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Jéssica Andrea Espinoza Araneda

Assimetria do balanço dos braços na doença de Parkinson e Caminhada Nórdica como estratégia de intervenção.

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Jéssica Andrea Espinoza Araneda

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BANCA AVALIADORA

_____

Dr. Luis Henrique Telles da Rosa

Departamento de Fisioterapia

Universidade Federal de Ciências da Saúde de Porto Alegre

_____

Dr. Clynton Lourenço Corrêa

Departamento de Fisioterapia

Universidade Federal do Rio de Janeiro

_____

Dr. Leonardo Alexandre Peyré-Tartaruga

Departamento de Educação Física, Fisioterapia e Dança

Universidade Federal do Rio Grande do Sul

Porto Alegre

2023

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Epígrafe

"Estar preparado é importante, saber esperar é ainda mais importante, mas aproveitar o momento certo é a chave da vida".

Arthur Schnitzler

RESUMO

A doença de Parkinson (DP) é um distúrbio neurodegenerativo crônico e progressivo, cuja prevalência está aumentando rapidamente como consequência do envelhecimento da população. O distúrbio da marcha é um dos sintomas mais comuns da doença e é a principal causa de quedas, limitação funcional e baixa qualidade de vida. Até o momento, as alterações nos parâmetros da marcha dos membros inferiores foram amplamente estudadas na DP. No entanto, o estudo do desempenho dos membros superiores durante a marcha tem recebido muito menos atenção na literatura. O balanço do braço (BB) ocorre naturalmente durante a marcha e estudos mostram que ele contribui para a recuperação da estabilidade, facilita o movimento dos membros inferiores e reduz o custo metabólico durante a marcha. Pessoas com DP geralmente apresentam diminuição da amplitude do BB no lado mais afetado do corpo, gerando assimetria do balanço do braço (ABB). Foi demonstrado que a ABB é um marcador motor precoce da doença, permitindo o diagnóstico diferencial em estágios iniciais e monitorando a progressão da doença. Além disso, as disfunções dos membros superiores são progressivas ao longo do tempo e podem afetar a qualidade da marcha, tornando seu estudo particularmente importante para melhorar o diagnóstico e o gerenciamento da DP. A caminhada nórdica (CN) é um esporte que consiste em caminhar com o uso ativo de dois bastões e, portanto, pode influenciar positivamente os parâmetros do BB e o desempenho da marcha em maior grau do que a caminhada livre. Considerando a importância dos parâmetros de BB para a marcha na DP, realizamos uma revisão sistemática com meta-análise para investigar as diferenças na ABB e em outros parâmetros de BB entre indivíduos com DP e saudáveis. Além disso, analisamos a relação entre a ABB, os parâmetros espaço-temporais da marcha dos membros inferiores e a progressão da doença. Os resultados mostraram, com moderada qualidade de evidência, que os indivíduos com DP têm maior ABB independentemente da fase da medicação (ON ou OFF) e do tipo de teste de marcha utilizado. A qualidade da evidência, muito baixa, sugere que também apresentam maior assimetria da velocidade do BB e menor amplitude tanto no braço mais afetado como no menos afetado. A meta-regressão indicou que à medida que a doença progride e os sintomas pioram, a ABB tende a diminuir. Em segundo lugar, criamos um protocolo de ensaio clínico com o objetivo de estudar os efeitos de um programa de CN sobre os parâmetros cinemáticos do BB em

comparação com a caminhada livre e sua influência no desempenho dos membros inferiores, mobilidade funcional e qualidade de vida. Este é o primeiro estudo voltado para os efeitos da CN sobre a assimetria e a amplitude do BB e sua influência sobre os parâmetros espaço-temporais da marcha, portanto, pode fornecer novas evidências para a compreensão dos efeitos da CN sobre os distúrbios da marcha na DP.

Palavras-chave: Braço; Assimetria do balanço do braço; Marcha; Doença de Parkinson, Caminhada Nórdica, Terapia de exercício, Reabilitação neurológica.

ABSTRACT

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder whose prevalence is rapidly increasing as a result of the aging population. Gait disturbance is one of the most common symptoms of the disease and is the main cause of falls, functional limitations, and poor quality of life. To date, changes in lower limb gait parameters have been widely studied in PD. However, the study of upper limb performance during gait has received much less attention in the literature. Arm swing (AS) occurs naturally during gait, and studies show that it contributes to the recovery of stability, facilitates lower limb movement, and reduces the metabolic costs of walking. People with PD generally have a decreased AS amplitude on the more affected side of the body, generating arm swing asymmetry (ASA). ASA has been shown to be an early motor marker of the disease, allowing differential diagnosis in the early stages and monitoring the progression of the disease. In addition, upper limb dysfunction is progressive over time and can affect gait quality, making its study particularly important for improving the diagnosis and management of PD. Nordic walking (NW) is a sport that consists of walking with the active use of two poles and can, therefore, positively influence AS parameters and gait performance to a greater extent than free walking. Considering the importance of AS parameters for gait in PD, we conducted a systematic review with meta-analysis to investigate the differences in ASA and other AS parameters between individuals with PD and their healthy peers. In addition, we analyzed the relationship between ASA, spatiotemporal parameters of lower limb gait, and disease progression. The results showed, with moderate quality of evidence, that individuals with PD have higher ASA independent of the phase of medication (ON or OFF) and the type of gait test used. Very low quality of evidence suggests that they also have higher ASA velocity and lower AS amplitude of both the most and least affected. Meta-regression indicated that ASA is inversely associated with disease duration and progression of motor symptoms. Secondly, we created a clinical trial protocol to study the effects of a NW program on the kinematic parameters of AS compared to free walking and its influence on lower limb performance, functional mobility and quality of life. This protocol is the first study focusing on the effects of NW on the asymmetry and amplitude of the AS and its influence on the temporospatial parameters of gait, so it may provide new evidence for understanding the effects of NW on gait disturbances in PD.

Key words: Arm; Arm swing asymmetry; Gait; Parkinson Disease, Nordic Walking, exercise therapy, neurological rehabilitation.

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CONTEXTUALIZAÇÃO

ARTIGO 1

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LISTA DE ABREVIATURAS E SIGLAS

ABB	Assimetria da Amplitude do BB
ABB	Assimetria do Balanço dos Braços
AEs	Adverse events
AS	Arm Swing
ASA	Arm Swing Asymmetry
ASI	Arm Symmetry Index
BB	Balanço dos Braços
CI	Confidence Interval
CL	Caminhada Livre
CN	Caminhada Nórdica
DP	Doença de Parkinson
FW	Free Walking
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
H&Y	Hoehn & Yahr
IMUs	Inertial Measurements Unit
iSAW	7-meter instrumented Stand and Walk Test
iTUG	Instrumented Timed Up and Go test
MDS	Sociedade Internacional de Parkinson e Distúrbios do Movimento
MMII	Membros Inferiores
MMSS	Membros Superiores
MoCA	Montreal Cognitive Assessment
NB	Núcleos Basais
NW	Nordic Walking
PD	Parkinson's disease
PDQ39	Parkinson's Disease Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Registry of Systematic Reviews
SMD	Standardized Mean Difference
SNc	Substância Negra porção *pars compacta*
SPIRIT	Standard Protocol Items for Clinical Trials
UPDRS	Escala Unificada de Avaliação da Doença de Parkinson

SUMÁRIO

1 INTRODUÇÃO

A doença de Parkinson (DP) é uma enfermidade neurodegenerativa, cuja prevalência está aumentando rapidamente. Globalmente, 9 milhões de pessoas recebem o diagnóstico da DP (1), e com o aumento da expectativa de vida na população idosa estima-se que este número ultrapasse os 12 milhões em 2040 (2). Fisiologicamente, a DP é caracterizada pela perda progressiva de neurônios dopaminérgicos na porção *pars compacta* da substância negra (SNc) do mesencéfalo, bem como pela presença de inclusões intracelulares conhecidas como corpos de Lewy em diferentes áreas cerebrais (3). Essas alterações repercutem diretamente no controle do processamento da informação pelos núcleos da base, desencadeando sinais clínicos clássicos como bradicinesia ou lentidão motora, tremor de repouso, instabilidade postural e alterações na marcha (3, 4). Os distúrbios da marcha representam o sintoma mais incapacitante nos acometidos pela DP, e são considerados um problema de saúde pública devido à sua estreita relação com quedas, dependência, baixa qualidade de vida e incapacidade física (5-7). A maioria dos estudos que abordam os distúrbios da marcha na DP referem-se principalmente às alterações nos parâmetros espaço-temporais e cinemáticos dos membros inferiores (MMII), os quais têm sido amplamente caracterizados (8, 9). No entanto, o estudo das alterações nos membros superiores (MMSS) é comparativamente muito menor, apesar de os MMSS desempenharem um papel importante na locomoção (10).

O balanço do braço (BB) é uma característica biomecânica específica da marcha humana e desempenha um papel importante na recuperação da estabilidade da marcha após uma perturbação (11). Além disso regula o movimento rotacional do corpo, promove a estabilidade dinâmica, e reduz o custo metabólico da caminhada (12-14). Estudos prévios mostraram que indivíduos com DP apresentam alterações significativas no movimento do BB, mesmo em estágios iniciais da doença (11, 15, 16). Essas alterações são caracterizadas por uma redução da amplitude e da velocidade máxima do BB, principalmente no lado mais afetado (17), o que resulta em uma assimetria entre os MMSS (18, 19). Curiosamente, estas alterações demonstraram ser resistentes à terapia dopaminérgica (20, 21). A assimetria da amplitude do BB (ABB) é uma característica relevante (22), podendo ser um marcador motor precoce para o diagnóstico e monitoramento da progressão da DP (23-25).

A reabilitação da marcha na DP centra-se frequentemente no treino do MMII e negligencia o papel dos MMSS (26). A ABB implica maior risco de queda (12, 27), maior custo energético e risco de congelamento da marcha (28). Nesse sentido, é importante a incorporação de estratégias de reabilitação que visem otimizar o BB e reduzir a assimetria. Melhorar os parâmetros do BB, principalmente amplitude e simetria, poderia contribuir para diminuir o momento angular em torno da vertical, e momento vertical de reação do solo, aumentando a velocidade da caminhada e o comprimento da passada, promovendo estabilidade e diminuindo o custo energético durante a caminhada (12, 14, 27, 29).

A caminhada nórdica (CN) é uma atividade física desportiva de natureza aeróbica, que se caracteriza pela caminhada com a utilização ativa de dois bastões, que gera uma demanda energética e mecânica tanto dos MMSS como dos MMII durante a sua prática (30, 31). O uso de bastões promove aumento na amplitude dos movimentos dos braços durante a caminhada, favorece a ativação muscular do MMSS, gerando ao mesmo tempo maior consumo energético com menor fadiga quando comparado a caminhada livre (CL) ou em esteira (32-34). Estudos mostram que a CN melhora os sintomas motores, o equilíbrio e os parâmetros da marcha relacionados aos MMII na DP (35-37). Desta forma, a CN pode ser uma atividade bastante promissora como estratégia para a reabilitação de pessoas com DP, especialmente nos parâmetros dos MMSS.

As disfunções do MMSS na DP são progressivas ao longo do tempo e podem deteriorar a qualidade da marcha (12, 19) Acreditamos que a investigação de tal característica seja relevante para facilitar o diagnóstico, monitoramento e tratamento da doença. Considerando que a CN favorece o uso ativo dos braços durante a caminhada, é possível levantar a hipótese de que um programa de treinamento CN em pessoas com DP poderia reduzir a assimetria e aumentar a amplitude do BB durante a caminhada e influenciar positivamente no desempenho dos MMII durante a marcha. A marcha é um componente essencial da mobilidade funcional e qualidade de vida (38). A mobilidade funcional é a capacidade fisiológica das pessoas de se movimentarem de forma independente e segura em vários ambientes para realizar suas atividades de vida diária e participar da comunidade (39). Portanto, as ações voltadas para a otimização da marcha, como a CN, poderiam melhorar a mobilidade funcional, o estado de saúde e a qualidade de vida das pessoas com DP.

Dentro desse contexto, o objetivo geral desta tese foi investigar a diferença na ABB entre indivíduos com e sem diagnóstico de DP, e estabelecer a relação com parâmetros espaço-temporais da marcha e progressão da doença. Também objetivamos criar um protocolo para um ensaio clínico randomizado que nos permita avaliar os efeitos de um programa de treinamento de CN e de CL nos parâmetros cinemáticos do BB e sua influência no desempenho do MMII, mobilidade funcional e qualidade de vida de pessoas com DP.

2 REVISÃO DE LITERATURA - CONTEXTUALIZAÇÃO

2.1 Doença de Parkinson

A doença de Parkinson (DP) é uma síndrome neurológica clínica crônica, progressiva, de início na idade adulta, com diversas causas e apresentações clínicas (40). Sua principal característica é a morte neuronal progressiva da substância negra, com consequente diminuição do neurotransmissor dopamina, causando alterações motoras típicas, como lentidão motora ou bradicinesia, tremor de repouso, rigidez e instabilidade postural (4). A idade média de início dos sintomas é aproximadamente 60 anos (41), com duração média do diagnóstico final até a morte de 10 anos (42).

2.2 Epidemiologia

Atualmente, a DP é a segunda doença neurodegenerativa mais prevalente depois da doença de Alzheimer (43) e estima-se que tanto a incidência como a prevalência global desta doença aumentem rapidamente, como consequência do crescimento populacional, já que a idade é o principal fator de risco (40, 44). No Brasil, a notificação da DP não é obrigatória, portanto, não há dados precisos sobre sua prevalência. De acordo com um estudo realizado numa cidade do interior do estado de Minas Gerais-Brasil, 3,3% das pessoas com mais de 60 anos têm DP, pelo que, extrapolando este valor para a população brasileira, mais de 630.000 pessoas teriam a doença (45, 46). No Chile, entre o período 1990-2016, a prevalência da DP aumentou 19,9%, colocando o Chile como o país latino-americano que registrou o maior aumento desta doença, seguido pelo Paraguai, El Salvador e Honduras (47). Neste contexto, a DP constitui atualmente um importante problema de saúde pública,

sendo que há perspectiva de que haja um aumento crescente de indivíduos acometidos pela doença em todo o mundo, exigindo, portanto, uma atenção aos impactos à nível populacional e econômico (40).

2.3 Etiopatogenia e fisiopatologia da Doença de Parkinson

Em 1817, o médico inglês James Parkinson descobriu pela primeira vez esta síndrome clínica chamada *Paralysis Agitans (*Parkinson*, 2002*) e mais tarde, em 1861, foi chamada de Doença de Parkinson por Jean-Martin Charcot, em homenagem ao seu descobridor (48). Sua etiologia permanece obscura e controversa. Em termos gerais, estudos acreditam que a DP pode ser decorrente da interação de fatores, sejam eles genéticos, ambientais, alterações mitocondriais, neuroinflamação, estresse oxidativo e alterações do próprio envelhecimento (40, 41, 49-51). Acredita-se que etiopatogenia seja multifatorial, ou seja, a combinação de predisposição genética com a presença de fatores tóxicos ambientais, além disso há contribuição do envelhecimento cerebral associada à perda neuronal progressiva (52).

A base fisiológica da DP é a disfunção dos núcleos basais (NB) devido à depleção de dopamina, um neurotransmissor do tipo catecolamina, cuja deficiência leva a uma cascata de alterações funcionais no circuito dos NB, que são, em última instância, responsáveis para o desenvolvimento das características cardinais da DP (53). Os NB são estruturas neurais subcorticales, incluem o estriado (caudado e putâmen), o globo pálido interno e externo, o núcleo subtalâmico, e o núcleo ventro-lateral do tálamo. Do ponto de vista funcional, essa rede interconectada inclui a SNc e a substância negra reticulada no mesencéfalo, e juntos eles desempenham uma variedade de funções, como programar e automatizar o movimento, seja ativando ou inibindo os movimentos (53). Além disso, eles têm uma importante participação em processos cognitivos. Os NB são segregados anatomicamente em circuitos: Motor, oculomotor, límbico e associativo ou cognitivo (53, 54).

2.4 Diagnóstico da doença de Parkinson

O diagnóstico da DP é clínico, sendo os sinais motores a base do diagnóstico. Os critérios aceitos para o diagnóstico da DP baseados em sinais clínicos foram introduzidos pela UK Parkinson Disease Society - Brain Bank (55) (Tabela 1).

Tabela 1

Critérios para o diagnóstico da DP UK Parkinson Disease Society - Brain Bank

I	A presença de bradicinesia (diminuição progressiva da amplitude e/ou velocidade do movimento) e pelo menos um outro sinal motor como: tremor de repouso, rigidez muscular e/ou instabilidade postural (não devido a alterações visuais, cerebelares, vestibulares ou proprioceptivas).
II	A ausência de critérios de exclusão da DP (outras causas que explicam os sinais e sintomas).
III	A existência de elementos característicos da doença durante o seguimento que apoiam o diagnóstico, tais como: início unilateral, curso progressivo, assimetria mantida dos sinais motores com maior envolvimento de um lado do corpo, resposta benéfica à terapia com levodopa e duração da doença superior a 10 anos.

A Sociedade Internacional de Distúrbios do Movimento (MDS) publicou em 2015, uma versão atualizada dos critérios de diagnóstico clínico da doença de Parkinson, conhecidos como Critérios de Diagnóstico Clínico da MDS para a Doença de Parkinson (MDS Clinical Diagnostic Criteria for Parkinson's Disease), com o objetivo de contribuir para o diagnóstico clínico padronizado tanto para a pesquisa quanto para a prática clínica. Os critérios incluem um processo de diagnóstico em duas etapas. Identificação do parkinsonismo, por meio da presença de bradicinesia com fadiga, além de rigidez ou tremor de repouso e 2. Determinação da DP como a causa do parkinsonismo. Essa última etapa se baseia em três elementos diagnósticos: critérios de apoio ao diagnóstico (características típicas da DP, que estão presentes em muitos pacientes, mas não em todos), critérios de exclusão absoluta (características que descartam a provável DP) e sinais de alerta (características que argumentam contra a DP, mas não são suficientes para descartar a provável DP). Os sinais de alerta podem ser equilibrados por critérios de apoio, de modo que a documentação de um critério de apoio pode compensar um sinal de alerta (Postuma et al.; 2015)

A DP é caracterizada como uma doença progressiva e geralmente o diagnóstico é feito quando sinais motores da doença se tornam evidentes (41). Entretanto já são identificados sinais de neurodegeneração em outras áreas do cérebro nas fases iniciais da doença quando os sinais motores clássicos não estão visíveis. Tais degenerações neuropatológicas resultam em sintomas não motores como sintomas neuropsiquiátricos, distúrbios do sono, sintomas autonômicos, gastrointestinais e sensoriais (56). Nesse sentido, a Sociedade Internacional de Parkinson e Distúrbios do Movimento (MDS) propôs 3 estágios para as fases iniciais da doença (57), em que aspectos motores e não motores podem estar presentes, mas ainda não são suficientes para estabelecer um diagnóstico (Tabela 2).

Tabela 2

Estágios para as fases iniciais da doença de acordo com a MDS

Estágio	Descrição
1.DP pré-clínica	Processo degenerativo já começou, mas os sinais e sintomas clássicos ainda não são evidentes
2. DP pro-drômica	Sinais e sintomas presentes, mas ainda insuficientes para o diagnóstico
3. DP em fase clínica	Sinais e sintomas clássicos estão presentes

Para as fases clínicas foram desenvolvidos instrumentos que permitem classificar as fases da doença com base principalmente em sinais e sintomas motores. A escala Hoehn & Yahr (H&Y) é um instrumento que mede o grau de incapacidade e classifica os pacientes em cinco estágios (58) (Tabela 3).

Tabela 3

Escala Hoehn & Yahr (H&Y)

Estágio	Descrição
Estágio 0	Nenhum sinal do quadro do paciente.
Estágio 1	Doença unilateral
Estágio 2	Envolvimento bilateral sem deficiência de equilíbrio
Estágio 3	Envolvimento bilateral leve a moderado, instabilidade postural, mas o paciente mantém a capacidade de viver de forma independente
Estágio 4	Deficiência grave, mas ainda capaz de ficar em pé e andar com ajuda
Estágio 5	Confinamento ao leito ou cama, a menos que seja assistido

A Revisão da Escala Unificada de Avaliação da Doença de Parkinson (MDS-UPDRS) patrocinada pela Sociedade de Distúrbios do Movimento (MDS) é um instrumento confiável e válido para monitorar a progressão da doença (59). Avalia os sinais, sintomas e determinadas atividades dos indivíduos por meio de autorrelato e observação clínica. É composto por 62 itens, divididos em quatro domínios (I: Experiências não motoras da vida diária; II: Experiências motoras da vida diária; III: Exame motor; IV: Complicações motoras). A classificação de cada item varia de 0 a 4 pontos, sendo que o valor máximo indica maior comprometimento e o mínimo, normalidade (59).

2.5 Tratamento medicamentoso na doença de Parkinson

Ainda não há tratamento disponível para curar a DP. O tratamento convencional visa reduzir os sintomas motores da doença, como bradicinesia, rigidez e tremor (60). Como primeira opção, o tratamento consiste na administração de levodopa (L-dopa), mas com o passar do tempo o tratamento perde eficácia, possivelmente porque a morte neuronal continua e, portanto, a dosagem deve ser aumentada (60) . Além disso, o tratamento crônico com L-Dopa (5-10 anos), gera alguns efeitos colaterais, como discinesias (entendidas como movimentos paradoxais anormais e exagerados, como tiques ou contrações e espasmos musculares distônicos) (61), que afetam seriamente as atividades diárias dos pacientes (62, 63). As discinesias ocorrem como parte de um fenômeno caracterizado por flutuações

motoras, quando a eficácia do tratamento com levodopa começa a diminuir ao longo do dia (64). De acordo com isso, diferenciam-se os estados “ON”, onde a resposta motora ao tratamento com L-dopa é máxima, e os estados “OFF”, onde seu efeito terapêutico é menor (65). Outros tratamentos, orais, transdérmicos ou subcutâneos, são inibidores da MAO-B, agonistas da dopamina, inibidores da COMT, amantadina ou anticolinérgicos (66). Outras terapias de segunda linha são a cirurgia funcional nos NB (estimulação cerebral profunda) e a infusão contínua de medicamentos como apomorfina ou levodopa (41). O início de uma ou outra terapia depende dos sintomas do paciente e às vezes é necessário agregar outros tratamentos para tratar aspectos não motores da doença, como antidepressivos ou analgésicos (67).

2.6 Tratamento não farmacológico – Reabilitação

Até agora, o tratamento farmacológico não é suficiente para impedir a evolução da doença, que é progressivamente incapacitante, principalmente quando os medicamentos já não são eficazes. Neste sentido, a reabilitação é essencial, é amplamente recomendada (66, 68) e tem como principal objetivo melhorar e/ou manter a qualidade de vida das pessoas com DP, ajudando a aumentar a mobilidade, melhorar o equilíbrio, a coordenação e manter a autonomia do paciente (69). Neste sentido, existe um conjunto crescente de evidências que revelam os benefícios da fisioterapia e do exercício para atenuar sinais motores e não motores, melhorar a função física e reduzir a incapacidade (69), principalmente através de estratégias direcionadas para melhorar postura, equilíbrio, marcha e capacidade física (5, 69).

2.7 Distúrbios da marcha na doença de Parkinson

Os distúrbios da marcha na DP são um dos sintomas mais comuns e incapacitantes da doença, e estão relacionados com quedas, limitação funcional e perda de qualidade de vida (5-7, 70).

O comprometimento da marcha está relacionado a conexões disfuncionais entre as regiões do NB, Área motora suplementar e mesencéfalo (71), o que altera a geração e execução de sequências motoras necessárias aos movimentos sequenciais e rítmicos da caminhada (72). O comprometimento de MMII e as alterações na marcha têm sido amplamente descritas na literatura (8, 9). Uma revisão sistemática, que

reuniu informações de 72 estudos e um total de 1.510 pessoas com DP e 1.517 indivíduos saudáveis, mostrou que pessoas com DP, em comparação com indivíduos saudáveis, apresentam menor velocidade autosselecionada, comprimento do passo, ritmo de equilíbrio e excursão do quadril, bem como maior cadência e ritmo de duplo apoio durante a caminhada. Essas mudanças não foram influenciadas pela idade, duração da doença, estágio da doença medido pelo H&Y e sintomas da doença medidos pela UPDRS (8).

A maioria dos estudos que analisam o comprometimento da marcha na DP concentram-se nos parâmetros espaço temporais e cinemáticos, principalmente relacionado aos MMII (7, 8, 73). Embora os braços desempenhem um papel importante na locomoção bípede (10), a análise dos parâmetros MMSS e o seu impacto na marcha em indivíduos com DP tem recebido menos atenção na literatura científica. O balanço dos braços (BB) é uma característica distintiva da marcha humana e é definido como um movimento rotacional rítmico dos braços, ocorrendo livremente no espaço, em direções opostas, principalmente no plano sagital durante a caminhada e corrida bípede (22). Estudos anteriores relatam que o BB contribui para a recuperação da estabilidade após uma perturbação, facilita o movimento das pernas e reduz o custo metabólico da caminhada (11-13).

A DP é por definição uma doença assimétrica. A diminuição da amplitude de BB é um dos sintomas mais frequentemente relatados (16, 21) e ocorre inicialmente no lado mais afetado do corpo. Esta diferença no movimento do BB entre o lado direito e esquerdo é conhecida como assimetria do BB (ABB) e é particularmente relevante (22). A ABB, diferentemente de outros parâmetros, tem sido considerada um marcador precoce de disfunção motora na DP, contribuindo assim para o diagnóstico precoce e diferencial, bem como para o monitoramento da progressão da doença (23, 24, 74). Além disso, é um preditor independente de quedas (12, 27) e implica um risco aumentado de desenvolvimento de congelamento da marcha (28). Curiosamente, alterações no BB demonstram ser resistentes à medicação dopaminérgica (Espinoza-Araneda et al., 2023; Navarro-López et al., 2022). Nesse sentido, é relevante a incorporação de estratégias de reabilitação que visem a otimização do BB e a redução de sua assimetria em pessoas com DP.

2.8 Caminhada Nórdica como estratégia de intervenção

Caminhada Nórdica (CN) é uma atividade física esportiva que tem origem no esqui de fundo na Finlândia na década de 1930 (Zurawik, 2016). É uma atividade principalmente de resistência aeróbica e consiste na realização de caminhada natural com o uso ativo de dois bastões, especialmente projetados para isso, que exige energética e mecanicamente tanto os MMSS quanto os MMII durante sua prática (Morsø, Hartvigsen, Puggaard, & Manniche, 2006; van Eijkeren et al., 2008).

Entre as inúmeras estratégias de reabilitação para a DP, a CN tem recebido atenção especial como uma alternativa emergente e promissora para estimular um estilo de vida ativo (31, 75), promover a melhora da marcha, da participação social, ea qualidade de vida em pessoas com DP (76-78). O uso dos bastões promove aumento do movimento do braço durante a caminhada, favorece a ativação muscular dos MMSS e envolve coordenação intencional entre os MMSS e os MMII, o que constitui uma opção interessante para otimizar os parâmetros da marcha dos membros superiores e inferiores, ao contrário da caminhada livre (CL) ou da caminhada em esteira (31, 33, 34, 79). Além disso, o uso dos bastões de forma rítmica pode atuar como uma pista sensorial, ativando circuitos intactos e evitando circuitos defeituosos dos NB, favorecendo a coordenação intersegmentar, organização temporal da marcha e estabilidade médio lateral (31, 78). Com base no exposto, é possível levantar a hipótese de que a CN poderia otimizar os parâmetros do BB, aumentando a amplitude e reduzindo a assimetria durante a caminhada em maior proporção quando comparado a CL. Além disso, melhorias no BB poderiam influenciar positivamente a execução dos MMII durante a caminhada, aumentando a velocidade, o comprimento do passo, a mobilidade funcional e assim contribuir para uma melhor qualidade de vida das pessoas com DP.

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4. OBJETIVOS

Artigo 1

Investigar a diferença na assimetria do balanço dos braços entre indivíduos com DP e pessoas saudáveis, e estabelecer a relação com parâmetros espaço temporais da marcha e progressão da doença.

Artigo 2

Criar um protocolo de ensaio clínico randomizado que permita avaliar os efeitos de um programa de treinamento de CN e de CL nos parâmetros cinemáticos do balanço dos braços e sua influência no desempenho dos membros inferiores mobilidade funcional e qualidade de vida de pessoas com DP.

5 ARTIGO 1

Arm Swing Asymmetry in People with Parkinson's disease and its Relationship with Gait: A Systematic Review and Meta-analysis

(Aceito para publicação no periódico Brazilian Journal of Physical Therapy – *Qualis A2, Fator de Impacto 3.4*)

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Arm Swing Asymmetry in People with Parkinson's disease and its Relationship with Gait: A Systematic Review and Meta-analysis

--Manuscript Draft--

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Corresponding Author:	Aline Pagnussat Federal University of Health Sciences of Porto Alegre Porto Alegre, Rio Grande do Sul BRAZIL
First Author:	Jéssica Andrea Espinoza Araneda, MSc
Order of Authors:	Jéssica Andrea Espinoza Araneda, MSc
	Cristian Alejandro Caparros Manosalva, MsC
	Paula Caballero Moyano, PhD
	Maira Jaqueline da Cunha, PhD
	Ritchele Redivo Marchese, MsC
	Aline Souza Pagnussat, PhD
Abstract:	Background: Individuals with Parkinson's disease present arm swing alterations that can adversely affect their locomotion. Objective: To identify differences in arm swing asymmetry (ASA) between individuals with Parkinson's disease (PD) and healthy individuals and to investigate the relationship between ASA, temporal-spatial gait parameters, and disease progression. Methods: A literature search was conducted in PubMed, Scopus, ProQuest, Web of Science, and EBSCOhost up to February 2023. Cross-sectional studies evaluating parameters of arm swing (AS) and ASA were included. Methodological quality was assessed using the Critical Appraisal Checklist, and the quality of the evidence was measured with a modified Grading of Recommendations Assessment, Development, and Evaluation. Results: Fourteen studies were included in the systematic review (1130 participants). Irrespective of the medication phase (ON or OFF) and the type of walk test employed, the meta-analysis showed moderate-quality evidence that individuals with PD have increased ASA amplitude (SMD= 0.84; 95% CI: 0.69, 0.99; I^2= 0%).Very low-quality evidence suggests higher ASA velocity (SMD=0.64; 95% CI:0.24, 1.05; I^2=59%) and lower AS amplitude on both the most affected (ES= -1.99, 95% CI:-3.04, -0.94, I2: 91%) and the least affected sides (ES=-0.75, 95% CI: -1.05, -0.44; I^2=66%). Meta-regression indicated that ASA is inversely related to disease duration (Z: -2.4892, P< .05) and motor symptoms progression (Z: -2.1336, P< .05). Conclusions: Regardless of the medication phase and the type of walk test employed, individuals with PD exhibited greater ASA and decreased AS amplitude than healthy individuals. ASA decreases as the disease progresses and symptoms worsen.
Suggested Reviewers:	
Opposed Reviewers:	
Response to Reviewers:	

Arm Swing Asymmetry in People with Parkinson's disease and its Relationship with Gait: A Systematic Review and Meta-analysis

Running title: “Arm swing asymmetry in Parkinson´s disease”

Authors: Jessica Espinoza-Araneda,[a,b], Cristian Caparrós-Manosalva,[a,b], Paula M Caballero,[b], Maira J da Cunha,[a,c], Ritchele R Marchese,[a,c], Aline S Pagnussat,[a,c,*].

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[a]Rehabilitation Sciences Graduate Program, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS, Brazil.

[b]Department of Human Movement Sciences, Faculty of Health Sciences, University of Talca, Talca, Chile

[c]Movement Analysis and Neurological Rehabilitation Laboratory, Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Porto Alegre, RS, Brazil.

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***Corresponding author:**

Aline Souza Pagnussat

Universidade Federal de Ciências da Saúde de Porto Alegre. 245, Sarmento Leite Street

Zip Code: 90050-170. Porto Alegre RS, Brazil. Phone: + 55-51-3303 8912. e-mail: alinespagnussat@gmail.com

ABSTRACT

Background

People with Parkinson's disease have alterations of the arm swing which is detrimental to walking.

Objective: To identify differences in arm swing asymmetry (ASA) between individuals with Parkinson's disease (PD) and healthy individuals and to investigate the relationship between ASA, temporal-spatial gait parameters, and disease progression.

Methods: A literature search was conducted in PubMed, Scopus, ProQuest, Web of Science, and EBSCOhost up to February 2023. Cross-sectional studies evaluating parameters of arm swing (AS) and ASA were included. Methodological quality was assessed using the Critical Appraisal Checklist, and the quality of the evidence was measured with a modified Grading of Recommendations Assessment, Development, and Evaluation.

Results: Fourteen studies were included in the systematic review (1130 participants). Irrespective of the medication phase (ON or OFF) and the type of walk test employed, the meta-analysis showed moderate-quality evidence that individuals with PD have increased ASA amplitude (SMD= 0.84; 95% CI: 0.69, 0.99; I^2= 0%).Very low-quality evidence suggests higher ASA velocity (SMD=0.64; 95% CI:0.24, 1.05; I^2=59%) and lower AS amplitude on both the most affected (ES= -1.99, 95% CI:-3.04, -0.94, I^2: 91%) and the least affected sides (ES=-0.75, 95% CI: -1.05, -0.44; I^2=66%).

Meta-regression indicated that ASA is inversely related to disease duration (Z: -2.4892, P< .05) and motor symptoms progression (Z: -2.1336, P< .05).

Conclusions: Regardless of the medication phase and the type of walk test employed, individuals with PD exhibited greater ASA and decreased AS amplitude than healthy individuals. ASA decreases as the disease progresses and symptoms worsen.

Keywords: Arm; Arm swing asymmetry; Gait; Parkinson Disease.

HIGHLIGHTS

- People with Parkinson´s disease (PD) has greater arm swing asymmetry than healthy individuals.
- People with PD have lower arm swing (AS) amplitude than healthy individuals.
- As PD progresses, symptoms worsen and gait cadence increases, AS asymmetry decreases.
- AS asymmetry and AS are relevant motor parameters for gait rehabilitation in PD.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that is rapidly increasing globally and is one of the leading causes of disability.[1] Epidemiological studies report that approximately nine million people have PD worldwide,[2] and this number is expected to double by 2040.[3] The progressive deterioration of dopaminergic neurons in the substantia nigra disrupts the function of the basal ganglia and results in clinical symptoms such as bradykinesia, rest tremor, rigidity, postural instability, and gait abnormalities.[4]

Gait abnormalities are common in PD and can be considered a public health concern due to their association with falls, dependence, and diminished quality of life.[5 6] Most studies on PD and gait impairments focus on lower limb temporospatial parameters and function.[7-9] In contrast, there are far fewer studies examining upper limb parameters and their impact on gait, despite the significant role of the upper limbs in bipedal locomotion.[10]

Regarding the upper limbs, modifications in arm swing (AS) parameters such as asymmetry and reduced amplitude, whether related to angular or linear displacement, are among the most frequently reported in people with PD.[11] AS refers to the natural swinging motion of the arms while walking and running, which mainly occurs in the sagittal plane.[12] AS contributes to the recovery of gait stability after a disturbance, favors the global stability of human gait, facilitates leg movements, and reduces the metabolic cost of walking.[10 13-17] AS abnormalities are present even in the early stages of the PD[18] and may be used as an independent predictor of falls in people with the disease.[12 15 19 20] The decrease in AS amplitude mainly occurs in the most affected side of the body and generates significant movement asymmetry.[12] The difference in the swinging motion between the left and right arms, known as arm

swing asymmetry (ASA), is particularly relevant. Among other gait parameters, ASA has been proposed as a more dependable indicator of motor dysfunction for early and differential diagnosis and for tracking the progression of PD over time.[21 22] Previous studies have demonstrated significant differences in ASA between individuals with early-stage PD and healthy individuals,[21] indicating its potential as a diagnostic tool. As upper limb dysfunctions are progressive over time, they can impact overall gait quality, making their study particularly relevant to improving the diagnosis and management of PD. However, the relationship between ASA, lower limb gait parameters, and the progression of PD requires further investigation.

Considering the importance of AS parameters for gait performance, especially in people with PD, this study investigated the differences in ASA and other AS parameters (ASA velocity and AS amplitude) between individuals with PD and their healthy counterparts. Additionally, we analyzed the relationship between ASA, lower limb spatiotemporal gait parameters, and disease progression.

METHOD

Data Sources and Searches

This study followed the recommendations for systematic reviews and meta-analysis contained in the PRISMA guidelines,[23] Cochrane Collaboration,[24] and the Guide for Meta-Analysis and Systematic Reviews of Observational Studies (MOOSE).[25] The study protocol was pre-registered in the International Prospective Registry of Systematic Reviews (PROSPERO Protocol n °CRD42022299839) before the data collection.

A systematic search was conducted in the PubMed, Scopus, ProQuest, Web of Science, and EBSCOhost databases between December 2020 and February 2023. For the literature search, the Boolean operator AND was used to combine specific search terms such as “Parkinson's Disease” and “arm swing”. Within these terms, additional synonyms or associated terms were combined using the OR operator (Supplementary material – Table S.1). Only potential original studies were considered. We did not include data from conferences, theses, dissertations, or non-peer-reviewed/unreviewed/unrefereed preprints.

Eligibility Criteria

Cross-sectional studies and clinical trials were considered (in the latter case, only baseline data were extracted), with no restriction on language or year of publication. The inclusion criteria were samples of people with PD of any age, sex, time of diagnosis, disease status and medication regimen, who were evaluated during either the ON or OFF medication phases; the presence of a group of healthy individuals matched by age and sex; and an evaluation of the temporospatial parameters of the AS, undertaken either in free or treadmill walking. The exclusion criteria were duplicate data, outcomes of interest not measured or not reported, samples of participants with secondary Parkinsonism and/or using deep brain stimulation devices.

Study Selection

The double selection method was used to identify relevant studies for the research. Two researchers (JAEA and CACM) conducted the first selection by independently reviewing titles and abstracts and removing duplicates. The remaining

studies were evaluated in the second selection by reading the full text and applying eligibility criteria. Any reviewer disagreements were resolved by consensus or by involving a third reviewer, PMCM.

Data Extraction and Quality Assessment

Two reviewers independently extracted data from the selected studies using a standardized form. The extracted data were: age, sex distribution, Hoehn and Yahr stage (H&Y), Unified Parkinson's Disease Rating Scale (UPDRS) part III-motor examination, disease duration, the pharmacological condition during evaluation (ON, OFF, or not treated) and outcome measures (ASA amplitude [%], ASA velocity [%], AS amplitude [in degrees/meters] on the most and less affected sides) and methods used for data acquisition, as well as the processing of AS and gait temporospatial variables. When confusing or incomplete data were found, the corresponding author was contacted by e-mail. The data were excluded from the analysis if the authors did not respond.

The methodological quality was analyzed using the Critical Appraisal Checklist from the Joanna Briggs Institute recommended for analytical cross-sectional studies.[26] The following criteria were qualitatively evaluated: clarity of the definition of the inclusion criteria, detail of the description of the included subjects, validity, and reliability of the exposure measures, objectivity and standardization of the criteria used to measure the treatment condition of confounding factors, validity, and reliability of outcome measures and adequate statistical analysis. For the risk of bias assessment, each component was evaluated and given a rating of "yes," "no," "unclear," or "not applicable." Based on the ratings, the risk of bias was categorized as high if three components received a "yes" rating, moderate if four to six

components received a "yes" rating, and low if seven to eight components received a "yes" rating.[26 27]

A modified version of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of the body of evidence of observational data.[28 29] The levels were categorized as “High,” “Moderate,” “Low,” and “Very Low”.[30 31] Because descriptive studies were included in each meta-analysis, all were initially categorized as “low.” The following criteria downgraded the quality of the evidence: (1) Risk of bias of included studies (if 25% or more of the included articles present a high risk of bias, that is, a lower score or equal to three points on the Critical Appraisal Checklist from the Joanna Briggs Institute), (2) Inconsistency (if I^2 was 50% or greater), (3) Indirectness (if the participants or outcomes of the included studies were heterogeneous); (4) Imprecision (if there was a wide 95% confidence interval including higher and lower AS parameters in either direction) and (5) Risk of publication bias (if Egger test p-value < 0.05). The level of certainty of the evidence was upgraded by one grade if there was a more significant effect size, and the meta-analysis did not present any previous limitation or bias that lowers the quality of evidence.[29 31]

Data Synthesis and Analysis

The mean and standard deviation of each AS parameter and the number of PD and healthy individuals were computed to estimate the pooled effect size. The median and interquartile range data were converted to the average and standard deviation following the formula from Luo et al.[32] and Wan et al.[33] The meta-analysis results are presented as the standardized mean differences, and the calculations were performed using the random-effects model. The Cochrane Q and I2

inconsistency tests assessed statistical heterogeneity between studies, whereby an I^2 index greater than 25% indicated moderate heterogeneity, while over 50% was classified as high heterogeneity.[24]

Based on the diversity of protocols used to assess AS parameters, we conducted a sensitivity analysis in which the medication status (ON/OFF) and the walking test used (free walking, iSAW or treadmill) were considered.

To determine potential moderating variables, we also performed a meta-regression for ASA, in which we considered the findings for disease duration, motor symptoms progression (UPDRS part III - motor examination), gait cadence, and stride length.

The publication bias was assessed using the Egger test in the linear regression analysis of the asymmetry of the Funnel plot.[34] The results of the meta-analyses are presented in the Forest plot as the standardized mean difference (SMD) with its corresponding 95% confidence interval (CI). The SMD was used to determine the overall effect size, interpreted according to Cohen[35] as follows: 0.2 - 0.5: small effect, 0.5 - 0.8: medium effect, and 0.8 or higher: large effect size. All statistical analyses were conducted using R v4.0.5 and Review Manager 5.4 software, with a significance level set at $P< 0.05$.

RESULTS

Study Selection

The electronic search strategy identified 539 studies. After screening titles and abstracts, we discarded 310 studies because they did not meet the eligibility criteria. The full text of thirty- nine articles was read, with twenty-five being excluded

because they a) included a sample of people evaluated after deep brain stimulation; b) did not report the AS temporal-spatial data; c) presented duplicate data from previous studies; and d) included participants without PD diagnosis (Figure 1). Thus, fourteen studies met the selection criteria and were considered in this systematic review. One study did not fully report the results related to the variable of interest.[21] We contacted the author by e-mail, with no response. Therefore, this study was excluded from the main analysis.

Study Characteristics

Fourteen studies were included for qualitative analysis, providing data from 1130 participants (Table 1). Regarding the distribution, 718 belonged to the PD group and 412 to the healthy control group. The mean age of participants ranged from 52.8 to 68.9 years. Most studies used H&Y to determine the stage of PD. The stages were presented as an average (between 1.3 and 2.6) or as a range (between I-IV). The average time of PD diagnosis ranged from 1.14 to 11.2 years. Most studies reported the degree of motor impairment using the UPDRS part III - motor examination. The average range was between 14 and 36.8 points in the ON medication phase and between 10 and 46.6 points in the OFF phase. One study did not report UPDRS data.[36]

Four studies evaluated participants during the ON-medication phase,[18 22 37 38] four during the OFF phase,[21 39-41] four during both phases[42-45] and two studies incorporated participants with untreated PD.[36 46] The walking tests used to measure AS parameters varied widely between studies. Four studies used the 7-meter instrumented Stand and Walk Test (iSAW) and instrumented Timed Up and Go test (iTUG),[42-44 46] eight studies used a free-walking test (range between 4 and 402

meters),[18 21 22 37-40 45] and two studies used a treadmill with a speed range between 2 km/h and 4 km/h; in these two latter cases, only data obtained at 3 km/h were considered in our analysis based on the average free walking speed reported for people with PD.[47] Regarding the instruments used to measure the AS parameters, five studies used inertial sensors, [42-46] six studies used camera systems,[18 21 22 37 39 40] two studies used ultrasonic emitters,[36 41] and one study used an optic sensor.[38]

Risk of Bias

The median Joanna Briggs Institute Critical Appraisal Checklist tool score was 6 (ranging from 5 to 8), which characterizes a moderate risk of bias (Supplementary material – Table S.2). The questions that received more "no" answers, indicating study limitations, were: "were the criteria for inclusion in the sample clearly defined?"[18 21 36 37 42 44-46] and “were the study subjects and the setting described in detail?[18 21 36 41 42 44-46] Other less frequent problems were observed in the questions: were strategies to deal with confounding factors stated?”[37 38 40 46] and “was appropriate statistical analysis used?”.[41 44]

Quantitative analysis

Among the fourteen studies selected for the systematic review, nine analyzed the ASA during walking based on the amplitude of motion measured in degrees and were incorporated into the meta-analysis.[18 22 36 38-43] The studies by Curtze et al.[42] and Gera et al.[43] included two independent groups with PD (Mild/severe and PD-gene mutations/PD-non gene mutations, respectively) and were evaluated under two different conditions (ON/OFF); therefore, four different pairwise comparisons were considered. The sample sizes of shared groups were divided approximately equally

between the comparisons keeping the means and standard deviation, according to the Cochrane recommendations for including several study groups.[48] Studies by Liu et al.,[40] Mirelman et al.,[18] and Roggendorf et al.[41] included two independent groups with PD (PD stage I-II/III-IV; PD-gene mutations/PD-no gene mutations and PD stage I/II, respectively); therefore, two different pairwise comparisons were considered. The control group sample sizes were distributed proportionally for each comparison.[48] The meta-analysis showed with moderate quality of evidence that people with PD presented a significantly higher ASA amplitude than healthy controls with a large effect size and low heterogeneity (SMD=0.84; 95% CI:0.69, 0.99; I^2= 0%; Figure 2). The Funnel Plot, designed to identify bias and determine the consistency of the ASA results, showed no bias in the results (Egger's regression intercept= 0.9266, P=0.89). The quality of the evidence was moderate due to the high effect size without downgrading criteria (Table 2).

In the sensitivity analysis, we considered factors that could have influenced the results of the ASA meta-analysis. We analyzed the influence of the pharmacological status (ON/OFF), and the types of gait tests used to measure the ASA. The ASA analysis revealed a large effect size in the subjects evaluated in the ON stage (ES= 0.86; 95% CI:0.67, 1.05; I^2:0%) and in the OFF stage (ES= 0.81; 95% CI:0.57, 1.06; I^2:1%). No significant differences in ASA were observed between the ON and OFF states (Q= 0.09; P=0.77; Figure 3A).

We identified three main ASA measurement tests: free walking, iSAW, and treadmill. Regardless of the test used, people with PD showed a significantly higher ASA amplitude than controls. The iSAW (ES= 0.54; 95% CI:0.27, 0.8; I^2:0%), free walking (ES= 0.95; 95% CI:0.75, 1.14; I^2:0%) and treadmill test (ES= 1.14; 95% CI:0.65, 1.63; I^2:14%) showed low heterogeneity and moderate to large effect sizes

(Figure 3B). Based on the test used to measure ASA during walking, the subgroup analysis showed statistically significant differences between them (Q= 7.34; P≤.05).

Other AS parameters

According to the meta-analysis of other AS parameters, there is very low-quality evidence indicating that people with PD have higher ASA velocity (ES= 0.64; 95% CI: 0.24, 1.05; I^2:59%) and lower AS amplitude (in degrees) on both the most affected (ES= -1.99; 95% CI:-3.04, -0.94; I^2: 91%) and the least affected sides (ES=-0.75; 95% CI: -1.05, -0.44; I^2=66%) (Supplementary material – Table S.3). The quality of evidence was downgraded because of inconsistency (high statistical heterogeneity; I^2>50%) (Table 2).

Meta-regression ASA

We conducted a meta-regression to analyze the relationship between the ASA amplitude and general gait parameters in people with PD. Five of the nine studies included in the ASA meta-analysis reported stride length and cadence data.[38-42] ASA amplitude did not significantly correlate with either cadence or stride length. The meta-regression could not include other gait parameters because too few studies incorporated such variables. Additionally, we observed that the disease duration and the motor performance assessed using the UPDRS inversely and significantly influenced the ASA amplitude in people with PD compared with healthy controls. In other words, ASA diminishes as the disease progresses and symptoms worsen (Supplementary material – Table S.4).

DISCUSSION

The aim of this systematic review was to determine the differences in ASA between individuals with PD and healthy controls and analyze its relationship with temporal-spatial gait parameters and disease progression.

The results showed moderate quality evidence that people with PD have higher ASA amplitude than healthy controls. With very low-quality evidence, people with PD showed higher ASA velocity and lower AS amplitude on both sides of the body compared to healthy controls. Meta-regression showed that ASA was inversely associated with disease duration and motor symptoms. On the other hand, ASA amplitude did not show a significant association with cadence and stride length. Our results suggest that PD alters the AS during gait asymmetrically and that ASA amplitude, ASA velocity, and AS amplitude are motor parameters capable of differentiating people with PD from those without the disease. In addition, as the disease progresses over time and motor symptoms increase, ASA reduces. Our results are consistent with previous studies,[38 49] that showed people with PD have significant differences in the AS amplitude and velocity and ASA during gait compared to healthy individuals.[38 40 49] Altered AS parameters compromise postural stability and gait efficiency[38] and can be detected early in the course of the disease. Thus, objectively evaluating these parameters could help the early and differential PD diagnosis. Additionally, AS parameters could be used to detect the onset of gait abnormalities,[38] prevent adverse consequences, monitor disease progression, and assess the effects of intervention strategies.[18 21 22 36 38]

Our sensitivity analysis showed that people with PD have more pronounced ASA in both the OFF and ON medication phases. Some studies have shown a

significant ASA and AS improvement in response to levodopa in subjects with moderate to severe PD.[39 42] However, other studies showed no such changes and argued that these parameters would be related to supraspinal control channels that are partially independent of dopaminergic control.[18 47 50] Future studies should address the effects of pharmacological and non-pharmacological therapy on AS parameters and gait at varying stages of the disease. On the other hand, irrespective of the type of walking test used (i.e., free walking, iSAW, or treadmill), individuals with PD exhibited higher ASA than controls. However, we found a greater magnitude of difference and increased heterogeneity in those studies that used a treadmill (Figure 3B). The speed used on the treadmill is a critical factor because it can influence spatiotemporal lower limb parameters.[51 52] Variability in individuals' ability to adapt to the treadmill can result in outcomes heterogeneity.

Our meta-regression showed that as the disease and symptoms progress, ASA decreases. PD is characterized by an initial asymmetric phase, where motor symptoms such as rigidity, bradykinesia, and tremor predominantly affect one side of the body. As the disease progresses, motor symptoms affect both sides more symmetrically, which could explain the decreased ASA with the progression of the disease.[53] We expected a significant correlation between ASA amplitude and lower limb gait parameters. We could only include cadence and stride length in the analysis due to the low number of studies incorporating AS and lower limb parameters. Previous studies show that as PD progresses, gait cadence increases and stride length decreases.[9] Consistently, motor symptoms become more symmetrical, and a decrease in ASA is expected. Higher cadence[9 50 54] and reduced step length have been associated with freezing of gait (FOG),[55] impaired gait coordination,[52] falls, and decreased quality of life.[51 53]

Limitations

This study has some limitations that need to be highlighted. According to GRADE, the certainty of evidence ranges from “very low” (for the other AS parameters) to “moderate” for the main outcome (ASA amplitude); therefore, these findings must be interpreted with caution. We have very little to moderate confidence in the estimated effect, mainly by the type of studies incorporated (observational) and the high heterogeneity. A small number of studies analyzed ASA and AS parameters during gait. The evaluation methods were diverse and may have been a source of data heterogeneity. However, no studies with a high risk of bias were included, and in the main analysis, the sources of heterogeneity were investigated.

Considering the relevance of ASA to gait, we expected to find associations with different temporal-spatial parameters. However, only cadence and stride length were included in the meta-regression; variables such as gait speed, step length, and others were not included in the analysis due to insufficient data. Future studies must focus on establishing the influence of ASA and AS on other gait parameters.

The findings of this study underscore the need for a more objective and quantitative evaluation of AS disorders in people with Parkinson's disease. Because the available instrument-based analysis systems are complex and costly, the increasing demand for objective measurement tools that can be used in clinical and unsupervised settings calls for the development and validation of cost-effective and minimally invasive instruments. Fortunately, the emergence of wearable sensors, smartphones,[56]and low-cost optical sensors,[38] among others, provides a new avenue for clinicians to monitor AS parameters and assess the efficacy of gait rehabilitation interventions.

CONCLUSION

People with PD have more pronounced ASA and a lower AS amplitude than healthy individuals, regardless of the ON/OFF medication phase and the walking test used. As the disease progresses and symptoms worsen, ASA tends to decrease. Hence, the assessment of ASA and AS should be considered significant motor parameters to examine gait abnormalities in PD. ASA and AS assessment can be used for early PD diagnosis, monitoring disease progression, and choosing therapeutic interventions for gait rehabilitation in people with PD.

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Table 1
Characteristics of the Included Studies

Study	Participants						ON/ OFF	Walk Test	Instrument	AS Parameters/ ASA Calculation Method	Lower Limbs Parameters
	Numbers of subjects Age(years)		PD Condition	H&Y	Motor UPDRS	Disease Duration (years)					
	HC	PD									
Curtze et al (2015)[42]	n= 64 65.4 (6.0)	n= 52 66.7 (5.5)	Mild PD	2.1 (0.3)	27.7 (12.2)	7.2 (3.9)	ON OFF	iSAW	IMU	AS (°) LAS Peak AS speed (°/s) ASA ROM (%) / Not specified	Gait cycle time Cadence RoM Leg Stride velocity Stride length Double support Time (%) Stance time (%) Swing time (%)
		n=52 66.3 (6.6)	Severe PD	2.6 (0.6)	31.8 (11.5)	10.4 (6.8)	ON OFF				
Gera et al (2020)[43]	n=15 62.7 (8.5)	n=17 57.2 (7.4)	PD gene mutations	2.1 (0.5)	29.0 (21.0)	11.2 (6.9)	ON OFF	ISAW	IMU	AS speed (°/s) LAS ASA RoM (%) ASA velocity (%) / Rogendorf	Stride length asymmetry
		n=17 60.9 (5.8)	PD no gene mutations	1.9 (0.3)	23.0 (14.5)	8.8 (7.1)	ON OFF				
Horak et al (2016)[44]	n=21 66.6 (6.4)	n= 100 66.(6.3)	Moderate PD	2.3 (0.5)	29.8 (11.9)	8.8 (5.8)	ON OFF	iSAW	IMU	Peak AS speed (°/s) ASA velocity (%) / Not specified	Cadence Stride velocity
Zampieri et al (2010)[46]	n= 60.2 (8.2)	60.4 (8.5)	Early PD untreated	1.6 (0.5)	20.0 (9.4)	1.14 (1.1)	-	iTUG	IMU	AS (°) MAS and LAS Peak MAS and LAS speed (°/s) ASA velocity (%) / Not specified	Cadence Stride velocity Stride length Double support time (%)
Cole et al (2010)[37]	n=17 65.1 (8.7)	n=17 66.9 (8.5)	PD Non fallers	1.6 (0.8)	26.9 (15.3)	3.9 (2.5)	ON	Free walking	MoCAP 3D	AS (m)	Cadence Gait speed Stride length Double support time (%) Stance time (%) Swing time (%)
		n=32 66.2 (8.7)	PD Fallers	1.8 (0.6)	34.5 (15.3)	6.2 (4.0)	ON				

(Continued)

Continued

Study	Participants						ON/ OFF	Walk Test	Instrument	AS Parameters/ ASA Calculation Method	Lower Limbs Parameters
	Numbers of subjects Age(years)		PD Condition	H&Y	Motor UPDRS	Disease Duration (years)					
	HC	PD									
Koh et al (2019)[39]	n=23 66.4 (5.9)	n=41 63.1 (7.9)	PD I-III	2.1 (0.3)	22.4 (8.5)	1.51 (1.8)	OFF	Free walking	MoCAP 3D	AS (m) MAS and LAS ASA amplitude (%) / Zifchock	Cadence Gait speed Stride velocity Stride length
Lewek et al (2010)[21]	n= 8 61.0 (12)	n=12 68.0 (8.2)	Early PD	1.3 (0.4)	11.3 (5.6)	2.0 (0.8)	OFF	Free walking	MoCAP 3D	AS (m) MAS and LAS ASA amplitude (%) / Zifchock	-
Ospina et al (2018)[22]	n=25 68.4 (9.4)	n=25 68.4 (8.0)	Early PD	I	36.8 (13.4)	Not reported	ON	Free walking	MoCAP 3D	AS (m) MAS and LAS AS speed (°/s) MAS and LAS ASA amplitude (%) / Zifchock	-
Sterling et al (2015)[45]	n=17 61.8 (8.7)	n=16 64.3 (9.4)	Early PD	1.8 (0.7)	14.0 (5.7)	2.47 (3.0)	ON OFF	Free walking	IMU	AS speed (°/s) MAS and LAS ASA velocity (%) / Zifchock	-
Mirelman et al (2016)[18]	n= 64 52.8 (14.2)	n=127 65.7 (6.9)	PD No Gen mutations	I-III	19.9 (10.7)	5.7 (4.2)	ON	Free walking	MoCAP 3D	AS (°) MAS and LAS ASA RoM (%) / Zifchock	Gait speed
		n= 67 64.9 (9.7)	PD Gen mutations	I-III	15.9 (6.9)	7.9 (6.2)	ON				
Plate et al (2015)[36]	n=60 55.3	n= 7 57.3	Early PD untreated	I-1,5	Not reported	< 3	-	Treadmill 3km/h	Ultrasound emitters	AS (°) MAS and LAS ASA RoM (%) / Kuhtz	-
Roggendorf et al (2012)[41]	n=25 65 (5)	n= 21 60 (11)	PD stage I	I	10 (5)	1.5 (1.2)	OFF	Treadmill 3km/h	Ultrasound emitters	AS (°) MAS and LAS ASA RoM (%) / Kuhtz	Cadence stride length Double support time (%) Stance time (%) Swing time (%)
		n=19 61 (12)	PD Stage II	II	18 (7)	4.6 (2.1)	OFF				

(Continued)

Table 1

Continued

Study	Participants						ON/ OFF	Walk Test	Instrument	AS Parameters/ ASA Calculation Method	Lower Limbs Parameters
	Numbers of subjects Age(years)		PD Condition	H&Y	Motor UPDRS	Disease Duration (years)					
	HC	PD									
Ferraris, et al (2022)[38]	n=13 56.3 (8.7)	n=16 68.9 (7.1)	PD Stage I-III	2.1 (0.9)	34 (6.5)	8.9 (7.6)	ON	Free walking	Optic sensor	AS (mm); AS area (mm^2); AS speed; AS (°); ASA RoM (%) /Zifchock	Step length (m); Step width (m); step velocity (m/s); Stride length (m); Double support (s); Stance duration (% of gait cycle); Gait velocity (m/s); Cadence (steps/min)
Liu et al (2022a)[40]	n= 48 61.5 (6.12)	n=39 -	PD Stage I-II	I-II	34.6 (10.7)	-	OFF	Free walking	2D Video	AS (°) MAS and LAS; AS velocity (°/s) MAS and LAS; ASA RoM (%); ASA velocity (%)	Step length (m) MAS and LAS; Swing phase (s) MAS and LAS, Cadence (steps/min); Gait velocity (m/s)
		n=29 -	PD Stage III-IV	III-IV	46.6 (12.9)	-	OFF				

Values are mean (SD). PD, Parkinson´s disease; HC, healthy control; H&Y, Hoehn and Yahr Scale (score); UPDRS, Unified Parkinson's Disease Rating Scale (score); AS, arm swing; LAS, least affected side; MAS, most affected side; ASA, arm swing asymmetry; RoM, range of motion; MoCAP, motion capture; IMU, Inertial measurement unit; I-SAW, Instrumented Stand and Walk (ISAW) Test; I-TUG, Instrumented Timed Up and Go test.

Table 2.
Certainty of evidence for meta-analyzed outcomes

Outcome	Study design	ES (95% CI)	p-value	N°studies / N° comparations N°Participants PD/HC	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Risk of publication bias[d]	Imprecision[e]	Certainty of the evidence[f]
ASA amplitude	Descriptive	0.84 (0.69 to 0.99) Large (+)	<.001	9/18 529/352	No	No	No	No	No	Moderate
ASA velocity	Descriptive	0.64 (0.24 to 1.05) Moderate	<.01	5/11 230/128	No	Very large (-)	No	No	No	Very low
AS MAS	Descriptive	-1.99 (-3.04 to -0.94) Large	<.01	10/17 520/344	No	Very large (-)	No	No	No	Very Low
AS LAS	Descriptive	-0.75 (-1.05 to -0.44) Moderate	<.01	9/13	No	Very large (-)	No	No	No	Very low

Notes: ASA = arm swing asymmetry; AS = arm swing; LAS = least affected side; MAS = most affected side; PD = Parkinson´s disease; HC = healthy control; ES= effect size; CI=confidence interval; (-) = Downgraded by one level; (+) = Upgraded by one level if there is a large effect size (0.8 or higher) without downgrading criteria.

[a] High risk of bias when 25% or more of the included articles present a score lower or equal to three points, assessed with the Critical Appraisal Checklist from the Joanna Briggs Institute.

[b] Very large inconsistency when I^2 was 50% or greater.

[c] Indirectness when the findings were clinically heterogeneous.

[d] Very Large risk of publication bias when the p- value of the Egger´s test was < 0.05.

[e] Very large imprecision when the upper or lower CI was 0.5 in either direction.

[f] Moderte certainty of the evidence= Moderately confident in the estimated difference; Very low certainty of the evidence= very little confidence in the estimated difference (Based on definitions provided by Balshem et al.; 2011)[30]

FIGURE LEGENDS

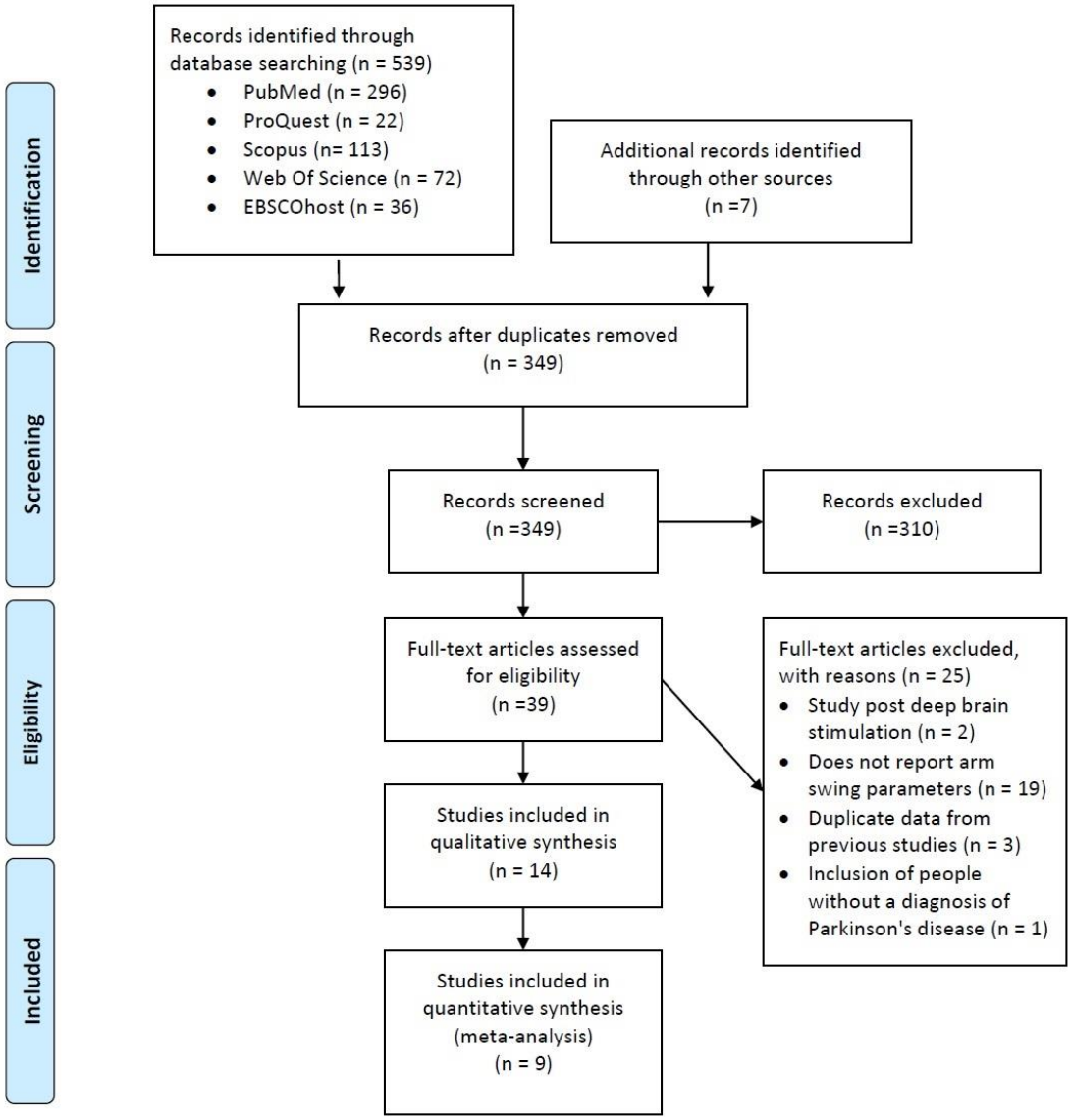

Figure 1. PRISMA flowchart.

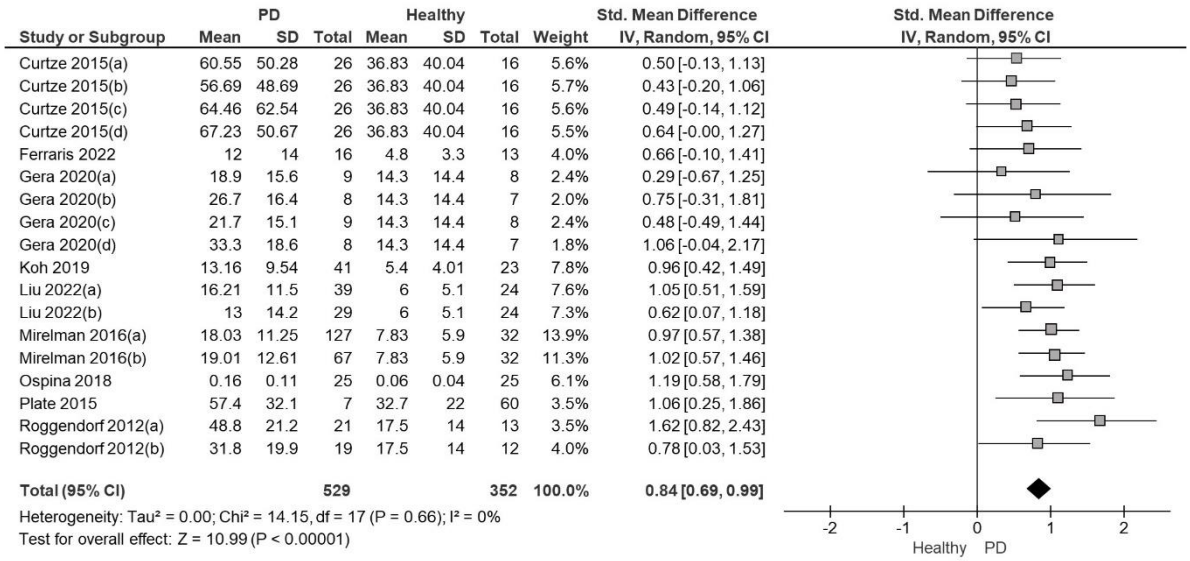

Figure 2. Forest plot from the meta-analysis of arm swing asymmetry during gait in people with Parkinson's disease versus healthy individuals.

Note: In studies with more than one PD group evaluated each comparison was included in separate pairs, with groups divided approximately equally between the comparisons[48]

Curtze 2015 (a): PD stage II, ON; (b): PD stage III.IV, ON; (c): PD stage II, OFF; (d): PD stage III-IV; OFF

Gera 2020 (a): PD GBA ON; (b) PD No GBA ON; (c): PD GBA, OFF; (d) PD No GBA, OFF

Liu 2022 (a): PD stage I-II, OFF; (b) PD stage III-IV, OFF

Mirelman 2016 (a): PD No gene mutations, ON; (b) PD gene mutations, ON

Roggendorf 2012 (a): PD stage I, OFF; (b): PD stage II, OFF.

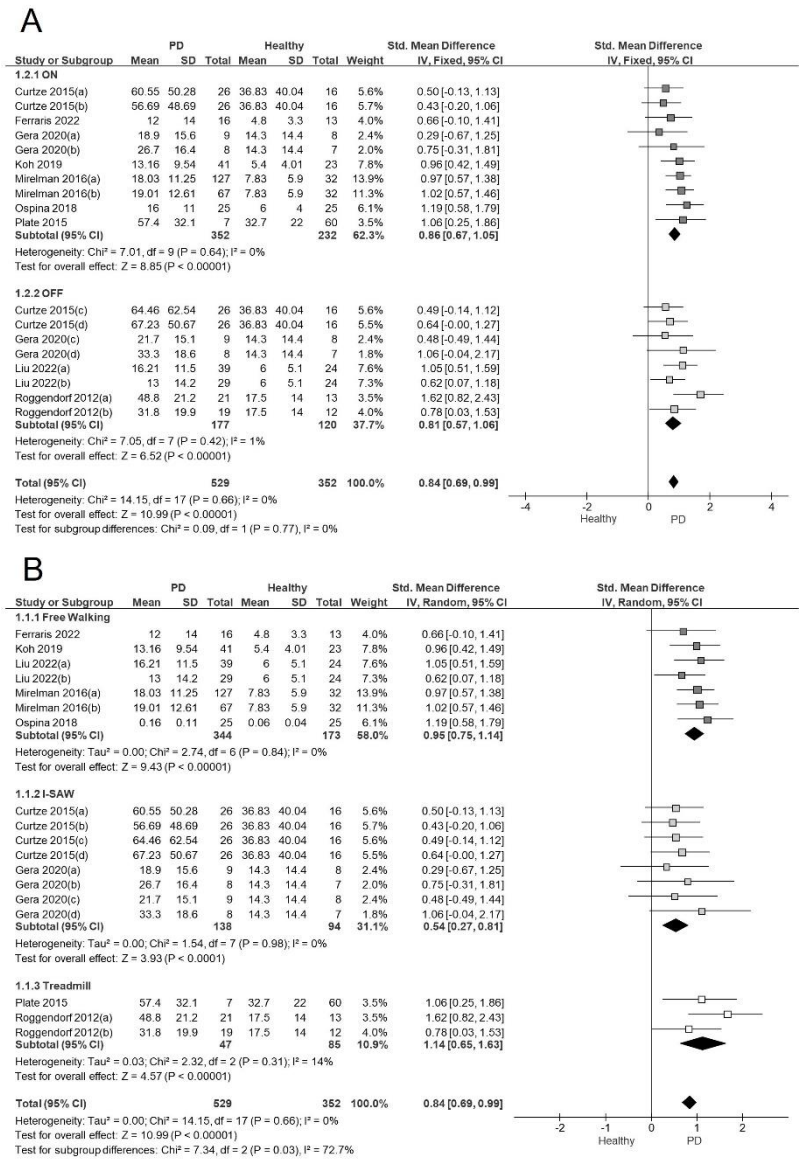

Figure 3. A) Forest plot sensitivity analysis showing effect sizes for arm swing asymmetry in relation to ON/OFF medication status in people with Parkinson's disease during walking. B) Forest plot sensitivity analysis showing effect sizes for arm swing asymmetry in relation to the methods used to determine ASA in people with Parkinson's disease during walking.

Note: In studies with more than one PD group evaluated each comparison was included in separate pairs, with groups divided approximately equally between the comparisons.[48]

Curtze 2015 (a): PD stage II, ON; (b): PD stage III.IV, ON; (c): PD stage II, OFF; (d): PD stage III-IV, OFF.

Gera 2020 (a): PD gene mutations ON; (b) PD No gene mutations ON; (c): PD gene mutations, OFF; (d) PD No gene mutation, OFF.

Mirelman 2016 (a): PD No gene mutations, ON; (b) PD gene mutations, ON.

Liu 2022 (a): PD stage I-II, OFF; (b) PD stage III-IV, OFF.

Roggendorf 2012 (a): PD stage I, OFF; (b): PD stage II, OFF.

Supplementary Material

Table S.1 Search Strategy Used in This Study

Pubmed (n=296)
#1(“Parkinson Disease”[Mesh] OR “Idiopathic Parkinson's Disease” OR “Lewy Body Parkinson's Disease” OR “Parkinson's Disease, Idiopathic” OR “Parkinson's Disease, Lewy Body” OR “Parkinson Disease, Idiopathic” OR “Parkinson's Disease” OR “Idiopathic Parkinson Disease” OR “Lewy Body Parkinson Disease” OR “Primary Parkinsonism” OR “Parkinsonism, Primary” OR “Paralysis Agitans”) AND #2("Arm"[MeSH] OR “Arms” OR “Upper Arm” OR “Arm, Upper” OR “Arms, Upper” OR “Upper Arms” OR “Arm swing” OR “asymmetry” OR “Arm swing asymmetry”) Search: #1 AND #2 Filters applied: Clinical Study, Clinical Trial, Controlled Clinical Trial, Evaluation Study, Observational Study, Randomized Controlled Trial, Validation Study.
Web of Knowledge: Web of Science (n=72)
(TI=(Parkinson*)) AND AB=(Arm swing*) Filters applied: Articles
Scopus (n=113)
TITLE-ABS-KEY ("Parkinson Disease" OR "Idiopathic Parkinson's Disease" OR "Lewy Body Parkinson's Disease" OR "Parkinson's Disease, Idiopathic" OR "Parkinson's Disease, Lewy Body" OR "Parkinson Disease, Idiopathic" OR "Parkinson's Disease" OR "Idiopathic Parkinson Disease" OR "Lewy Body Parkinson Disease" OR "Primary Parkinsonism" OR "Parkinsonism, Primary" OR "Paralysis Agitans") AND TITLE-ABS ("Arm" OR "Arms" OR "Upper Arm" OR "Arm, Upper"

OR "Arms, Upper" OR "Upper Arms" OR "Arm swing" OR “Asymmetry” OR "Arm swing asymmetry") AND (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "cp") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "cr") OR EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "dp") OR EXCLUDE (DOCTYPE , "ed")) AND (EXCLUDE (EXACTKEYWORD , "Human") OR EXCLUDE (EXACTKEYWORD , "Male") OR EXCLUDE (EXACTKEYWORD , "Humans")) AND (EXCLUDE (SRCTYPE , "p") OR EXCLUDE (SRCTYPE , "b") OR EXCLUDE (SRCTYPE , "k") OR EXCLUDE (SRCTYPE , "d") OR EXCLUDE (SRCTYPE , "Undefined"))
EBSCOhost (n=36)
(Ti(“Parkinson Disease” OR “Idiopathic Parkinson's Disease” OR “Lewy Body Parkinson's Disease” OR “Parkinson's Disease, Idiopathic” OR “Parkinson's Disease, Lewy Body” OR “Parkinson Disease, Idiopathic” OR “Parkinson's Disease” OR “Idiopathic Parkinson Disease” OR “Lewy Body Parkinson Disease” OR “Primary Parkinsonism” OR “Parkinsonism, Primary” OR “Paralysis Agitans”) AND AB(“Arm swing” OR “Arm swing asymmetry”) Filters applied: Peer-reviewed, scientific journal, article
ProQuest (n=22)
(Ti(“Parkinson Disease” OR “Idiopathic Parkinson's Disease” OR “Lewy Body Parkinson's Disease” OR “Parkinson's Disease, Idiopathic” OR “Parkinson's Disease, Lewy Body” OR “Parkinson Disease, Idiopathic” OR “Parkinson's Disease” OR “Idiopathic Parkinson Disease” OR “Lewy Body Parkinson Disease” OR “Primary Parkinsonism” OR “Parkinsonism, Primary” OR “Paralysis Agitans” AND (Ab“Arm"[MeSH] OR “Arm swing” OR “Arm swing asymmetry”)) Filters applied: Peer-reviewed, scientific journal, article

Table S.2. Assessment of Risk of Bias in Included Studies Using the Critical Appraisal Checklist of the Joanna Briggs Institute

		Cole et al., 2010	Curtze et al., 2015	Gera et al., 2019	Horak et al., 2016	Koh et al., 2019	Mirelman et al., 2016	Ospina et al., 2018	Plate et al., 2015	Lewek et al., 2010	Roggendorf et al., 2012	Sterling et al., 2015	Zampieri et al., 2010	Ferraris et al.,2022	Liu et al., 2022
1	**Were the criteria for inclusion in the sample clearly defined?**	N	N	Y	N	Y	N	Y	N	N	Y	N	N	Y	Y
2	**Were the study subjects and the setting described in detail?**	Y	N	Y	N	Y	N	Y	N	N	N	N	N	Y	Y
3	**Was the exposure measured in a valid and reliable way**	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	**Were objective, standard criteria used for measurement of the condition?**	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	**Were confounding factors identified?**	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
6	**Were strategies to deal with confounding factors stated?**	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
7	**Were the outcomes measured in a valid and reliable way?**	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	**Was appropriate statistical analysis used?**	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
	Total score	6	6	8	5	8	6	8	6	6	6	6	5	6	7

Y = Yes; N = No

Table S.3 Other Arm Swing Parameters in People with Parkinson's disease Versus Healthy Controls

Outcome Measure	k/p	PD (n)	HC (n)	Effect estimate SMD (95% CI)	I^2 (*p*-value)	Z-value	*p*-value
ASA velocity (%)	5/11	230	128	0.64(0.24, 1.05)	59% (<0.01)	3.13	< 0.01*
Arm swing LAS (°)	9/13	416	297	-0.75(-1.05, -0.44)	66% (<0.01)	-4.86	< 0.01*
Arm swing MAS (°)	10/17	520	344	-1.99(-3.04, -0.94)	91% (<0.01)	-3.71	< 0.01*

HC = Healthy controls; MAS = Most Affected Side; LAS = Least Affected Side; k/p: number of studies/number of pairs; n: sample of subjects; SMD: Standardized Mean Difference; CI: Confidence Intervals; I^2: I-squared inconsistency test; * Statistical significance

Table S.4

Meta-regression of moderators of clinical and gait parameters on ASA in subjects with Parkinson's disease.[a]

Moderator	K	Slope	SE	95%CI	Z-value	p-value
UPDRS (score)	15	-0.0183	0.0086	-0.0350, - 0.0015	-2.1336	0.0329 *
Duration disease (y)	16	-0.0712	0.0286	-0.1273, - 0.0151	-2.4892	0.0128*
Cadence (steps/s)	10	-0.0086	0.0054	-0.0192, 0.0020	-1.5878	0.1123
Stride Length (m)	8	-0.0031	0.0055	-0.0139, 0.0077	-0.5643	0.5726

Abbreviations: k = number of studies; CI, confidence intervals. * Statistical significance

[a] The table presents the results for each potentially moderating factor for ASA.

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 (Supplementary material, Table S.1)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7

Topic	No.	Item	Location where item is reported
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10 (Figure 1)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	10
Study characteristics	17	Cite each included study and present its characteristics.	10-11 (Table 1)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	11-12 (Supplementary material, Table S.2)

Topic	No.	Item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2, 3; Supplementary material, Table S3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-13Supplementary material, Table S.2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12-13, Supplementary material, Table S.3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	13, Figure 3A, 3B, Supplementary material, Table S.4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	13, Table 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14-17
	23b	Discuss any limitations of the evidence included in the review.	16-17
	23c	Discuss any limitations of the review processes used.	16
	23d	Discuss implications of the results for practice, policy, and future research.	17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	18
Competing interests	26	Declare any competing interests of review authors.	18

Topic	No.	Item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

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To: "Aline Pagnussat" alinespagnussat@gmail.com
From: "Brazilian Journal of Physical Therapy" aizzalasa.bjpt@gmail.com
Subject: Decision on submission to Brazilian Journal of Physical Therapy

Manuscript Number: BJPT-D-22-00468R3

Arm Swing Asymmetry in People with Parkinson's disease and its Relationship with Gait: A Systematic Review and Meta-analysis

Dear Professor Pagnussat,

Thank you for submitting your manuscript to Brazilian Journal of Physical Therapy.

I am pleased to inform you that your manuscript has been accepted for publication.

My comments, and any reviewer comments, are below.
Your accepted manuscript will now be transferred to our production department. We will create a proof which you will be asked to check, and you will also be asked to complete a number of online forms required for publication. If we need additional information from you during the production process, we will contact you directly.

We appreciate and value your contribution to Brazilian Journal of Physical Therapy. We regularly invite authors of recently published manuscript to participate in the peer review process. If you were not already part of the journal's reviewer pool, you have now been added to it. We look forward to your continued participation in our journal, and we hope you will consider us again for future submissions.

Kind regards,
Rafael Zambelli Pinto and Guy Simoneau
Editor-in-Chief

Brazilian Journal of Physical Therapy

Editor and Reviewer comments:

6 ARTIGO 2

Nordic walking and arm swing asymmetry in people with Parkinson's disease: Protocol for Randomized Clinical Trial.

(Formatado conforme normas do periódico BMJ Open Sport & Exercise Medicine – *Qualis A4, Fator de Impacto 4.8*)

Running head: Nordic Walking and Arm swing asymmetry in Parkinson's disease

Title: Nordic walking and arm swing asymmetry in people with Parkinson's disease: Protocol for Randomized Clinical Trial.

Authors: Jessica Espinoza-Araneda, Msc[1,2,7], Cristian Caparros-Manosalva, Msc[1,2,7], Maira J da Cunha, PhD[1,3], Gabriel Nasri Marzuca-Nassr, PhD[5,7], Nicole B. Fritz Silva, PhD[6,7], Aline S Pagnussat, PhD[1,3,4,7].

Filiation

[1]Rehabilitation Sciences Graduate Program, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Brazil

[2]Department of Human Movement Sciences, Faculty of Health Sciences, University of Talca, Talca, Chile

[3]Movement Analysis and Neurological Rehabilitation Laboratory, Universidade Federal de Ciências da Saúde de Porto Alegre, UFCSPA, Brazil

[4]Department of Physical Therapy, Georgia State University, GSU, USA

[5] Universidad de La Frontera, Facultad de Medicina, Departamento de Ciencias de la Rehabilitación, Temuco, Chile

[6] Health Department. University of Los Lagos. Puerto Montt, Chile.

[7] Interuniversity Center for Healthy Aging RED21993

ABSTRACT

Background: People with Parkinson's disease (PD) face disruptions in arm swing motion during walking, including a reduction in amplitude and an increase in asymmetry. Both conditions are detrimental to gait performance. Nordic Walking (NW) is a walking modality that uses poles and can positively affect the parameters of Arm Swing (AS). This study aims to compare a NW with a free walking (FW) protocol and investigate their effects on AS asymmetry, AS amplitude, and gait parameters in people with PD.

Methods: Twenty-four people with PD, stages 1-3 on the Hoehn and Yahr scale, will be randomly assigned to the NW training (n=12) or FW training group (n=12). The primary outcomes are amplitude asymmetry of AS (%) and AS amplitude (deg). We will also analyze temporospatial measurements during walking, functional mobility, and quality of life. Blinded researchers will conduct evaluations at baseline (T0), post-intervention (T1), and in one-month follow-up (T2). Participants will complete 24 supervised NW or FW training sessions for 12 weeks.

Discussion: This is the first study to address the effects of NW on the asymmetry of AS, AS amplitude, and its influence on gait parameters. We hypothesize that an NW program in PD will reduce the asymmetry and increase the AS amplitude during gait to a greater extent than free walking. The results of this study may provide new evidence to understand the effects of NW on gait in people with PD.

Keywords Parkinson disease; arms swing; gait, Nordic Walking, exercise therapy, neurological rehabilitation.

What is already known on this topic

- People with Parkinson's disease (PD) have greater arm swing asymmetry and lower amplitude, and these alterations affect gait performance and increase the risk of falling.
- Nordic walking (NW) is a sport consisting of walking with the active use of two poles, therefore it can positively affect the parameters of Arm Swing (AS) and gait performance to a greater extent than free walking

What this study adds

- This is the first study to address the effects of NW on the Asymmetry and amplitude of AS and its influence on temporospatial gait parameters.
- The results of this study may provide new evidence to understand the effects of NW on gait in people with PD in comparison to free walking

How this study might affect research, practice or policy

- We highlight the importance of upper limb performance during locomotion in people with PD and the study of new rehabilitation strategies which is limited in the literature and clinical practice
- This study provides a detailed protocol of NW training for clinicians working with people with PD, which will allow replication of our clinical trial if the NW is an effective intervention.

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder and one of the leading causes of disability.[1] Gait disturbances are frequent in PD and strongly related to falls, dependency, and low quality of life.[2 3] Changes in lower limbs' gait parameters are widely studied in PD.[4] However, gait kinematic parameters of upper limbs are little addressed in the literature.

According to a recently published meta-analysis, people with PD present lower AS amplitude and velocity and greater asymmetry during gait compared with healthy peers.[5] These changes are considered early features of PD,[6] and an independent predictor of falls.[7] During locomotion, movements of the upper and lower limbs influence each other.[8] When these movements are asymmetrical, it implies a higher energy cost and a greater probability of developing freezing of gait.[9] Improvements in AS parameters would contribute to decrease angular momentum around vertical and vertical ground reaction moment caused by the rotation of the whole- body on the vertical axis, increasing the walking speed and step length, promoting stability, and decreasing energy costs during walking.[8 10 11]

Nordic walking (NW) is considered an outdoor sport modality, which consists of walking rhythmically with the use of two poles. NW technique have shown that the sequence of active movements demands mechanically and energetically both the upper and lower limbs during walking unlike other strategies such as free walking (FW) or treadmill walking.[12 13] In addition, using the poles rhythmically could promote mid-lateral stability and act as an external sensory signal, optimizing intersegmental coordination and temporal organization of gait.[14] No studies have evaluated the effects of NW on the kinematic parameters of AS. Considering that NW favors the active use of the upper limbs during walking, we hypothesize that a NW training

program in PD will reduce the asymmetry and increase the AS amplitude during gait to a greater extent than free walking. On the other hand, improvements in AS could positively influence the performance of lower limbs during walking, increasing gait speed, step length, functional mobility, and quality of life.

MATERIAL AND METHODS

Study design

This is a protocol for a randomized controlled clinical trial, 1:1, parallel, single-blinded (evaluators), of superiority, conducted according to the recommendations of Standard Protocol Items for Clinical Trials 2013 (SPIRIT-2013).[15] The study will be registered in clinicaltrial.gov.

Study Setting

The study will be carried out in the Laboratory of Human Movement Sciences, athletic track, and trails of the University of Talca, Chile.

Participants

People with PD belong to PD groups, community rehabilitation centers, and/or the Neurological Clinic of the School of Kinesiology of the University of Talca, Talca-Chile. Table 1 shows the inclusion and exclusion criteria.

Table 1

Inclusion and exclusion criteria

Inclusion criteria	● Diagnosis of idiopathic PD, confirmed by a neurologist following the criteria of the Parkinson's Disease Society Brain Bank Criteria ● Age between 50-80 years ● Disease stage between I and III according to Hoehn and Yahr (H&Y) ● Able to walk without technical aids.
Exclusion criteria	● Cognitive impairment (Score < 26 in the Montreal Cognitive Assessment; MoCA). ● Surgery less than 3 months or deep brain stimulation (DBS). ● Any comorbidity that has a contraindication to moderate to high physical exercise intensity. ● Participate in any walking training 2 or more times per week. ● Diagnosis of any other neurological or musculoskeletal condition that can cause motor compromise and interfere with locomotion.

Note: All information will be obtained through medical history reported by participants and corroborated by medical records or participant´s physician.

Sample size calculation

The sample size was calculated using G*Power 3.1.9.4 software, accepting an alpha risk of 0.05 and a beta risk of 0.2 for a one-sided contrast. A minimum of 22 participants will be required considering the difference in AS amplitude in people with PD (0.2 m ± 0.08 m) compared to people without PD (0.29 ± 0.08 m) with an effect size of 1.125.[16] Considering a loss of 10%, 24 participants will be included (12 in the NW group and 12 in the FW group).

Recruitment, randomization, blinding, and treatment allocation

The study will be submitted to the analysis and approval of the Bioethics Committee of the University of Talca Chile. A physiotherapist (R1) will make the invitation to participate through social media, telephone contact, and visits to the meeting places. Through a presentation, all the information and explanation of the study's nature, purpose, and procedure will be delivered, as well as any inconveniences and risks of participation. For those willing to participate, the physiotherapist will carry out the process of reading and signing the informed consent. Subsequently, to verify the inclusion and exclusion criteria, a brief questionnaire containing biodemographic and

health history, the H&Y scale will be applied to establish the stage of the disease,[17] and to assess cognitive status, MoCA will be applied.[18] All information reported by participants will be corroborated by medical records or the participant´s physician. Those who meet the selection criteria will be invited to the Human Movement Sciences Laboratory of the University of Talca to carry out the baseline evaluations. After the baseline evaluation, an assistant (R2) who will not participate in the evaluations, intervention, or data analysis will assign a number to each participant and perform a randomization process into blocks of four participants to assign them to study groups using a digital research randomizer (https://www.random.org). Participants will be allocated to the intervention group with NW or the intervention group with FW, with an allocation index of 1:1. The distribution will be blinded to the evaluators (R3, R4) and statisticians (R5).

Interventions

The lack of standardized protocols for NW prescription has made it difficult to compare different studies. Based on this, the framework for NW exercise prescription for PD will be used.[19]

The NW training will be supervised by a physiotherapist instructor from the Chilean School of Nordic Walking Fittrek, Chile (R6). A physiotherapist will carry out the FW program (R8). Patients will be asked to abstain from engaging in a direct physical therapy program that involved therapeutic gait training during the intervention and follow-up period.

The training will be developed in the athletics track and trails of the University of Talca, Chile, with a demarcation of 400 m to control the distance traveled in each training. The participants will be trained in groups (NW or FW), on alternate days, in

the morning, according to the peak of action of the pharmacological treatment, that is, between 30 minutes and two hours after ingesting the medication, which will be recorded in each session.

The extension for both groups will be 12 weeks, two times a week, completing 24 one-hour sessions. The NW group will carry out the first 4 sessions of induction to the technique. The FW group will complete the same number of sessions. The first four will be an induction to gait training (Details of the induction phase for both groups in Supplementary Material 1).

The training sessions will be organized in 3 phases: 1. warm-up phase, 2 training phase; 3 stretching phase and return to calm. The general structure of the training sessions is described in Table 2.

Table 2

General structure of the training sessions

Phase	**Time (min)**	**Description**
1. Warm-up	5-10	General joint mobility exercises, progressive walking exercises in place, free walking at a comfortable speed, and travel in different directions
2. Training phase	40-50	NW or FW, at intervals, progressing to a continuous walk on varying terrains (grass, gravel, land)
3. Calm down phase	5-10	Muscle stretching and breathing exercises.

The protocol will be standardized for both groups. The training phase differs in the NW program in the use of poles during training. The poles will be telescopic, made of aluminum, with a cork handle and removable strap, a flexible hard metal tip and height adjustment between 100 and 125 cm, and a weight not exceeding 380 g.

The NW program was closely monitored for each participant, continuously assessing gait pattern, NW technique, and exercise response during training.

The NW technique will be controlled in each session by checking four critical elements according to the Fittrek standard power technique:[20] Correct posture when walking, coordinated steps, pendulum movement of the arms from the shoulder, and effective push of the poles from the moment of nailing until reaching hip height with the hand. In addition, releasing and recovering the pole will be encouraged once the hand passes over the hip during walking. The trainer will focus on promoting the amplitude of the stride and the AS without losing the naturalness of the gait in a rhythmic and coordinated way, increasing the speed when walking. Errors will be corrected session by session, such as decreased width of the AS and step, height adjustment of the pole to facilitate AS, vertical support of the poles and forward support, tendency to drag the tips of the poles, overload of the arm extensor, lack of waist dissociation and lack of coordination. In the case of technical errors, the progression will be restarted with technique induction exercises, and their correction will be checked (Supplementary Material 1). Trainers will review the objectives with participants weekly and provide direct augmentative feedback on the results achieved in terms of walking speed and distances covered session by session (Knowledge of results). On the other hand, they will also receive feedback regarding the quality of the NW or FW technique (knowledge of execution). Learning will be facilitated through modeling, visual feedback via video, visual cues, and verbal attention instruction. The trainers will review the objectives with participants on a weekly basis. The work intensity for both groups will be between 60% and 80% of the reserve heart rate (RHR) and in a range between 11 and 15 of the Borg perception of effort scale (RPE). To monitor the training intensity, a Polar Ft1 brand heart rate

monitor will be placed on the thorax at the level of the xiphoid process. Gait intensity will also be modulated by perceived gait speed, using the following descriptors: comfortable: self-selected gait speed; intermediate: between comfortable speed and maximum speed; fast: maximum walking speed; Maxima: maximum trot. Training will progress according to the Peyré-Tartaruga proposal, 2022,[19] which considers a systematic increase in the duration of the walk, speed, and intensity. The details of the training prescription both for the familiarization and training of NW and FW are presented in Supplementary material 2.

Outcome Measures

Two physiotherapists (R3-R4), blinded to the study groups, will conduct the evaluations at T0 (baseline assessment), T1 (after 12 weeks of intervention), and T2 (one-month follow-up). Participants will be evaluated between 30 minutes and 2 hours after taking the medication, during the "ON" phase. Outcome measures will be administered using standardized procedures and the same testing order at all time points. Baseline assessments to characterize the sample and prescribe training are described in the supplemental material 3. Evaluations will be divided into two days to avoid fatigue (Figure 1).

Primary outcomes are the amplitude of the AS (range of motion) [deg], and asymmetry of the amplitude of AS between left and right swings (0% means no asymmetry) [%] during walking.

Secondary outcomes are temporospatial measurements during walking: gait speed [m/s], step length [m], functional mobility and quality of life.

Kinematic of the AS during walking

The AS parameters will be acquired through 2 TrignoTM IMU sensors (Delsys Inc., Boston, EMA, USA), placed at wrist level, fixed with a semi-elastic velcro strap 30 mm above the styloid, and oriented according to right-handed coordinate systems (x forward, y left, and z vertical). The sensors have a triaxial accelerometer (max outputs ±16 g), a triaxial gyroscope (max outputs ±2000°/s), and a magnetometer (10 Hz). Data capture will be performed at a 148Hz sampling rate on both IMUs synchronized in the same time window with EMGWorks 4.3.1 acquisition software (Delsys Inc., Boston, MA, USA).

Each participant will walk through an 8m long and 3m wide corridor, free of obstacles in comfortable shoes at a self-selected preferred speed. Three repetitions will be performed, stopping at each end for 3 seconds and then turning.[21] The analysis of the variables will be carried out between two and six meters of the corridor to avoid the influence of acceleration and deceleration on the walk. Participants will be accompanied and can rest at the end of the corridor if necessary.

AS is defined as a rotational movement of the arm, occurring during walking, and running in bipeds with a periodicity of around 1–2 Hz and in opposite directions (anterior and posterior). The hand and arm move freely through space in opposite directions with most of the movement in the sagittal plane of the body frame.[22] The AS parameters will be extracted with a validated AS algorithm, for both upper limbs, with a periodicity between 0.3 and 3 Hz and a minimum amplitude of 5°.[22] Only rotations around the frontal and sagittal axis will be considered because longitudinal rotations can be influenced by body turns.

To determine the AS of each member, only the gyroscope functions (gross angular velocity of the 3 axes of the IMU) and the capture frequency will be configured[23] and

exported in txt format for its post-processing in Matlab 2017a. The gyroscope data will be filtered with a 2nd order Butterworth low pass filter with a cutoff frequency of 3 Hz to omit noise and possible filter from the obtained signal.

The AS asymmetry will be determined according to the symmetry index considering the phases with oscillation detected in both arms simultaneously with the following equation: $ASI = [(L-R) / \max(L, R)] \times 100$; where L will correspond to the amplitude or peak of the angular velocity of the left arm and R to the right arm. An ASI of 0% will be considered to determine an identical symmetry between the left and right arm.[22]

Temporospatial measures during walking

Gait temporospatial parameters (gait speed and step length) will be acquired under the same test conditions and simultaneously to obtain the AS parameters using a wireless IMU sensor model G-walk® (BTS, Italy) fixed with a semi-elastic belt between the fifth lumbar and second sacral vertebrae. Data will be recorded using the G-Studio software (BTS, Italy) at a capture frequency of 100 Hz, and transmitted via Bluetooth to a computer. Data processing will be carried out through a specific software (BTS G-Studio), validated in different populations.[24]

Functional Mobility

Functional mobility will be measured through the Timed up and go (TUG). The test measures the function of the lower limbs, mobility, and risk of falling. The participant will be instructed to get up from a chair (without using their arms), walk to a mark 3 m away, turn around, and sit back in the chair. The time in seconds it takes to complete the circuit, if the time is greater than 11 seconds, indicates a risk of falling.[25]

Quality of life

Quality of life will be assessed through the Parkinson's Disease Questionnaire (PDQ39). This is an instrument composed of 39 questions divided in to 8 domains related to aspects of quality of life. Each item can be answered according to five predetermined responses (never, rarely, sometimes, frequently, and always). The score ranges from 0 to 4 points and the total score ranges from 0 to 100 points. A lower score reflects a better quality of life. The instrument has been validated for the Spanish version.[26]

Other outcomes

Adherence will be monitored by recording attendance at training sessions. Fully adherent participants will be considered those who attend more than 80% of the training program sessions. To promote adherence, if a participant is absent for two sessions without justification, he or she will be contacted by telephone to record the reasons for the absence and to motivate him or her to return if possible.

Data management

The data of the participants obtained both in the recruitment and evaluation and follow-up will be compiled and stored in a single computer destined for the study, which will have restricted access with a password only to the principal investigator (JEA) and a co-responsible person (CCM). The informed consent will be filed and stored in a filing cabinet to which only the investigators responsible and co-responsible for the trial will have access. The information and records of each participant will be extracted in a data form in which an identifier number will be used to protect the confidentiality of the participant in the analysis and review of data. The

principal investigator (JEA) and a co-responsible person (CCM) will be the custodians of the documentation and it will be stored for a period of 5 years. The quality control of the data and records will be the responsibility of the principal investigator and co-responsible, who will verify that the data were correctly extracted and are suitable for further analysis.

Statistical analysis

The statistical package SPSS version 25 (Chicago, IL, USA) and the statistical package Graphpad Prism version 8 (San Diego, CA, USA) will be used. Descriptive data analysis will be calculated for all variables in both groups at baseline (T0). The normality distribution for each continuous variable will be verified through the Shapiro-Wilk test. Levene's test of homogeneity of variance will be used to assess the effects of the randomization procedure. To investigate differences in AS parameters, a repeated measures analysis of variance (AnovaRM) will be performed with 2 factors (time x group), to test the differences in the effect of 2 intervention protocols in times (T0), post-intervention (T1) and a follow-up one month after the intervention (T2). To determine intra- and inter-group differences, a Bonferroni post hoc test will be applied. To estimate the relationship between kinematic parameters and asymmetry of AS with lower limb parameters, Pearson's correlation coefficient will be used. Subsequently, a multiple regression analysis will be performed.

In the case of a non-normal distribution, data will be presented as the median and interquartile range, and nonparametric tests will be used. Adverse effects comparison between the two groups will be made by using the chi-square test. For the treatment of absent longitudinal data (missing data), an imputation method using regression will

be used. All results with a p-value < 0.05 will be considered statistically significant. Additionally, the size of the effect will be obtained with Cohen's d test.

Data-monitoring

This study will be supervised by a doctoral thesis committee, made up of 2 members. The main author must present the study design to the committee before starting the enrollment of the participants.

Adverse events

Adverse events (AEs) are those that have deleterious or unfavorable results that occur during the evaluation or before, during or after exercise, such as nausea, headache, falls, and disabling pain. AEs and those not related to the intervention (such as exacerbation of pre-existing diseases or worsening of PD symptoms) will be monitored in each session and reported in the results. If the patient or physiotherapist notices AEs that require medical attention, the physiotherapist in charge of the training will apply a care protocol and inform the principal investigator, who will collect a complete description of the event on a form designed for that. The intervention will be interrupted if the adverse event makes it impossible for the participant to perform physical exercise. The reasons will be explained and given all the necessary guidance and accompaniment to attend a medical check-up at the care center. In addition, the information and records obtained in the different evaluations will be permanently and irretrievably removed from the databases to maintain the confidentiality of the participant. Therefore, they will not be considered in the subsequent analysis.

Audit and inspections

The data and documents will be accessible to auditors from the Scientific Ethics Committee of the University of Talca-Talca-Chile. The principal Investigator will answer questions during inspections. All parties involved will keep the data of the participants confidential.

DISCUSSION

NW is a physical exercise modality that can be used as a non-pharmacological strategy to reduce the functional decline in people with PD. Some studies have reported the effects of NW on motor and non-motor symptoms,[27] functional mobility,[28] [29] quality of life,[30] balance,[31] and walking in PD.[27] [29] NW seems to be superior to free walking for improving locomotion and quality of life. However, a recent systematic review highlighted the high heterogeneity of the studies in terms of methodological quality, selection criteria, training prescription, and comparison groups, which makes it very difficult to replicate their results.[32]

Our study protocol provides a structured program that follows the recommendations for evaluating and intervening with NW in people with PD.[19] Both training programs (NW and FW) are identical in intensity, volume, and duration. Also, we considered all the critical elements for exercise prescription, such as specificity, overload, individualization, and progression. In our protocol, NW group participants will undergo a familiarization period using the poles. Both groups will be assessed in a one-month follow-up, and we will register any adverse events. These are aspects that have, sometimes, not been considered in previous trials.

We highlight the importance of investigating the upper limb parameters during locomotion in people with PD. The decrease in AS and its asymmetry are prevalent

dysfunctions and influence the performance of the lower limbs while walking. The increase in the AS amplitude increases cadence, gait speed, and stride length.[8 10] The NW differs from free walking by the active use of the poles, which favors the upper limb activity. We hypothesize that NW can increase the AS amplitude, reduce its asymmetry, and positively influence gait parameters. Previous studies have shown that NW improves spatiotemporal gait parameters and ground reaction force compared to free walking in healthy subjects,[33] as well as self-selected gait speed in people with PD to a greater extent than free walking.[28] The literature argues that these effects may be a consequence of using poles. However, this relationship has not been demonstrated.

To our knowledge, this is the first study to address the effects of NW on the kinematics parameters of AS and its influence on temporospatial gait parameters. However, this study may have some limitations. For example, the sensorimotor compromise some participants may have present to a greater extent, such as bradykinesia, rigidity, and incoordination, may prevent the correct execution of the NW technique. To overcome this limitation, our protocol will include people with mild to moderate compromise, and we will ensure a period of NW familiarization to acquire the correct technique. We believe that this study provides a detailed protocol to clinicians that will allow for the reproduction of our clinical trial results.

PUBLICATION AND DISSEMINATION POLICY

Once the results are available, the results will be communicated to the participants, the groups of people with PD, community rehabilitation centers, and the Physiotherapy Clinic of the University of Talca. It is planned to participate in professional meetings, and congresses and publish this protocol and the trial results

in scientific journals, especially related to the area of neurorehabilitation, physical therapy, and geriatrics. Information that could reveal the identity of the participants will never be included.

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Conflicts of interest: The authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1: Trial Flow chart

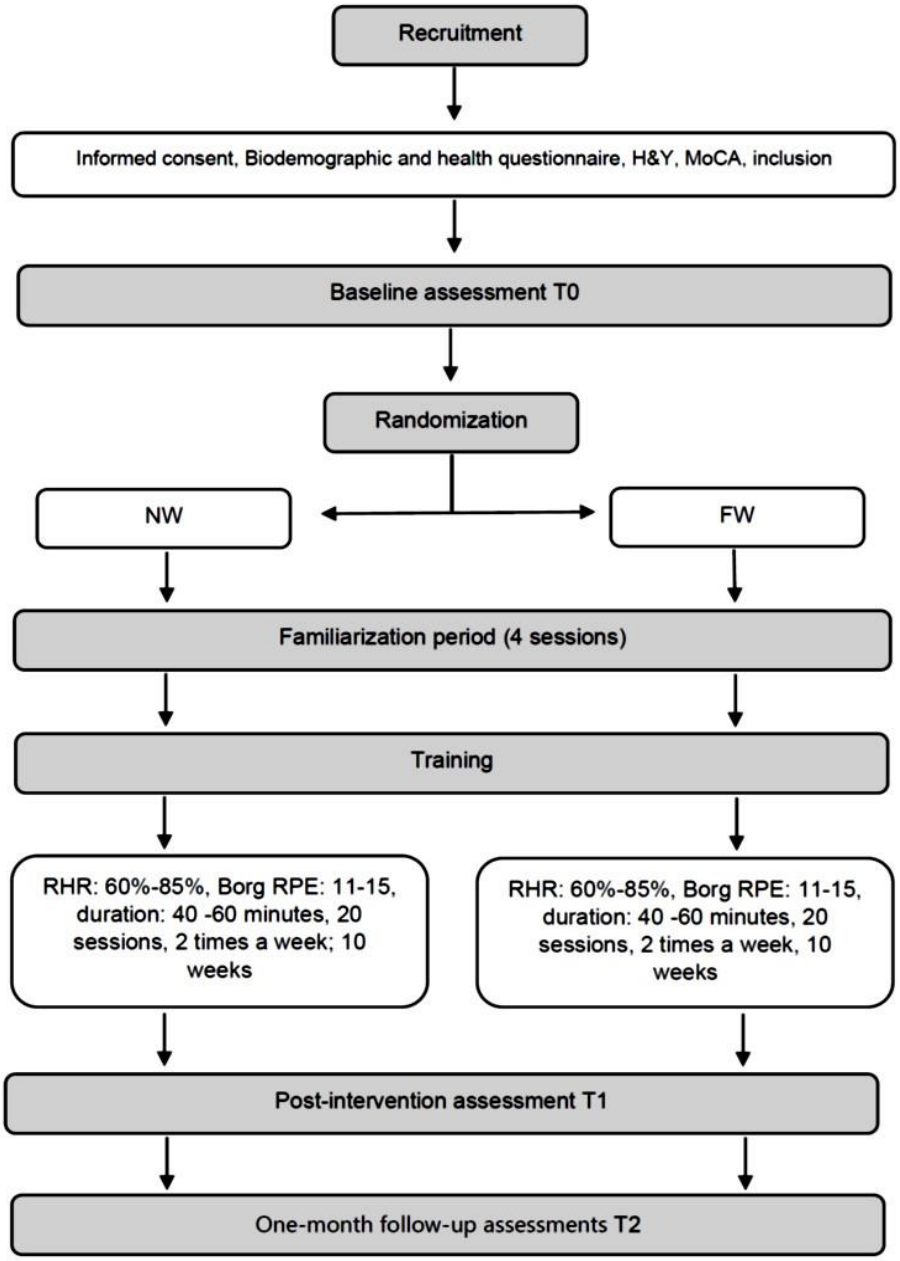
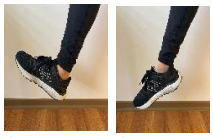
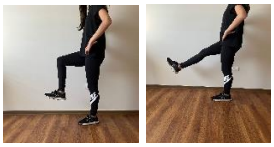
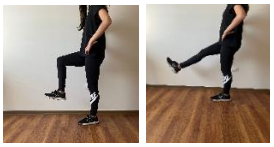
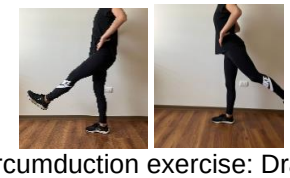
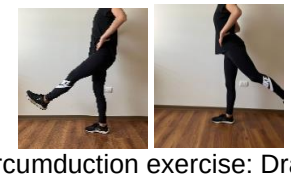


Figure 1. Trial Flow chart: H&Y: Hohen and Yahr scale; MoCA: Montreal Cognitive Assessment; NW: Nordic Walking; FW: Free walking, RHR: Reserve heart rate; RPE: Rating of perceived exertion.

SUPPLEMENTARY MATERIAL

Table S.1

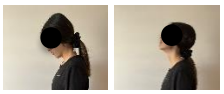
Description of the gait induction phase for both groups

Session 1	
Nordic Walking	**Free Walking**
The instructor will present to the training group and will explain the purpose and structure of the sessions.	The instructor will present to the training group and will explain the purpose and structure of the sessions.
The instructor will educate about the perception of effort and the use of the Borg scale. Education self-assessment heart rate, use of monitoring watch	The instructor will educate about the perception of effort and the use of the Borg scale. Education self-assessment heart rate, use of monitoring watch
Warm-up	
1.Respiratory exercise Inhale, expand the abdomen, hold for 3 seconds, and exhale (3 repetitions).	**1.Respiratory exercise** Inhale, expand the abdomen, hold for 3 seconds, and exhale (3 repetitions).
2. General mobility exercises a. Ankle flexion-extension exercise: In pairs, lean on your partner's right shoulder, raise your foot with an extended knee, and perform ankle flexion-extensions (1 set/10 repetitions for each ankle). Then, perform ankle circumductions (1 set/10 repetitions for each ankle).	**2. General mobility exercises** a. Ankle flexion-extension exercise: In pairs, lean on your partner's right shoulder, raise your foot with an extended knee, and perform ankle flexion-extensions (1 set/10 repetitions for each ankle). Then, perform ankle circumductions (1 set/10 repetitions for each ankle).
	
b. knee extension exercises: In pairs, lean on your partner's right shoulder. Flex the hip to 90°, extend the knee, and return. Change sides (1 set/10 repetitions for each leg))	b. knee extension exercises: In pairs, lean on your partner's right shoulder. Flex the hip to 90°, extend the knee, and return. Change sides (1 set/10 repetitions for each leg)
	
c. Hip flexion extension exercises: In pairs, lean on your partner's right shoulder. Swing your leg back and forth, keeping your knee extended. (1 set/ 10 repetitions for each leg)	c. Hip flexo extension exercises: In pairs, lean on your partner's right shoulder. Swing your leg back and forth, keeping your knee extended. (1 set/ 10 repetitions for each leg)
	
d. Waist circumduction exercise: Draw an imaginary circle with your waist (1 set/ 5 repetitions for each side)	d. Waist circumduction exercise: Draw an imaginary circle with your waist (1 set/ 5 repetitions for each side)

e. Place your hands on your shoulders. With both elbows, make circular movements backward gently and slowly, then repeat the movement but forwards. (1 set/ 5 repetitions for each direction)

f. Arm swing exercise: Swing one arm in front and the other back as much as possible, alternating. (1 set/20 repetitions)

g. Head tilt forward and backward: Look up and lift your chin, bringing your head back to do slight neck extensions. (1 set/5 repetitions)



h. Turn your head: Turn your head gently to each side. Try looking over your shoulder and pause in the center (1 set/5 repetitions for each side)

e. Place your hands on your shoulders. With both elbows, make circular movements backward gently and slowly, then repeat the movement but forwards. (1 set/ 5 repetitions for each direction)

f. Arm swing exercise: Swing one arm in front and the other back as much as possible, alternating. (1 set/20 repetitions)

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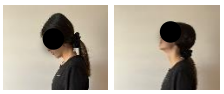


h. Turn your head: Turn your head gently to each side. Try looking over your shoulder and pause in the center (1 set/5 repetitions for each side)

Training phase

3. Postural awareness: Cervical spine

Align the cervical spine by bringing the chin to the chest until reaching a neutral position (1 set/ 3 repetitions)

4. Postural awareness: Lumbopelvic movement

Move the pelvis in anteversion, move through a neutral position, and move the pelvis toward retroversion, recognizing neutral position. Activation of the core by contracting abdominal muscles (1 set/10 repetitions)

3.Postural awareness: Cervical spine

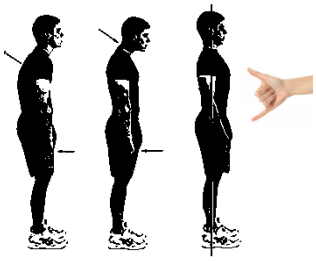
Align the cervical spine by bringing the chin to the chest until reaching a neutral position (1 set/ 3 repetitions)

4. Postural awareness: Lumbopelvic movement

Move the pelvis in anteversion, move through a neutral position, and move the pelvis toward retroversion, recognizing the neutral position. Activation of the core by contracting abdominal muscles (1 set/10 repetitions)

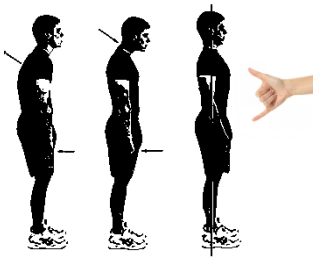
5. Postural awareness: Lumbar spine

Hold your hand, then extend only the thumb and little finger, as indicated in the figure. Place the tip of the thumb on the xiphoid process of the sternum and the little finger on the navel. Extend your body until your thumb moves away from your little finger. (1 set/ 10 repetitions)



5. Postural awareness: Lumbar spine

Hold your hand, then extend only the thumb and little finger, as indicated in the figure. Place the tip of the thumb on the xiphoid process of the sternum and the little finger on the navel. Extend your body until your thumb moves away from your little finger. (1 set/ 10 repetitions)



6. Postural awareness during walking

Walk while maintaining correct posture (cervical and lumbar spine in the neutral position, core activation, look ahead) (5 set/50 meters).

6. Postural awareness during walking

Walk while maintaining correct posture (cervical and lumbar spine in the neutral position, core activation, look ahead) (5 set/50 meters).

7. Awareness of the phases of walking

a. Show heel contact, foot strike, and foot takeoff phases.

b. In pairs, lean on your partner's shoulders and walk on your heels (3 set/5 repetitions for each leg)
c. In pairs, lean on your partner's shoulders and walk on tiptoe (3 set/5 repetitions for each leg)
d. Alone, practice the phases of walking with each leg, exaggerating heel strike (3 set/5 repetitions for each leg)
e. Practice the phases of walking with each leg, exaggerating the takeoff pace. Verbal command: "push the sand when you take off your foot" (3 set/5 repetitions for each leg)
f. Free walk, raising awareness of the phases of walking (3 sets / 30 meters)

7. Awareness of the phases of walking

a. Show heel contact, foot strike, and foot takeoff phases.

b. In pairs, lean on your partner's shoulders and walk on your heels (3 set/5 repetitions for each leg)
c. In pairs, lean on your partner's shoulders and walk on tiptoe (3 set/5 repetitions for each leg)
d. Alone, practice because ofwalking with each leg, exaggerating heel strike (3 set/5 repetitions for each leg)
e. Practice the phases of walking with each leg, exaggerating the takeoff pace. Verbal command; "push the sand when you take off your foot" (3 set/5 repetitions for each leg)
f. Free walk, raising awareness of the phases of walking (3 sets / 30 meters)

8. Awareness of the dissociation of the shoulder and pelvic girdles during walking

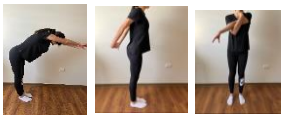
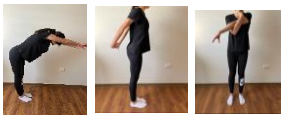
a. Show how the shoulder and pelvic girdle rotate during walking.

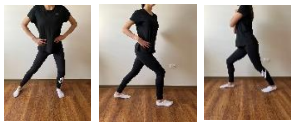
b. Walk without rotating the shoulder and pelvic girdles (2 sets/30 meters).
c. Walking by rotating the shoulder and pelvic girdle (2 sets/30 meters).

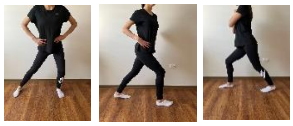
8. Awareness of the dissociation of the shoulder and pelvic girdles during walking

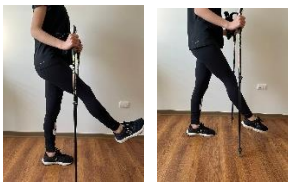
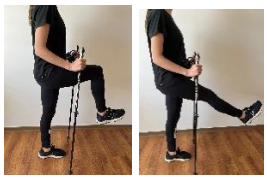
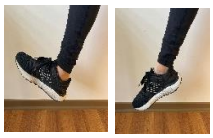
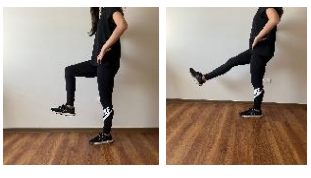
a. Show how the shoulder and pelvic girdle rotate during walking.

b. Walk without rotating the shoulder and pelvic girdles (2 sets/30 meters).
c. Walking by rotating the shoulder and pelvic girdle (2 sets/30 meters).

d. Walking exaggerating the rotation between the shoulder and pelvic girdle (2 sets/30 meters). e. As a couple, face to face. Stretch your arms in front, with your palms facing inward, without touching palms, rotate your trunk, and try to reach your partner's opposite palm, colliding with it (2 set/10 repetition for each arm).	d. Walking exaggerating the rotation between the shoulder and pelvic girdle (2 sets/30 meters). e. As a couple, face to face. Stretch your arms in front, with your palms facing inward, without touching palms, rotate your trunk, and try to reach your partner's opposite palm, colliding with it (2 set/10 repetition for each arm).
9. Awareness of Arm swing (AS) while walking a. Show the normal AS during walking. The movement is rhythmic, of medium amplitude, pendulum towards flexion and extension of the arm.  b. Walking with arms at your side without arm swing (1 set/30 meters) c. With your feet shoulder-width apart, twist your torso to the left. The arms should hang freely at the sides and will follow the movement of the body effortlessly, causing the arms to swing. Once the turn is complete, turn to the right. As you turn from side to side, your arms will begin to hit your body lightly. d. Walking at normal speed, begin to increase speed and gradually increase the arm swing to the maximum you can (2 set/30 meters)	**9. Awareness of Arm swing (AS) while walking** a. Show the normal AS during walking. The movement is rhythmic, of medium amplitude, pendulum towards flexion and extension of the arm.  b. Walking with arms at your side without arm swing (1 set/30 meters) c. With your feet shoulder-width apart, twist your torso to the left. The arms should hang freely at the sides and will follow the movement of the body effortlessly, causing the arms to swing. Once the turn is complete, turn to the right. As you turn from side to side, your arms will begin to lightly hit your body. d. Walk at normal speed, begin to increase speed, and gradually increase the arm swing to the maximum you can (2 sets/30 meters)
10. Educating and recognizing different walking speeds: Self-selected speed Intermediate speed Maximum speed. Walking at different speeds (2 sets/30 meters at each speed).	**10. Educating and recognizing different walking speeds:** Self-selected speed Intermediate speed Maximum speed. Walking at different speeds (2 sets/30 meters at each speed).
Calm down phase	
11. Respiratory exercise Inhale, expanding the abdomen, hold for 3 seconds and exhale (3 repetitions).	**11. Respiratory exercise** Inhale, expanding the abdomen, hold for 3 seconds and exhale (3 repetitions).
12. Stretching exercises Leg and shoulder stretching exercises: 3 sets/15 seconds on each side. 	**12. Stretching exercises** Leg and shoulder stretching exercises: 3 sets/15 seconds on each side. 





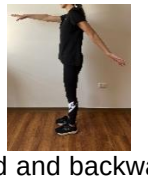
Session 2	
Nordic Walking	**Free Walking**
Warm-up	
Induction on the use of Nordic Walking poles Height adjustment of the poles **1. Respiratory exercise:** Inhale, expand the abdomen, hold for 3 seconds, and exhale (3 repetitions).	**1. Respiratory exercise:** Inhale, expand the abdomen, hold for 3 seconds, and exhale (3 repetitions).
2. General mobility exercises with poles a. Supported with the poles, raise your foot with an extended knee and perform ankle flexion extensions (1 set/10 repetitions for each ankle). Then, perform ankle circumductions (1 set/10 repetitions for each ankle).  b. Supported with the poles. Rise on tiptoe and then rest on heels (1 Set/10 repetitions)  c. Knee extension exercises: Supported with the poles. Flex the hip to 90°, extend the knee, and return. Change sides (1 set/10 repetitions for each leg).  d. Hip flexor extension exercises: Supported with the poles, Swing your leg back and forth, keeping your knee extended. (1 set/ 10 repetitions for each leg)	**2. General mobility exercises** a. Ankle flexion-extension exercise: In pairs, lean on your partner's right shoulder, raise your foot with an extended knee, and perform ankle flexion-extensions (1 set/10 repetitions for each ankle). Then, perform ankle circumductions (1 set/10 repetitions for each ankle).  b. In pairs, lean on your partner's right shoulder. Rise on tiptoe and then resto n heels (1 set/10 repetitions)  c. knee extension exercises: In pairs, lean on your partner's right shoulder. Flex the hip to 90°, extend the knee, and return. Change sides (1 set/10 repetitions for each leg)  d. Hip flexo extension exercises: In pairs, lean on your partner's right shoulder. Swing your leg back and forth, keeping your knee extended. (1 set/ 10 repetitions for each leg)

e. Waist circumduction exercise: Supported with the poles, draw an imaginary circle with your waist (1 set/ 5 repetitions for each side).

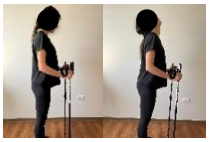
f. Front spine stretch: With the poles in your hands, bring your arms in front, stretch your spine, and try to form a line between your arms, head, and spine.

g. With the poles, swing your arms, back and forth, both simultaneously.

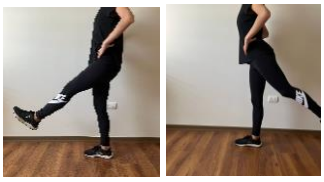
h. Arm swing exercise with poles: Swing one arm in front and the other back as Much as possible, alternating. (1 set/20 repetitions)



i. Head tilt forward and backward: Look up and lift your chin, bringing your head back to do slight neck extensions. (1 set/5 repetitions)



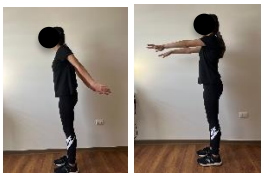
j. Turn your head: Turn your head gently to each side. Try looking over your shoulder and pause in the center (1 set/5 repetitions for each side)



e. Waist circumduction exercise: Draw an imaginary circle with your waist (1 set/ 5 repetitions for each side)

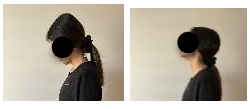
f. Front spine stretch: Bring your arms in front, stretch your spine, and try to form a line between your arms, head, and spine.

g. Swing your arms back and forth, both at the same time.

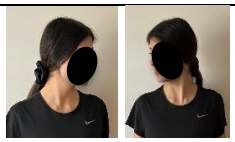


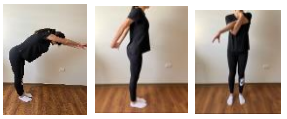
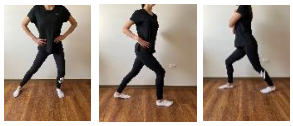
h. Arm swing exercise: Swing one arm in front and the other back as much as possible, alternating. (1 set/20 repetitions)

i. Head tilt forward and backward: Look up and lift your chin, bringing your head back to do slight neck extensions. (1 set/5 repetitions)



j. Turn your head: Turn your head gently to each side. Try looking over your shoulder and pause in the center (1 set/5 repetitions for each side)

	
Training phase	
3. Postural awareness during walking without poles: Walk while maintaining correct posture (cervical and lumbar spine in the neutral position, core activation, look ahead) (3 set/50 meters): - Look straight ahead - Avoid looking at the ground -Shoulders back and relaxed, - Natural movement of the shoulder girdle - Wide pendulum movement of the arms from the shoulder (Avoid bending the elbow excessively, 70% shoulder movement, 30% elbow movement) - Avoid vast stride (Avoid knee hyperextension) - Support the foot following the heel, sole, and toe sequence).	**3. Postural awareness during walking:** Walk while maintaining correct posture (cervical and lumbar spine in the neutral position, core activation, look ahead) (3 set/50 meters): Look straight ahead. - Avoid looking at the ground -Shoulders back and relaxed, - Natural movement of the shoulder girdle - Wide pendulum movement of the arms from the shoulder (Avoid bending the elbow excessively, 70% shoulder movement, 30% elbow movement) - Avoid vast stride (Avoid knee hyperextension) - Support the foot following the heel, sole, and toe sequence).
4. Active use of the poles First exercise: on grass Body erect, arms stretched out at the sides of the body, hands relaxed, do not hold the handle, toe of the poles backward. Start walking, with normal gait and arm swing. 2 sets 100 meters.	**4. Arm swing normal** Body erect, arms stretched out at the sides of the body, hands relaxed. Start walking, with normal gait and arm swing. 2 sets 100 meters.
5. Active use of the poles Second exercise: Same position as above. Walking will slightly increase the amplitude of the stride, thereby increasing the movement of the arms. Try to reach the navel with your hand forward. The tips of the poles are still dragging, but they will begin to snag on the ground spontaneously. (2 set/100 meters).	**5. Arm swing active** Body erect, arms stretched out at the sides of the body, hands relaxed. Start walking, with a normal gait. Walk at your usual speed and start increasing your stride length. You should feel the amplitude of your arm swing increase. (2 set/100 meters).
6. Active use of the poles Third Exercise: It is the same starting position. Walk while with stride slightly widened. Now start lightly gripping the grips, gently touching them with your fingers, and holding them without straining. Begin to get used to walking with poles. (2 set/100 meters)	**6. Arm swing active + waist dissociation**. Body erect, arms stretched out at the sides of the body, hands relaxed. Start walking with a normal gait. Then, increase your stride length. You should feel the amplitude of your arm swing increase. Then, add a slight rotation of the pelvic and shoulder girdle until the arm reaches the navel level. 2 set/100 meters).
Calm down Phase	
7. Respiratory exercise Inhale, expanding the abdomen, hold for 3 seconds and exhale (3 repetitions).	**7. Respiratory exercise** Inhale, expanding the abdomen, hold for 3 seconds and exhale (3 repetitions).

8. Stretching exercises. Leg and shoulder stretching exercises: 3 sets/15 seconds on each side. 	**8. Stretching exercises.** Leg and shoulder stretching exercises: 3 sets/15 seconds on each side.  
Session 3	
Nordic Walking	Free Walking
Induction on the use of Nordic Walking poles Height adjustment of the poles	
Warm-up	
1. Respiratory exercise Inhale, expand the abdomen, hold for 3 seconds, and exhale (3 repetitions).	**1. Respiratory exercise** Inhale, expand the abdomen, hold for 3 seconds, and exhale (3 repetitions).
2. General mobility exercises with poles Sequence of joint mobility exercises described in session 2.	**2. General mobility exercises** Sequence of joint mobility exercises described in session 2.
Training phase	
3. Walk while maintaining correct posture Cervical and lumbar spine in the neutral position, core activation, look ahead. (3 set/50 meters).	**3. Walk while maintaining correct posture** Cervical and lumbar spine in the neutral position, core activation, look ahead. (3 set/50 meters).
4. Active use of the poles First exercise: on grass Body erect, arms stretched out at the sides of the body, hands relaxed, do not hold the handle, toe of the poles backward. Start walking relaxedly, with normal gait and arm swing (2 sets 100 meters).	**4. Stride length and Arm swing** Body erect, arms stretched out at the sides of the body, hands relaxed. Start walking relaxedly, with a normal gait. Walk at your usual speed and start increasing your stride length. You should feel the amplitude of your arm swing increase (2 set/100 meters).
5. Active use of the poles Second exercise: Same position as above. Walking will slightly increase the amplitude of the stride, thereby increasing the movement of the arms. Try to reach the navel with your hand forward. The tips of the poles are still dragging, but they will begin to snag on the ground spontaneously (2 set/100 meters).	**5. Arm swing active + waist dissociation.** Body erect, arms stretched out at the sides of the body, hands relaxed. Start walking relaxedly, with a normal gait. Then, increase your stride length. You should feel the amplitude of your arm swing increase. Then, add a slight rotation of the pelvic and shoulder girdle until the arm reaches the level of the navel (2 set/100 meters).

6. Active use of the poles Third Exercise: It is the same starting position. Walk while with stride slightly widened. Now start lightly gripping the grips, gently touching them with your fingers, and holding them without straining. Begin to get used to walking with poles (2 set/100 meters).	**6. Recognizing different walking speeds:** Walking with the correct posture Coordinated gait The pendulum movement of the arms from the shoulder. Walk at your self-selected speed, awareness of perceived exertion, and increased heart rate. 1 set/ 100 metros.
7. Active use of the poles Fourth Exercise: Grasp the handle firmly, keeping the angulation of the cane. Lift the tip of the pole, advance with your arm to the height of your navel and drive it into the ground. The pole will stick close to the body's center of gravity. As your body progresses, push the pole toward the ground for the entire stroke until your hand reaches your hip. Slightly relax the pressure on the grip, maintaining control of the pole. The pole does not let go (2 sets/100 meters). The instructor will provide personalized feedback, each participant will be filmed, and the checklist will be made: 1. Walking with the correct posture 2. Coordinated gait 3. Pendulum movement of the arms from the shoulder. 4. Effective thrust from sticking the pole until reaching hip height with the hand. Feedback on the correct NW technique will be given through demonstration, video filming, and verbal instruction.	**7. Recognizing different walking speeds:** Walking with the correct posture Coordinated gait. The pendulum movement of the arms from the shoulder. Walk at your intermediate speed. Awareness of perceived exertion and increased heart rate. 1 set/ 100 metros. Walk at your maximum speed. Awareness of perceived exertion and increased heart rate. 1 set/ 100 metros. The instructor will provide personalized feedback, each participant will be filmed, and the checklist will be made: 1. Walking with the correct posture 2. Coordinated gait 3. Pendulum movement of the arms from the shoulder. Feedback on the correct walking technique will be given through demonstration, video filming, and verbal instruction.
Calm down Phase	
8. Respiratory exercise	**8. Respiratory exercise**
9. Stretching exercises Sequence of stretching exercises described in session 2.	**9. Stretching exercises** Sequence of stretching exercises described in session 2.
Session 4	
Nordic Walking	**Free Walking**
Induction on the use of Nordic Walking poles Height adjustment of the poles.	
Warm-up	
1. Respiratory exercise Sequence of respiratory exercises described in session 2.	**1. Respiratory exercise** Sequence of respiratory exercises described in session 2.

2. General mobility exercises with poles Sequence of joint mobility exercises described in session 2.	**2. General mobility exercises with poles** Sequence of joint mobility exercises described in session 2.
3. Active use of the poles First exercise: on grass Body erect, arms stretched out at the sides of the body, hands relaxed, do not hold the handle, toe of the poles backward. Begin to walk relaxed with a normal stride and arm swing. 2 sets of 50 meters	**3. Lower limb activation for walking** Stand in a line of two people. The person behind stands on the shoulders of the partner and walks on the heels, 1 set of 10 meters, and changes.
4. Active use of the poles Second exercise: Same position as above. Walking will slightly increase the amplitude of the stride, thereby increasing the movement of the arms. Try to reach the navel with your hand forward. The tips of the poles are still dragging, but they will begin to snag on the ground spontaneously. (2 set/50 meters)	**4. Lower limb activation for walking** Stand in a line of two people. The person behind leans on the shoulders of the partner and walks on toes, 1 set 10 meters, and changes.
5. Active use of the poles Third Exercise: It is the same starting position. Walk while with stride slightly widened. Now start lightly gripping the grips, gently touching them with your fingers, and holding them without straining. Begin to get used to walking with poles. (2 set/50 meters)	**5. Lower limb activation for walking** Hold a two-person line. The person behind leans on the shoulders of the partner and walks on the side edge of the feet. 1 set, 10 meters, and change
6. Active use of the poles Fourth Exercise: Grasp the handle firmly, keeping the angulation of the cane. Lift the tip of the pole, advance with your arm to the height of your navel and drive it into the ground. The cane will stick close to the body's center of gravity. As your body progresses, push the pole toward the ground for the entire stroke until your hand reaches your hip. Slightly relax the pressure on the grip, maintaining control of the pole. The pole does not let go. (2 set/50 meters)	**6. Walk while maintaining correct posture** Cervical and lumbar spine in the neutral position, core activation, look ahead (3 set/50 meters). Look straight ahead - Avoid looking at the ground -Shoulders back and relaxed, - Natural movement of the shoulder girdle - Wide pendulum movement of the arms from the shoulder (Avoid bending the elbow excessively, 70% shoulder movement, 30% elbow movement) - Avoid vast stride (Avoid knee hyperextension) - Support the foot following the heel, sole, and toe sequence).
7. Active use of the poles Fifth Exercise: Letting go of the pole back. Stand with the tips of your sticks at toe level and your arms outstretched. While still wielding the pole and keeping the pole stuck in the ground, simulate the displacement when you walk with the poles. Take small steps forward. When your hand reaches thigh height, feel the tension in your wrist. When you move further back, the tension increases. If you release the handle	**7. Arm swing active + waist dissociation** Body erects, arms stretched out at the sides of the body, hands relaxed. Begin to walk relaxed with a normal stride and arm swing. Then, increase your stride length. You should feel the amplitude of your arm swing increase. Then, add a slight rotation of the pelvic and shoulder girdle until the arm reaches the level of the navel. (2 set/100 meters)

slightly, the tension will be reduced. 1 set/ten repetitions.	
8. Active use of the poles Sixth Exercise: Regaining the pole Stand with the tips of your sticks at toe level and your arms outstretched. While still wielding the pole and keeping the pole stuck in the ground, simulate the displacement when you walk with the poles. Take small steps forward. When your hand reaches thigh height, feel the tension in your wrist. When you move further back, the tension increases. If you release the handle slightly, the tension is reduced. Continue the journey until the height of the buttocks. From there, the reverse movement will begin. Pull the strap and take the pole back into the grip, bringing it to the next forward support. Maintain the angulation of the pole. (1 set/ 10 repetitions)	**8. Walking with the correct posture** Coordinated gait The pendulum movement of the arms from the shoulder. Walk at a self-selected speed. Awareness of perceived exertion and increased heart rate. 1 set/ 100 meters.
9. Walking with the poles a. Walking with the correct posture b. Coordinated gait c. Pendulum movement of the arms from the shoulder. d. Effective thrust from sticking the pole until reaching hip height with the hand.	**9. Recognizing different walking speeds** a. Walk at intermediate speed. Awareness of perceived exertion and increased heart rate. 1 set/ 100 meters. b. Walking with the correct posture Coordinated gait. The pendulum movement of the arms from the shoulder. c. Walk at maximum speed. Awareness of perceived exertion and increased heart rate. 1 set/ 100 metros.
The instructor will provide personalized feedback, each participant will be filmed, and the checklist will be made: a. Walking with the correct posture b. Coordinated gait c. Pendulum movement of the arms from the shoulder. d. Effective thrust from sticking the pole until reaching hip height with the hand. Feedback on the correct NW technique will be given through demonstration, video filming, and verbal instruction.	The instructor will provide personalized feedback, each participant will be filmed, and the checklist will be made: a. Walking with the correct posture b. Coordinated gait c. Pendulum movement of the arms from the shoulder. Feedback on the correct walking technique will be given through demonstration, video filming, and verbal instruction.
Calm down Phase	
10. Respiratory exercise	**10. Respiratory exercise**
11. Stretching exercises Sequence of stretching exercises described in session 2.	**11. Stretching exercises** Sequence of stretching exercises described in session 2.

SUPPLEMENTARY MATERIAL

Table S.2

Prescription of the NW and FW training program per session.

Session	Nordic Walking			Free Walking		
	General prescription	Intensity according to perceived walking speed	Training volume based on 6MWT distance coefficient (%)	General prescription	Intensity according to perceived walking speed	Training volume based on % of theoretical distance of 6MWT
S1	I: 60% RHR; Borg: 11(Relatively easy). T: -Warm-up:5' -Target zone: 50' cool-down: 5 ' T: Specific introductory exercises to the NW.	50' comfortable	A= 50 B= 50 C=50	I: 60% RHR; Borg: 11(Relatively easy). T: Warm-up:5' Target zone: 50' cool-down: 5' T: Specific introductory exercises to the FW.	50' comfortable	A= 50 B= 50 C=50
S2	I: 60% RHR; Borg: 11(Relatively easy). T: Warm-up:5' Target zone: 50' cool-down: 5 ' T: Specific introductory exercises to the NW.	50' comfortable	A= 50 B= 50 C=50	I: 60% RHR; Borg: 11(Relatively easy). T: Warm-up:5' Target zone: 50' cool-down: 5' T: Specific introductory exercises to the FW.	50' comfortable	A= 50 B= 50 C=50
S3	I: 60% RHR; Borg: 11(Relatively easy). T: Warm-up:5' Target zone: 50' cool-down: 5 '	50' comfortable	A= 50 B= 50 C=50	I: 60% RHR; Borg: 11(Relatively easy). T: Warm-up:5' Target zone: 50' cool-down: 5 '	50' comfortable	A= 50 B= 50 C=50

	T: Specific introductory exercises to the NW			T: Specific introductory exercises to the FW		
S4	I: 60% RHR; Borg: 11(Relatively easy). T: Warm-up:5' Target zone: 50' cool-down: 5 ' T: Complete technique od NW.	50' comfortable	A= 50 B= 50 C=50	I: 60% RHR; Borg: 11(Relatively easy). T: Warm-up:5' Target zone: 50' cool-down: 5' Specific introductory exercises to the FW	50' comfortable	A= 50 B= 50 C=50
S5	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 44' cool-down: 11'	5´ heating 20' comfortable 24' intermediary 11' stretching	A= 50 B= 70 C=110	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 50' cool-down: 5'	5´ heating 20' comfortable 24' intermediary 11'stretching	A= 50 B= 70 C=110
S6	I: 60% RHR-70%; Borg: 11(Relatively easy) - 14 (something hard). T: Warm-up:5' Target zone: 45' cool-down: 10'	5' heating 20' comfortable 10' intermediary 15' fast 10' stretching	A= 50 B= 70 C=110	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 45' cool-down: 10'	5' heating 20' comfortable 10' intermediary 15' fast 10' stretching	A= 50 B= 70 C=110
S7	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 40' cool-down: 10'	5´ heating 20' comfortable 20' intermediary 10' stretching	A= 60 B= 80 C=120	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 40' cool-down: 10'	5´ heating 20' comfortable 20' intermediary 10' stretching	A= 50 B= 70 C=110

S8	I: 60%-70%RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 45' cool-down: 10'	5' heating 25' comfortable 20' fast 10' stretching	A= 65 B= 85 C=125	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 40' cool-down: 10'	5' heating 25' comfortable 20' fast 10' stretching	A= 65 B= 85 C=125
S9	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 44' cool-down: 11'	5' heating 20' comfortable 24' intermediary 11' stretching	A= 65 B= 85 C=125	I: 60% -70%RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 44' cool-down: 11'	5' heating 20' comfortable 24' intermediary 11' stretching	A= 65 B= 85 C=125
S10	I: 60% -70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 45' cool-down: 11'	5´ heating 20' comfortable 24' intermediary 5' fast 10' stretching	A= 65 B= 85 C=125	I: 60% -70%RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 45' cool-down: 11'	5´ heating 20' comfortable 24' intermediary 5' fast 10' stretching	A= 65 B= 85 C=125
S11	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 45' cool-down: 10'	5´ heating 20' comfortable 10' intermediary 15' fast 10' stretching	A= 55 B= 75 C=115	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5' Target zone: 45' cool-down: 10'	5' heating 20' comfortable 10' intermediary 15' fast 10' stretching	A= 55 B= 75 C=115
S12	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5'	5' heating 20' comfortable 10' intermediary 15' fast 10' stretching	A= 60 B= 80 C=120	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5'	5´ heating 20' comfortable 10' intermediary 15' fast 10' stretching	A= 60 B= 80 C=120

	Target zone: 45’ cool-down: 10’			Target zone: 45’ cool-down: 10’		
S13	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 45’ cool-down: 10’	5´ heating 20’ comfortable 10’ intermediary 15’ fast 10’ stretching	A= 65 B= 85 C=125	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 45’ cool-down: 10’	5´ heating 20’ comfortable 10’ intermediary 15’ fast 10’ stretching	A= 65 B= 85 C=125
S14	I: 60% -80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 70 B= 90 C=130	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10 ‘	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 70 B= 90 C=130
S15	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 75 B= 95 C=145	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 75 B= 95 C=145
S16	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10’	10´ heating 40 ´comfortable 10 ´stretching	A= 65 B= 85 C=125	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10’	10´ heating 40 ´comfortable 10 ´stretching	A= 65 B= 85 C=125
S17	I: 60%-80% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’	5´ heating 20’ comfortable 10’ intermediary 15’ fast 10’ stretching	A= 65 B= 85 C=125	I: 60%-80% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’	5´ heating 20’ comfortable 10’ intermediary 15’ fast 10’ stretching	A= 65 B= 85 C=125

	Target zone: 45’ cool-down: 10’			Target zone: 45’ cool-down: 10’		
S18	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10’	5´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 70 B= 90 C=130	I: 60% -80%RHR; Borg: 11(Relatively easy) - 13 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10’	5´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 70 B= 90 C=130
S19	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10’	10´ heating 25 ´comfortable 10 ´intermediary 3’ fast 3’ jog 10’ stretching	A= 75 B= 95 C=135	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:5’ Target zone: 41’ cool-down: 10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 75 B= 95 C=135
S20	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10’	10´ heating 25’ comfortable 20’ fast 10’ stretching	A= 75 B= 95 C=135	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10’	10´ heating 25’ comfortable 20’ fast 10’ stretching	A= 75 B= 95 C=135
S21	I: 60% -70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10’	10´ heating 20’ comfortable 20’ fast 10’ stretching	A= 80 B= 100 C=140	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10’	10´ heating 20’ comfortable 20’ fast 10’ stretching	A= 80 B= 100 C=140
S22	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog	A= 90 B= 110 C=150	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog	A= 90 B= 110 C=150

	Target zone: 41’ cool-down: 10’	10’ stretching		Target zone: 41’ cool-down: 10’	10’ stretching	
S23	I: 60%-80%RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:10’ Target zone: 41’ cool-down: 10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 90 B= 110 C=150	I: 60%-80% RHR; Borg: 11(Relatively easy) - 15 (hard). T: Warm-up:10’ Target zone: 41’ cool-down: 10’	10´ heating 25’ comfortable 10’ intermediary 3’ fast 3’ jog 10’ stretching	A= 90 B= 110 C=150
S24	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10’	10´ heating 20’ comfortable 20’ fast 10’ stretching	A= 100 B= 120 C=160	I: 60%-70% RHR; Borg: 11(Relatively easy) - 13 (something hard). T: Warm-up:5’ Target zone: 40’ cool-down: 10 ‘	10´ heating 20’ comfortable 20’ fast 10’ stretching	A= 100 B= 120 C=160

Supplementary material 3

Baseline assessments to characterize the sample and prescribe training

Characterization of the sample

A personal interview will be carried out to collect biodemographic and health data such as age, sex, educational level, time of diagnosis of the disease, medication, dose, Sleep quality, diet, physical activity level, and history of falls in the last year.

Motor and non- motor Symptoms of PD

After the biodemographic and health data collection, the Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) will be applied, following the established protocol.[1] It is a validated and reference instrument to evaluate the progression of motor and non-motor symptoms in PD.

Vital parameters and anthropometric evaluation

To safeguard the safety of the participants and prescribe the training individually, the vital parameters of heart rate, blood pressure, and respiratory rate will be assessed. The heart rate will be used to determine the intensity of training based on the Tanaka model to establish the maximum heart rate based on age[2] and the calculation of the Reserve Heart Rate (RHR) to determine the range of intensity of the training[3].

The anthropometric profile will begin with the measurement of weight in kilograms (kg) using an OMRON-514C scale and height in centimeters (cm) using a SECA 206 wall-mounted stadiometer, data that allows calculating the body mass index (BMI) through the weight/height^2 ratio (kg/cm^2). The upper limb length from the acromion to the tip of the middle finger and the lower limb length from the greater trochanter to the ground plane shall also be measured (m).

10-meter walk test (10MWT)

The 10MWT is a validated performance measure used to assess walking speed in meters per second (m/s) over a short distance in different health conditions[4] and correlates with functional mobility and mortality[5]. The individual walks for 14 meters straight path, with the time measured for the intermediate 10 meters to allow for acceleration and deceleration. Start timing when the toes pass the 2-meter mark and stop timing when the toes pass the 12-meter mark. The total time to travel the intermediate 10 meters is recorded. The speed is calculated based on the ratio between 10 meters and the total time required in m/s. The protocol will be applied in two conditions, at self-selected walking speed (SSWS) and maximum speed randomly. Each participant will complete 3 trials for each condition, which will be averaged.

Locomotor Rehabilitation Index

From the SSWS (mechanical gait marker) obtained in the 10MWT and the calculation of the optimal walking speed (OWS), defined as the walking speed where the metabolic cost is lowest (OWS= $\sqrt{[0.25 \times g \times l]}$; where g, gravital acceleration (9.81ms-2); l, lower limb length), the Locomotor Rehabilitation Index (LRI) will be determined, which expresses the relationship between the SSWS and OWS (LRI=100 x SSWS/OWS).[6] Is a complementary analysis of spatiotemporal parameters in gait assessment.
According to this index, when the SSWS and OWS are coincident, walking is functional and healthy. The walking speed obtained in the 10MWT will also allow to determine the intensity of the training[6], using the following descriptors: comfortable: self-selected gait speed; intermediate: between comfortable speed and maximum speed; fast: maximum walking speed; Maxima: maximum trot.

6-minute walk test (6MWT)

The 6MWT is a sub-maximal exercise test used to assess aerobic capacity and endurance through the maximum distance covered in 6 minutes. After resting for 10 minutes, the test will be applied according to the protocol of the American Thoracic Society (ATS).[7] The test will be carried out in a corridor of 30 meters in length, flat and straight. The participant must walk for six minutes at a fast pace that allows the patient

to perform as many meters as possible in this time. The sensation of dyspnea (choking), blood pressure, heart rate, oxygen saturation, and meters reached will be recorded. The theoretical maximum distance will be obtained using the reference values for the Chilean population described by Osses et al, 2010, according to sex, height, and BMI.[8] Based on this, the participants will be divided into each group according to the distance coefficient. **Group A** whose coefficient is less than 0.85, **group B**, those who walk with a coefficient between 0.86 to 1.2, and **group C** with a coefficient over 1.2, and will progress according to the Peyré-Tartaruga proposal.[6]
After this phase of evaluation, the participants will be summoned again to complete the kinematic evaluation of the gait.

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7 CONCLUSÃO GERAL

O objetivo desta tese foi verificar possíveis diferenças na ABB entre indivíduos com e sem DP e analisar sua relação com parâmetros espaço-temporais da marcha e de progressão da doença. Adicionalmente, também objetivamos propor um protocolo de ensaio clínico controlado e randomizado para investigar o efeito do treinamento de CN sobre os parâmetros cinemáticos do BB e sua influência sobre os parâmetros da marcha em membros inferiores, mobilidade funcional e qualidade de vida.

Com base no primeiro artigo, é possível concluir que pessoas com DP têm maior amplitude da ABB e velocidade, bem como menor amplitude de BB em comparação com indivíduos sema doença, independentemente da fase de medicação ON/OFF e do teste de marcha utilizado. À medida que a doença progride e os sintomas pioram, a ABB tende a diminuir. A ABB não mostrou associação significativa com a cadência e o comprimento da passada. Isso sugere que a DP altera o BB durante a marcha de forma assimétrica e que a assimetria da amplitude e da velocidade, bem como a amplitude do BB, seriam parâmetros motores capazes de diferenciar pessoas com DP de pessoas sem a doença. Por fim, nossos resultados mostraram que à medida que a doença progride e os sintomas aumentam, a ABB diminui.

Ainda há poucos estudos que abordam os distúrbios dos membros superiores e sua influência sobre os membros inferiores durante a marcha na DP, em diferentes estágios da doença, em diferentes fases farmacológicas e após diferentes estratégias de reabilitação da marcha. Estudos futuros devem se concentrar na análise da influência do ABB e do BB nos parâmetros dos membros inferiores durante a marcha e na avaliação da terapia farmacológica e não farmacológica sobre o BB e os parâmetros da marcha em diferentes estágios da doença. Além disso, os resultados destacam a necessidade de pesquisas que avaliem os distúrbios do BB de forma objetiva. Os sistemas de análise baseados em instrumentos são complexos e caros para serem implementados na clínica e em ambientes não supervisionados, exigindo a validação de instrumentos econômicos e minimamente invasivos que permitiriam aos clínicos monitorarem os parâmetros do BB e avaliar a eficácia das estratégias de reabilitação da marcha na DP. Atualmente, surgiram dispositivos como sensores portáteis, smartphones, sensores ópticos de baixo custo, entre outros, que permitiriam

expandir o estudo do BB e dos distúrbios dos membros inferiores, bem como os efeitos das estratégias de reabilitação.

No segundo estudo, levantamos a hipótese de que a CN poderia aumentar a amplitude do BB, reduzir a assimetria e impactar positivamente os parâmetros da marcha em pessoas com DP. A CN difere da caminhada livre pelo uso ativo de bastões, o que favorece a atividade dos membros superiores e tem se mostrado uma modalidade de exercício físico que pode ser usada como uma estratégia não farmacológica para reduzir o declínio funcional em pessoas com DP. Este é o primeiro estudo destinado a avaliar os efeitos da CN nos parâmetros cinemáticos do BB e sua influência nos parâmetros espaço-temporais dos membros inferiores na marcha. Acreditamos que este estudo fornece um protocolo detalhado que permitirá a replicação de resultados obtidos pelo futuro ensaio clínico que será realizado.

Até o momento, vários estudos demonstraram que a CN é uma atividade fácil e segura, com efeitos benéficos em diferentes condições de saúde. A CN é uma atividade esportiva incipiente no Chile, não existindo nenhum programa de CN, nem grupos de pesquisa nessa linha de trabalho na Universidade de Talca. Portanto, considero que esta tese, além de cumprir com seu papel como requisito para concessão do título de doutor, servirá como base para iniciar uma linha de pesquisa pioneira e promissora, com o objetivo de avaliar os efeitos da CN em diferentes parâmetros de saúde e grupos populacionais na cidade e na Univerdidade de Talca – Chile.

8 IMPACTOS DO TRABALHO

Do ponto de vista clínico, a ABB e o BB devem ser considerados parâmetros motores relevantes no exame das anormalidades da marcha na DP. A avaliação objetiva desses parâmetros pode contribuir para o diagnóstico diferencial e precoce da DP. Além disso, os parâmetros BB podem ser usados para detectar o início das anormalidades da marcha, evitar consequências adversas, como quedas, monitorar a progressão da doença e avaliar os efeitos das estratégias de intervenção em pessoas com DP.

Por fim, a criação de um protocolo de ensaio clínico sobre os efeitos da CN nos parâmetros de BB e na marcha permitirá a replicação dos resultados e melhorará a

qualidade metodológica dos estudos clínicos que usam a CN como estratégia de intervenção na DP.

ANEXOS

ANEXO A

Submission guidelines BMJ Open Sport & Exercise Medicine

Please review the below article type specifications including the required article lengths, illustrations, table limits and reference counts. The word count excludes the title page, abstract, tables, acknowledgements, contributions, and references. Manuscripts should be as succinct as possible, yet if you feel your manuscript warrants additional length, consult the editorial office and/or mention the reason in your Cover letter.

We encourage authors to submit previous reviews by other journals and specify what action they took to address reviewer comments. Submitting previous reviews may significantly reduce article processing times. When you submit a previously reviewed manuscript to BMJ Open Sport & Exercise Medicine, please name the journal and submission ID in the cover letter and append any previous reviews and your responses.

For further support when making your submission please refer to the resources available on the BMJ Author Hub. Here you will find information on writing and formatting your research through to the peer review process and promoting your paper.

Protocol

A study protocol's purpose is to keep researchers and funding bodies current in their fields by exposing them to research activity that would otherwise go unnoticed. This can help to avoid redundant work and, hopefully, enable collaboration. Protocol publication in its entirety also makes more information available than trial registries currently require and increases transparency, making it easier for others (editors, reviewers, and readers) to see and understand any deviations from the protocol that may have occurred during a study.

BMJ Open Sport & Exercise Medicine will consider protocols for any study design, including observational studies and systematic reviews.

Protocol manuscripts should report planned or ongoing research studies. If data collection is complete we will not consider the protocol. The inclusion of pilot data supportive of the protocol is encouraged.

Protocols for studies that will require ethical approval, such as trials, will not be considered without having received that approval.

Additional material may be presented as supplementary information, which will be published in a single PDF file in the Appendix should your protocol be accepted.

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Word count: up to 4000 (excluding references and tables)

Abstract: up to 250, unstructured

Tables/illustrations: up to 6 tables and/or figures

References: up to 30

Include the key messages of your protocol after your abstract using the following headings. These key points should be no more than 3-5 sentences and should be distinct from the abstract; be succinct, specific and accurate!

What is already known on this topic - summarise the state of current scientific knowledge and/or clinical practice on your intended study's subject

What this study adds - summarise the report's take home messages, highlighting their scientific and/or clinical relevance.

How this study might affect research, practice or policy - summarise the intended study's potential impact and implications.

This will be published as a summary box after the abstract in the final published protocol.

10 tips on preparing your scientific manuscript for BMJ Open Sports & Exercise Medicine

Read our instructions for authors carefully. Familiarize yourself with our style guide, formatting requirements and word count limits.

Look at our recent publications to get an idea of what topics are currently being explored. For our journal, the topic must have relevance for clinicians with the key question 'will the findings change what practitioners do?''

Gather background information. Conduct a thorough literature review of your topic and ensure your paper reflects the current state of the literature. Make sure to include only the most relevant, trustworthy and up-to-date sources. It is also important to reflect on contradictory sources if it is a relevant discovery of the literature review.

Write clearly and concisely. Aim for clarity and brevity. Avoid jargon and use simple language and assumptions on the knowledge base of the reader. Clearly expand any acronyms used earlier on in your paper. Ensure your paper is directed to our broad audience.

Create a catchy title and abstract. Capture the reader's attention with a compelling title and concise, informative abstract. Your title should also accurately reflect your paper. As you conduct your literature review note any particular naming conventions for your type of paper and reflect this, if appropriate.

For your introduction, we encourage short introductions when the rationale of the study is obvious, i.e. it may be as short as 3 short paragraphs if that addresses the question “Why we did it”.

We encourage the use of the headings Introduction, Methods, Results, Discussion, and subheadings where appropriate.

Organize your data and results in tables and diagrams to present the data in an easy-to-understand format. As we are an online journal, we can include colour Figures in your manuscript without additional costs.

Discuss the results and implications and explain the significance of the findings. We find it hard to imagine a discussion that has fewer than two subheadings.

Edit and proofread your paper. Check for spelling, grammar and punctuation errors. Have someone review the manuscript before submitting it. You may also wish to use the language editing and translation services provided by BMJ Author Services.

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Keywords are specific terms that define what your paper is about. Keywords are important for search engine optimisation and enhance the discoverability of your work and its impact. They also help editors to identify peer reviewers for your manuscript.

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Main text separated under appropriate headings and subheadings using the following hierarchy: BOLD CAPS, bold lower case, Plain text, Italics

Tables should be in Word format and placed in the main text where the table is first cited. Tables should also be cited in numerical order

Acknowledgments, Competing Interests, Funding and all other required statements

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Figures must be uploaded as separate files (view further details under the Figures/illustrations section). All figures must be cited within the main text in numerical order and legends should be provided at the end of the manuscript.

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Acronyms and abbreviations should be used sparingly and fully explained when first used. Abbreviations and symbols must be standard. SI units should be used throughout, except for blood pressure values which should be reported in mm Hg.

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Please ensure that any specific patient/hospital details are removed or blacked out (e.g. X-rays, MRI scans, etc). Figures that use a black bar to obscure a patient's identity are not accepted.

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Tables should be in Word format and placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as Excel files within the manuscript are NOT accepted. Tables in Excel should be copied and pasted into the manuscript Word file.

Tables should be self-explanatory and the data they contain must not be duplicated in the text or figures. Any tables submitted that are longer/larger than 2 pages will be published as online only supplementary material. Video: How to improve your graphs and tables

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Data citations: Wang G, Zhu Z, Cui S, at al. Glucocorticoid induces incoordination between glutamatergic and GABAergic neurons in the amygdala. Dryad Digital Repository [dataset]. August 11, 2017. https://doi.org/10.5061/dryad.k9q7h.

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Legal material: Toxic substances Contro Act: Hearing on S776 Before the Subcommittee of the Environment of the Senate Comm. on Commerce, 94th Congress 1st September (1975).

Law references: The two main series of law reports, Weekly Law Reports (WLR) and All England Law Reports (All ER) have three volumes a year e.g., Robertson v Post Office [1974] 1 WLR 1176

Acknowledgements

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Additional information such as figures, tables, raw data and methodology statements, may be submitted and published alongside your manuscript as ‘supplemental material’. Supplemental material shall only be accepted subject to the following criteria:

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