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REVIEW

Dose–Response Effects of Exercise Training on Circulating Brain-Derived Neurotrophic Factor (BDNF): A Systematic Review and Meta-analysis of Randomised Controlled Trials

Gang Huang[1] · Liang Tan[2] · Lianghao Zhu[3] · Qinghua Meng[4,5] · Chunyu Bao[4,5] · Xuequan Feng[6]

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Abstract

Brain-derived neurotrophic factor (BDNF) is involved in neuroplasticity, but circulating BDNF is not a validated surrogate for brain BDNF. We synthesised randomised controlled trials comparing chronic exercise with a non-exercising control. Change-score standardised mean differences (Hedges' g) were pooled using restricted maximum likelihood and Hartung–Knapp inference. The analysis included 48 trials, 56 exercise-versus-control comparisons and 2361 unique participants. Shared control sample sizes were apportioned across comparisons, with trial-cluster robust sensitivity analyses. Exercise increased circulating BDNF on average ($g = 0.41$, 95% CI 0.25 to 0.57; $p < 0.001$), with substantial heterogeneity ($I^2 = 67.0\%$; 95% prediction interval − 0.54 to 1.36). Serum-based comparisons yielded $g = 0.27$ (95% CI 0.10 to 0.44) and plasma-based comparisons $g = 0.69$ (0.37 to 1.00); the matrix moderator was significant in the primary analysis ($p = 0.017$) but not under trial-cluster robust inference ($p = 0.065$). Population, modality and intervention duration were not significant primary moderators. In the joint dose model (33 comparisons from 29 trials), neither total prescribed exercise volume ($\beta = 0.037$ per 1000 min, $p = 0.614$) nor vigorous versus moderate intensity ($\beta = -0.190$, $p = 0.361$) was associated with the BDNF effect. Weekly-volume and quadratic analyses did not establish a dose–response relationship. The overall effect remained positive after restricting sampling to approximately ≥ 24 h after exercise ($g = 0.35$, 95% CI 0.12 to 0.58). Egger's test indicated small-study effects ($p = 0.011$). The certainty of evidence was very low. Chronic exercise is associated with an average increase in circulating BDNF, but heterogeneity, methodological limitations and uncertain moderator effects prevent a biomarker-specific exercise prescription or an inference of increased central BDNF.
PROSPERO registration: CRD420261448624.

Keywords Brain-derived neurotrophic factor · Exercise · Physical activity · Dose–response · Meta-analysis · Neuroplasticity

Gang Huang and Liang Tan have contributed equally to this work and share first authorship.

✉ Qinghua Meng
745112962@qq.com

✉ Chunyu Bao
chunyubao730102@tjus.edu.cn

✉ Xuequan Feng
fengxuequan@126.com

[1] School of Exercise and Health, Tianjin University of Sport, Tianjin 301617, China

[2] Faculty of Physical Culture, Gdansk University of Physical Education and Sport, 80-336 Gdansk, Poland

[3] Key Laboratory of Psychological and Physiological Regulation in Competitive Sports, Tianjin University of Sport, Tianjin, China

[4] Tianjin University of Sport, Tianjin 301617, China

[5] Tianjin Sports Injury and Rehabilitation Virtual Simulation Teaching Center, Tianjin 301617, China

[6] Department of Neurosurgery, Tianjin First Central Hospital, Tianjin 300384, China

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Introduction

Brain-derived neurotrophic factor (BDNF) is a widely distributed neurotrophin in the mammalian brain and a key driver of activity-dependent neuroplasticity [1]. Acting mainly through the tropomyosin receptor kinase B (TrkB), it promotes neuronal survival and differentiation, dendritic and axonal growth, synaptogenesis, and long-term potentiation in the hippocampus and cortex [2]. These actions underpin learning and memory, synaptic and structural plasticity, and the regulation of mood and stress [3]. BDNF is therefore increasingly seen as a common biological link between physical activity and cognitive and mental health [4, 5].

BDNF can be measured in serum and plasma, but these measurements reflect different biological pools and pre-analytical processes rather than an interchangeable measure of brain neurotrophic activity [6, 7]. Peripheral BDNF has been studied in relation to depression [8] and exercise-related changes in hippocampal volume [9]. However, these associations do not establish that a change in peripheral concentration quantitatively represents a change in brain BDNF. This distinction is central to interpreting an exercise intervention assessed only with blood measurements.

Experimental work provides a biological rationale for exercise-induced neurotrophic adaptation. In animal models, exercise increases hippocampal Bdnf expression, and BDNF–TrkB signalling contributes to plasticity and memory [5, 10]. Candidate pathways include PGC-1α/FNDC5 signalling [11] and β-hydroxybutyrate-mediated regulation of Bdnf expression [12], together with cathepsin B-related muscle–brain communication [13]. The wider mechanistic literature also considers IGF-1 and other exercise-responsive signals [14]. Human cerebral arteriovenous sampling demonstrates that the brain can release BDNF during exercise [15], but it does not validate resting serum or plasma BDNF as a quantitative surrogate for central concentrations after a training programme. BDNF Val66Met affects activity-dependent secretion [16] and has been associated with differences in training responses [17]. These mechanisms support plausibility, not an assumption that every peripheral BDNF change originates in the brain.

Despite this mechanistic rationale, human trials report heterogeneous effects, and previous reviews report heterogeneous peripheral BDNF responses, including changes in resting concentrations after repeated training [18–24]. Important questions remain about population differences, assay and blood-matrix effects, and the independent contributions of exercise intensity and volume. Absolute concentrations differ across assays and matrices; standardising the effect scale facilitates pooling but does not remove biological or measurement heterogeneity. Dose is also multidimensional: session duration, frequency, programme length and intensity should not be represented as if prescribed minutes alone fully describe the training stimulus.

The present review estimates the average effect of chronic exercise on circulating BDNF and evaluates heterogeneity by population, blood sample matrix, exercise modality and intervention duration. It examines prescribed exercise volume and harmonised intensity jointly and in exploratory models, with sensitivity analyses for sampling timing, assumed pre–post correlations and shared-control dependence. Age is examined using a 45-year operational threshold, alternative cut-offs and continuous-age models. Certainty is evaluated for the peripheral-BDNF outcome as a body of evidence rather than for individual studies or exploratory subgroups.

Methods

Protocol, Registration and Reporting

The review was reported in accordance with PRISMA 2020 [25] and registered with PROSPERO (CRD420261448624). The analysis plan and the distinction between primary, exploratory and sensitivity analyses are described in Supplementary Text S1. The PRISMA checklist is provided in Supplementary Table S1.

Eligibility Criteria

Studies were selected using the PICOS framework, in line with Supplementary Table S2. Population: human participants of any age and sex, either apparently healthy or living with a chronic clinical condition (e.g., multiple sclerosis, Parkinson's disease, dementia/mild cognitive impairment, stroke, type 2 diabetes, metabolic syndrome, depression, or haemodialysis). Intervention: a structured chronic exercise programme lasting at least two weeks, classified as aerobic training (AT), resistance training (RT), high-intensity interval training (HIIT), moderate-intensity continuous training (MICT), combined/multimodal training (CT) or aerobic-plus-resistance training (AT + RT). For subgroup analysis, these were grouped into four categories: aerobic (AT and MICT), resistance, HIIT, and combined/multimodal (CT and AT + RT). Comparator: a non-exercising control condition (habitual lifestyle, usual care or wait-list). Outcome: peripheral-blood (serum or plasma) BDNF concentration reported as mean ± SD, or convertible to it, at baseline and after the intervention. Study design: randomised controlled trials with two or more arms.

We excluded acute single-session studies without a training period, interventions with unequal co-interventions,

reports without usable BDNF summary data, and non-randomised or non-human studies. Graph-only reporting was not itself an exclusion if usable numerical estimates could be recovered. Trials comparing exercise modalities without an eligible non-exercising control did not contribute to quantitative synthesis. For multiple reports of one cohort, the most complete eligible report was retained. Selected exercise arms and trial-specific selection details are documented in Supplementary Table S3.

Search Strategy, Study Selection and Data Extraction

We searched six electronic databases — five international databases (PubMed, Embase, Web of Science Core Collection, MEDLINE and the Cochrane Library [CENTRAL]) and one Chinese-language database (China National Knowledge Infrastructure [CNKI]) — from database inception to 18 June 2026, with no language restriction. The search combined controlled vocabulary and free-text terms for the exposure and outcome, for example ("brain-derived neurotrophic factor" OR "BDNF") AND ("exercise" OR "physical activity" OR "training" OR "aerobic" OR "resistance" OR "HIIT") AND (randomised OR trial). We hand-searched the reference lists of eligible studies and relevant reviews and performed forward citation tracking. The full, database-specific search strings appear in Supplementary Table S4.

Two reviewers independently screened records and extracted participant characteristics, exercise prescriptions, blood matrix, assay/kit, sampling interval and BDNF summary statistics (Supplementary Tables S3 and S5). Graph digitisation, SE-to-SD conversion and author-provided data are documented in the notes to Supplementary Table S5.

Total prescribed volume was session duration × weekly frequency × programme length; weekly volume was session duration × weekly frequency. Missing dose values were not imputed from the intensity file. Prescriptions and numeric summaries were matched by study and exercise arm. Intensity was harmonised categorically from the native metric using ACSM guidance as a framework [26]. HRR, HRmax, VO_2-based measures, resistance loading and perceived exertion were not universally converted to %HRmax. Representative values were retained on their native scales. The main joint model used moderate and vigorous categories; other/unclear prescriptions were retained in a three-category sensitivity model (Supplementary Table S5).

Risk of Bias and Certainty of Evidence

Risk of bias was assessed using RoB 2 [27], covering randomisation, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result (Supplementary Text S2 and Fig. S1). Certainty was assessed with GRADE [28] for the effect on peripheral circulating BDNF. Randomised evidence started at high certainty; risk of bias, inconsistency, indirectness, imprecision and publication bias were judged separately. The assessment considered the contribution of trials with methodological limitations, effect dispersion, confidence intervals and possible missing evidence. Observed power, an objective assay and an Egger p value were not used as automatic decision rules. Imprecision concerned the direction of the average biomarker change; clinical importance was not inferred without a validated BDNF threshold.

Effect-Size Calculation and Statistical Analysis

For each comparison, mean change was endpoint minus baseline BDNF. Change-score SD was calculated as $\sqrt{(SDpre^2 + SDpost^2 - 2r \times SDpre \times SDpost)}$, with $r = 0.5$ in the primary analysis and $r = 0.3$ and 0.7 in sensitivity analyses. Hedges' g standardised the between-arm difference in change [29]; positive values indicate a greater increase in circulating BDNF with exercise. Effect sizes were calculated using meta::metacont with the exact small-sample correction [30]. For multi-arm trials, the control sample size was divided by the number of retained exercise comparisons; control means and SDs were unchanged. The apportioned n entered the pooled SD, small-sample correction and sampling variance. This is an approximate shared-control strategy, not an assumption that all 56 estimates are independent. Original control participants were counted once in the overall participant total.

Random-effects models used REML estimation and Hartung–Knapp inference [31]. Heterogeneity was summarised by τ^2 and model-based I^2 [32, 33]; 95% prediction intervals described the estimated spread of effects across comparable settings [34]. Subgroup analyses considered population, serum versus plasma, four exercise modalities and duration ≤ 8 versus > 8 weeks. Formal moderator tests evaluated between-subgroup differences. The unclear-matrix comparison was excluded only from matrix-specific models. Matrix stratification and extended dose models were exploratory, not prespecified confirmatory tests. Model-specific comparison and trial counts are reported.

The 45-year cut-off was an operational classification, not a validated BDNF breakpoint or a conventional definition of old age. Longitudinal evidence of cognitive change at ages 45–49 provides context for considering midlife [35], but does not establish a corresponding BDNF threshold. We examined 40-, 45-, 50- and 60-year cut-offs, continuous age and a joint age–population model (Supplementary Table S6). Non-numerical age entries and references to another table were treated as missing, not interpreted as ages. Age analyses used 52 comparisons from 46 trials when

two eligibility-bound proxies were included; a sensitivity analysis excluded these proxies, leaving 50 comparisons from 44 trials.

The main joint dose model entered total volume (per 1000 min, centred at 1080 min) and intensity category simultaneously (Supplementary Table S7). Weekly minutes (per 60 min/week, centred at 120 min/week) replaced total volume in a sensitivity model. Exploratory models examined volume × intensity, a quadratic total-volume term and a three-category intensity variable. Separate graphical models assessed each exposure alone and its interaction with population or blood matrix (Supplementary Table S8); they were not the jointly adjusted main model. The main joint model is presented as the principal intensity-adjusted analysis in this report, but remains exploratory rather than a prespecified confirmatory analysis.

Trial-cluster robust variance estimation (CR2, with small-sample degrees-of-freedom corrections) was used as a sensitivity analysis, retaining the primary working weights [36]. It does not replace an explicit shared-control covariance model. Trial-cluster robust results are reported in Supplementary Table S9. Funnel-plot inspection (Supplementary Fig. S2) and comparison-level Egger-type regression assessed small-study effects, not proof of publication bias [37, 38]. Leave-one-comparison-out and leave-one-trial-out analyses removed one comparison or all comparisons from one trial, respectively (Supplementary Fig. S3 and Table S10). Correlation and sampling-time sensitivities are shown in Supplementary Fig. S4 and Table S11; approximately ≥ 24 h includes reports of "about one day" and does not guarantee an exact 24-h interval. Observed-power values are descriptive approximations based on the observed effect and SE [39], not prospective power for $g = 0.20$ or a certainty criterion. Analyses used R 4.3.1 with meta 8.2–1, metafor 4.8–0 and clubSandwich 0.7.0 [30, 40]. Two-sided $p < 0.05$ was the nominal threshold; exploratory tests were not multiplicity-adjusted.

Results

Study Selection and Study Characteristics

The search (from database inception to 18 June 2026) identified 3477 records across the six databases: 3472 from the five international databases (PubMed 247, Embase 610, Web of Science 998, MEDLINE 575 and Cochrane CENTRAL 1042) and 5 from CNKI. After we removed duplicates and screened titles, abstracts and full texts (see Fig. 1), 48 randomised controlled trials met the inclusion criteria and provided 56 exercise-versus-control comparisons (K = 56) for the meta-analysis, one of which was reported in Chinese. Trials that provided only head-to-head comparisons of two exercise modalities were screened and are discussed qualitatively but, lacking a non-exercise arm, contributed no exercise-versus-control comparison to the pooling. Reasons for full-text exclusion, grouped by category, are given in the PRISMA flow diagram (Fig. 1).

The 48 trials contributed 56 exercise-versus-control comparisons and 2361 unique participants: 1316 in exercise arms and 1045 controls. Six multi-arm trials shared a control across their selected exercise arms. Healthy samples contributed 35 comparisons from 27 trials and clinical samples 21 comparisons from 21 trials. The exercise modalities were aerobic (23 comparisons), resistance (8), HIIT (7) and combined/multimodal (18); 22 comparisons lasted ≤ 8 weeks and 34 lasted > 8 weeks. Serum was used in 40 comparisons from 37 trials, plasma in 15 comparisons from 10 trials, and the matrix was unclear for one comparison. Prescribed total and weekly exercise volume were available for 53 comparisons from 46 trials, ranging from 180 to 5925 min and from 50 to 450 min/week. Four comparisons from two trials lacked usable numerical ages in the source text; two further trials reported age eligibility bounds rather than mean ages. Detailed characteristics, selected arms and BDNF measurement information are provided in Supplementary Tables S3 and S5.

Risk of Bias

Of the 48 trials, 7 were judged at low risk of bias, 36 raised some concerns and 5 were at high risk. Randomisation/allocation concerns occurred in 31 trials and concerns about deviations from intended interventions in 38; these judgements do not equate inability to blind participants with bias by itself. Low-risk, some-concerns and high-risk trials contributed 19.1%, 69.6% and 11.2% of the primary random-effects weight, respectively. Study- and domain-level judgements are shown in Supplementary Fig. S1, with criteria in Supplementary Text S2.

Overall Effect of Exercise on Circulating BDNF

Across 56 comparisons, chronic exercise increased circulating BDNF on average (Hedges' $g = 0.41$, 95% CI 0.25 to 0.57; $p < 0.001$). Heterogeneity remained substantial ($\tau^2 = 0.2175$; $I^2 = 67.0\%$), and the 95% prediction interval was − 0.54 to 1.36. Thus, a positive average effect did not imply a positive effect in every setting. Trial-cluster CR2 inference retained the same point estimate with a 95% CI of 0.229 to 0.588 ($p < 0.001$). The pooled and subgroup estimates are displayed in Fig. 2; robust-inference results are provided in Supplementary Table S9.

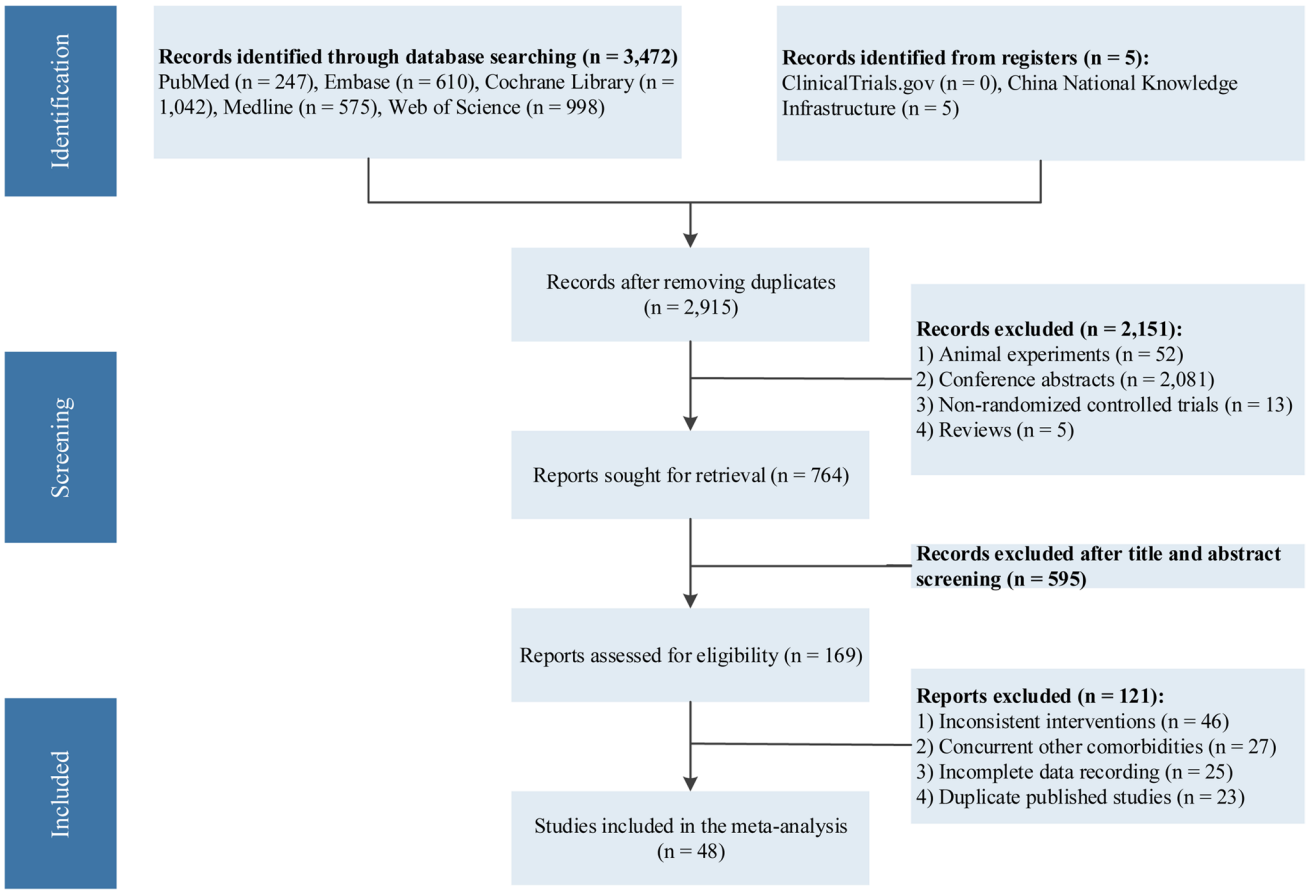


Fig. 1 Study selection. Note. Counts refer to records, reports and trials. The 48 included trials contribute 56 exercise–control comparisons

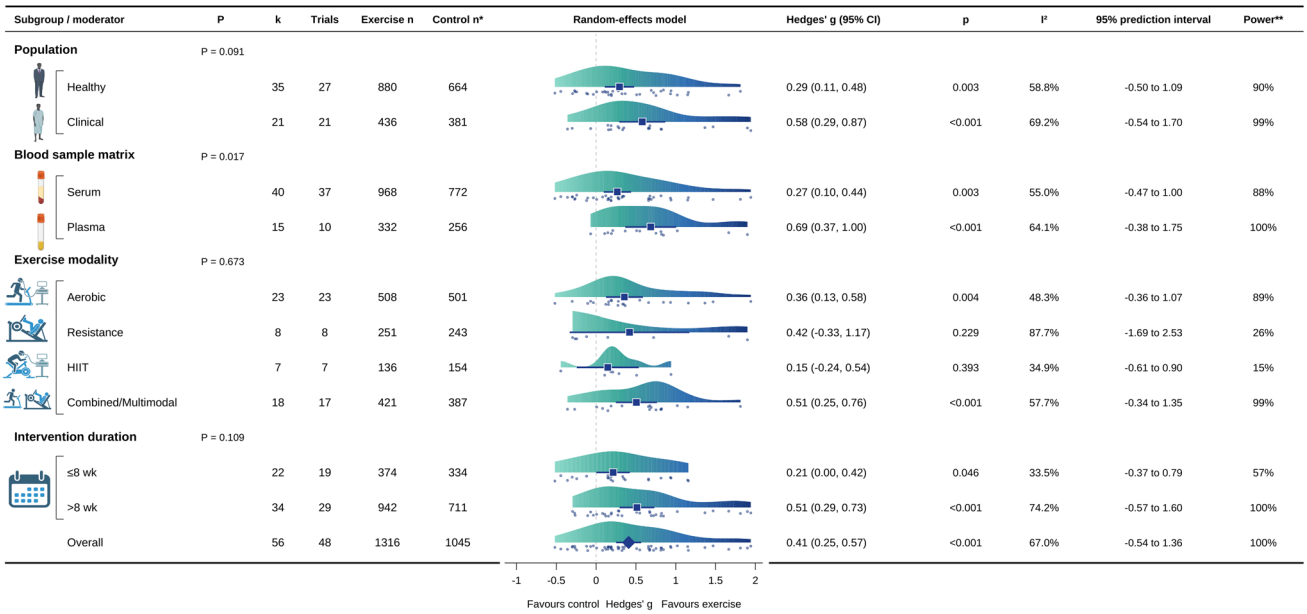


Fig. 2 Overall and subgroup effects on circulating BDNF. Note. REML–HK estimates and 95% CI; k denotes comparisons. *Controls are counted once within each subgroup; subgroup totals are not additive. **Observed power is descriptive. Moderator P differs from pooled-effect p. CI, confidence interval; prediction intervals summarise heterogeneity

Subgroup Analyses

Serum-based comparisons yielded $g = 0.27$ (95% CI 0.10 to 0.44; k = 40), whereas plasma-based comparisons yielded $g = 0.69$ (0.37 to 1.00; k = 15). The primary matrix moderator test was significant ($p = 0.017$; Fig. 2). However, the trial-cluster CR2 contrast was 0.420 (95% CI − 0.029 to 0.869; $p = 0.065$), so the evidence for a matrix difference was sensitive to the inferential method. Healthy and clinical samples yielded $g = 0.29$ (0.11 to 0.48) and 0.58 (0.29 to 0.87), respectively; their primary between-group test was not significant ($p = 0.091$), nor was the CR2 test ($p = 0.132$). These observational comparisons between trials do not establish that any matrix or population responds better causally.

Aerobic training yielded $g = 0.36$ (95% CI 0.13 to 0.58; $p = 0.004$) and combined/multimodal training $g = 0.51$ (0.25 to 0.76; $p < 0.001$). Resistance training ($g = 0.42, -0.33$ to 1.17; $p = 0.229$) and HIIT ($g = 0.15, -0.24$ to 0.54; $p = 0.393$) had confidence intervals spanning zero and compatible with either increases or decreases in circulating BDNF relative to control. The formal modality moderator test was not significant ($p = 0.673$). Shorter interventions yielded $g = 0.21$ (0.00 to 0.42 after rounding; $p = 0.046$) and longer interventions $g = 0.51$ (0.29 to 0.73; $p < 0.001$), without a significant duration moderator ($p = 0.109$). Therefore, the subgroup estimates do not demonstrate superiority of a particular modality or duration.

Age analyses included 52 comparisons from 46 trials with usable age information, including two eligibility-bound proxies (Supplementary Table S6). Nominal cut-off tests gave $p = 0.057$, 0.041, 0.030 and 0.016 at 40, 45, 50 and 60 years, respectively; the 45-year contrast was not significant under CR2 inference ($p = 0.056$). Continuous age was not significant (β = 0.062 per 10 years, 95% CI − 0.009 to 0.133; $p = 0.084$), including when both bound proxies were excluded (50 comparisons; β = 0.067, − 0.005 to 0.140; $p = 0.067$). These exploratory results do not identify a unique biological age threshold.

In the joint age–population model (52 comparisons), the ≥ 45-year age contrast was 0.339 (95% CI 0.012 to 0.665; $p = 0.042$), and the clinical-versus-healthy contrast was 0.255 (− 0.075 to 0.584; $p = 0.127$). The corresponding CR2 p values were 0.0497 and 0.147. This model does not establish a biological breakpoint or an individual-level age effect (Supplementary Table S6).

Dose–Response Analyses

The main joint dose model included 33 comparisons from 29 trials with both prescribed-volume data and moderate/vigorous intensity classification. Neither total volume (β = 0.037 per 1000 min, 95% CI − 0.112 to 0.187; $p = 0.614$) nor vigorous versus moderate intensity (β = − 0.190, − 0.608 to 0.228; $p = 0.361$) was significant; the omnibus moderator test was $p = 0.571$. Replacing total volume with weekly minutes gave β = 0.104 per 60 min/week (− 0.235 to 0.443; $p = 0.536$), with an intensity contrast of − 0.152 (− 0.589 to 0.285; $p = 0.483$). The corresponding CR2 tests were also non-significant (Supplementary Tables S7 and S9).

Separate overall models were non-significant for total volume (β = 0.056 per 1000 min, 95% CI − 0.059 to 0.171; $p = 0.332$; 53 comparisons; Fig. 3), vigorous versus moderate intensity (β = − 0.210, − 0.602 to 0.182; $p = 0.284$; 35 comparisons; Fig. 4) and weekly volume (β = 0.075 per 60 min/week, − 0.070 to 0.221; $p = 0.303$; 53 comparisons; Fig. 5). The clinical-versus-healthy total-volume slope difference was 0.251 per 1000 min (0.018 to 0.485; $p = 0.036$), but CR2 inference gave a wider interval (− 0.091 to 0.593; $p = 0.128$). The matrix slope interaction was not significant ($p = 0.086$). Intensity interactions were $p = 0.662$ for population and $p = 0.702$ for matrix; weekly-volume interactions were $p = 0.790$ and $p = 0.514$, respectively.



Fig. 3 Total exercise volume and BDNF. Note. **A**, overall; **B**, population; **C**, blood matrix. Bubbles show weighted comparisons; bands are 95% CI. These models do not adjust for intensity. Population interaction: HK $p = 0.036$; CR2 $p = 0.128$. Joint models: Table S7; plotted-model coefficients: Table S8.

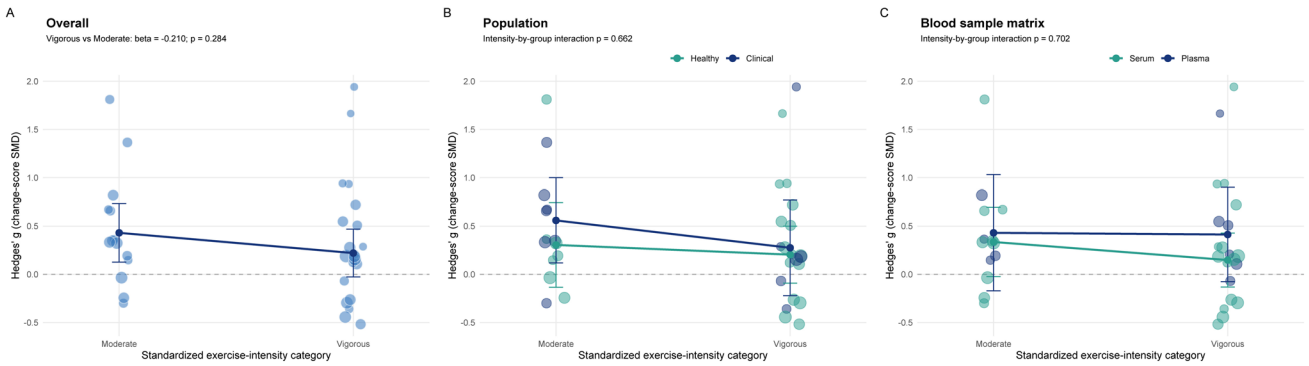


Fig. 4 Exercise intensity and BDNF. Note. **A**, overall; **B**, population; **C**, blood matrix. Lines join category estimates; bars are 95% CI. Light, mixed and unclear prescriptions are excluded. These are not continuous %HRmax-equivalent doses. Classifications: Table S5; joint models: Table S7; plotted-model coefficients: Table S8



Fig. 5 Weekly exercise volume and BDNF. Note. **A**, overall; **B**, population; **C**, blood matrix. Bubbles show weighted comparisons; bands are 95% CI. These models do not adjust for intensity. Weekly-volume units are 60 min/week; joint models are in Table S7; plotted-model coefficients are in Table S8

The volume × intensity term was not significant ($p = 0.231$), and the quadratic total-volume coefficient was − 0.039 (95% CI − 0.126 to 0.048; $p = 0.362$). These exploratory models did not detect the tested form of non-linearity and do not establish a ceiling or its absence. In the three-category intensity sensitivity (53 comparisons), the total-volume coefficient remained non-significant ($\beta = 0.043, -0.073$ to 0.159; $p = 0.459$; omnibus $p = 0.344$). Full model coefficients and counts are retained in Supplementary Table S7.

Publication Bias, Sensitivity Analyses and Certainty of Evidence

Comparison-level Egger regression indicated small-study effects ($p = 0.011$; Supplementary Fig. S2). This does not establish selective publication as the cause, particularly because shared controls and the relationship between standardised effects and their SEs complicate interpretation. In leave-one-comparison-out analyses, pooled g ranged from 0.355 to 0.427; in leave-one-trial-out analyses, it ranged from 0.355 to 0.453. All intervals excluded zero (Supplementary Fig. S3 and Table S10). Varying the pre–post correlation gave $g = 0.349$ (95% CI 0.213 to 0.485) at $r = 0.3$, 0.409 (0.252 to 0.566) at $r = 0.5$ and 0.512 (0.319 to 0.706) at $r = 0.7$. Restricting sampling to approximately ≥ 24 h retained 27 comparisons from 21 trials and yielded $g = 0.351$ (0.122 to 0.580; $p = 0.004$); the sampling-category moderator was not significant ($p = 0.854$). These timing and correlation sensitivities are shown in Supplementary Fig. S4. Omitting Briken yielded $g = 0.41$ (95% CI 0.25 to 0.57), without changing the pooled direction (Table S10).

The certainty of evidence for the average peripheral-BDNF effect was very low (Supplementary Table S12). Randomised evidence was downgraded once for risk of bias, once for substantial unexplained inconsistency and once for suspected publication bias. No additional downgrade was applied for indirectness of the peripheral biomarker outcome or for imprecision in the direction of the average change. Both HK and CR2 intervals excluded no change, but no validated threshold supported an inference of clinically important benefit. Funnel asymmetry was considered alongside

the predominance of small trials, with heterogeneity and SMD–SE coupling acknowledged as alternative explanations. No subgroup-specific certainty ratings were assigned.

Discussion

This synthesis of 48 trials and 56 comparisons found an average increase in circulating BDNF after chronic exercise ($g = 0.41$), with substantial variation across settings. The primary serum/plasma moderator was significant, but its interval included no difference under trial-cluster robust inference. Population, modality and duration did not show significant primary moderator tests. Neither prescribed volume nor harmonised intensity was significant in the joint model. An exploratory total-volume-by-population interaction reached the nominal threshold in one model but was not retained under CR2 inference. These findings support an average peripheral biomarker response, not a reliable hierarchy of populations or exercise prescriptions.

The average effect is compatible with previous syntheses of exercise and resting peripheral BDNF [19, 24], including work in ageing and neurodegenerative populations [18, 22, 23]; findings in healthy samples are also heterogeneous [20]. Matrix-specific analyses, joint consideration of volume and intensity, sampling information and shared-control sensitivities help interpret this variability. Standardising the effect measure addresses scale differences but does not make assays biologically equivalent or remove pre-analytical variation. A positive pooled mean does not ensure a positive BDNF response in a new population or programme.

The relationship between peripheral and central BDNF warrants consideration beyond a general limitation. Rasmussen et al. demonstrated cerebral BDNF release during exercise [15]. That observation establishes that the brain can contribute to blood BDNF under the studied conditions; it does not calibrate a resting blood assay against regional brain concentrations or establish that a training-induced blood change is brain-derived. Serum BDNF is strongly influenced by platelet release during clotting [7], whereas plasma measurements depend on platelet contamination, activation and processing [6]. Experimental blood-processing studies show that clotting conditions [7] and centrifugation strategy [6] affect measured concentrations. Thus, serum and plasma should not be treated as interchangeable, and neither matrix is a direct assay of neuronal BDNF or TrkB activity. Our matrix contrast concerns standardised effects across different trials, not a within-person validation of either matrix as a central surrogate.

Cefis et al. [41] organise exercise-induced brain BDNF regulation around neuronal activity, haemodynamic signals and circulating exercise-related mediators. Activity-dependent calcium signalling and transcriptional regulation can influence Bdnf expression; cerebral perfusion and endothelial signalling provide additional routes. These processes need not produce proportional changes in a blood assay. The review also emphasises that skeletal-muscle BDNF expression does not by itself establish muscle as the principal source of circulating BDNF. Complementary experimental studies implicate PGC-1α/FNDC5 [11] and β-hydroxybutyrate [12], as well as cathepsin B [13], in exercise-related signalling. Together, they broaden the mechanistic rationale [13, 14] without demonstrating that these pathways mediated the pooled human blood response.

The serum/plasma finding is therefore methodological as well as biological. Different platelet handling, assay targets and sampling intervals can affect the standardised response, and plasma studies were fewer than serum studies. The primary contrast ($p = 0.017$) weakened with cluster-robust inference ($p = 0.065$). It would be inappropriate to conclude that plasma demonstrates a stronger central response or is a superior surrogate on this evidence. Similarly, a significant effect within aerobic or combined training but not within resistance or HIIT is not itself a significant difference between modalities; the formal modality test was $p = 0.673$.

The absence of a significant joint volume–intensity association does not establish the absence of biological dose dependence. These study-level models assess associations across programmes whose participants, assays and exercise prescriptions differ. A coarse moderate/vigorous classification can obscure within-category differences; interval workbout intensity is not the same as session-average intensity, and resistance load cannot be translated into a universal cardiovascular percentage. Prescribed minutes also do not measure completed workload. Baseline fitness, adherence, frequency, progression and recovery may modify the response, but their contribution was not demonstrated by the present results. They should be regarded as candidate explanations for future testing rather than established causes of a null association.

The quadratic analysis did not detect non-linearity ($p = 0.362$), but a quadratic term is not a direct test of every possible plateau or ceiling. A physiological ceiling might depend on baseline fitness or prior exposure and therefore need not occur at the same prescribed volume in every population; this possibility remains hypothetical. Our findings do not justify asserting that a ceiling occurs even at low doses, that subgroup slopes cancel one another, or that additional exercise specifically benefits clinical populations. The nominal population slope interaction in Fig. 3 ($p = 0.036$) was not significant with trial-cluster CR2 inference ($p = 0.128$), which further limits that interpretation. Exercise recommendations should therefore rest on established health and functional outcomes rather than an optimum BDNF dose inferred from these aggregate data.

Several limitations remain. Peripheral BDNF cannot establish a central neurotrophic effect. Assay and sampling information is incomplete: four comparisons fall into a possible < 24 h carry-over category and 25 have unclear or variable timing. Methodological limitations, substantial heterogeneity and suspected missing evidence yield very low certainty about the effect magnitude. The split-control approach does not fully remove within-trial dependence; CR2 adjusts inference but retains the working weights. The joint dose model contains only 33 comparisons and uses a coarse intensity classification. Age analyses rely on incomplete reporting and two eligibility-bound proxies, which were excluded in sensitivity analysis. One comparison involved graph digitisation (1/48 trials; 1/56 comparisons), which may introduce extraction error; data-source details are provided in Supplementary Table S5. The non-significant subgroup estimates have confidence intervals spanning zero and remain compatible with increases or decreases in circulating BDNF relative to control; they neither demonstrate equivalence nor establish the absence of an effect.

Future trials should report achieved intensity, completed volume, baseline fitness and adherence, alongside a reproducible description of blood matrix, assay, clotting and centrifugation, fasting and time since the last exercise bout. Standardised resting measurements would help separate chronic adaptation from acute carry-over. Adequately powered dose-finding and multi-arm trials, analysed with appropriate dependence structures, are needed to test whether volume or intensity has causal effects on BDNF. Individual-participant-data analyses could investigate age, sex and genotype without relying solely on trial-level averages. Concurrent functional and cognitive outcomes would also be needed before treating a peripheral BDNF response as clinically meaningful.

Conclusion

Across 48 trials and 56 exercise-versus-control comparisons, chronic exercise was associated with an average increase in circulating BDNF ($g = 0.41$, 95% CI 0.25 to 0.57), but the certainty of this evidence was very low. The prediction interval included no effect, and serum/plasma and population-specific volume findings were sensitive to trial-cluster inference. Joint analyses did not establish independent associations of prescribed volume or moderate/vigorous intensity with the BDNF effect. The evidence does not identify an optimal biomarker-specific exercise prescription or demonstrate increased central BDNF.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12035-026-06272-2.

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Data Availability The datasets analysed for this study, including the study-level dataset and dose–response outputs, are included in the Supplementary Material and are available from the corresponding author on reasonable request.

Declarations

Ethics Approval Ethical review and approval were not required for this study because it is a secondary analysis of previously published, aggregated data and did not involve new data collection from human participants or animals.

Consent to Participate Not applicable. This study is a secondary analysis of previously published, aggregated data and did not involve the collection of new data from human participants.

Consent for Publication Not applicable.

Competing interests The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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