# Changes of Brain-Derived Neurotrophic Factor (BDNF) levels after different exercise protocols: a systematic review of clinical studies in Parkinson's disease

**Supplementary File 1. Search strategies**

**Pubmed**

Search: ((Parkinson*[Title/Abstract] OR PD[Title/Abstract]) AND (exercise[Title/Abstract] OR "physical activity"[Title/Abstract] OR training[Title/Abstract] OR sport*[Title/Abstract] OR rehabilit*[Title/Abstract] OR "physical therapy"[Title/Abstract] OR physiotherapy[Title/Abstract]) AND (BDNF[Title/Abstract] OR plastic*[Title/Abstract] OR synap*[Title/Abstract] OR neuro*[Title/Abstract] OR cognit*[Title/Abstract] OR biomarker*[Title/Abstract])) NOT ((rat[Title] OR animal[Title] OR mouse[Title] OR mice[Title]) NOT review[Title]) Filters: from 2003/1/1 - 2022/12/31 Sort by: Most Recent

**Scopus**

( TITLE ( ( parkinson* OR pd ) AND ( exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy ) AND ( bdnf OR plastic* OR synap* OR neuro* OR cognit* OR biomarker* ) ) OR ABS ( ( parkinson* OR pd ) AND ( exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy ) AND ( bdnf OR plastic* OR synap* OR neuro* OR cognit* OR biomarker* ) ) AND NOT TITLE ( ( rat OR animal OR mouse OR mice ) not AND review ) ) AND PUBYEAR > 2002 AND PUBYEAR < 2023

**Web of Science**

(Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) (Title) or (Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) (Abstract) not (rat OR animal OR mouse OR mice) NOT review (Title)

**ClinicalTrial.gov**

(Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) in Record Title OR (Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) in Abstract NOT (rat OR animal OR mouse OR mice) NOT review in Record Title - (Word variations have been searched)

**Embase**

(Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) in Record Title OR (Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) in Abstract NOT (rat OR animal OR mouse OR mice) NOT review in Record Title - (Word variations have been searched)

**CINHAL**

(Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) in Record Title OR (Parkinson* OR PD) AND (exercise OR "physical activity" OR training OR sport* OR rehabilit* OR "physical therapy" OR physiotherapy) AND (BDNF OR plastic* OR synap* OR neuro* OR cognit* OR biomarker*) in Abstract NOT (rat OR animal OR mouse OR mice) NOT review in Record Title - (Word variations have been searched)

**Supplementary File 2.** Measurement of BDNF by study

| Author and year | Sample | Unit | Timing of post-exercise BDNF measurement |
|---|---|---|---|
| Angelucci et al. 2016 | Serum | pg/mL | At 8:00-9:00 a.m. |
| Da Silva Germanos et al. 2019 | Plasma | pg/ml | Not specified |
| De Oliveira et al. 2020 | Plasma | ng/mg | At 10-11 a.m. |
| Frazzitta et al. 2014 | Serum | ng/mL | At 7:00 am, away from exercise |
| Freidle et al. 2022 | Serum | pg/mL | Within 2-3 weeks after the end of the intervention[a] |
| Harro et al. 2022 | Serum | ng/mL | On a non-exercise day[a] |
| Landers et al. 2019 | Plasma | pg/mL | Between 48 and 72 hours from active participation in the trial[a] |
| O'Callaghan et al. 2019 | Serum | ng/ml | Not specified |
| Pondé et al. 2019 | Serum | pg/mL | Not specified |
| Sajatovic et al. 2017 | Serum | pg/mL | Not specified |
| Schaeffer et al. 2022 | Serum | ng/mL | Away from the exercise[a] |
| Segura et al. 2020 | Plasma | pg/mL | Not specified |
| Soke et al. 2021 | Serum | pg/ml | At 8-9 am, the day after the end of the intervention |
| Stuckenschneider et al. 2021 | Serum | ng/mL | Not on exercise days[a] |
| Szymura et al. 2020 | Serum | ng/mL | At 8-10 a.m., 2 days after the completion of the programme |
| Zoladz et al. 2014 | Serum | pg/mL | One week after the end of the training[a] |

[a]Personal communication from the authors

**Supplementary File 3.** Studies not included in this review and reason for exclusion

| Authors, year | Reason for exclusion |
|---|---|
| Angelucci et al., 2015 [1] | Not physical training |
| Angelucci et al., 2015 [1] | Abstract (duplicate) |
| Azevedo et al., 2022 [2] | Observational study |
| Bastioli et al., 2022 [3] | Animals |
| Bekinschtein et al., 2020 [4] | Review |
| Biagioni et al., 2018 [5] | Abstract |
| Campos et al., 2016 [6] | Review |
| Dias Belchior et al., 2017 [7] | Not BDNF measures |
| Farshbaf et al., 2016 [8] | Review |
| Farshbaf et al., 2016 [8] | Review (duplicate) |
| Ferreira et al., 2018 [9] | Review |
| Fontanesi et al., 2016 [10] | Not BDNF measures |
| Franzén et al., 2018 [11] | Protocol |
| Franzén et al., 2019 [12] | Protocol |
| Goldberg et al., 2015 [13] | Review |
| Harper et al., 2019 [14] | Not BDNF measures |
| Harpham et al., 2023 [15] | Not BDNF measures |
| Hirsch et al., 2016 [16] | Review |
| Hooper et al., 2016 [17] | Animals |
| HU et al., 2005 [18] | Not physical training |

| | |
|---|---|
| Karim et al., 2022 [19] | Measure of BDNF <12h (5-60 min) |
| Khalil et al., 2017 [20] | Cross-sectional |
| Marusiak et al., 2015 [21] | Not BDNF measures |
| Mattson et al., 2004 [22] | Animals |
| Migdadi et al., 2018 [23] | Abstract |
| Monteiro-Junior et al., 2015 [24] | Review |
| Norwitz et al., 2020 [25] | Not BDNF measures |
| Pagnussat et al., 2018 [26] | Not physical training |
| Patterson et al., 2022 [27] | Protocol |
| Radak et al., 2007 [28] | Review |
| Rothman et al., 2012 [29] | Review |
| Szymura et al., 2019 [30] | Abstract |
| Tuon et al., 2014 [31] | Animals |
| van Wegen et al., 2020 [32] | Protocol |
| Wang et al., 2022 [33] | Animals |
| Wu et al., 2011 [34] | Animals |
| Yang et al., 2014 [35] | Animals |


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**Supplementary File 4.** Type, intensity, frequency and duration of exercise components by study arm

| Author and year | Study arm[a] | Activity | Type of activity | MET | Sessions week | Min session |
|---|---|---|---|---|---|---|
| Angelucci et al. 2016 | Multimodal | Relaxation, breathing | Others | 1.5 | 5 | 10 |
| | | Flexibility | Others | 2.0 | 5 | 15 |
| | | Mobility | Others | 2.3 | 5 | 20 |
| | | Postural | Others | 2.5 | 5 | 20 |
| | | Treadmill | Aerobic | 3.0 | 5 | 20 |
| | | Stationary bike | Aerobic | 3.0 | 5 | 20 |
| | | Wii Fit Balance Board | Balance | 2.3 | 5 | 20 |
| | | Coordination | Others | 2.5 | 5 | 25 |
| Da Silva Germanos et al. 2019 | Multimodal | Aquatic exercises: stretching, mobility | Others | 2.5 | 2 | 10 |
| | | Aquatic exercises: strengthening, gait, balance, proprioception | Resistance | 5.0 | 2 | 20 |
| | | Aquatic exercises: dual task | Aerobic | 3.0 | 2 | 20 |
| De Oliveira et al. 2020 | Multimodal | Mobility, coordination | Others | 2.5 | 2 | 8 |
| | | Deep water running (endurance) | Aerobic | 5.0 | 2 | 35 |
| | | Coordination | Balance | 3.0 | 2 | 13 |
| | | Stretching, relaxation | Others | 2.0 | 2 | 8 |
| Frazzitta et al. 2014 | Multimodal | Cardiovascular exercises | Aerobic | 2.5 | 5 | 15 |
| | | Stretching, mobility | Others | 2.3 | 5 | 15 |
| | | Postural | Others | 2.5 | 5 | 15 |
| | | Stabilometric platform with a visual cue | Balance | 2.5 | 5 | 15 |
| | | Treadmill training with both a visual and an auditory cue | Aerobic | 2.8 | 5 | 30 |
| | | Occupational therapy | Others | 2.0 | 5 | 40 |
| Freidle et al. 2022 | Multimodal | HiBalance: sensory integration, motor agility, anticipatory postural adjustments and stability limits | Balance | 3.0 | 2 | 50 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Functional aerobic (home exercises) | Aerobic | 3.5 | 1 | 20 |
| | | Strength exercises (home exercises) | Resistance | 3.5 | 1 | 20 |
| | Speech and communication | HiCommunication: voice sound level, articulatory precision, word retrieval, memory | Others | 1.3 | 2 | 50 |
| | | Voice, speech function (home exercises) | Others | 1.3 | 1 | 30 |
| Harro et al. 2022 | Endurance | Warm up (nordic walking) | Aerobic | 2.5 | 2 | 10 |
| | | Nordic walking | Aerobic | 5.0 | 2 | 43 |
| | | Cool down (nordic walking) | Aerobic | 2.5 | 2 | 10 |
| Landers et al. 2019 | Multimodal (High intensity) | Treadmill, overground walking on the indoor track, stair climber, bike, recumbent bike, rowing machine | Aerobic | 4.5 | 4 | 30 |
| | | Strengthening the major muscle groups of the trunk and upper/lower extremities | Resistance | 4.5 | 4 | 30 |
| | | Postural, dynamic gait, sensory orientation | Balance | 3.0 | 4 | 15 |
| | | Stretching | Others | 2.3 | 4 | 15 |
| | | Home exercise (same exercises) | Aerobic | 4.0 | 2 | 18 |
| | | Home exercise (same exercises) | Resistance | 4.0 | 2 | 18 |
| | | Home exercise (same exercises) | Balance | 3.0 | 2 | 9 |
| | | Home exercise (same exercises) | Others | 2.3 | 2 | 9 |
| | Multimodal (Low intensity) | Treadmill, overground walking on the indoor track, stair climber, bike, recumbent bike, rowing machine | Aerobic | 2.7 | 4 | 15 |
| | | Strengthening the major muscle groups of the trunk and upper/lower extremities | Resistance | 3.0 | 4 | 15 |
| | | Step touch task | Balance | 2.5 | 4 | 10 |
| | | Stretching | Others | 2.3 | 4 | 10 |
| | | Home exercise (same exercises) | Aerobic | 3.0 | 2 | 11 |
| | | Home exercise (same exercises) | Resistance | 3.0 | 2 | 11 |
| | | Home exercise (same exercises) | Balance | 2.5 | 2 | 8 |
| | | Home exercise (same exercises) | Others | 2.3 | 2 | 8 |
| O'Callaghan et al. 2019 | Aerobic + Resistance | Warm up | Aerobic | 2.5 | 3 | 8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Stretching | Others | 2.3 | 3 | 2 |
| | | 12 stations in a circuit | Aerobic | 4.0 | 3 | 27 |
| | | Resistance stations | Resistance | 4.0 | 3 | 12 |
| | | Cool down | Aerobic | 2.5 | 3 | 8 |
| | | Stretching | Others | 2.3 | 3 | 2 |
| | High-Intensity Interval Training | Warm up | Resistance | 3.0 | 3 | 10 |
| | | Power clean and press, step and press, squat, pull-down to squat, high pull, bent over row | Resistance | 7.0 | 3 | 20 |
| | | Cool down | Resistance | 3.0 | 3 | 5 |
| Pondé et al. 2019 | Aerobic | Treadmill | Aerobic | 3.0 | 2 | 40 |
| | | Motor imagery | Others | 1.1 | 2 | 14 |
| Sajatovic et al. 2017 | Aerobic + Resistance (peer support) | Warm up | Aerobic | 2.5 | 3 | 5 |
| | | EXCEED: fast-paced, low-resistance cycling | Aerobic | 4.0 | 3 | 20 |
| | | EXCEED: progressive sequence of resistance bands | Resistance | 3.5 | 3 | 20 |
| | | Cool down | Aerobic | 2.5 | 3 | 5 |
| | Aerobic + Resistance | Warm up | Aerobic | 2.5 | 3 | 5 |
| | | SGE: fast-paced, low-resistance cycling | Aerobic | 4.0 | 3 | 20 |
| | | SGE: progressive sequence of resistance bands | Resistance | 3.5 | 3 | 20 |
| | | Cool down | Aerobic | 2.5 | 3 | 5 |
| Schaeffer et al. 2022 | Aerobic | Exergaming | Aerobic | 4.0 | 3 | 45 |
| Segura et al. 2020 | Aerobic | Warm up | Aerobic | 2.5 | 3 | 10 |
| | | Stationary tandem bicycle | Aerobic | 6.0 | 3 | 20 |
| | | Cool down | Aerobic | 2.5 | 3 | 5 |
| | | Stretching | Others | 2.3 | 3 | 10 |
| Soke et al. 2021 | Aerobic + Resistance | Warm up | Aerobic | 2.5 | 3 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Treadmill | Aerobic | 4.5 | 3 | 20 |
| | | Cool down | Aerobic | 2.5 | 3 | 5 |
| | | Task-oriented training (TOT): circuit with a series of workstations | Resistance | 4.0 | 3 | 33 |
| | Aerobic | Warm up | Aerobic | 2.5 | 3 | 5 |
| | | Treadmill | Aerobic | 4.5 | 3 | 20 |
| | | Cool down | Aerobic | 2.5 | 3 | 5 |
| Stuckenschneider et al. 2021 | Multimodal | Coordination | Balance | 2.5 | 2 | 20 |
| | | Wall pushups, holding medicine balls with outstretched arms, squats, or crunches | Resistance | 4.1 | 2 | 20 |
| | | Walking or running exercises | Aerobic | 4.1 | 2 | 20 |
| Szymura et al. 2020 | Aerobic | Warm up | Aerobic | 2.5 | 3 | 5 |
| | | Wii Fit Balance Board | Balance | 3.3 | 3 | 50 |
| | | Cool down | Aerobic | 2.5 | 3 | 5 |
| Zoladz et al. 2014 | Aerobic | Warm up | Aerobic | 2.5 | 3 | 10 |
| | | Interval training | Aerobic | 3.5 | 3 | 40 |
| | | Cool down | Aerobic | 2.5 | 3 | 10 |

[a]Definition of exercise intervention according Zhou B et al. in Aging Neurosci 2022
Abbrevations: MET, Metabolic Equivalent of Task.

**Supplementary File 5.** Pre-post exercise BDNF levels of experimental and comparison group in controlled studies only

| Author and year | Study arm[a] | BDNF before the exercise[b] | BDNF after the exercise[b] | SMD[c] | (95% CI) | |
|---|---|---|---|---|---|---|
| Frazzitta et al. 2014 | Multimodal | 21.6 (3.4) | 24.8 (6.4) | 0.64 | (-0.16 | 1.45) |
| | Control | 22.9 (4.0) | 22.6 (4.3) | | | |
| Freidle et al. 2022 | Multimodal | 38010.8 (7956.7) | 37169.4 (5928.3) | 0.14 | (-0.26 | 0.54) |
| | Speech and communication | 37805.3 (8044.6) | 35945.8 (6208.5) | | | |
| Landers et al. 2019 | Multimodal (high intensity) | 1960.2 (1529.5) | 2580.7 (1411.2) | -0.07 | (-0.85 | 0.70) |
| | Multimodal (low intensity) | 960.3 (1482.9) | 1697.5 (1368.1) | | | |
| O'Callaghan et al. 2019 | Aerobic + Resistance | 1300.1 | 1338.0 | 0.32 | (-0.42 | 1.06) |
| | Control | 1470.3 | 861.4 | | | |
| | High-Intensity Interval Training | 685.0 | 783.9 | 0.48 | (-0.44 | 1.40) |
| | Control | 699.9 | 627.9 | | | |
| Sajatovic et al. 2017 | Aerobic + Resistance (peer support) | | | 0.54 | (-0.24 | 1.32) |
| | Aerobic + Resistance | | | | | |
| Segura et al. 2020 | Aerobic | 20.6 (120.0) | 207.1 (120.0) | 1.85 | (0.61 | 3.09) |
| | Control | 260.0 (150.0) | 149.6 (150.0) | | | |
| Soke et al. 2021 | Aerobic + Resistance | 1397.0 | 1507.5 | 0.03 | (-0.68 | 0.74) |
| | Aerobic | 1487.6 | 1411.2 | | | |
| Szymura et al. 2020 | Aerobic | 21.2 (8.4) | 30.4 (6.3) | 1.45 | (0.64 | 2.25) |
| | Control | 30.1 (8.0) | 25.8 (11.7) | | | |

[a]Definition of exercise intervention according Zhou B et al. in Aging Neurosci 2022; [b]Mean (Standard deviation). For O'Callaghan et al. 2019, Soke et al. 2021 the median is reported**;** [c]Standardized Mean Difference (Hedges' g); for the studies by O'Callaghan et al. 2019, Sajatovic et al. 2017, Soke et al. 2021 data was derived from Jiecheng et al. 2023

**Supplementary File 6.** Pre-post exercise BDNF levels separately by study arm in controlled and non-controlled studies

| Author and year | Study arm[a] | BDNF before the exercise[b] | BDNF after the exercise[b] | SMD[c] | (95% CI) | |
|---|---|---|---|---|---|---|
| Angelucci et al. 2016 | Multimodal | 2188.4 (1718.8) | 2356.5 (1666.7) | 0.10 | (-0.83 | 1.02) |
| Da Silva Germanos et al. 2019 | Multimodal | 493.9 | 933.3 | - | | |
| De Oliveira et al. 2020 | Multimodal | 0.2 (0.1) | 0.4 (0.3) | 1.00 | (0.02 | 1.98) |
| Frazzitta et al. 2014 | Multimodal | 21.6 (3.4) | 24.8 (6.4) | 0.61 | (-0.15 | 1.37) |
| | Control | 22.9 (4.0) | 22.6 (4.3) | -0.07 | (-0.95 | 0.81) |
| Freidle et al. 2022 | Multimodal | 38010.8 (7956.7) | 37169.4 (5928.3) | -0.12 | (-0.52 | 0.28) |
| | Speech and communication | 37805.3 (8044.6) | 35945.8 (6208.5) | -0.26 | (-0.66 | 0.15) |
| Harro et al. 2022 | Endurance | 34.8 | 32.3 | - | | |
| Landers et al. 2019 | Multimodal (high intensity) | 1960.2 (1529.5) | 2580.7 (1411.2) | 0.42 | (-0.36 | 1.20) |
| | Multimodal (low intensity) | 960.3 (1482.9) | 1697.5 (1368.1) | 0.52 | (-0.33 | 1.37) |
| O'Callaghan et al. 2019 | Aerobic + Resistance | 1300.1 | 1338.0 | - | | |
| | Control | 1470.3 | 861.4 | - | | |
| | High-Intensity Interval Training | 685.0 | 783.9 | - | | |
| | Control | 699.9 | 627.9 | - | | |
| Pondé et al. 2019 | Aerobic | 88.8 (111.8) | 202.6 (183.4) | 0.75 | (-0.26 | 1.76) |
| Sajatovic et al. 2017 | Aerobic + Resistance (peer support) | 26.8 (15.6) | 90.0 (166.4) | 0.53 | (-0.25 | 1.32) |
| | Aerobic + Resistance | 26.8 (15.6) | 90.0 (166.4) | 0.53 | (-0.19 | 1.26) |
| Schaeffer et al. 2022 | Aerobic | 23.9 (7.5) | 25.2 (7.3) | 0.18 | (-0.50 | 0.85) |
| Segura et al. 2020 | Aerobic | 20.6 (120.0) | 207.1 (120.0) | 1.55 | (0.26 | 2.85) |
| | Control | 260.0 (150.0) | 149.6 (150.0) | -0.74 | (-1.82 | 0.35) |
| Soke et al. 2021 | Aerobic + Resistance | 1397.0 | 1507.5 | - | | |
| | Aerobic | 1487.6 | 1411.2 | - | | |
| Stuckenschneider et al. 2021 | Multimodal | 33.6 (9.7) | 34.3 (11.8) | 0.07 | (-0.91 | 1.05) |
| Szymura et al. 2020 | Aerobic | 21.2 (8.4) | 30.4 (6.3) | 1.24 | (0.48 | 1.99) |
| | Control | 30.1 (8.0) | 25.8 (11.7) | -0.43 | (-1.21 | 0.35) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Zoladz et al. 2014 | Aerobic | 10977.0 (2618.9) | 14206.0 (4350.9) | 0.90 | (0.06 | 1.74) |

[a]Definition of exercise intervention according Zhou B et al. in Aging Neurosci 2022; [b]Mean (Standard deviation). For the studies by Da Silva Germanos et al. 2019, Harro et al. 2022, O'Callaghan et al. 2019, Soke et al. 2021 the median is reported. [c]Standardized Mean Difference (Cohen's d)

## Supplementary File 7. Sensitivity analysis

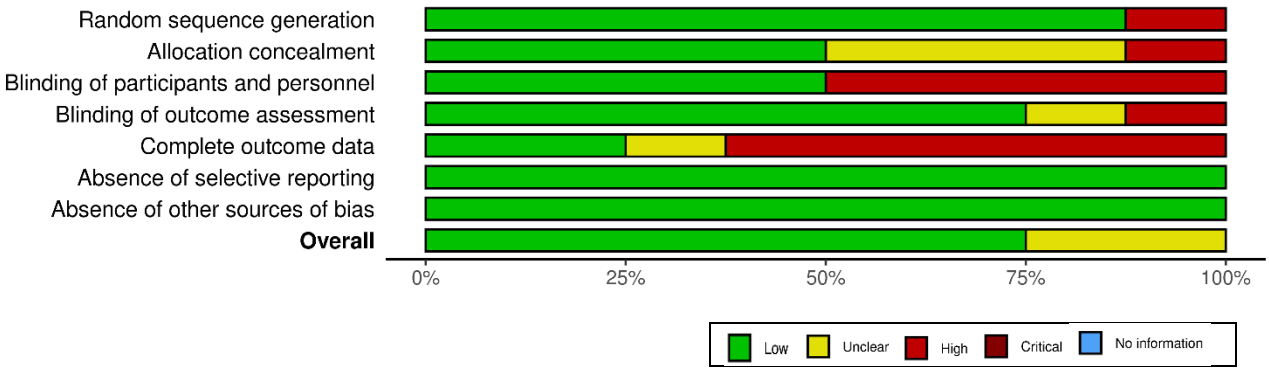
Meta-regression of between-group differences in intensity, volume and type of exercise on changes in BDNF levels (controlled studies only)

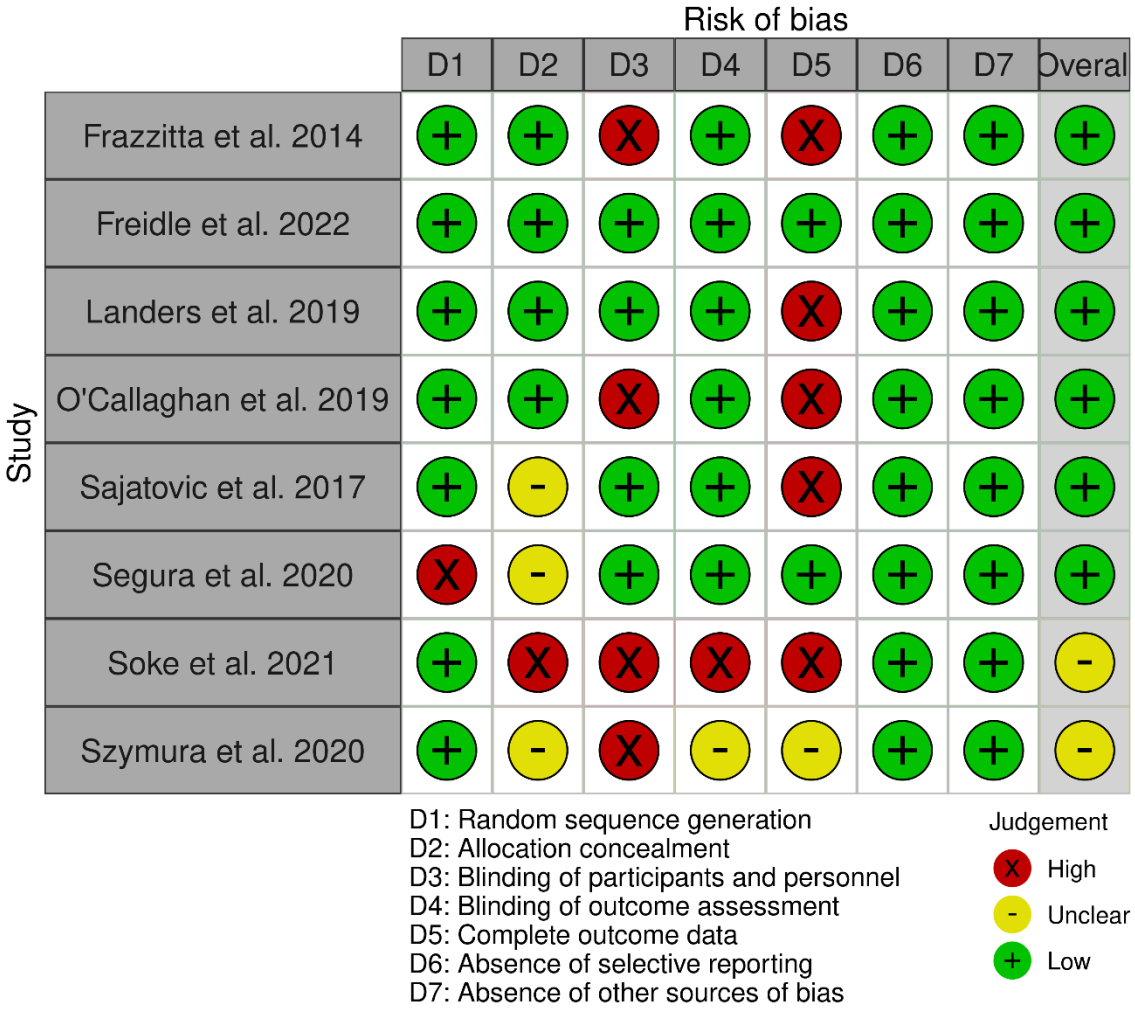
| | 5 studies | | | | 9 studies | | | |
|---|---|---|---|---|---|---|---|---|
| | **Coefficient** | **(95% CI)** | | **P value** | **Coefficient** | **(95% CI)** | | **P value** |
| **Δ Time-weighted average of MET** | 0.41 | (0.02 | 0.81) | 0.042 | 0.14 | (-0.04 | 0.32) | 0.124 |
| **Δ Total MET-hours (x100)** | -0.26 | (-2.23 | 1.71) | 0.797 | -0.04 | (-0.94 | 0.87) | 0.934 |
| **Type** | | | | | | | | |
| **Identical (Aerobic + Resistance)** | Reference | | | | Reference | | | |
| **Aerobic** | 1.25 | (-0.93 | 3.43) | 0.262 | 0.58 | (-0.64 | 1.79) | 0.350 |
| **Balance** | 0.81 | (-1.29 | 2.91) | 0.449 | 0.45 | (-0.80 | 1.70) | 0.476 |
| **Resistance** | | | | | 0.00 | (-1.31 | 1.31) | 0.999 |

Linear regression of intensity, volume and type of exercise on change in BDNF (study arms of controlled and non-controlled studies)

| | **Coefficient** | **(95% CI)** | | **P value** |
|---|---|---|---|---|
| **Time-weighted average of MET** | 0.26 | (0.15 | 0.38) | 0.000 |
| **Total MET-hours (x100)** | 0.52 | (-0.02 | 1.06) | 0.059 |
| **Type** | | | | |
| **Aerobic** | 1.10 | (0.50 | 1.70) | 0.002 |
| **Balance** | 0.93 | (0.10 | 1.77) | 0.031 |
| **Aerobic + Resistance** | 0.79 | (0.14 | 1.43) | 0.020 |

**Supplementary File 8.** Risk of bias assessment using Cochrane risk of bias tool (RoB)



**Supplementary File 9.** Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I)