

**Supplementary Table S2. Interventions, Measures, and Key Findings**

| Author,<br>Year of<br>publication         | Exercise or Physical Activity        |   | Comparison   | BDNF<br>Sample/<br>Detection<br>method | Symptoms-<br>Measures   | Result   |   |
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|   | Frequency;<br>duration               | Intervention  |  |  |   | Change in BDNF   | Symptoms vs BDNF  |
| <b>Adults with Neurological Disorders</b> |                                      |   |  |  |   |  |   |
| 1. Amato et al., 2021 [52]                | 12 weeks (2 x/week); 90 mins/session | Stretching exercise: lactate threshold training (combined balance and stretching exercise to produce a modest amount of lactate)  | Pre vs. Post vs. 9 months follow up  | Plasma/ ELISA                          | Fatigue-VAFS  | The BDNF level increased significantly immediately after the intervention program but not at 9-month post intervention follow up                       | Immediately after the intervention, fatigue decreased and BDNF level increase significantly               |
| 2. Azevedo et al., 2022 [53]              | One session; 60 mins                 | Aerobic exercise- Walking on a treadmill with increasing speed during the first 15 min to reach 60-65% Max HR. Continue with the same intensity (15 min) and decrease speed for cool down (5 min) | Participants with vs. without depression and PD participants with vs. without fatigue              | Serum/ ELISA                           | Depressive symptoms- BDI<br>Fatigue- PFS                      | mBDNF level increased after the exercise regardless groups.  | Symptoms (fatigue and depression) were used for grouping. Exercise increase mBDNF level regardless groups |
| 3. Bansi et al., 2013 [54]                | 3-week (5x/week); 20 mins            | Aerobic exercise: Cycling on an aquatic bike (Training intensity: 70% Heart Rate peak (60% VO <sub>2</sub> peak) (n=28)   | Cycling on an ergometer (Training intensity: 70% Heart Rate peak (60% VO <sub>2</sub> peak) (n=24) | Serum/ Multiplex flow cytometry        | Fatigue- The multidimensional FSMC                            | No significant differences of BDNF between the land vs water ergometer groups. In the water group, BDNF significantly increased after the intervention | The increasing of BDNF were observed, fatigue was not changed after the intervention.                     |
| 4. Bartlett et al., 2020 [55]             | 9 months (2x/week); 60 mins          | Multimodal exercise: Supervised aerobic, resistance and endurance training combined with other interventions in rehabilitation program. (n=18)  | Usual Care Control (n=11)  | Serum/ ELISA                           | Sleep-PSQI, sleep diary, ESS<br>Anxiety, and depression- HADS | The BDNF level slightly increased from baseline in the intervention group.   | Changes in BDNF level and symptoms after the intervention were not significant                            |

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| 5. Devasahayam et al., 2020 [56] | One session                             | Aerobic exercise: Maximal GXT on a TBRs- 80 SPM for 2 minutes, increasing the load by one level every 2 mins until exhaustion or level 10. (n=14)   | Age/sex matched healthy control (n=7)  | Serum/ELISA                   | Fatigue-FSS<br>HRQoL-SF-36)   | Serum BDNF level increased after the intervention but not significant.   | In MS group, higher elevation in BDNF was significantly correlated with walking speed and lower vitality (measured by SF-36)                                       |
| 6. Belchior et al., 2017 [57]    | 8-week (2x/week); 10-30 mins/session    | Aerobic exercise: Walking on a treadmill- Start with 10 minutes of walking at baseline velocity on a flat treadmill. Every week, increase by 5 minutes until reaching 30 minutes. (n=10)                      | Usual Care Control (n=12)  | Plasma/NA                     | Depression-GDS<br>HRQoL-SF-36<br>cognitive function-MMSE                  | No significant change in BDNF level post-intervention changes.   | Association between BDNF and symptoms was not investigated   |
| 7. Harro et al., 2022 [58]       | 20-week (2-3x/week); 60-65 mins/session | Aerobic exercise: NW training— supervised NW exercise training (6 week) and independent NW (14 weeks)   | before, post supervised phase and 3 month follow up  | Serum/ELISA                   | Fatigue-PFS   | BDNF level increased significantly at 3 month follow up from baseline and post supervised phase  | No significant change in fatigue. The association between BDNF level and fatigue was not studied   |
| 8. Landers et al., 2019 [59]     | 8 weeks (3-4x/week); 90 mins/session    | Multimodal exercise: High-intensity multimodal exercise boot camp (HIBC)- Multimodal exercise- moderate to high intensity aerobic, strength training, balance training, and active rest and stretching (n=13) | Low-intensity, Control group- 60 mins of aerobic, strength, balance, and stretching (n=11) | Serum/ELISA<br>DNA/Genotyping | Fatigue-PFS<br>Depression-BDI<br>QoL-Parkinson's Disease Questionnaire-39 | BDNF levels significantly increased post-intervention but decreased at the 6-month follow-up compared to baseline in both HIBC and control groups. | Fatigue decreased significantly post intervention only in the HIBC group. The association between BDNF level and symptoms was not investigated.                    |
| 9. Ozkul et al., 2018 [60]       | 8-week; 105 min/session                 | Multimodal exercise: combined aerobic and Pilates exercise- a) aerobic training: walking on a treadmill to reach 60-80% of maximum Heart; b) Pilates training after 15 min rest. (n=18)                       | Usual care control (n=18) vs. Healthy volunteers (n=18)                                    | Serum/ELISA<br>Serum          | Fatigue-FSS   | The BDNF level increase post intervention in both groups but was significant only in the exercise group.   | Fatigue severity decreased significantly only in exercise group but increase in the control group. The association between BDNF and symptoms was not investigated. |

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| 10. Liu et al., 2020 [61]             | 4-week (5x/week)                  | Strength training: isotonic weight training machines: 2 sets of 12 reps of a weight 40-50% 1 Repetition Maximum (n=30)   | Aerobic (stationary bicycle training): paddle rate at the intensity of 5-6 on a 10-scale of perceived exertion for 30 min (n=31) | Serum/ELISA  | Cognitive function-MMSE and MoCA<br>Depression-GDS | The BDNF level increase in both groups but not significant  | Cognitive function improved significantly for both exercise groups. Both depression and BDNF level were not significantly change for both groups            |
| 11. Zhang et al., 2023 [62]           | 12-week (3x/week); 60 min/session | Multimodal exercise: Traditional Chinese Exercise (TCE) + Rhythm Training Group (RTG)- joint stretching, aerobic exercise and acupoint massage (n=14)  | Walking Group- Relaxation phase (10 min) and 3 km walk (WG) (n=14)<br><br>Education Control group (n=14)                         | Serum/ELISA  | Depression-HDS                                     | BDNF level increased in both TCE+RTG and WG groups but significantly decreased in the control group   | Participants in both exercise groups (TCE+RTG and WG groups) showed significant reduction of depression score and increasing BDNF level at 12 weeks         |
| <b>Adults with chronic conditions</b> |                                   |  |  |              |  |   |   |
| 12. De Araujo et al., 2019 [63]       | 8-week (3x/week); 90 min/session  | Multimodal exercise: Treadmill endurance (30 min at 60% 6MWT, progress by dyspnea) and muscular training: 2 sets of 10-15 reps for lower limbs, 2 sets of 2 minutes for upper limbs.                                       | Pre vs. Post 1 <sup>st</sup> session vs. Pre 24 <sup>th</sup> session  | Plasma/ELISA | Depression-BDI, HRQoL-mMRC<br>Dyspnea-SGRQ         | Plasma BDNF level significantly decreased immediately after the first exercise session.   | Dyspnea decreased significantly. No significant change of the depression score. Change in plasma BDNF was not related to change in depression and dyspnea   |
| 13. Deus et al., 2021 [64]            | 6-month (3x/week); 60 min/session | Strength training: Resistance training (RT)immediately before each dialysis session (n=81)   | Usual care control (CTL) (n=76)  | Serum/ELISA  | Depression-BDI, HRQoL-SF-36                        | BDNF increased for RT group but decreased for CTL group.  | Depression decreased, and vitality and emotional well-being improved in the exercise group. High BDNF was linked to lower depression and better well-being. |
| 14. Gomes et al., 2014 [65]           | 12-week (3x/week)                 | Aerobic exercise: Acute (2 min at 1 mph, 18 min at 2 mph, 30 min rest) following by chronic: 40-65 min aerobic exercise (5 min warm-up/cool-down), 30 min treadmill at 70% HRmax, increasing to 80% HRmax by week 8 or 12. | Pre-post intervention  | Plasma/ELISA | Pain-VAS for pain                                  | Acute exercise: BDNF increases immediately and lasts up to 30 min during recovery.<br><br>Chronic exercise: BDNF significantly increases after 12 weeks compared to baseline. | Pain decreased significantly while the BDNF level increased significantly after the 12 weeks exercise compared to baseline.                                 |

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| 15. Jablochko et al., 2019 [66]  | 15-week (2x/week); 60 mins/session  | Strength training: Resistance training: 10 min warm-up and stretching. Progress from 40% to 80% of 1RM, with 15-20 reps to 5-8 reps, 1-2 sets, and 1 min rest. (n=41) | Relaxation therapy: 25 min guided relaxation (n=34)<br><br>Healthy Volunteers (n=25) | multiplex electrochemiluminescence assay panel Plasma | Pain- VAS<br>Anxiety and Depression-HADS<br>HRQoL-SF-36<br>Quality of Life, Fibromyalgia-FIQ<br>Fatigue-MFI | FM participants had higher BDNF than controls.<br><br>BDNF increased post-intervention in both groups, but not significantly. | Pain and fatigue decreased significantly in the exercise groups.<br><br>No significant association between BDNF change and symptoms.   |
| 16. Lee et al., 2014 [67]        | 12-week                             | Aerobic exercise: 50 minutes of moderate aerobic exercise in weight reduction program   | Pre-post intervention: Participants were grouped by BDNF change (minor vs. greater)  | Serum/ELISA   | Depression-Zung Self-Rating Depression Scale  | The BDNF level increased significantly after the intervention   | Depression score decreased, but not significantly. Larger BDNF change linked to smaller depression decrease.<br><br>Significant reduction in depression was seen in the greater BDNF change group. |
| 17. Ribeiro et al., 2021 [68]    | 6 weeks (3x/week)                   | Others: Whole-Body Vibration Training (WBVT)- 3-11 min of dynamic squatting on a synchronic vibrating platform (FitVibe®ExcelPro, GymnaUniphy, Belgium). (n=17)       | Usual care Control (n=15)  | Plasma/ELISA  | Fibromyalgia Symptoms-FIQ and VAS<br>Sleep-PSQI<br>Depression-BDI   | BDNF level increase significantly in the intervention group but decrease in the control group                                 | The intervention group showed significant reduction of pain, sleep problem, and depression and increasing BDNF level   |
| 18. Žlibinaitė et al., 2020 [69] | 6 months (3x/week); 50 mins/session | Aerobic exercise: supervised aerobic exercise training on cycle ergometry to achieve 60-70% of maximum HR (n=13)  | Usual Care Control (n=13)  | Serum/ELISA   | Mood State-Brunel Mood Scale  | BDNF level decreased after the program. The control group had a larger reduction of BDNF level.                               | No significant changes in exercise group. In control group, depression and confusion increased significantly and BDNF level decreased.   |

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| 19. Maguire et al., 2023 [70] | One session; 80 mins | Aerobic exercise: Moderate intensity cycle-ergometer aerobic training (MI-ET) and upper limb robotic or sensor-based motor training (RT) (n=10)                               | Low-intensity gait and balance circuit training (LI-CT) (n=7)  | Serum/ ELISA   | Balance measured with the Mini BESTest Fatigue-FSS                               | Serum BDNF levels showed no significant change from pre to post-training in either group.                           | Change in BDNF levels was not related to changes in balance and fatigue  |
| <b>Adults with Cancer</b>     |                      |   |  |  |  |   |  |
| 20. Cartmel et al., 2021 [48] | 6-month              | Aerobic exercise: Home based moderate-intensity aerobic exercise- Weekly phone consultation with certified cancer exercise trainer to increase the PA to 150 min/week. (n=74) | Attention control health education- Weekly telephone attention control health education. (n=70)      | Serum/ ELISA   | Depression- CES-D  | Free-BDNF level decreased but the total BDNF level increased after the program compared to baseline.                | Depression decreased in the exercise arm. Greater decline of depression score associated with a greater increase in free-BDNF (weak association) but not the total BDNF    |
| 21. Hartman et al., 2019 [49] | 12 weeks             | Physical activity: Personalized physical activity- One in-person visit to set activity goals, two phone calls, and emails every 3 days with reminders and content. (n=43)     | Wellness Contact Control Group- Health education through e-mails every 3 days (n=44)                 | Plasma/ High-sensitivity immunoassay                         | Anxiety, depression, fatigue, physical function- PROMIS Cognitive functions- SDT | No between-group differences in changes in BDNF.  | The exercise group had greater reductions in anxiety. BDNF mediation on exercise effects on cognition was not studied due to the lack of significant effect on BDNF levels |
| 22. Miklja et al., 2022 [71]  |                      | No intervention.  | Low tolerance (Light activity daily) vs. High tolerance (Moderate to high activity for 10+ min/day.) | Plasma/ Circulating BDNF- ELISA DNA/ BDNF <sup>Fval66m</sup> | Pain, sleep, fatigue, depression, and anxiety- PROMIS version 1.0                | Glioma patients with high exercise tolerance had a lower mean plasma BDNF than low exercise tolerance participants. | High exercise tolerance reported higher quality of life. However, the amount of exercise and symptoms were not related to the BDNF polymorphism and circulating BDNF level |

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| 23. Zimmer et al., 2018 [50]  | 8-month                             | Multimodal exercise: Personalized exercise recommendation- 3-week rehabilitation to set activity goals (9-15 MET h/week), with adjustments at 1 week, 4, and 8 months. One phone follow-up after 1 month. | pre-post intervention   | Serum/ELISA                     | Fatigue- MFI-20 Cognitive function- EORTC QLQ-C30  | BDNF level significantly increased after 8 months.   | Fatigue decreased, self-perceived cognitive function increased and BDNF increased significantly after 8 months                       |
| <b>Older Adults</b>           |                                     |   |   |                                 |  |  |  |
| 24. Gmiat et al., 2018 [72]   | 12-week (3x/week); 60 mins/session  | Aerobic exercise: Beginners (first time) NW (n=11)  | Advanced group (regular NW for more than 4 years) (n=24)  | Serum/ELISA                     | Depression- BDI<br>Cognition- D2 test of attention, Trial Making Test A&B<br><br>HRQoL-SF-36 | The BDNF level increase post 12-week NW among participants in advanced group but decrease among participants in beginners' group | The advanced group showed improved depression, quality of life, and cognition, with no link between symptoms and BDNF change         |
| 25. Pereira et al., 2013 [73] | 10-week (3x/week); 60 mins/session  | Strength training: Muscle strength training at 50% of 1RM, then adjusted after 2 weeks to 75% of 1RM. (n=229)   | Aerobic exercise training-Walking and free exercise to maintained at 65-80% of the age maximum HR (n=222) | Plasma/ELISA                    | Depression- GDS  | The BDNF level increase significantly post intervention only in the strengthening group.   | Depression decreased significantly post intervention for both groups. The effect of the exercise was not mediated by the BDNF level. |
| 26. Ruiz et al., 2015 [74]    | 8-week (3x/week); 40-45 min/session | Multimodal exercise: Structured, supervised light to moderate intensity exercise that consisted of Aerobic on cycle ergometer, strength resistance and stretching exercise training. (n=20)               | Standard Care (n=20)  | Serum/Quantitative Immunoassays | Depression- GDS<br>Cognition- MMSE   | The BDNF increase after the program in the exercise group but not significant.   | No significant relationships among change in BDNF, depression and cognitive function.  |
| 27. Yeh et al., 2015 [75]     | 3 months (3x/week); 50 min/session  | Aerobic exercise: Aerobic exercise with music for 64% maximal HR (n=41)   | Usual Care (n=26)   | Serum/Multiplex                 | Depression- BDI  | The BDNF level increase significantly after the program in the intervention group  | The intervention group showed reduced depression scores and increased BDNF levels, but the BDNF-depression link was not examined.    |

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| 28. Takahashi et al., 2019 [51]  | 8 weeks   | Physical activity: Increasing PA above usual lifestyle under free-living condition (n=19)   | Usual care control (n=19)   | Serum/ELISA  | Depression-GDS  | The serum BDNF increased significantly in the active group.   | Depression score decreased for both groups but not significant. The association between BDNF and depression was not studied.  |
| 29. Vedovelli et al., 2017 [76]  | 3-month (3x/week); 60 min/session                                 | Multimodal exercise: Combination of aerobic exercises (e.g., walking, cycling) and muscle-strengthening activities (e.g., resistance training using body weight or weights). (n=20) | Usual care Control (n=9)  | Serum/ELISA  | Depression-BDI<br>Anxiety-BAI                                       | BDNF level increased significantly at 1 month and 3-month post intervention                         | Depression and anxiety significantly reduced and BDNF level increased at 1-month and 3-month post intervention in the exercise group  |
| <b>Healthy young adults</b>      |   |   |   |              |   |   |   |
| 30. Cahn et al., 2017 [77]       | 3-month   | Stretching training: Yoga and meditation retreat with daily mindfulness, yoga, breath-focused and non-doing meditation, and a vegetarian diet.                                      | Pre vs. post intervention   | Plasma/ELISA | Depression, Anxiety and Somatic symptoms-Brief Symptom Inventory-18 | BDNF level increased after a 3-month intervention.  | Self-reported anxiety and depression decreased, while BDNF increased after the 3-month program, with higher BDNF levels linked to reduced anxiety.                            |
| 31. Cullen et al., 2020 [78]     | One session; 2 hours  | Aerobic exercise: Submaximal cycling (45 min) to reach 60% VO2 max follow by self-paced maximal effort (15 min) and recovery (30 min)   | Three sleep conditions: control (sleep 7–9 hours), partial deprivation (sleep 4 hours), and full deprivation (24 hours no sleep). | Plasma/ELISA | Fatigue, Mood State - Modified Profile of Mood States questionnaire | BDNF level increased from baseline during and after exercise  | Exercise during different types of sleep deprivation did not impact BDNF levels. BDNF was associated with liveliness but was not influenced by the type of sleep deprivation. |
| 32. Piacentini et al., 2016 [79] | 12 weeks (3 times/week); start at 20 mins and increased by 5 mins | Aerobic exercise: Intensified training- increase time and intensity cycle training by 70% from the normal training  | Normal training-normal volume and intensity of cycle training. Recovery training-low intensity.                                   | Plasma/ELISA | Mood State POMS-24  | BDNF level increased post intervention but no significant different among the 3 training conditions | Exercise induced mood disturbance was not associated with a change in plasma BDNF concentrations  |

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| 33. Suzuki et al., 2014 [80]     | 9 weeks     | Multimodal exercise: Military training- military-style physical exercises, including endurance running, strength training, obstacle courses, combat drills, and fatigue-inducing activities, with extended periods of sleep deprivation. | Before, during and after training  | Plasma/ ELISA         | Fatigue- VAS<br>Sleep-Wrist motion and pulse wave interval                       | Plasma BDNF concentration significantly decreased.                             | Fatigue increased during training but decreased afterward. No significant link was found between BDNF changes and symptoms (fatigue, sleep, stress).                      |
| 34. Verbickas, et al., 2017 [81] | One session | Aerobic exercise: Sprint Interval exercise (SIE): 12 bouts of 5-second all-out cycling sprints with 3 minutes rest between each. The resistance set at 7.5% of body weight. (n=10)   | Stretch-shortening exercise (SSE): 200 drop jumps from height of 0.5 m and immediate maximum rebound with a 30-second interval between each jump. (n=10) | Serum/ ELISA          | Fatigue- isometric torque and central activation ratio                           | BDNF increased at 2 min after SIE and decreased at 24 hours after SIE and SSE. | Associations were found on high baseline BDNF level with smaller change of central fatigue.<br><br>Larger change in BDNF 24 hours associated with a lower central fatigue |
| 35. Verbickas, et al., 2018 [82] | One session | Others: High-volume drops jump exercise- 200 intermittent drop jumps   | Baseline, immediately after 100 and 200 drop jumps, and then at 1 h and 24 h post-exercise   | Serum/ ELISA<br>Serum | Neuromuscular fatigue- isometric torque and central activation ratio<br>Pain-VAS | Serum BDNF was decreased by 1 hour and 24 hours after exercise.                | Change in BDNF levels was not associated with changes in peripheral fatigue or central fatigue  |

**Note:** BDNF, Brain-Derived Neurotrophic Factors; ELISA, Enzyme-Linked Immunosorbent Assay; VAS, Visual Analogue for fatigue scale; HR, Heart Rate; PD, Parkinson's Disease; BDI, Beck Depression Inventory; PFS-Parkinson Fatigue Scale-16; mBDNF, Mature isoform BDNF; FSMC, Fatigue Scale for Motor and Cognitive Function; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; GXT, graded exercise test; TBRs, total body recumbent stepper; SPM, steps per minute; FSS, Fatigue Severity Scale; HRQoL Health related quality of life; SF-36, 36-Item Short Form Survey; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; NW, Nordic Walking; MICT, Moderate-intensity continuous training; HIIT, High-intensity interval training; FSS, Fatigue Severity Scale; MoCA, Montreal Cognitive Assessment; HDS, Hamilton Depression Scale; mMRC, modified medical research council scale; SGRQ, St. George Respiratory Questionnaire; VAS-Visual Analog Scale; FIQ, Fibromyalgia impact questionnaire; MFI, Multidimensional Fatigue Inventory (MFI); BCSB, Brief Cognitive Screening Battery, SVF, Semantic Verbal Fluency; CDT, Clock Drawing Test; FAB, Frontal Assessment Battery; DES-D, Center for Epidemiologic Studies Depression Scale; PROMIS, Patient-reported outcomes measurement information system; SDT, Oral Symbol Digit test from the NIH Toolbox; PCR, Polymerase Chain Reaction; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life; BAI, Beck Anxiety Inventory; POMS-24, Profile of Mood States-24