herfurth et al., 2015), younger, less overweight, with less comorbidities and at the earlier illness stages. Third, the effects of NW appear to depend on the training protocol, including the level of technical skills due to the professional instruction and the regular coaching (Reuter et al., 2011) as well as the training length and intensity. Indeed, a supervised, high-intensity (five times per week for four weeks) indoor training on treadmills produced the largest reduction in the motor symptom severity in our exploratory meta-analysis (Bang and Shin, 2017).

There are various speculations regarding the possible mechanisms that facilitate the motor improvements after NW. One proposed model suggests that the conscious focus on the rhythmic movement may be regulated by the frontal cortex rather than the defective dopamine circuitry in the basal ganglia (van Eijkeren et al., 2008). NW may also improve various motor functions, including the trunk stability (Gougeon et al., 2017), the lower-body muscle flexibility (Cugusi et al., 2015), the coordination between upper and lower limbs (Bang and Shin, 2017) and the power generation and absorption in knee (Zhou et al., 2018) that together lead to better balance and mobility.

It is likely that the social and the cognitive aspects of NW play an important role in any motor improvements in PD. NW encouraged the social interactions with other PD patients leading to more acceptance of own illness and forming of walking groups beyond the study duration (Reuter and Ebersbach, 2012; van Eijkeren et al., 2008). NW is relatively simple to learn because it does not require additional cognitive load (Gougeon et al., 2017), tends to improve alertness and planning abilities (Ebersbach et al., 2014) and lowers pain (Reuter et al., 2011). Therefore, it can be speculated that the social and the cognitive aspects of NW are related to improvements in the motor functioning in PD.

Although promising, the clinical relevance of NW remains unclear for a number of reasons according to the current and the recent systematic reviews (Bombieri et al., 2017; Cugusi et al., 2017). First, our review relies on data from 13 primary studies with poor to moderate quality and small sample sizes. The majority of the studies inadequately described their methods. Thus, multiple assumptions were made regarding the NW protocols in terms of the mode of training (individual or group) and professional instruction before and during training. Since inadequate reporting of methods and results is common in primary studies and in systematic reviews regarding the complementary therapies in PD (Kedzior and Kaplan, 2019), the authors of future primary studies should include sufficient methodological details in their articles or online supplementary materials. Second, although our exploratory meta-analysis suggests that NW produced a large reduction in the motor symptom severity, the outcomes of NW were probably affected by the placebo and the expectation effects in the $k = 9$ out of the 13 studies due to the lack of randomisation, adequate control conditions or blinding of assessors. Third, the statistically significant improvements in various NW outcomes may not be clinically relevant. While the 5-point reduction in the motor symptom severity on UPDRS III was considered clinically meaningful in one RCT (Bang and Shin, 2017), most studies failed to report either the effect sizes of any improvements or adequate descriptive statistics to compute such effect sizes. A comparison of effect sizes may be more meaningful than hypothesis testing in studies with small

sample sizes and complex designs (pre- and post-data from two or more independent groups). Fourth, the longer-term maintenance of any benefits of NW may require regular and supervised training (Ebersbach et al., 2010; Krishnamurthi et al., 2017). Fifth, some benefits of NW may not be superior to other exercise programs. However, the compliance with the NW protocol was excellent suggesting that patients liked to perform this training regularly. Furthermore, NW is relatively cheap, convenient and easy to learn. Taken together, NW may contribute to the maintenance of the overall mobility at the early stages of PD in addition to pharmacotherapy. Since the quality of studies was poor to moderate, future single-blind RCTs should investigate the clinical relevance of the NW outcomes and the training parameters (mode and intensity) necessary to optimise the benefits of NW in PD.

Limitations. Although the current review is of a high methodological quality according to the AMSTAR2 scale (Supplementary Information File, Table S6) and the PRISMA Checklist (Supplementary Information File, Table S7), there are some limitations in our work. While the current review is the largest review to date with $k = 13$ studies, it includes only four new observational studies relative to the recent systematic reviews (Bombieri et al., 2017; Cugusi et al., 2017). One reason for such a small number of studies published in this field to date could be the publication bias against small studies with statistically non-significant results. Future systematic reviews should consider extending their literature searches to identify unpublished resources and/or studies in smaller journals not listed in international databases. Furthermore, our data synthesis relies on the outcomes of statistical tests in studies with small sample sizes. The outcomes of NW relative to control conditions should be quantified using a meta-analysis of post-NW outcomes controlled for baseline scores in single-blind RCTs. Our inspection of the effect sizes in five studies suggests that any heterogeneity among the immediate outcomes of NW could be explained by the training mode and intensity and the ON- or OFF-phases of the antiparkinsonian medications.

5. Conclusions

NW may contribute to the maintenance of the overall mobility at the early stages of PD in addition to pharmacotherapy. The longer-term maintenance of any motor or non-motor benefits of NW may require regular and supervised training. Although NW may not be superior to other exercise programs, it is relatively cheap, convenient and easy to learn. Since the quality of studies was poor to moderate, future single-blind RCTs should investigate the clinical relevance of the NW outcomes and the training parameters (mode and intensity) necessary to optimise the benefits of NW in PD.

Author's contributions

The first author designed the study. Both authors selected the studies, coded and synthesised all data. The first author wrote the manuscript. Both authors read and approved the final manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbmt.2020.01.003>.

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