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The feasibility, safety, physiological and clinical effects of high-intensity interval training for people with Parkinson's: a systematic review and meta-analysis

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Abstract

Background:
Exercise is important for people with Parkinson's (PwP), with high-intensity interval training (HIIT) proposed as a feasible and effective exercise modality. However, no literature synthesis for PwP has been undertaken.
Objectives:
To evaluate the feasibility, safety, physiological and clinical effects of HIIT for PwP.
Methods:
Systematic searches of Medline, Embase, CINAHL, Web of Science, and Google Scholar were undertaken. Studies that included ≥ 2 weeks of HIIT for PwP and reported sufficient detail for full quality assessment were eligible. Quality was assessed with the TESTEX scale or the Downs and Black tool according to study design. Feasibility and safety data, physiological and clinical outcomes were extracted. Meta-analyses explored the pooled effects of HIIT on $VO_{2peak/max}$ compared to moderate-intensity continuous exercise (MICE) and usual care.
Results:
Eleven articles were identified (seven controlled/comparator studies and four single group) including 117 HIIT participants predominantly of mild-to-moderate disease severity. HIIT programmes were professionally supervised and between 6 weeks and 24 months. Overall, study quality was deemed to be moderate to good. Following screening, nine studies reported 90–100% programme completion; however, only one was > 12 weeks in duration. Adverse events were uncommon. HIIT improved $VO_{2peak/max}$ compared to usual care, but not to MICE. Increased brain-derived neurotrophic factor (BDNF) and improved motor symptoms were also reported.
Conclusion:
Up to 12 weeks of supervised HIIT appears to be feasible and safe for some people with mild-to-moderate disease severity. HIIT improves cardiorespiratory fitness and may increase BDNF and improve motor symptoms in PwP. Future studies should explore safe ways to facilitate access and long-term adherence.

Keywords (separated by '-') Exercise - Neurodegenerative - Physical - Activity - Cardiorespiratory

Footnote Information

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REVIEW

The feasibility, safety, physiological and clinical effects of high-intensity interval training for people with Parkinson's: a systematic review and meta-analysis

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Abstract

Background Exercise is important for people with Parkinson's (PwP), with high-intensity interval training (HIIT) proposed as a feasible and effective exercise modality. However, no literature synthesis for PwP has been undertaken.

Objectives To evaluate the feasibility, safety, physiological and clinical effects of HIIT for PwP.

Methods Systematic searches of Medline, Embase, CINAHL, Web of Science, and Google Scholar were undertaken. Studies that included ≥ 2 weeks of HIIT for PwP and reported sufficient detail for full quality assessment were eligible. Quality was assessed with the TESTEX scale or the Downs and Black tool according to study design. Feasibility and safety data, physiological and clinical outcomes were extracted. Meta-analyses explored the pooled effects of HIIT on $VO_{2peak/max}$ compared to moderate-intensity continuous exercise (MICE) and usual care.

Results Eleven articles were identified (seven controlled/comparator studies and four single group) including 117 HIIT participants predominantly of mild-to-moderate disease severity. HIIT programmes were professionally supervised and between 6 weeks and 24 months. Overall, study quality was deemed to be moderate to good. Following screening, nine studies reported 90–100% programme completion; however, only one was > 12 weeks in duration. Adverse events were uncommon. HIIT improved $VO_{2peak/max}$ compared to usual care, but not to MICE. Increased brain-derived neurotrophic factor (BDNF) and improved motor symptoms were also reported.

Conclusion Up to 12 weeks of supervised HIIT appears to be feasible and safe for some people with mild-to-moderate disease severity. HIIT improves cardiorespiratory fitness and may increase BDNF and improve motor symptoms in PwP. Future studies should explore safe ways to facilitate access and long-term adherence.

Keywords Exercise · Neurodegenerative · Physical · Activity · Cardiorespiratory

Parkinson's disease (Parkinson's) is a debilitating neurodegenerative disorder, characterised by tremor, rigidity, bradykinesia, and postural instability, along with a wide range of non-motor symptoms [1]. Parkinson's is the fastest growing neurological condition globally, affecting an estimated 6.1 million people [2] including 1% of people over the age of 60 [3]. Exercise is considered to be an important aspect of Parkinson's management, having been evinced to stimulate neuroprotection [4] and amelioration of motor and non-motor symptoms, [5, 6] with higher intensity exercise theorised to provide greater benefits [7, 8]. Additionally, a lack of regular exercise can lead to reduced aerobic fitness compared to healthy controls [9], potentially increasing the risk of additional health and wellbeing complications. However, people with Parkinson's (PwP) face barriers to exercise participation including perceived lack of time, low outcome expectation and fear of symptom exacerbation [10].

High-intensity interval training (HIIT) is a low-volume, high-intensity exercise modality consisting of short periods of high-intensity exercise interspersed with periods of rest or active recovery. Compared to traditional endurance exercise, HIIT has been evinced to promote similar or greater physiological adaptations in both healthy and clinical populations with reduced exercise volume and total time commitment [11–13]. HIIT, therefore, could be apposite for PwP.

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While recent reviews have investigated the effects of exercise therapies [14], intensive exercise [15], and aerobic exercise [5] for PwP, no systematic pooling of evidence involving HIIT interventions has been undertaken. Therefore, by undertaking a comprehensive synthesis of available evidence, this review aimed to provide an overview of the feasibility and safety of HIIT through the assessment of data, such as eligibility, programme completion, and adverse events. A secondary aim was to evaluate the effects of HIIT on physiological and clinical health outcomes in PwP.

Methods

The review was undertaken and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16]. Review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42021290258. The final search strategy was peer-reviewed by an information specialist with reference to an amended PICO model: as the review involved no specific comparator or outcome, these aspects were not included in the search strategy to ensure sensitivity.

Searches

A systematic literature search of Medline, Web of Science, CINAHL, Embase, and PsycINFO databases was undertaken up to the 23rd November 2021, with grey literature identified using Google Scholar. Database searching involved a combination of phrases, subject headings, and Boolean operators (Appendix B). Backward and forward citation chasing was undertaken using identified systematic reviews [5, 14, 15] and original articles.

Article type

All published original articles and grey literature that reported sufficient information to enable a full quality assessment were included. There were no restrictions regarding date or article language.

Participants

Participants were > 17 years, diagnosed with Parkinson's. Articles that included healthy individuals or those with differing neurodegenerative conditions were excluded.

Study design

All study design types involving any modality of HIIT for PwP, or exercise training that included HIIT within a broader programme were included. Programmes with non-exercise components were excluded, except combined exercise and education programmes. Programmes had to be of at least 2 weeks in duration to be included. Eligible articles described exercise target intensity as ≥ 75% of maximal heart rate (HR_{max}) or equivalent [17], including programmes that involved interval exercise of target intensity in part (such as 65%-85% HR_{max}). Where classification was based on description or other data, such as being described as "high intensity", or "maximal effort" inclusion was discussed by authors. Articles that included any type or no comparator were included.

Outcomes

Feasibility data such as programme recruitment, attendance, completion, patient experience and achieved exercise intensity, safety data such as adverse effects and events, and physiological and clinical health-related outcomes were included.

Selection process

Following the literature search and removal of duplicates, titles, and abstracts were screened and full texts examined by two authors (CH and HG). A third author (LC) was designated to resolve disagreements regarding inclusion but was not required. Reasons for exclusion of articles were reported. Mendeley Desktop version 1.19.8 and Rayyan online software were utilised.

Data extraction

The following were extracted and tabulated for each study; lead author and date, aspects of study design including trial type, HIIT protocol, frequency and duration of intervention, supervision, setting, and control group activities along with outcome data. Participant characteristics included number, age, sex, pharmacotherapy, on/off symptom state, disease stage, and duration of Parkinson's.

Quality assessment

Each paper was assessed for risk of bias by two authors (CH and either LC, HG, or JM) with either the Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) scale [18] or the Modified Downs and Black quality assessment tool [19] dependent on study design. Two assessment tools were utilised to ensure that all study types were assessed appropriately. The TESTEX scale consists of 15 items, 5 relating to study quality and 10 pertaining to reporting, including factors, such as randomisation and intention-to-treat analysis. Studies with a TESTEX score of 12–15 were considered to be high quality, 7–11 to be good

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quality, and ≤ 6 low quality [20]. The TESTEX scale was applied to studies with a control or comparator group. The Modified Downs and Black assessment tool was applied to single group pre/post-design studies, and a single-subject case study. Validated as a suitable assessment tool for non-randomised studies [21], the Modified Downs and Black tool consists of 27 items, relating to reporting (10 items, 1 item double weight), external validity (3), internal validity (13), and study power (1). For this study, 24–28 points was considered high quality, 19–23 good, 14–18 fair, and < 14 poor [22].

Data extraction and analysis

Data relating to individual health-related outcomes, feasibility, and safety were extracted and tabulated. Meta-analyses were undertaken to explore the pooled effects of HIIT on $VO_{2peak/max}$ (ml/kg/min) compared to usual care and MICE. The strength of meta-analysed evidence was evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [23]. The GRADE tool assesses strength of evidence according to risk of bias, inconsistency, indirectness of evidence, imprecision, and publication bias. Quantitative data analysis included calculation of mean pre- to post-intervention changes (in preference to final values comparison to eliminate between subject variability). If unreported, standard deviation changes were calculated with the application of an imputed correlation coefficient with additional sensitivity analysis [24]. Meta-analysis was undertaken with an inverse variance weighting method with fixed effects model to calculate weighted mean difference (WMD) and 95% confidence intervals (95% CI) between HIIT and comparator groups [24]. Analysis was undertaken with Review Manager v5.4, with $P < 0.05$ considered statistically significant. I^2 values (%) were calculated to evaluate statistical heterogeneity, with the following thresholds applied as recommended in the Cochrane Handbook for Systematic Reviews [24]; 0%–40% might not be important, 30%-60% may represent moderate heterogeneity, 50%–90% substantial heterogeneity, and 75%-100% considerable heterogeneity. No publication bias assessment or sensitivity analysis was undertaken due to the limited number of studies in meta-analysis.

Results

Study identification and selection (Fig. 1)

Database searches identified 3644 articles, with one additional article identified through manual searching. Following removal of duplicates, 2803 articles were screened. Full-text examination was undertaken with 74 articles following a review of titles and abstracts. Eleven articles met inclusion criteria for qualitative analysis, of which four were deemed suitable for two separate meta-analyses. The majority of excluded articles ($n = 51$) that underwent full-text examination were omitted due to exercise programmes not including HIIT. Articles that included HIIT for PwP but were excluded due to other criteria are listed in Appendix C.

Study and participant characteristics

Study characteristics

Of the 11 identified articles, one was a randomised controlled trial with usual care control group [25], three were randomised exercise comparator trials [26–28], one was a randomised controlled pilot study [29], one was a pseudo-randomised controlled trial [30], three were single group (pre/post-design) studies [31–33], one was a randomised controlled pilot study with additional comparator [34], and one was a single-subject case study [35]. Nine articles were fully published, and two were grey literature (PhD thesis, [35] MSc thesis [27]). Two articles reported data from the HIIT group of the same intervention, but utilised different comparators [29, 34]. Eight studies included only HIIT, whilst three included an HIIT component as part of a mixed-intensity aerobic programme [25, 30, 31]. Of the seven studies that included a comparator, four consisted of MICE [26–28, 34], and three of usual care [25, 29, 30].

Exercise programmes

HIIT modalities included cycle ergometry, [25, 27, 30–33, 35] and also running [28], high-intensity walking [26], and resistance training [29, 34]. HIIT work: rest ratio ranged between 3 min work: 3 min active recovery [26] and 15 s work: 45 s at preferred intensity [33]. Programme duration ranged between 3 weeks [32, 35] and 24 months, [28] the most common duration being of 12 weeks ($n = 3$), with frequency being predominantly thrice-weekly. When compared to MICE, total exercise time was less in HIIT in three out of four studies [27, 28, 34] and the same in one [26], while total exercise volume was less in HIIT than MICE in all four comparator studies. Seven studies calculated target exercise intensity as % of $HR_{peak/max}$, one as % of peak power output [27] (PPO), one as % of peak workload [30] (PWL), one as perceived maximum effort [33] ("as fast as possible"), and one as rate of perceived exertion [28] (RPE [36]). HIIT target intensity ranged between 75% HR_{max} [25, 31] and 100% HR_{peak} [32, 35]. Individualised target intensity was established through incremental exercise testing in five studies [27, 29, 30, 32, 35], while three [25, 26, 31] utilised age-predicted formulas. All programmes were described as

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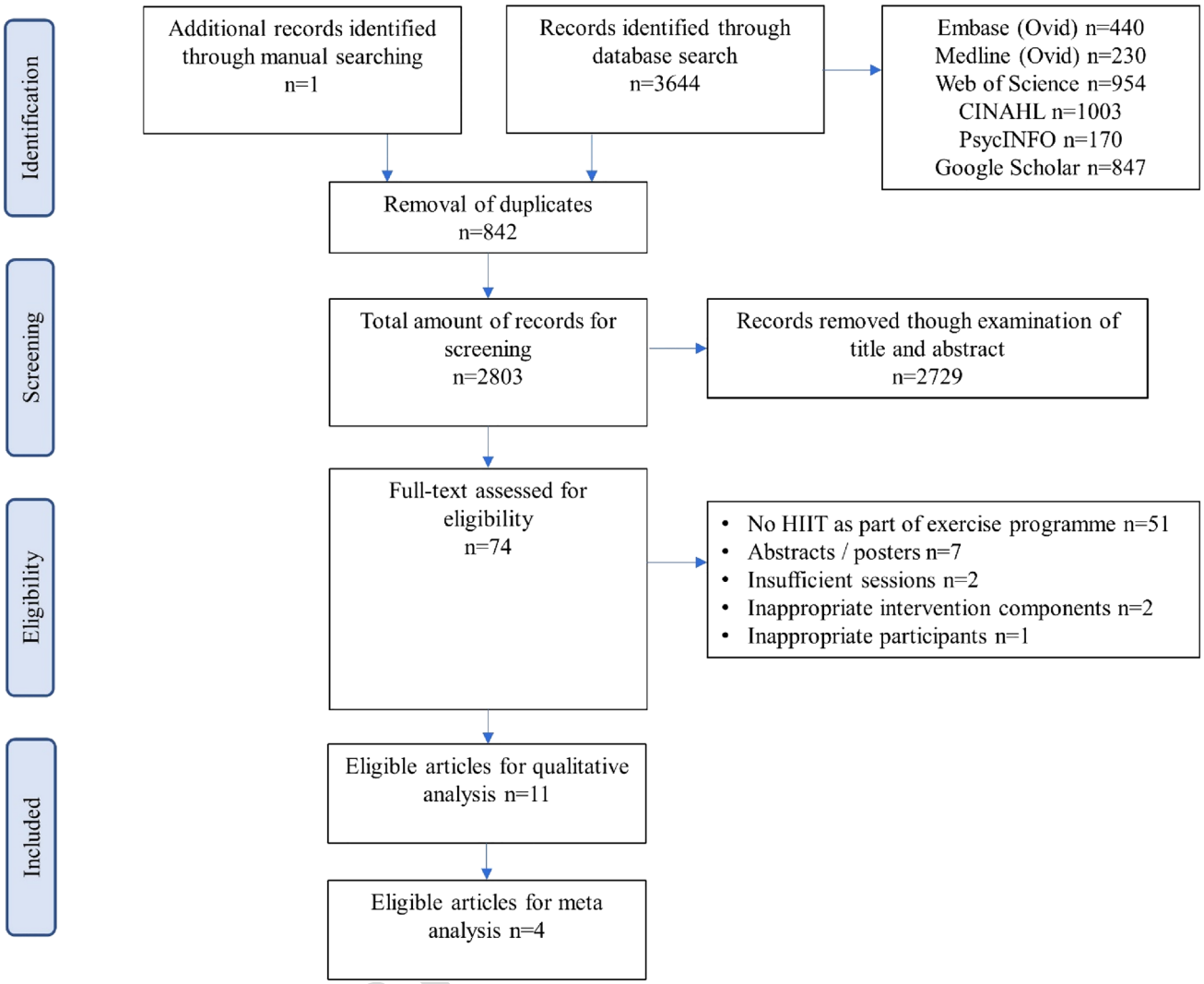

Fig. 1 Study identification and selection PRISMA flow diagram

being supervised, either in full or part by exercise professionals. Exercise programme locations were a variety of settings, commonly described as "gym", "fitness centre", or "laboratory".

Outcomes

Overall, studies reported over 40 individual physiological and clinical outcomes. Primary outcomes included relative $VO_{2peak/max}$ and haematological parameters including brain-derived neurotrophic factor (BDNF). Secondary outcomes included sub-sections of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Parkinson's Disease Questionnaire 39 (PDQ-39), and functional measures such as the Six-Minute Walk Test (6-MWT). Feasibility and safety data, such as achieved intensity, programme completion, and adverse effects and events, were also reported in varying detail.

Participant characteristics

Studies included 117 participants allocated to HIIT, and 111 allocated to usual care/comparator groups. The minimum sample size was one, [35], while the maximum was 43 [26] consisting of 22 HIIT participants and 21 continuous exercise comparators. Ten studies included both male and female participants, with a higher percentage of female participants in four [25, 27–29]. Mean HIIT participant ages ranged from 63 years [33] to 72 years [25]. Parkinson's stage was defined by either the Hoehn and Yahr or modified Hoehn and Yahr scale in all studies, with inclusion criteria commonly being of stages 1–3 only (mild-to-moderate severity). Only one study [32] included

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participants of Hoehn and Yahr stage 4 (severe disability). All studies excluded PwP with a history of cardiac or cardiorespiratory dysfunction. No changes in treatment were reported in any study. Additionally, seven studies [25–27, 30, 31, 33, 35] specified "on/off" state during training or assessment. Table 1 shows study and participant characteristics for controlled/comparator studies, while Table 2 shows single group studies.

Quality assessment (Tables 3 and 4)

Seven studies were assessed with the TESTEX scale [25–30, 34] and four with the Modified Downs and Black assessment tool [31–33, 35]. Two studies were rated as high quality [25, 29], five as good [26–28, 30, 34], two as fair [31, 32], and two as poor [33, 35]. Common limitations included lack of assessor blinding, allocation concealment, activity monitoring in control groups, and adjustment for confounders within statistical analysis. Generally, more recent studies and those assessed by the TESTEX were of higher quality. Overall study quality was deemed to be moderate to good, with a mean TESTEX score of 10.9 /15 and 12.3/28 for the Modified Downs and Black assessment tool.

Feasibility

Recruitment

Of the 11 studies, three did not report recruitment data [31, 33, 35]. The remaining studies reported differing aspects of recruitment and eligibility in varying levels of detail; Uc et al. [26] recruited 43 out of 73 PwP following telephone screening and in-person evaluation, while Demonceau et al. [30] reported that 52 participants were recruited who accepted and met inclusion criteria out of 120 initially contacted. Haas et al. [32] reported 18 out of 37 participants were recruited following telephone screening, while Harvey et al. [29]/O'Callaghan et al. [34] reported that 20 participants began the intervention out of 32 approached, with two excluded due to medical criteria and 10 not consenting. Marusiak et al. [25] recruited 20 participants from 22 approached, with one ineligible on medical grounds, while Duplea [27] recruited 18 PwP of 48 approached, with 23 declining to participate and seven ineligible after assessment. Fernandez et al. [28] recruited 27 of 29 assessed, with two participants not having confirmed diagnosis. Overall, pooled data from seven studies revealed that 46% of initial contacts were either ineligible for or did not consent to participate in HIIT.

HIIT programme completion and attendance

All studies reported HIIT programme completion rates, with five [25, 27, 31, 32, 35] reporting 100% completion. Fernandez et al. [28] reported 92% completion, with one death unrelated to the exercise programme. Harvey et al. [29]/O'Callaghan et al. [34] reported 90% completion, with one dropout due to unrelated illness. Seventeen of 22 participants completed a 24-month intervention undertaken by Uc et al. [26], with three of the five dropouts due to exercise related knee pain. Demonceau et al. [30] reported 80% programme completion with 4 dropouts; one through lack of time, one unrelated surgical intervention, one adverse event, and one lack of interest. Ten studies reported data regarding HIIT programme attendance, with three [32, 33, 35] reporting 100% attendance, and the other seven ranging from 73% [26] to 97.7% [25].

Aspects of HIIT intensity

Three studies reported mean achieved intensity of HIIT fast phase, with Harvey et al. [29]/O'Callaghan et al. [34] reporting 88.8% HR_{max}, Marusiak et al. [25] RPE 18, 68% HR_{max} (target 75%), and Duplea [27] 92% HR_{max}. Uc et al. [26] and Uygur et al. [33] reported mean achieved HIIT intensity across both slow and fast phases (69.2% HR_{max} and 13.2 RPE, respectively). Similarly, Demonceau et al. [30] reported that 30.1 of 36 sessions were completed at 70–80% PWL across fast and slow phases. Zoladz et al. [31] reported that 33% of participants achieved a mean exercise intensity of > 75% HR_{max} across all varied intensity sessions. Conducting a single group HIIT feasibility study, Haas et al. [32] reported that 12 out of 18 participants achieved > 75% of their age-predicted target intensity during maximal exercise testing.

Patient experience

On study [32] conducted interviews assessing participant experience of HIIT. Key themes can be seen in Table 6.

Safety

Of the eight studies that reported adverse effects and events, four reported none [27, 32, 33, 35], while Harvey et al. [29]/O'Callaghan et al. [34] reported a single adverse event in the form of a drop in blood pressure, although the participant continued with the intervention. Demonceau et al. [30] reported five adverse events and effects in the HIIT group (light knee sprain, knee pain, headache, tiredness, and hypotension), including one (hypotension) that resulted in participant withdrawal after 10 of 12 weeks. Uc et al. [26] reported

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Table 1 Study and participant characteristics (controlled/comparator studies)

	Intervention	Participants								
Study/design	HIIT group	Control/comparator group	Exercise setting and supervision	Sample size (n) initial allocation	Age (years) mean (SD)	Gender (F/M)	PD duration (years) mean (SD) unless stated	H & Y stage	Medication/ changes	On/off state
Uc [26] Randomised comparator trial	HIIT only 24 months, thrice-weekly Intervallic walking, 3-min intervals at 80–90% HR_{max}, interspersed with 3-min reduced pace intervals at 60–70% $HR_{max.}$ 15–45 min in total	MICE 24 months, thrice-weekly Walking, 15–45 min at 70% HR_{max}	"Community setting" Supervised by "trainers"	EG: 22 CG: 21	EG: 65 (5.2) CG: 68 (7.5)	EG: 7/15 CG: 6/15	EG: 5.3 (3.5) CG: 8 (6.3)	1–3	Dopaminergic(3 in CG group no treatment) Changes NR	Either during training
Demonceau [30] Pseudo RCT	Mixed programme including HIIT 12 weeks including 7 weeks of HIIT once weekly Cycle ergometer, 30-s to 3-min intervals at 70–80% PWL interspersed with 30–90 s active recuperation at 50% PWL. 16–24 min in total	Usual care	Laboratory/ Hospital Supervised by "physiotherapist"	EG: 20 CG: 15	EG: 65 (8.0) CG: 63 (6.0)	EG: 6/14 CG: 5/10	(Median/IQR) EG: 5 (2.5–8) CG: 5 (3–7)	1–3	Dopaminergic Changes NR	On during assessments
Harvey [29] Randomised controlled pilot study	HIIT only 12 weeks, thrice-weekly Whole-body movements with resistance machines, 4 lots of 4 × 45-s intervals at 85% HR_{max} interspersed with 15-s rest period. 3.5-min rest period after every 4 intervals	Usual care	Gym based Supervised by "senior physiotherapist" & "exercise scientist"	EG: 10 CG: 10	EG: 68 (7.9) CG: 69 (6.0)	EG: 4/6 CG: 4/6	NR	1–3	"Anti Parkinsonian" No changes	NR

Table 1 (continued)

Study/design	Intervention	Participants								
	HIIT group	Control/comparator group	Exercise setting and supervision	Sample size (n) initial allocation	Age (years) mean (SD)	Gender (F/M)	PD duration (years) mean (SD) unless stated	H & Y stage	Medication/ changes	On/off state
Marusiak [25] RCT	Mixed programme including HIIT 8 weeks including 2 weeks of HIIT thrice-weekly Cycle ergometer, 8 × 3-min intervals "fast phase" at 75% HR_{max} interspersed with 2-min "slow phase"	Usual care	Laboratory Supervised by "training supervisor"	EG: 10 CG: 10	EG: 72 (10.0) CG: 74 (9.0)	EG: 4/ 6 CG: 7/3	EG: 9 (5.0) CG: 8 (4.0)	1.5–3	"Anti Parkinsonian" No changes	On during training/off during assessments
O'Callaghan [34] Randomised controlled pilot study with comparator	HIIT only Same EG participants as Harvey [29]	MICE 12 weeks, thrice-weekly Aerobic exercise, 45–60 min at 60–80% HR_{max} Separate delayed start CG (usual care)	Gym based Supervised by "senior physiotherapist" & "exercise scientist"	EG: As Harvey CG: 16 with separate usual care CG of 16	EG: As Harvey CG: 70 (7.2)	EG: As Harvey CG: 4/9	NR	1–3	As Harvey	NR
Duplea [27] (MSc thesis) Randomised comparator trial	HIIT only 10 weeks, thrice-weekly Cycle ergometer, 10 × 1-min intervals at 80% PPO interspersed with 1-min active recuperation at 10% PPO	MICE 10 weeks, thrice-weekly, Cycle ergometer, 30–50 min at 60% PPO	Gym based Supervised by "certified YMCA instructor"	EG: 9 CG: 9	EG: 67 (10.0) CG: 70 (7.0)	EG: 4/5 CG: 3/5	NR	1–3	"Regular PD medication" Changes NR	On during training and assessments

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Table 1 (continued)

Study/design	Intervention			Participants							
	HIIT group	Control/comparator group	Exercise setting and supervision	Sample size (n) initial allocation	Age (years) mean (SD)	Gender (F/M)	PD duration (years) mean (SD) unless stated	H & Y stage	Medication/ changes	On/off state
Fernandez [28] Randomised comparator trial	HIIT only 12 weeks, thrice-weekly Jogging or running, 7 × 1-min intervals at 15–17 RPE, interspersed with 2-min active recuperation at 9–11 RPE	MICE 12 weeks, thrice-weekly Walking or jogging, 26 min at 11–14 RPE	Setting NR 2 sessions supervised by "exercise specialist". 1 unsupervised	EG: 13 CG: 14	EG: 68 (8.9) CG: 70 (7.7)	EG: 5/7 CG: 3/6	EG: 6 (40.3) CG: 6.7 (39.9)	1–3	Dopaminergic No changes	NR

EG exercise group, *CG* control/comparator group, *NR* Not recorded, *HIIT* high-intensity interval training, *MICE* moderate-intensity continuous exercise, *HRmax* maximum heart rate, *HRpeak* peak heart rate, *PWL* peak workload, *PPO* peak power output, *RPE* rate of perceived exertion, *NT* no treatment, *SD* standard deviation, *PD* Parkinson's Disease, *H & Y* Hoehn and Yahr, *SEM* standard error of the mean, *On* symptoms controlled by medication, *Off* symptoms not controlled by medication

three adverse effects in the HIIT group, all in the form of knee pain resulting in dropout from a 24-month programme, while there were none within an MICE comparator group.

Effects of HIIT on physiological and clinical outcomes

CCS = Controlled/comparator studies.

SGS = Single group studies.

Maximal exercise capacity

CCS: Five studies measured changes in relative $VO_{2peak/max}$ [25, 27, 29–31]. Demonceau et al. [30] and Harvey et al. [31] found no differences compared to usual care, while Uc et al. [26] and Duplea [27] reported no differences compared to MICE. However, Demonceau et al. [30], Harvey et al. [29], and Duplea [27] reported significant within-group improvements in the HIIT group, (mean change [SD where reported]; + 2.8, + 3.1 [± 2.4] and + 4.3 ml/kg/min, respectively) with Duplea [27] also reporting improvements in the MICE comparator (+ 2.2 ml/kg/min). Uc et al. [26] reported no significant differences in either HIIT or MICE group. Meta-analyses exploring the pooled effect of HIIT on $VO_{2peak/max}$ (ml/kg/min) evinced a significant improvement compared to usual care (Fig. 2a; WMD: 2.25; 95% CI 0.25–4.25; $p = 0.03$; $n = 2$), but not to MICE (Fig. 2b; WMD: 1.09; 95% CI − 0.61 to 2.80; $p = 0.21$; $n = 2$). Statistical heterogeneity in both analyses was rated as "not important" ($I^2 = 0\%$, $p = 0.88$ and $I^2 = 0\%$, $p = 0.61$, respectively).

The strength of meta-analysed evidence according to the GRADE tool [23] was assessed to be moderate for HIIT compared to usual care—downgraded due to lack of randomisation, allocation concealment, and intention-to-treat (ITT) analysis in one study [30]. Compared to MICE, strength of evidence was assessed to be low, downgraded due to both imprecision and the risk of bias through lack of allocation concealment and ITT analysis.

Demonceau et al. [30] evinced improvements in PWL following HIIT (+ 0.3 watts/kg), although there were no differences when compared to a usual care group. Duplea [27] reported improvements in PPO in both HIIT and MICE groups (+ 15 and + 11 watts, respectively) with no between-group differences.

SGS: Haas et al. [32] reported no improvement in VO_{2max} following HIIT.

Haemodynamic variables

CCS: Harvey et al. [29] explored changes in cardiac index, finding no differences between HIIT and usual care groups. Fernandez et al. [28] reported no changes in systolic blood

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Table 2 Study and participant characteristics (single group studies)

Study/design	Intervention	Participants							
	HIIT group	Exercise setting and supervision	Sample size (n) initial allocation	Age (years) Mean (SD) unless stated	Gender (F/M)	PD duration (Years) Mean (SD) unless stated	H & Y stage	Medication/changes	On/off state
Zoladz [31] Single group pre/post-design study	Mixed programme including HIIT 8 weeks, including 2 weeks of HIIT thrice-weekly Cycle ergometer, 8×3-min intervals "fast phase" at 75% HR_{max} interspersed with 2-min "slow phase"	Setting NR Supervised by "training supervisor"	12	Mean (SEM) 70 (3.0)	5/7	7.5	1–3	Dopaminergic Changes NR	On during training/off during assessments
Haas [32] Single group pre/post-design study	HIIT only 3 weeks, twice weekly Cycle ergometer, 10×1-min intervals at HR_{peak} interspersed with 1-min zero workload	Laboratory Supervised by "experienced physiotherapists"	6	63 (7.4)	2/4	NR	1–4	Type NR Changes NR	NR
Uygur [33] Single group pre/post-design study	HIIT only 6 weeks, twice weekly Recumbent cycle, 20×15 s intervals at maximal effort "as fast as possible" interspersed with 45 s active recuperation at preferred pedal rate	Setting NR Supervised by "experienced trainer"	14	63 (8.8)	4/10	3.3 (28.9)	1–3	Type NR No changes	On during training and assessments
Osborn [35] (Doctoral thesis) Single-subject case study	HIIT only 3 weeks, twice weekly Cycle ergometer, 10×1-min intervals at HR_{peak} interspersed with 1-min zero workload	Gym based Supervised by "family member"	1	70	1/0	5	3	Dopaminergic No changes	No on/off phase

NR Not recorded, *HIIT* high-intensity interval training, *HRmax* maximum heart rate, *HRpeak* peak heart rate, *SD* standard deviation, *PD* Parkinson's Disease, *H & Y* Hoehn and Yahr, *SEM* standard error of the mean, *On* symptoms controlled by medication, *Off* symptoms not controlled by medication

Table 3 TESTEX quality assessment scale (Controlled/comparator studies)

	Criteria Study		Uc [26]	Demonceau [30]	Harvey [29]	Marusiak [25]	O'Callaghan [34]	Duplea [27]	Fernandez [28]
Study quality	Eligibility criteria specified		1	1	1	1	1	1	1
	Randomisation		1	0	1	1	1	1	0
	Allocation concealment		0	0	0	1	0	0	0
	Groups similar at baseline		1	1	1	1	1	1	1
	Assessor blinding		1	0	1	0	1	1	1
Reporting	Outcome measures assessed in 85% of patients	Adherence > 85%	1	0	1	1	0	1	1
		Adverse events reported	1	1	1	0	0	1	1
		Exercise attendance reported	1	1	1	1	0	0	1
	Intention to treat analysis		0	0	1	1	0	0	0
	Between group statistical comparisons	Primary outcome	1	1	1	1	1	1	1
		At least 1 secondary outcome	1	1	1	1	1	1	1
	Point measures and measures of variability		1	1	1	1	1	1	1
	Activity monitoring in control groups		0	0	0	1	0	0	0
	Relative exercise intensity remained constant		1	1	1	1	1	1	0
	Exercise volume & energy expenditure		0	1	1	1	1	1	1
	Totals	Total/15	11	9	13	13	9	11	10
		Quality	Good	Good	High	High	Good	Good	Good

Where items were not applicable, 0 points were awarded

pressure (SBP) or diastolic blood pressure (DBP) following HIIT, while Duplea [27] reported no changes in SBP or DBP in either the HIIT or MICE group. Fernandez et al. [28] reported between-group differences in endothelial reactivity in favour of the HIIT group with an increase of 4.05%, compared to a 1.29% reduction in the MICE comparator ($p = 0.004$). Fernandez et al. [28] also examined changes in pulse wave velocity, reporting no improvements following HIIT or MICE.

Haematological parameters

CCS: O'Callaghan et al. [34] investigated the impact of HIIT on levels of BDNF compared to MICE, finding that HIIT stimulated significant within-group improvements (increases in 82.4% of participants), with no improvement in the comparator group.

SGS: Zoladz et al. [31] reported BDNF increases of 34%, a 7% reduction in serum levels of inflammatory cytokine tumour necrosis factor alpha (TNFα), and a 21% decrease in serum vascular cell adhesion molecule-1 following HIIT. No changes in blood platelets, serum cortisol level, plasma F2 isoprostanes level, or plasma syndecan-1 level were found [31].

Walking capacity and cycle endurance

CCS: Three studies evaluated distance walked during the submaximal 6-MWT. Only Fernandez et al. [28] found significant HIIT group improvements compared to a comparator (MICE; $p = 0.046$), while both Demonceau et al. [30] and Harvey et al. [29] found no significant improvements in the HIIT group (+31 m, and median + 15.5 m [IQR − 17 to

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Table 4 Downs and Black quality assessment tool (Single group studies)

	Criteria	Study	Zoladz [31]	Haas [32]	Uygur [33]	Osborn [35]
Reporting	Is the hypothesis/aim/objective of the study clearly described?		1	1	1	1
	Are the main outcomes to be measured clearly described in the Introduction or methods section?		1	1	1	1
	Are the characteristics of the patients included in the study clearly described?		1	1	1	1
	Are the interventions of interest clearly described?		1	1	1	1
	Are the distributions of principal confounders in each group of subjects to be compared clearly described? (2 marks)		1	1	0	0
	Are the main findings of the study clearly described?		1	1	1	1
	Does the study provide estimates of the random variability in the data for the main outcomes?		1	1	1	0
	Have all important adverse events that may be a consequence of the intervention been reported?		0	1	1	1
	Have the characteristics of patients lost to follow-up been described?		0	1	1	0
	Have actual probability values been reported		1	1	1	0
External validity	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?		1	0	0	0
	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?		1	0	0	0
	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?		0	0	1	0
Internal validity—bias	Was an attempt made to blind study subjects to the intervention they have received?		0	0	0	0
	Was an attempt made to blind those measuring the main outcomes of the intervention?		0	0	0	0
	If any of the results of the study were based on "data dredging", was this made clear?		0	0	0	0
	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case–control studies, is the time period between the intervention and outcome the same for cases and controls?		0	0	0	0
	Were the statistical tests used to assess the main outcomes appropriate?		1	1	1	0
	Was compliance with the intervention/s reliable?		0	1	0	1
	Were the main outcome measures used accurate (valid and reliable)?		1	1	1	1
Internal validity—confounding	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case–control studies) recruited from the same population?		1	0	0	0
	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case–control studies) recruited over the same period of time?		1	0	0	0
	Were study subjects randomised to intervention groups?		0	0	0	0
	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?		0	0	0	0
	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?		0	1	0	0
	Were losses of patients to follow-up taken into account?		0	0	1	0
Power	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?		0	0	0	0

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47.5], respectively), with no differences compared to usual care control groups.

SGS: Osborn [35] reported an 8-m improvement in the 6-MWT within the case study participant. Examining cycling endurance, Haas et al. [32] reported a significant improvement of + 54.5 s.

Gait speed

CCS: Utilising the 7-Metre Walk Test, Uc et al. [26] reported no improvements in gait speed in either HIIT or MICE group.

SGS: Uygur et al. [33] evinced improvements in the 10-Metre Walk Test, with a 15.9% reduction in total time taken, while Osborn [35] reported a 1.28 m/s improvement in the single participant.

Mobility, balance, and balance confidence

CCS: Neither study [28, 30] that assessed mobility and balance with the Timed-Up-and-Go Test (TUG) found improvements in either the HIIT group or MICE/usual care group, respectively.

SGS: Uygur et al. [33] evinced improvements in the TUG, with a 0.54 s (15.59%) reduction in time taken. Osborn [35] reported a -0.25 s change in the single subject, while Utilising the Mini-Balance Evaluation Systems Test (Mini BESTest), Osborn [35] reported an eight-point improvement. Uygur et al. [33] reported no significant improvement (+ 10.81%) in the Activities of Balance Confidence Scale. However, Uygur et al. [33] did evince significant improvements in both simple reaction time (− 13.15%) and the Four-Square Step Test (dynamic balance; − 17.04%) following HIIT.

MDS-UPDRS

CCS: Examining changes in the UPDRS part III (motor symptom examination), Duplea [27] found improvements in both the HIIT and MICE groups (12.8 and 8.2 points, respectively, non-significant between groups). Marusiak et al. [25] reported improvements in the bradykinesia subsection following HIIT compared to usual care ($p < 0.001$). Marusiak et al. [25] also evinced HIIT group improvements in the UPDRS part II (motor aspects of daily living), although no between-group differences were found, whilst finding no change in the Activities of Daily Living Scale.

Table 4 (continued)

Criteria	Study	Zoladz [31]	Haas [32]	Uygur [33]	Osborn [35]
	Totals	14	14	13	8
	Total/28				
	Quality	Fair	Fair	Poor	Poor

Where items were not applicable, 0 points were awarded

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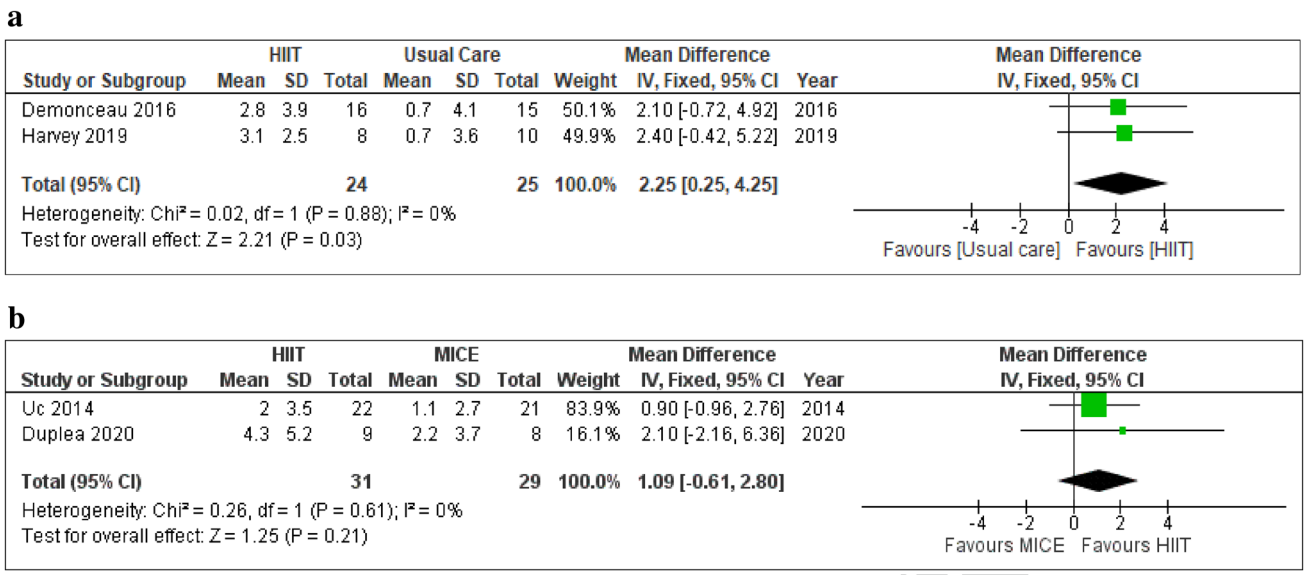

Fig. 2 **a** Meta-analysis: $VO_{2peak/max}$ (mL/kg/min) HIIT v usual Care. **b** Meta-analysis: $VO2_{peak/max}$ (ml/kg/min) HIIT v MICE

SGS: Uygur et al. [33] reported a 20.14% (3.5 point) improvement in the UPRDS part III, and a 15.1% improvement in the UPDRS bradykinesia sub-section.

Lower body strength parameters

CCS: Fernandez et al. [28] evinced improvements in the Sit-to-Stand Test (functional lower extremity strength) in both the HIIT and MICE groups, with no between-group differences. Examining knee extensor and flexor strength, Demonceau et al. [30] found no improvements in peak torque in either group.

SGS: Similarly, Haas et al. [32] reported no improvements in either knee extensor or flexor strength after six sessions of cycle ergometer HIIT.

Quality of life and emotional state

CCS: Duplea [27] reported improvements in depression (Beck Depression Inventory) in both the MICE and HIIT group, although there were no between-group differences. Examining changes in quality of life utilising the PDQ-39, Harvey et al. [29] and Demonceau et al. [30] reported no improvements in either HIIT or usual care group. Marusiak et al. [25] examined changes in the UPDRS "emotional state" section, finding a significant improvement in the HIIT group, but no between-group differences.

SGS: Haas et al. [32] reported no improvements in the PDQ-39, while, similarly, Uygur et al. [33] reported no improvement in the Short Form 36 Health Survey.

A summary of key results can be seen in Table 5 (comparator/controlled studies) and Table 6 (single group studies). AQ6

Discussion

This review aimed to evaluate the feasibility, safety, physiological and clinical effects of HIIT for PwP by undertaking a comprehensive synthesis of existing evidence. Results suggest that HIIT could be at least as beneficial for a number of outcomes as lower intensity continuous forms of exercise. High programme completion rates and a few adverse events in programmes of up to 12 weeks indicate feasibility for this population.

Feasibility and implications for programme delivery

High exercise attendance and low dropout rates are encouraging regarding the feasibility of HIIT for this population. Additionally, the lack of adverse effects and events in interventions of up to 12 weeks would suggest HIIT programmes of this duration to be a safe exercise option for PwP. The one exception was Demonceau et al. [30] who reported five adverse events/effects including "hypotension" and a "light knee sprain". However, minor adverse effects such as

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Table 5 Overview of key results by study—controlled/comparator studies

Study/design	Quality TESTEX score	Physiological outcomes (Mean (±SD) unless stated)	Clinical outcomes (Mean (±SD) unless stated)	Feasibility and safety of HIIT
Uc [26] Randomised comparator trial	11 (Good)	**VO_{2max} (ml/kg/min):** Change from baseline: HIIT group: 2.0 (±3.5) non-significant, MICE group: 1.1 (±2.7), non-significant Between group non-significant	**Gait speed – 7-Metre Walk Test (s):** change from baseline: HIIT group: -0.92 (±1.1), non-significant, MICE group: -0.70 (±1.0), non-significant Between group non-significant	**Recruitment rate**: 43 eligible of 76 screened and evaluated **Programme completion in HIIT group**: 17 of 22 **Attendance in HIIT group**: 73% **HIIT intensity**: 69.2% HR_{max} (mean of both fast/slow phase) **Adverse events/effects in HIIT group**: 3 (knee pain all resulting in dropout)
Demonceau [30] Pseudo RCT	9 (Good)	**VO_{2peak} (ml/kg/min):** HIIT group: pre 23.4 (±5.2), post 26.2 (±6.5), $p=0.02$. Usual care group: pre 23.5 (±6), post 22.8 (±6.7), non-significant Between group non-significant **Peak workload (w/kg):** HIIT group: pre 1.68 (±0.45) post 1.98 (±0.61) $p<0{,}001$. Usual care group: pre 1.72 (±0.57), post 1.68 (±0.52), non-significant Between group non-significant	**6 Minute Walk Test (m):** HIIT group: pre 553 (±67) post 584 (±91), non-significant. Usual care group: 541 (±65), post 532 (±70), non-significant. Between group non-significant **Timed-Up-and-Go Test (s):** HIIT group: pre 1.8 (±0.3) post 1.7 (±0.2), non-significant. Usual care group: pre 1.8 (±0.2) post 1.8 (±0.2), non-significant. Between group non-significant **Quality of life (PDQ-39**) HIIT group: pre 28 (±12) post 27 (±15), non-significant. Usual care group: pre 20 (±13), post 19 (±13), non-significant. Between group non-significant **Lower body strength: Knee flexor/extensor peak torque.** No improvements	**Recruitment rate**: 52 accepted & met eligibility criteria of 120 contacted **Programme completion in HIIT group**: 80% **Attendance in HIIT group**: Mean 31.3 sessions (of 24–36) **HIIT intensity**: 30.1 sessions completed at target intensity (70–80% PWL) **Adverse events/effects in HIIT group**: 5 (light knee sprain, knee pain, headache, tiredness and hypotension). Hypotension led to participant dropout
Harvey [29] Randomised controlled pilot study	13 (High)	Change from baseline; **VO_{2peak} (ml/kg/min):** HIIT group: 3.1 (±2.54), $p=0.029$. Usual care group: 0.7 (±3.56), non-significant. Between group non-significant **Cardiac index (L/min/m^2):** HIIT group median 1.8, IQR − 1.8 to 5.2, non-significant. Usual care group: median − 0.2, IQR − 2.8 to 6.5, non-significant. Between group non-significant	Change from baseline; **6 Minute Walk Test (m):** HIIT group median 15.5, IQR − 17.0 to 47.5, non-significant. Usual care group: median 48.5, IQR − 15.8 to 75.3, non-significant. Between group non-significant **Quality of life (PDQ-39):** HIIT group median 1.0, IQR − 8.3 to 15.3, non-significant. Usual care group: − 0.5, IQR − 5.2 to 5.8, non-significant. Between group non-significant	**Recruitment rate**: 20 participated from 32 approached **Programme completion in HIIT group**: 90% **Attendance in HIIT group**: 79.1% of those who completed the intervention **HIIT intensity**: HIIT fast phase: Mean 88.8% of maximal (Target 85%) **Adverse events/effects**: 1 (Drop in blood pressure, continued intervention)

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Table 5 (continued)

Study/design	Quality TESTEX score	Physiological outcomes (Mean (±SD) unless stated)	Clinical outcomes (Mean (±SD) unless stated)	Feasibility and safety of HIIT
Marusiak [25] RCT	13 (High)	N/A	**UPDRS (Bradykinesia):** HIIT group improvement, $p = 0.015$, between-group $p = 0.0003$ **UPDRS (part II):** HIIT group improvement, p = 0.004, between-group non-significant **UPDRS (emotional state)**: HIIT group improvement, p = 0.005, between-group non-significant **Activities of Daily Living Scale**: No improvement in either group	**Recruitment rate**: 20 participated from 22 approached (1 medical grounds, 1 other) **Programme completion in HIIT group**: 100% **Attendance in HIIT group**: 97.7% **HIIT intensity**: Mean 68% HR_{max} for "fast phase", (Target 75%) RPE 18 **Adverse effects/events**: NR
O'Callaghan [34] Randomised controlled pilot study with additional comparator	9 (Good)	**Serum brain-derived neurotrophic factor**: HIIT group $p = 0.01$ (increase in 82.4% of participants), MICE group non-significant	N/A	HIIT group as Harvey et al. (2019)
Duplea [27] Randomised comparator trial	11 (Good)	**VO_{2max} (ml/kg/min):** HIIT group: pre 23.6 (±7.4) post, 27.9 (±8.6), $p < 0.05$. MICE group: pre 18.0 (±6.0), post 20.2 (±4.1), $p < 0.05$. Between group non-significant **Peak power (watts):** HIIT group: pre 173 (±54), post 188 (±55), $p < 0.05$. MICE group: pre 130 (±44), post 141 (±63), $p < 0.05$. Between group non-significant **SBP/DBP**: No changes in either group	**Fatigue (PFS-15);** HIIT group: pre 42 (±18), post 39 (±16), non-significant. MICE group: pre 47 (±16), post 44 (±15) non-significant. Between group non-significant **UPDRS part III**; HIIT group: 12.8 (±1.6) point improvement, $p < 0.05$ MICE group: -8.2 (±1.7) improvement, $p < 0.05$ Between group non-significant **Beck Depression Inventory**; HIIT group: pre 11 (±9), post 5 (±5), $p < 0.05$. MICE group: pre 12 (±6), post 8 (±6), $p < 0.05$. Between group non-significant	**Recruitment rate:** 18 participated of 48 assessed (23 declined, 7 not eligible) **Programme completion in HIIT group:** 100% **Attendance in HIIT group**: 90% **HIIT intensity**: Mean 92% HR_{max} in fast phase (Target 85%) **Adverse effects/events**: 0

Table 5 (continued)

Study/design	Quality TESTEX score	Physiological outcomes (Mean (±SD) unless stated)	Clinical outcomes (Mean (±SD) unless stated)	Feasibility and safety of HIIT
Fernandez [28] Randomised comparator trial	10 (Good)	**Endothelial reactivity:** HIIT group: +4.05%. MICE group: -1.29%, between-group $p=0.004$ **SBP/DBP**: No change in either group **Pulse wave velocity**: No change in either group	**SittoStand Test**: HIIT group: 27.2% improvement, $p<0.05$. MICE group: 21.5% improvement, $p<0.05$. Between group non-significant **Timed-Up-and-Go Test (s)**: HIIT group: median (IQR) pre 7.5 (6.29–12.5) post 7.63 (5.7–18.21), non-significant. MICE group: pre 8 (5.88–15.23) post 8.07 (5.68–17.08), non-significant. Between group non-significant **6 Minute Walk Test**: HIIT group improvement, $p<0.05$. MICE group non-significant. Between group $p=0.046$ (exact figures not reported)	**Recruitment rate**: 27 participated of 29 volunteers. (2 unconfirmed diagnosis) **Programme completion in HIIT group**: 92% (1 death, unrelated to exercise) **Attendance in HIIT group**: 87.5% **HIIT intensity**: NR **Adverse effects/events**: NR

NR not recorded, *SD* standard deviation, *IQR* inter-quartile range, *HIIT* high-intensity interval training, *MICE* moderate-intensity continuous exercise, *VO2max* maximal oxygen uptake, *HRmax* maximum heart rate, *UPDRS* unified Parkinson's disease rating scale, *PDQ-39* Parkinson's disease questionnaire 39, *PFS-15* Parkinson's disease fatigue scale 15, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ml/kg/min* millilitres per kilogramme per minute, *L/min/m²* litres per minute per metre squared, *w* watts, *m* minutes, *s* seconds

"headache" and "tiredness" were also included, with only one leading to withdrawal from the programme. Whether these occurrences were a direct consequence of HIIT is unclear.

In the one longer duration study [26], the 23% drop-out and low attendance rate could indicate that extended engagement in HIIT programmes is challenging for some PwP. Therefore, exploring protocols to facilitate long-term participation would appear to be pertinent. One potential method to support ongoing engagement in exercise is to facilitate the adoption of home-based programmes. In this review, all HIIT was professionally supervised and delivered within clinical settings. In agreement with focus group evidence presented by Haas et al. [32], Paul et al. [37] reported that adequate supervision when undertaking exercise was a programme attribute deemed important by PwP. Therefore, whilst face-to-face delivery could reduce opportunities for participation and long-term engagement [38], unsupervised HIIT cannot be recommended until evidence regarding its feasibility and acceptability is available.

When considering recruitment and eligibility data, studies almost uniformly included participants of mild-to-moderate disease severity. Therefore, existing evidence does not support the use of HIIT for PwP with greater disease severity. Furthermore, 46% of initial contacts did not participate. As reasons for non-participation were not always reported, it is unclear as to how many people were ineligible through health-related criteria, or simply declined through lack of interest or logistical reasons. Also, the possibility that accepters were more likely to be interested in exercise could have resulted in participation bias, [39] restricting the generalisability of results.

With regard to exercise type and intensity, cycle ergometry, resistance training, and running appear to be well tolerated, and some studies reported that participants were able to achieve target HIIT intensity [27, 29]/[34]. However, other studies either did not report intensity [28, 32, 35] or reported the mean of combined programme elements [25, 26, 30, 31, 33]. Due to these ambiguities, quantifying the proportion of PwP who could successfully achieve HIIT is problematic. Consequently, this review cannot delineate more specific conclusions other than to suggest that 12 weeks of thrice-weekly supervised HIIT, appears to be feasible and safe for some PwP of mild-to-moderate disease severity.

Physiological and clinical outcomes

Meta-analysis evinced a significant effect of HIIT on $VO_{2peak/max}$ compared to usual care. This result is congruent with previous research suggesting the benefits of HIIT

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Table 6 Overview of key results by study—single group studies

Study/design	Downs and Black score	physiological outcomes [mean (±SD) unless stated]	Clinical outcomes [Mean (±SD) unless stated]	Feasibility and safety of HIIT
Zoladz [31] Single group study (pre/post)	14 (Fair)	**Serum brain-derived neurotrophic factor**: Increase of 34%, $p=0.03$ **Serum TNFα**: 7% reduction $p=0.03$ **Serum vascular cell adhesion molecule-1 level**: Decrease of 21%, $p=0.001$ **Blood platelets, serum cortisol level, Plasma F2 isoprostanes level or plasma syndecan-1 level**: All non-significant	N/A	**Recruitment rate**: NR **Exercise programme completion**: 100% **Attendance**: NR **Exercise intensity**: NR for only HIIT sessions (33% achieved mean > 75% HR_{max} across all mixed-intensity sessions) **Adverse events/effects:** NR
Haas [32] Single group study (pre/post)	14 (Fair)	**VO_{2max} (ml/kg/min)**: pre 28.81 (±7.05) post 29.85 (±4.96, non-significant **Inspiratory muscle strength (Maximal inspiratory pressure):** pre 57.83 (±17.46) post 65.83 (±20.79), non-significant	**Cycle endurance (s):** pre 518.3 (±59.7) post 572.8 (±89.5) Significant (exact p value not reported) **Lower body strength (knee; Nm):** Extensor pre 1.27 (0.27) post 1.27 (0.47), Flexor pre 1.0 (0.3) post 0.96 (0.19), both non-significant **Timed-Up-and-Go Test**: pre 10.99 (±1.8) post 10.84 (±1.59), non-significant **Quality of life (PDQ-39):** pre 25.34 (±10.35) post 32.53 (±13.84), non-significant	**Recruitment rate**: 18 participated of 37 screened **Exercise programme completion** (n = 6) 100% **Attendance**: 100% **Exercise intensity**: 12/18 participants achieved target intensity ≥ 75% HR_{max} during exercise testing. NR during HIIT **Adverse events/effects**: 0 **Qualitative data – patient experience:** Themes to emerge; ""Enjoyable", "Preferred to low intensity exercise", "Improved wellbeing", "Perceived to increase muscle strength and activity levels", "Cause temporary muscle soreness", "A group setting would assure motivation" and "Needs facilitation and staff expertise"

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Table 6 (continued)

Study/design	Downs and Black score	physiological outcomes [mean (±SD) unless stated]	Clinical outcomes [Mean (±SD) unless stated]	Feasibility and safety of HIIT
Uygur [33] Single group study (pre/post)	13 (Poor)	**N/A**	**UPDRS-III**: pre 17.53 (±6.43) post 14.00 (±5.62) % change − 20.14, p < 0.001 **UPDRS bradykinesia**: pre 7.19 (±2.52) post 6.08 (±1.77) % change − 15.01, p = 0.049 **Gait speed—10 m walk test** (s): pre 3.42 (±0.88) post 2.88 (±0.66) % change − 15.59, *p* < 0.001 **Timed-Up-and-Go Test (s)**: pre 7.29 (±1.60) post 6.19 (±1.51) % change − 15.06, p < 0.01 **Functional Reach Test (cm):** pre 27.12 (±4.95) post 33.28 (±6.10) % change 22.71 *p* = 0.002 **Activities Specific Balance Confidence Scale**: pre 79.95 (±16.10) post 88.59 (±10.80) % change 10.81, non-significant **Simple reaction time (s):** pre 0.285 (±0.077) post 0.247 (±0.055) % change -13.15, *p* = 0.021 **Four-Square Step Test (s):** pre 9.11 (±4.51) post 7.56 (±3.08) % change -17.04, *p* = 0.009 **Short Form 36 Health Survey**: pre 58.15 (±23.46) post 62.00 (±22.09) % change 6.62, non-significant	**Recruitment rate**: NR **Exercise programme completion**: 100% **Attendance**: 100% **Exercise intensity**: Mean achieved intensity for slow/fast phase: RPE 13.2 "somewhat hard" **Adverse events/effects**: 0
Osborn [35] Single-subject case study (pre/post)	8 (Poor)	N/A	**Timed-Up-and-Go Test (s):** 0.25 improvement in single subject **Balance (Mini BESTest):** 8-point improvement **Gait speed—10 m walk test**: 1.28 m/s improvement **6 Minute Walk Test:** 8 m improvement	**Recruitment rate**: NR **Exercise programme completion**: 100% **Attendance**: 100% **Exercise intensity**: NR **Adverse events/effects**: 0

NR not recorded, *SD* standard deviation, *IQR* inter-quartile range, *HIIT* high-intensity interval training, *MICE* moderate-intensity continuous exercise, *TNFα* tumour necrosis factor alpha, *VO2max* maximal oxygen uptake, *HRmax* maximum heart rate, *PDQ-39* Parkinson's disease questionnaire 39, *BESTest* balance evaluation systems test, *UPDRS* unified parkinson's disease rating scale, *ml/kg/min* millilitres per kilogramme per minute, *L/min/m*^{2} Litres per minute per metre squared, *w* Watts, *m* minutes, *s* seconds

to maximal aerobic capacity [40]. However, whether the 2.25 ml/kg/min (9.8%) increase in $VO_{2peak/max}$ compared to usual care evinced by this study could be considered as clinically meaningful is debatable. In cardiac patients, an improvement of 6% has been associated with a 7% reduction in all-cause mortality [41], while Harvey et al. [29] considered a change of 2 ml/kg/min to be clinically meaningful. Due to the increased likelihood of comorbid cardiovascular and cerebrovascular disease in PwP [42], an improvement of 2.25 ml/kg/min would appear to be of considerable importance. HIIT does not appear to be more beneficial than MICE, which is unsurprising as MICE has also been found to improve VO_{2max} within this population [5]. However, HIIT still appears to provide similar benefit to MICE despite reduced exercise volume and overall time commitment, constituting important considerations for exercise adherence.

The lack of overall improvement in the 6-MWT would initially appear to be inconsistent with increases in $VO2_{peak/max}$. Congruently, the two studies that examined both outcomes [29, 30] found HIIT group improvements in $VO_{2peak/max}$, but not in the 6-MWT. This suggests that increased aerobic fitness does not necessarily equate to improvements in walking capacity in PwP. Although the 6-MWT is evinced to be a predictor of VO_{2max} in healthy adults [43], a similar association in Parkinson's has yet to be established. This could be explained by other factors, such as disease-related postural instability influencing 6-MWT time. A further consideration is that exercise modality could have been influential; Fernandez et al. [28] were the only study to report significant HIIT group differences, having utilised a modality comparable to the 6-MWT in the form of jogging or running. In contrast, studies that reported no improvement utilised other modalities [29, 30, 35]. Additionally, Haas et al. [32] reported improvements in cycling endurance following cycle ergometry. This evidence supports HIIT specificity—a key consideration when targeting patient-centric rehabilitative goals.

HIIT appears to stimulate increases in BDNF that are possibly greater than MICE. This result is pertinent, as PwP exhibit lower levels of BDNF than healthy people—a factor thought to play an important role in disease pathology [44]. Reduced BDNF has been associated with motor impairment, depression, and cognitive impairments in PwP [45–47], while animal models of Parkinson's have shown BDNF to provide neuroprotection [48] and improve synaptic plasticity [46]. In healthy humans, continuous high-intensity exercise has been theorised to stimulate greater acute and long-term increases in BDNF than exercise of lower intensity [7, 51], and whilst only two studies [31, 34] in this review investigated BDNF (including one single group study [31]), findings that HIIT appears to have a similar positive effect in PwP are encouraging. Theories as to how HIIT increases BDNF include induced hypoxia, thought to be a precursor to BDNF proliferation [51]. The reduction in inflammatory biomarkers evinced by Zoladz et al. [31] appear to be compatible with increases in BDNF, as BDNF has been theorised to participate in anti-inflammatory processes [52]. Neuroinflammation has been highlighted as an important therapeutic target for Parkinson's [53]; therefore, further investigation into the effects of HIIT on BDNF and inflammatory biomarkers would seem to be of relevance. Furthermore, the lack of overall improvement in haemodynamic variables could have been a consequence of autonomic dysfunction associated with Parkinson's [54], leading to the blunting of classic cardiac adaptations to exercise [9]. However, improvements in endothelial reactivity compared to MICE found by Fernandez et al. [28] indicate this to be a parameter warranting further investigation.

Significant within-group UPDRS part III improvements were reported in three studies [25, 27, 33] following HIIT, including one controlled study [25] that also evinced improvements compared to usual care. This evidence is contrary to a recent meta-analysis [15] that found "intensive" exercise programmes did not stimulate improvements. However, although defined as "intensive", the review also included programmes of MICE at 50–60% HR_{max}, and no specific exercise intensity subgroup analysis was undertaken. Moreover, Ridgel and colleagues [55] undertook a randomised comparator trial evidencing UPDRS-III improvements following "forced exercise" compared to "voluntary" exercise. Furthermore, a recent exercise comparator trial [7] found greater improvements following high-intensity treadmill exercise, than both MICE and usual care in people with de-novo Parkinson's. Interestingly, the programmes that elicited the greatest UPDRS-III improvements in this study, included HIIT phases of higher intensity (92% HR_{max} [27], maximal effort [33]). The results evinced by Duplea [27] were also significantly greater than the MICE comparator. Therefore, as with BDNF, a similar intensity dose response relationship possibly exists. Given this similarity, and the evinced correlation between reduced BDNF and motor impairment, the suggestion that motor improvements could have been in part a consequence of increased BDNF would seem plausible. However, whilst encouraging, there is currently no evidence to indicate that BDNF and motor improvements translate to important outcomes such as activities of daily living.

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As HIIT appears to have a positive influence on UPDRS-III, the reason for the lack of uniform improvement in the TUG is not immediately obvious. However, the traditional TUG has been criticised as being insensitive to change in early stage Parkinson's, when motor symptoms are less evident [56]. Therefore, given the early-to-moderate disease stage of HIIT participants, this factor could have been influential.

The lack of improvement in quality of life (QOL) is contrary to a recent meta-analysis of 20 studies [57] that examined the effect of exercise on QOL for PwP, reporting significant improvements. However, within the present review, included studies could have been limited by the number of participants. For example, the results of Haas et al. [32] appear to have been skewed by an outlier whose PDQ-39 score worsened by almost 42%. Results from Duplea (2020) appear to be more congruent with previous research [58], evincing improvement in the depression of both HIIT and MICE groups.

Review limitations

This review provides a comprehensive examination of not just effectiveness, but also feasibility and safety of HIIT for PwP. However, several limitations should be acknowledged. First, the number of randomised controlled trials and HIIT participants included in the review was limited. Also, study designs were heterogenous which allowed for only narrative synthesis to assess effectiveness for the majority of outcomes, while the strength of meta-analysed $VO_{2max/peak}$ evidence was moderate for HIIT compared to usual care and low compared to MICE. Therefore, conclusions should be interpreted with caution. Also, whilst the inclusion of grey literature where there was sufficient detail for quality assessment enabled a comprehensive review, lack of peer review may lead to bias. Furthermore, due to intervention heterogeneity, development of specific HIIT protocol recommendations to maximise outcome is not possible.

Implications for clinical practice and future research

This review presents the most comprehensive evidence to date that HIIT could be feasible, safe, and at least as effective as MICE at improving various physiological and clinical parameters for some PwP with mild-to-moderate disease severity. Therefore, HIIT could offer a time-efficient, low-volume exercise alternative to improve cardiorespiratory fitness, and potentially motor symptoms, BDNF and target specific patient-centric goals. Future research should aim to further elucidate the effects of differing HIIT modalities and protocols on physiological and clinical outcomes and explore ways to encourage initial engagement and long-term participation.

Conclusion

Thrice-weekly, professionally supervised HIIT of up to 12 weeks appears to be feasible and safe for some PwP with mild-to-moderate disease severity. HIIT improves cardiorespiratory fitness and may increase BDNF and improve motor symptoms in PwP. Future quality studies are needed to research the effects of differing HIIT protocols on physiological and clinical parameters, and to explore safe methods to facilitate access and long-term adherence. AQ7

Appendix

Appendix A

See Tables 7 and 8

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Table 7 PRISMA checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review	Title page, 2
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	3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	4
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	4,5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	Appendix B
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	5
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	6
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	5
	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	5
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	6
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	6,7

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Table 7 (continued)

Section and topic	Item #	Checklist item	Location where item is reported
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))	6,7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	6
	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	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression)	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	7
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	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	Appendix C
Study characteristics	17	Cite each included study and present its characteristics	10-12
Risk of bias in studies	18	Present assessments of risk of bias for each included study	15-17
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	24-26

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Table 7 (continued)

Section and topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	10-12
	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	17,18
	20c	Present results of all investigations of possible causes of heterogeneity among study results	17,18
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	NA due to small amount of studies
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	NA due to <10 studies in meta-analysis
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	17,18
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	27-30
	23b	Discuss any limitations of the evidence included in the review	31
	23c	Discuss any limitations of the review processes used	31
	23d	Discuss implications of the results for practice, policy, and future research	32
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	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	33
Competing interests	26	Declare any competing interests of review authors	33
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	N/A (Corresponding author for more information)

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Table 8 PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
Information sources and methods			
Database name	1	Name each individual database searched, stating the platform for each	4/Appendix B
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched	N/A
Study registries	3	List any study registries searched	N/A
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done	N/A
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, and setting up email alerts for references citing included studies)	4
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others	N/A
Other methods	7	Describe any additional information sources or search methods used	4
Search strategies			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run	Appendix B
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use	5
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used	N/A
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	4
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches and email alerts)	N/A
Dates of searches	13	For each search strategy, provide the date when the last search occurred	Appendix B
Peer review			
Peer review	14	Describe any search peer review process	4
Managing records			
Total Records	15	Document the total number of records identified from each database and other information sources	8
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources	5

PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews

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720 # Appendix B

721 See Table 9

Table 9 Search strategy per database

Database	Searches (22/11/2021)
Embase (Ovid)	1 exp Parkinson disease/ 2 Parkinson*.mp. 3 shaking palsy.mp. 4 1 or 2 or 3 5 high intensity interval training.mp. 6 HIIT.mp. 7 HIT.mp. 8 high intensity exercis*.mp. 9 interval exercis*.mp. 10 intermittent exercis*.mp. 11 high intensity interval exercis*.mp. 12 sprint interval training.mp. 13 aerobic interval training.mp. 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 1315 4 and 14
Medline (Ovid)	1 exp Parkinson disease/ 2 Parkinson*.mp. 3 shaking palsy.mp. 4 1 or 2 or 3 5 high intensity interval training.mp. 6 HIIT.mp. 7 HIT.mp. 8 high intensity exercis*.mp. 9 interval exercis*.mp. 10 intermittent exercis*.mp. 11 high intensity interval exercis*.mp. 12 sprint interval training.mp. 13 aerobic interval training.mp. 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 1315 4 and 14
Web of Science	1 TS=(parkinsons disease). 2 ALL=(parkinson*). 3 ALL=(shaking palsy). 4 ((#1) OR #2) OR #3. 5 ALL=(High intensity interval training). 6 ALL=(HIIT). 7 ALL=(HIT). 8 ALL=(High intensity exercis*). 9 ALL=(interval exercis*). 10 ALL=(intermittent exercis*). 11 ALL=(High intensity interval exercis*). 12 ALL=(sprint interval training). 13 ALL=(aerobic interval training). 14 (((((((#5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13. 15 (#4) AND #14.
CINAHL	1 SU parkinson's disease or parkinson disease or parkinsons disease or pd or parkinsons or parkinsonism. 2 TX Parkinson*. 3 TX shaking palsy. 4 S1 OR S2 OR S3. 5 TX high intensity interval training or hiit or high intensity exercise or high intensity workout. 6 TX HIT. 7 TX interval exercis*. 8 TX intermittent exercis*. 9 TX high intensity interval exercis*. 10 TX sprint interval training. 11 TX aerobic interval training. 12 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11. 13 S4 AND S12.
PsycINFO	1 su(parkinsons disease). 2 parkinson*. 3 shaking palsy 4. su(parkinsons disease) OR parkinson* OR (shaking palsy). 5 high intensity interval training. 6 HIIT. 7 HIT 8. high intensity exercis*. 9 interval exercis*. 10 intermittent exercis*. 11 high intensity interval exercis*. 12 sprint interval training. 13 aerobic interval training. 14 (high intensity interval training) OR HIIT OR HIT OR (high intensity exercis*) OR (interval exercis*) OR (intermittent exercis*) OR (high intensity interval exercis*) OR (sprint interval training) OR (aerobic interval training). 15 4 AND 14
Google Scholar	1 Advanced search “Parkinson’s” AND “high intensity interval” OR “HIIT”

722 # Appendix C

723 See Table 10

Table 10 Excluded studies that included HIIT for PwP, and reasons for exclusion

Article	Reason for exclusion
Fiorelli et al. 2019 Uygur et al. 2015	Only examined the acute effects of a single HIIT session
Ridgel et al. 2016 Rose et al. 2013	Included inappropriate intervention components
Marusiak et al. 2015	Included inappropriate participants
Gobert et al. 2021 Gobert and McDowell 2020 Malczynska et al. 2019 Malczynska et al. 2020 Marusiak et al .2017 Pascal 2018 Pascal 2018b	Reported insufficient information for a full quality assessment

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Declarations

Conflict of interest None to declare.

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