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Systematic Review

Exercise-Induced Changes in Circulating Exerkines Associated with Brain Health: A Systematic Review and Meta-Analysis in Healthy Populations

Songxin Tang [1], Raquel Pedrero-Chamizo [1,*], Eva Gesteiro [1], Carlos Quesada-González [1,2], Margarita Pérez-Ruiz [1] and Marcela González-Gross [1]

[1] ImFINE Research Group, Department of Health and Human Performance, Facultad de Ciencias de la Actividad Física y del Deporte-INEF, Universidad Politécnica de Madrid, C/Martín Fierro 7, E-28040 Madrid, Spain; songxin.tang@alumnos.upm.es (S.T.); eva.gesteiro@upm.es (E.G.); carlos.quesada@upm.es (C.Q.-G.); margarita.perez@upm.es (M.P.-R.); marcela.gonzalez.gross@upm.es (M.G.-G.)

[2] Department of Mathematics Applied to Information and Communication Technologies, Universidad Politécnica de Madrid, 28040 Madrid, Spain

* Correspondence: raquel.pedrero@upm.es; Tel.: +34-910677952

Abstract

Exerkines are released in response to physical exercise and play a key role in promoting health, such as taking part in modulating brain morphology and function. Expression levels of some of them are associated with an increase in neuroplasticity and a decrease in the risk of brain-related diseases such as dementia and depression. Therefore, our objective is to investigate the response of exerkines in healthy individuals and its potential to promote brain health. The search was performed in five databases. Randomized controlled trials of humans and animals of all ages who performed acute and/or long-term exercise and assessed the effects of exerkines were included. Human data were used for quantitative analysis, and animal experiments were included as part of the qualitative analysis. No meta-analyzes were conducted on animal data; preclinical findings are presented solely to contextualize mechanisms and are not used for clinical inference. Eventually, the sample consisted of 3321 individuals, with an age range from 10 to 89 years. Meta-analysis reveals that both acute and chronic exercise induced increases in the brain-derived neurotrophic factor and insulin-like growth factor 1 in older adults. Other exerkines such as cathepsin B and vascular endothelial growth factor have also demonstrated potential power for brain health. In conclusion, physical exercise by altering the levels of exerkines may be a feasible strategy for healthy individuals aiming at healthy aging of the brain. Moreover, it is advisable to analyze additional exerkines or multiple simultaneous applications to assess the cerebral effects during physical exercise. PROSPERO registration number: CRD42023438803.

Keywords: exercise; myokine; BDNF; IGF-1; cognitive function; brain health

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1. Introduction

Regular physical exercise (PE) promotes cardiovascular health [1], reduces the risk of chronic diseases [2,3], and improves brain health [4–7]. A growing body of research has shown that PE is not only effective in reducing the risk of neurodegenerative diseases [8], but also beneficial in promoting healthy aging of the brain [9]. In this context, a heterogeneous group of signaling molecules termed "exerkines" encompassing proteins, mRNA, and miRNA were studied, either directly or via extracellular vesicles, in response

to PE stimuli [10]. These factors originate from skeletal muscle (myokines), cardiac (cardiokines), adipose tissue (adipokines), liver (hepatokines), as well as neurons (neurokines), and are involved in mediating organ crosstalk to metabolic equilibrium [11]. For instance, the brain-derived neurotrophic factor (BDNF) has been shown to rise in levels after PE and is strongly associated with improving brain health [12–15]. Moreover, the BDNF and insulin-like growth factor 1 (IGF-1) can act synergistically and may play a crucial role in regulating neuroplasticity and preventing neurodegenerative diseases [11,12,16–19]. However, based on our knowledge, no investigator has yet conducted a comprehensive quantitative analysis of IGF-1 responses before and after PE. Importantly, the concept of exerkines is not restricted to classical neurotrophic or metabolic factors but broadly encompasses circulating signaling molecules whose release is modulated by exercise and which mediate systemic inter-organ communication [20]. Within this framework, tumor necrosis factor-alpha (TNF-α), although classified as a pro-inflammatory cytokine, has also been shown to exhibit acute, exercise-responsive fluctuations distinct from its role in chronic inflammation. Transient TNF-α signaling is involved in skeletal muscle remodeling, immune regulation, and metabolic adaptation, suggesting it is as a myokine-like communicator rather than solely a pathological marker. Meanwhile, other exerkines or candidate exerkine that are able to cross the blood–brain barrier (BBB), such as cathepsin B (CTSB) [20], fibroblast growth factor 21 (FGF21) [21], and kynurenine [22], have not been systematically reviewed in terms of the contribution of exercise-induced exerkines to brain health.

With the global population aging and the increase in lifestyle diseases, understanding how changes in exerkines affect the brain health of people at various ages is important for public health strategies and personal health management. Consequently, we anticipate providing a clue for further research on the applications of "exercise as medicine" and "healthy aging of the brain".

The aims of this review and meta-analysis are: (a) to analyze the responses of exerkines to acute and long-term PE in a healthy population, (b) to study the quantitative changes in BDNF and IGF-I before and after exercise, (c) to examine the specific biological effect of each selected exerkine, and (d) to synthesize how these exercise-induced molecular signals translate into systemic biomarkers that reflect potential brain health adaptations. In addition, evidence from animal models is included exclusively to provide mechanistic context (e.g., hippocampal expression of BDNF/IGF-1/VEGF; pathways such as CTSB and FNDC5/irisin). We do not conduct meta-analyses of animal data, and we do not assume direct extrapolation to humans; these findings are presented as a hypothesis-generating context to complement the human results.

This review follows a hybrid design, combining a confirmatory meta-analysis for well-established markers (BDNF, IGF-1) with an exploratory systematic synthesis of emerging exerkines.

2. Methods

2.1. Protocol and Registration

This review (PROSPERO registration number: CRD42023438803) was carried out and reported based on the "Preferred Reporting Items for Systematic Reviews and Meta Analyses statement" (PRISMA) [23].

2.2. Data Strategy

Studies in 5 databases were reviewed: PubMed, Web of Science, EMBASE, PsycINFO (accessed through Ovid) and COCHRANE, from inception to 10 April 2024. The following boolean operators (AND/OR/NOT) and search terms (including MeSH) were used: "exercise" AND "exerkine" OR "myokine" OR "cardiokine" OR "hepatokine" OR "neu-

rokine" OR "baptokine" AND "brain health". The full search strategy is presented in Supplementary Materials, S1. Reference lists, Google Scholar, and gray literature were manually scanned, with the aim of expanding our results.

2.3. Selection Criteria

For selection, studies had to meet the following inclusion criteria based on the PICOS framework [24]: (a) Participants and conditions: all-age human participants and animal subjects were required to be free of diagnosed neurological, metabolic, or cardiovascular disease, and were with healthy brain conditions [25] (e.g., characterized by the preservation of optimal brain integrity, mental and cognitive function, and the absence of overt neurological disorders) across the lifespan (e.g., children, adolescents, young adults, middle-aged adults, older adults). (b) Intervention: randomized control trials (RCT) including a single bout (acute) and/or multiple bouts (chronic) of supervised exercise interventions (e.g., endurance exercise, resistance exercise, combined exercise). (c) Comparator: age/gender-matched healthy humans and animals without exercise interventions that received usual care, health education, puzzle, and/or placebo. (d) Outcome: exerkines were examined, with at least one of them serving as the main outcome of interest: angiopoietin, apelin, adiponectin, β-aminoisobutyric acid (BAIBA), BDNF, CTSB, FGF21, fibronectin type III domain-containing protein 5 (FNDC5), fractalkine (CX3CL1), growth differentiation factor-8 (GDF8), growth hormone (GH), glycosylphosphatidylinositol-specific phospholipase D (GPLD1), hydroxybutyrate dehydrogenase (HBDH), IGF-1, interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-10 (IL-10), irisin, lactate, musclin protein (MSC), osteocrin protein (Ostn), vascular endothelial growth factor (VEGF) and 3-Hydroxybutyric Acid (3-HB).

The exclusion criteria were: (a) participants with rehabilitation, disease, injured, or disabled; (b) intervention with cognitive training, mindfulness training, balance training, or stretching training only; (c) nutritional intervention was performed in either the intervention or control group.

2.4. Search Procedure

Two independent reviewers who assessed the titles and abstracts of identified articles were involved in the evaluation process. Duplicate and irrelevant titles and abstracts were excluded from further consideration. Subsequently, the full-text articles that qualified were independently retrieved by the reviewers, as potential candidates for further evaluation. In the event of any disagreements, a discussion was conducted to reach a consensus. If a disagreement persisted, a third reviewer was consulted to make a final decision.

2.5. Data Extraction

The following data was extracted from each human study: (a) name of the first author; (b) year of publication; (c) country; (d) study design; (e) participant characteristics; (f) exercise characteristics; (g) control group characteristics; (h) primary outcomes (i.e., pre- and post-intervention exerkine levels in each study, in addition, only baseline and immediate post-exercise values were extracted for acute exercise); and (i) brain-related outcomes.

Exerkines were extracted as mean ± standard deviation (SD), or converted to mean ± SD. The change in exerkines was determined by subtracting the difference in change between the exercise and control groups, utilizing a pooled SD of change in both groups.

Some adjustments were performed to harmonize data from different studies: (a) the median and range were reported instead of the mean and SD, a formula from Hozo et al. [26] was used for conversion; (b) the standard error was provided instead of the SD, a formula from Altman and Bland [27] was used; (c) data were reported only by figures, a software (WebPlotDigitizer 5, San Francisco, CA, USA) was applied to extract them; (d) no data were

provided to identify the mean and SD, the corresponding authors were contacted; (e) exerkine levels were expressed in units other than pg/mL, which were converted to pg/mL.

2.6. Quality Assessment

A PEDro scale was applied to evaluate the methodological quality of included studies in humans [28]. There are 10 items that were scored in each study. The scores of 0–3, 4–5, 6–8 and 9–10 are considered poor, fair, good and excellent, respectively. A quality of evidence of the overall effect was evaluated by The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system [29]. Disagreement was resolved by discussing with the third reviewer. To limit analytic bias, studies with a PEDro score < 6 were excluded.

2.7. Statistical Analysis

A random-effects meta-analysis was implemented to calculate the effect size, computed with standardized mean differences (SMD) along with 95% confidence intervals (CI) in the levels of BDNF and IGF-1 between exercise groups and control groups. SMD were computed using Hedges' g, a bias-corrected form of Cohen's d.

According to the data of the BDNF, subgroup analyses were conducted based on gender (male and female), age (<18, 18–29.9, 30–59.9 and ≥60 years), baseline BMI (≤25 and >25), physical activity levels (low, moderate and high, among studies that reported physical activity levels, 70% of the studies used the international physical activity questionnaire [30] which was self-reported), blood biomarkers (serum and plasma), types of exercise [endurance, resistance, combined and high-intensity interval training (HIIT)] [31], length (≤12 and >12 weeks), frequency (≤3 sessions/week and >3 sessions/week), and duration (≤30 min/session and 30–60 min/session).

Because the included biomarkers represent biologically distinct signaling molecules rather than repeated testing of a single outcome, analyses were interpreted as estimation of effect magnitude rather than confirmatory hypothesis testing. Therefore, no formal multiplicity correction was applied, consistent with recommendations for exploratory biomarker syntheses.

In total, two primary meta-analyses were conducted, corresponding to BDNF and IGF-1 outcomes. Other exerkines identified in the systematic review were synthesized qualitatively and were not subjected to pooled statistical testing. No additional confirmatory subgroup meta-analyses were performed. Stratified observations (e.g., acute vs. chronic exercise) were interpreted descriptively

Heterogeneity among studies was calculated using I^2 and the Cochran statistic [32]. Heterogeneity is considered high when I^2 = 75–100%, moderate when I^2 = 50–90%, and low when I^2 = 0–25% [32]. Risk of publication bias was examined by Egger's regression test and funnel plots, with a $p < 0.1$ proposing the presence of bias [33]. Sensitivity analysis was performed by the leave-one-out method with the DerSimonian–Laird model to examine crucial studies which have significant impact on BDNF and IGF-1 between studies [34].

Meta-regression was performed to explore the factors that may influence the effect size to interpret potential sources of heterogeneity across trials. All analyses were performed with STATA software (Version 17; StataCorp., College Station, TX, USA). Statistical significance was set at $p < 0.05$ unless specified elsewhere.

2.8. Role of Preclinical Evidence and Qualitative Synthesis Approach

Preclinical studies were included to summarize mechanistic observations that cannot be measured directly in living humans (e.g., tissue-level expression and pathway activation). These studies were synthesized qualitatively in a separate subsection following the SWiM reporting guidance for narrative/alternative syntheses [35]. No pooling or quantitative

comparisons with human trials were performed, and no clinical inferences were drawn from the animal data.

3. Results

3.1. Flowchart of Studies Through the Review

The article selection process is shown in Figure 1. Complete reasons for exclusion from each study are shown in Supplementary Materials, S2. Of the selected studies, 42 articles met the criteria, and then secondary screening was performed according to the reference lists of 42 articles. If an eligible article was found in a reference list, the reference list from the article was screened, and the cycle proceeded until no additional eligible article was found. Finally, 74 articles were included in this review (42 articles in humans and 32 in animals), among which present meta-analysis comprise 37 articles from human experiments (Figure 1).

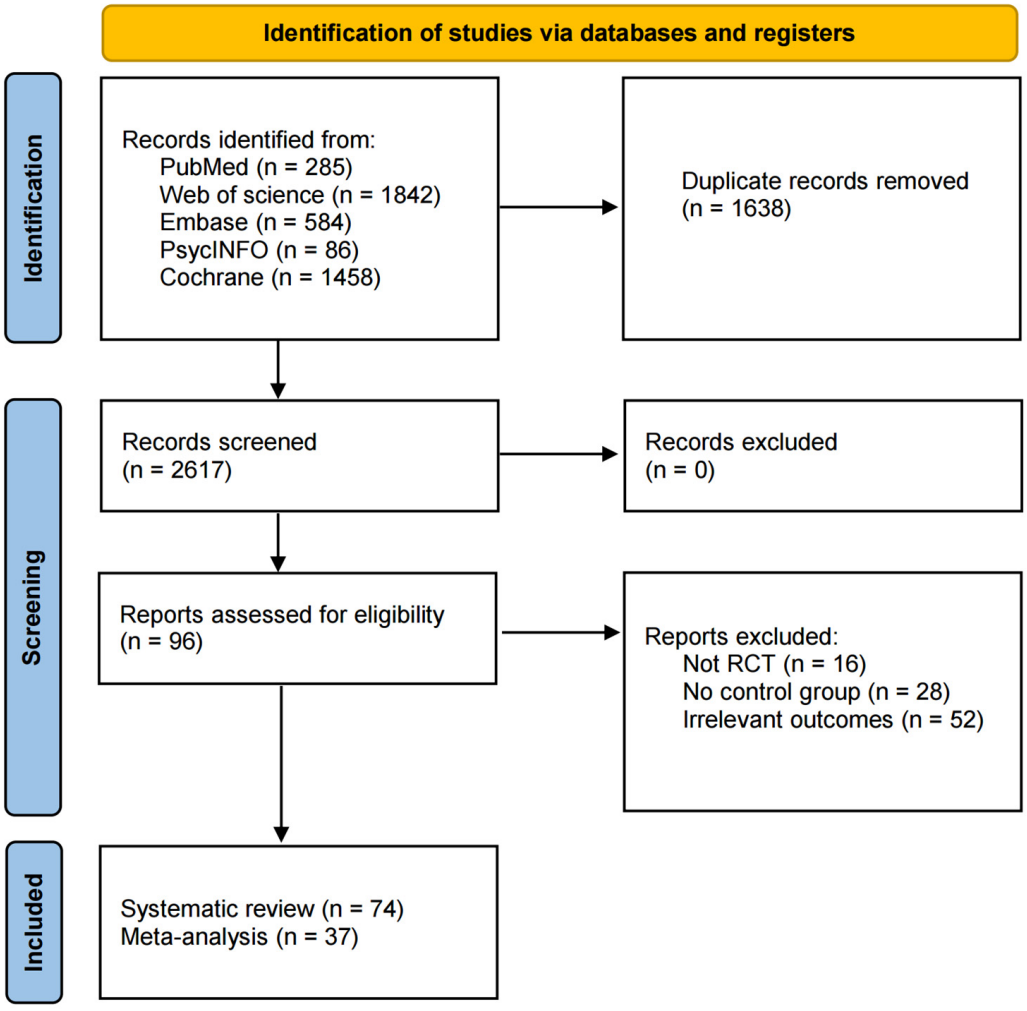


Figure 1. Flow chart depicting the search process.

3.2. Characteristics of Included Studies

3.2.1. Participants and Subjects

The characteristics of the 42 RCTs performed on humans are summarized in Table 1. The sample consisted of 3321 individuals (1665 in exercise groups and 1656 in control groups), with an age range from 10 to 89 years. A total of 34 studies reported the number of participants by gender in each group. Of these 34 studies, 56.4% of the individuals were male. These selected studies were from the United States (n = 8), Germany (n = 7), South

Korea (n = 7), China (n = 4), Spain (n = 3), and other eleven countries all with less than 3 studies.

Table 2 shows the characteristics of the 32 RCTs selected in animals. Age ranges from adolescence to old age, and 84% of the studies employed male-only subjects. All exercise protocols were voluntary, and 97% of the protocol adopted the mode of aerobic exercise.

3.2.2. Interventions in Humans

PE interventions were classified according to length as acute (one single session or a bout of PE), short-term ($\leq$4 weeks), and long-term (>4 weeks).

In human experiments where acute interventions were executed, the following modes of exercise emerged: aerobic exercise [13,14,36–47], resistance training [36,48], HIIT [49], and combined exercise [50].

Long-term interventions in humans were conducted for 5 to 48 weeks; the modes of exercise were aerobics [12,51–65], resistance training [63,66–70], combined exercise [64,71,72], Tai Chi [73,74], and taekwondo [75,76].

3.2.3. Interventions in Animals

The following evidence from animal studies is reported solely to provide mechanistic context. These findings are not pooled with human data and are not used for clinical inference. Among animal experiments, the lengths of intervention were one single exercise session [77,78], short-term trail [61,79–102], and long-term intervention [103–108].

3.3. Acute and Chronic Effects of Physical Exercise on Exerkine Levels in Healthy Humans

Among the included studies, a total of eleven exerkines (or candidate exerkines) were observed, including BDNF, CTSB, FGF21, GH, IGF-1, IL-6, irisin, klotho, kynurenine, TNF-α, and VEGF. Of these, BDNF and IGF-1 were used in the present meta-analysis.

3.3.1. BDNF

Across older adults, acute exercise was associated with a pooled increase in circulating BDNF (SMD = 3.02, 95% CI = 1.83–4.21), whereas chronic exercise tended to associate with a smaller increase (SMD = 0.71, 95% CI = −0.08–1.50) (Figure 2). Adolescents equally benefited from chronic exercises as evidenced by a pooled elevation in the BDNF (SMD = 1.28, 95% CI = 0.39–2.17). However, in adults, both young and older subgroups showed significant increases in BDNF levels (young adults: SMD = 1.74, 95% CI 1.21–2.28; older adults: SMD = 3.02, 95% CI 1.83–4.21). Notably, these effects were observed following acute exercise, whereas no significant changes were found after chronic exercise interventions.

Subgroup analysis was performed on the BDNF (Table 3). Briefly, trials with acute exercise show significant subgroup effects for the type of exercise (p = 0.01) and a tendency for age (p = 0.06). Meanwhile, chronic interventions indicate that significant subgroup effects were observed in gender, type of exercise, and blood biomarkers (all $p \leq 0.01$), as well as a tendency for the physical activity level (p = 0.07).

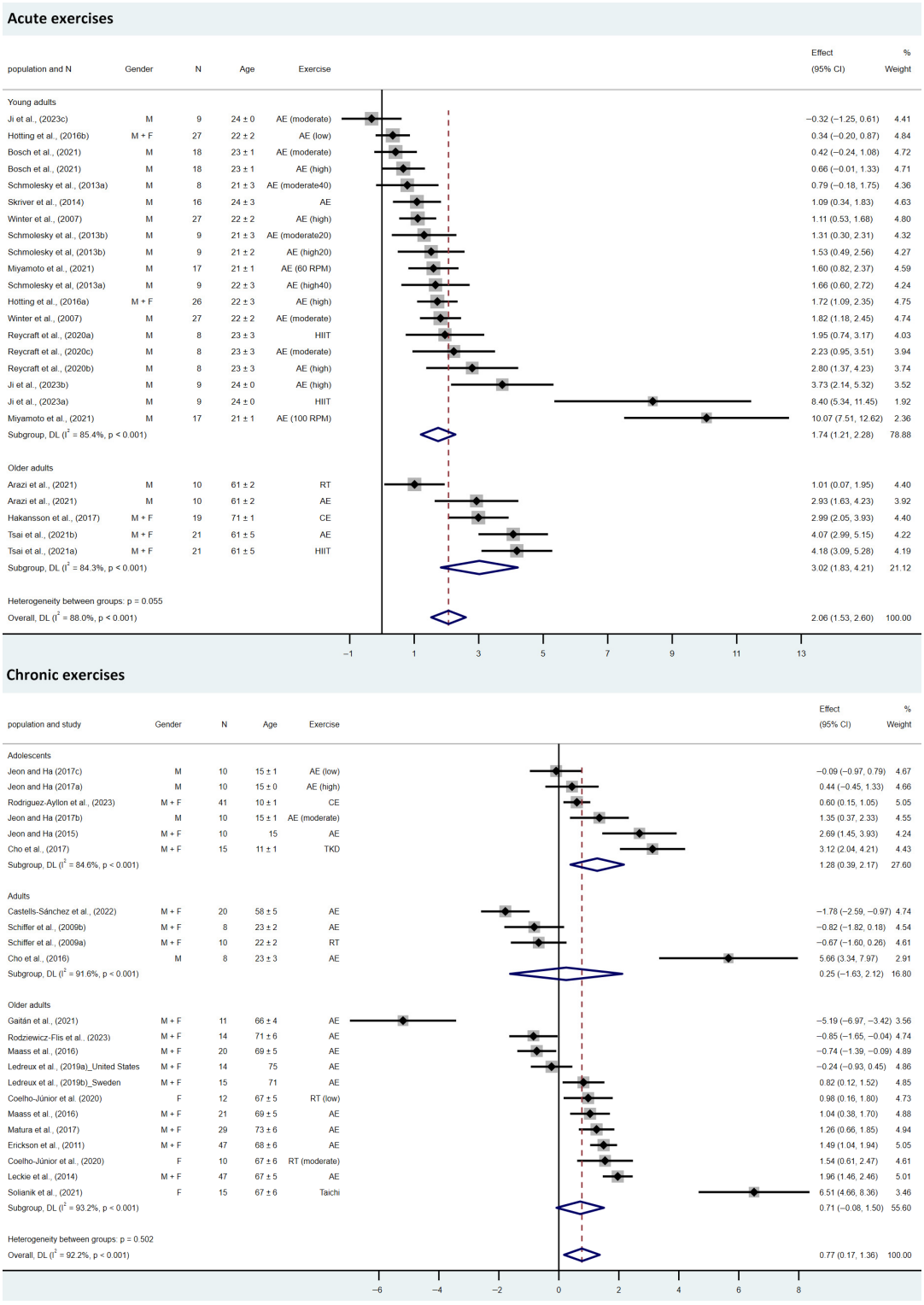


Figure 2. Responses of circulating BDNF to acute and long-term physical exercises in different age groups (results shown as standardized mean differences, weights and between-subgroup heterogeneity test are from random-effects DerSimonian–Laird model). *AE*, aerobic exercise; *CE*, combined exercise; *CI*, confidence interval; *F*, female; *high*, high-intensity; *high20*, high-intensity exercise for 20 min; *high40*, high-intensity exercise for 40 min; *HIIT*, high-intensity interval training; *low*, low-intensity; *M*, male; *modeate40*, moderate-intensity exercise for 40 min; *moderate*, moderate-intensity; *moderate20*, moderate-intensity exercise for 20 min; *RPM*, revolutions per minute; *RT*, resistance training; effect (95% CI) represents the standardized mean difference calculated as Hedges' g. Black dots, effect size; horizontal short lines, 95 CI; Blue diamonds, pooled effect size; solid vertical line, line of no effect.

Table 1. Summary of the included studies in humans.

Author, Year, and Country	Design	Participant *N* (Female), Mean Age ± SD	Intervention Components	Exerkines (The Change Between Pre- and Post-Exercise)	Brain-Related Outcomes
Acute interventions					
Arazi et al., 2021 (Iran) [36]	RP	Healthy older adults AE (with interval): 10 (0), 61 ± 2 RT: 10 (0), 61 ± 2 CON: 10 (0), 61 ± 1	--- AE: 3 × 10 min with 120 s interval of running with 65–70% of HR_{max} [208–0.7 (age)] --- RT: 65–70% of 1 RM --- Time: total 45 min in all conditions	--- Serum BDNF AE, +13%; RT, +16%; CON, +0.9% --- Serum IGF-1 AE, +4%; RT, +4%: CON, +0.2%	N/A
Bosch et al., 2021 (Switzerland) [13]	RC	Healthy young adults N = 18 (0), 23 ± 1	--- Cycle ergometer with a pedaling cadence of 60–80 RPM --- AE (H): 75% of HR_{max} for 21 min --- AE (M): 65% of HR_{max} for 30 min	Serum BNDF AE (H): +2470 pg/mL AE (M): +2270 CON: +1890	--- AE (M) improved memory (accuracy, efficiency and decoding) --- In AE (M), correlation between BDNF and delayed memory retention
Chang et al., 2017 (Taiwan, China) [46]	RC	Healthy young adults N = 30 (13), 23 ± 2	Cycle ergometer with 60–70% of HRR for 30 min	No difference in serum BDNF after AE	AE improved cognitive functions (response time & accuracy)
Hakansson et al., 2017 (Sweden) [50]	RC	Healthy older adults N = 19 (11), 71 ± 1	CE (self-weight exercise combined with aerobic exercise) with 11–13 RPE, total 35 min	Significantly increased in serum BDNF after CE	Working memory correlation with lower baseline BDNF and post-CE BDNF
Hötting et al., 2016 (Germany) [37]	RP	Healthy young adults AE (H): 26 (13), 22 ± 3 AE (L): 27 (13), 22 ± 2 CON: 28 (14), 23 ± 2	Exercise on a cycling ergometer with 80% of HR_{max} ± 5 beats/min (H) or less than 57% of HR_{max} (L) for 30 min	Serum BDNF AE (H), +14% AE (L), −5% CON, −8%	AE (H) protected memory
Hwang et al., 2016 (United States) [45]	RP	Healthy young adults AE: 29 (15), 23 ± 3 CON: 29 (17), 24 ± 3	Running on a treadmill with 85–90% of VO_{2max} for 20 min	Significantly increased in serum BDNF after AE	--- AE (H) improved cognitive function (test in Stroop and TMT) --- Significant correlation between the change in BDNF and shorter completion times in TMT
Ji et al., 2023 (Korea) [38]	RC	Healthy young adults N = 9 (0), 24 ± 0	--- Cycle ergometer --- HIIT: four 30 s of "all out" followed by 4 min of recovery, total 18 min --- AE (H): 85% HRR for 30 min --- AE (M): 55% HRR for 30 min	--- Serum BDNF HIIT, +52%; AE (H), +24% AE (M), −2%; CON, 0% --- Serum CTSB HIIT, +184%; AE (H), +87% AE (M), −23%; CON, +5% --- Serum FGF21 HIIT, +44%; AE (H), +12% AE (M), +2%; CON, −8%	N/A

Table 1. *Cont.*

Author, Year, and Country	Design	Participant *N* (Female), Mean Age ± SD	Intervention Components	Exerkines (The Change Between Pre- and Post-Exercise)	Brain-Related Outcomes
McDonnell et al., 2013 (Australia) [47]	RC	Healthy adults N = 25 (16), 27 ± 8	--- Cycle ergometer with a pedaling cadence of 50 RPM --- AE (L): 58 ± 5% of age-predicted HR_{max} (220 − age), 11 ± 2 RPE, total 30 min --- AE (M): 76 ± 16% of age-predicted HR_{max}, 15 ± 1 RPE, total 15 min	Trend to decrease serum BDNF after any condition	AE (L) improved neuroplasticity within the motor cortex
Miyamoto et al., 2021 (Japan) [39]	RC	Healthy adults N = 17 (0), 21 ± 1	Cycle ergometer with 40% of VO_{2max} for 40 min	Serum BDNF AE (60 RPM), +4% AE (100 RPM), +24% CON, −7%	N/A
Reycraft et al., 2020 (Canada) [14]	RC	Healthy young adults N = 8 (0), 23 ± 3	--- Treadmill running --- HIIT: four 30 s of "all out" efforts interspersed with 4 min of recovery, total 18 min --- AE (H): 85% of VO_{2max} for 30 min --- AE (M): 65% of VO_{2max} for 30 min	--- Plasma BDNF HIIT, +196%; AE (H), +53% AE (M), +53%; CON, −4% --- Plasma Irisin HIIT, −12%; AE (H), −8% AE (M), −2%; CON, +6%	N/A
Schmolesky et al., 2013 (United States) [40]	RP	Healthy young adults AE (H for 40 min): 9 (0), 22 ± 3 AE (H for 20 min): 9 (0), 21 ± 2 AE (M for 40 min): 8 (0), 21 ± 3 AE (M for 20 min): 9 (0), 21 ± 3 CON: 10 (0) Age 20 ± 2 in CON (40 and 20 min)	Cycle ergometers with 60% and 80% of HRR for 20 min and 40 min (four exercise conditions)	Serum BDNF AE (H for 40 min), +28% AE (H for 20 min), +26% AE (M for 40 min), +30% AE (M for 20 min), +41% CON (40 min), −11% CON (20 min), −14%	N/A
Schwarz et al., 1996 (United Stated) [41]	RC	Healthy young adults N = 10 (0), 28 ± 5	--- Exercise on a cycling ergometer --- AE (H): 79 ± 5.7% VO_{2max} for 10 min --- AE (M): 46 ± 4.9% VO_{2max} for 10 min	--- Serum GH AE (H), +343%; AE (M), +57% CON, +26% --- Serum IGF-1 AE (H), +13%; AE (M), +8% CON, −6%	N/A

Table 1. *Cont.*

Author, Year, and Country	Design	Participant *N* (Female), Mean Age ± SD	Intervention Components	Exerkines (The Change Between Pre- and Post-Exercise)	Brain-Related Outcomes
Skriver et al., 2014 (Denmark) [42]	RP	Healthy young adults AE: 16 (0), 24 ± 3 CON: 16 (0), 24 ± 4	Cycling ergometer with 10 mmol/L or above of intensity in lactate and workload ranged from 200 to 315 W, total 20 min	--- Plasma VEGF AE, +2.22 pg/mL; CON, +0.04 pg/mL --- Plasma BDNF AE, +0.37 pg/mL; CON, +0.02 pg/mL --- Plasma IGF-1 AE, +80 pg/mL; CON, +20 pg/mL	Positive correlation between BDNF change with memory
Slusher et al., 2018 (United States) [49]	RC	Healthy young adults N = 13 (0), 24 ± 1	HIIT with sprint intensity on a cycle ergometer for 10 × 20 s with 10 s of active recovery against 5.5% of the participant's body weight, total 15 min	Significantly increased after HIIT	HIIT improved executive function
Tsai et al., 2021 (Taiwan, China) [43]	RC	Healthy late-middle-aged and older adults N = 21 (11), 61 ± 5	--- Stationary adjustable bicycle --- HIIT: 24 min of training (1 min of 70–75% of HRR alternated with a 2 min of 9–11 RPE active recovery period) --- AE: 50–55% of HRR --- Time: total 30 min in all conditions	--- Serum BDNF HIIT, +18%; AE, +23%; CON, −4% ---Serum Irisin HIIT, +8%; AE, +4%; CON, 0%	--- No correlations among the change in BDNF and irisin and the change in neuro-cognitive performance --- In AE, significant correlations between the change in irisin and reaction time --- AE improved accuracy rate --- AE and HIIT improved reaction time
Tsai et al., 2014 (Taiwan, China) [48]	RP	Healthy young adults RT (H): 20 (0), 22 ± 2 RT (L): 20 (0), 23 ± 3 CON: 20 (0), 23 ± 2	--- RT (H): 80% of 1 RM --- RT (L): 50% of 1 RM --- Time: total 40 min in all conditions	--- Serum GH RT (H), +1145%; RT (L), +458% CON, +73% --- Serum IGF-1 RT (H), +12%; RT (L), +6% CON, −2%	RT with both high- and L-improved executive function
Winter et al., 2007 (Germany) [44]	RC	Healthy sports young adults N = 27 (0), 22 ± 2	--- AE (H): running with blood lactate level ≤ 2 mmol/L, the median of HR was 140 beats/min, total 10 min --- AE (M): running with blood lactate level > 10 mmol/L, the median of HR was 184 beats/min, total 40 min	Serum BDNF AE (H), +12%; AE (M), +15% CON, +4%	Relationship between more sustained BDNF during learning after AE (H) and better short-term learning success
Chronic intervention					
Cassilhas et al., 2010 (Brazil) [66]	RP	MMSE score > 23 older adults RT (high-load): 20 (0), 68 ± 1 RT (moderate-load): 19 (0), 69 ± 1 CON: 23 (0), 67 ± 1	--- RT (high-load): 80% of 1 RM --- RT (moderate-load): 50% of 1 RM --- Length: 60 min/session, 3 sessions/wk for 6 months	Serum IGF-1 RT (high-load), +35%; RT (moderate-load), +41,120 pg/mL CON, −10%	RT improved mood and anxiety

Table 1. *Cont.*

Author, Year, and Country	Design	Participant *N* (Female), Mean Age ± SD	Intervention Components	Exerkines (The Change Between Pre- and Post-Exercise)	Brain-Related Outcomes
Guazzarini et al., 2024 (Italy) [73]	RP	Healthy older adults Tai Chi: 14 (10), 70 ± 7 CE: 14 (10), 70 ± 5 CON: 14 (8), 72 ± 5	Intensity: N/A Length: 2 sessions/wk for 6 months	Plasma Irisin Tai Chi, +70%; CE, +55%; CON, −30%	Tai Chi practice at six months positive correlation between irisin with a verbal memory test
Castells-Sánchez et al., 2022 (Spain) [52]	RP	Healthy late-middle-aged adults AE: 25 (13), 58 ± 5 CON: 15 (7), 57 ± 6	--- Healthy late-middle-aged adults --- AE: 25 (13), 58 ± 5 --- CON: 15 (7), 57 ± 6	--- Plasma BDNF AE, −16%; CON, +5% --- Plasma TNF-α AE, +8%; CON, −1%	In AE group, sex differences were found in total white matter, parietal, temporal lobe, and dorsolateral prefrontal cortex volumes
Cho et al., 2017 (Korea) [76]	RP	Healthy children Taekwondo: 15 (6), 11 ± 1 CON: 15 (6), 11 ± 1	--- Main exercise (involved basic movements, poomsae, kicking and gymnastic) with 11–15 RPE --- Length: 60 min/session, 5 sessions/wk for 4 months	--- Serum BDNF Taekwondo, +15%; CON, +2% --- Serum VEGF Taekwondo, +9%; CON, +3% --- Serum IGF-1 Taekwondo, +8%; CON, +3%	Taekwondo improved cognitive function (color-word test)
Cho et al. 2019 (Korea) [75]	RP	Healthy older adults Taekwondo: 19 (19), 69 ± 4 CON: 18 (18), 69 ± 4	--- Main exercise (involved Taekwondo basic movement, poomsae, kicking and taekwondo gymnastics) with 50–80% of HR_{max} --- Length: 60 min/session, 5 sessions/wk for 4 months	--- Serum BDNF Taekwondo, +13%; CON, +2% --- Serum VEGF Taekwondo, +5%; CON, −2% --- Serum IGF-1 Taekwondo, +7%; CON, 0%	Taekwondo improved cognitive function (color-word test)
Cho et al., 2016 (Korea) [53]	RP	Overweight or obese young adults AE: 8 (0), 23 ± 3 CON: 8 (0), 22 ± 2	--- Running on a treadmill with 70% of HRR --- Length: 40 min/session, 3 sessions/wk for 2 months	Serum BDNF AE, +21%; CON, +1%	N/A
Coelho-Júnior et al. 2020 (Brazil) [68]	RP	Healthy older adults RT (M): 10 (10), 67 ± 6 RT (L): 12 (12), 67 ± 5 CON: 14 (14), 67 ± 5	--- RT (M): traditional RT (exercise machines and free weights) with 5–6/10 RPE --- RT (L): traditional RT combined with power training using elastic bands with 2–3/10 RPE --- Length: approx. 60 min/session, 2 sessions/wk for 22 wks	Serum BDNF RT (M), +5%; RT (L), +2% CON, −3%	Both RT programs improved global cognitive function, including short-term memory and dual-task performance

Table 1. *Cont.*

Author, Year, and Country	Design	Participant *N* (Female), Mean Age ± SD	Intervention Components	Exerkines (The Change Between Pre- and Post-Exercise)	Brain-Related Outcomes
Erickson et al. 2011 (United States) [12]	RP	Older adults with normal cognitive function, depression score, and no neurologic disease or infarction history AE: 60 (44), 68 ± 6 CON: 60 (36), 66 ± 5	--- Walking with 60–75% of HRR --- Length: 50 min/session, 3 sessions/wk for 1 year	Serum BDNF AE, +11%; CON, +3%	--- AE increased hippocampal volume --- Association between the change in BDNF and the change in hippocampal volume --- Association between higher aerobic fitness level after AE and better memory performance
Gaitán et al., 2021 (United States) [54]	RP	Cognitively healthy older adults AE: 11 (5), 66 ± 4 CON: 12 (6), 64 ± 5	--- Moderate–vigorous intensity on treadmill --- Length: 3 sessions/wk for 26 wks	--- Plasma CTSB AE, +32%; CON, +22% --- Plasma BDNF AE, −47%; CON, −19% --- Serum klotho AE, 0%; CON, −6%	Positive correlation between the change in CTSB with cognitive function
Jeon and Ha 2015 (Korea) [56]	RP	Healthy adolescents AE, N = 10; CON, N = 10 No gender reported, mean age 15	--- AE on treadmill with 40–60% of VO_{2max} until burned 200 kcal --- Length: 3 sessions/wk for 2 months	--- Serum BDNF AE, +18%; CON, +4% --- Serum IGF-1 AE, +50%; CON, +3%	N/A
Jeon and Ha 2017 (Korea) [55]	RP	Healthy adolescents AE (H): 10 (0), 15 ± 0 AE (M): 10 (0), 15 ± 1 AE (L): 10 (0), 15 ± 1 CON: 10 (0), 15 ± 0	--- AE on treadmill with 40% (L) of VO_{2max} for 43 min/session, or with 55% (M) of VO_{2max} for 33 min/session, or with 70% (H) of VO_{2max} for 26 min/session, until burned 200 kcal --- Length: 4 sessions/wk for 3 months	--- Serum BDNF AE (H), +19%; AE (M), +7% AE (L), +1%; CON, +2% --- Serum IGF-1 AE (H), +8%; AE (M), −1% AE (L), +1%; CON, +6%	AE (H) improved working memory
Leckie et al., 2014 (United States) [57]	RP	Older adults without cognitive impairment AE: 47 (32), 67 ± 5 CON: 45 (27), 66 ± 6	--- Walking with 60–75% of HRR --- Length: 50 min/session, total 1 year	Serum BDNF AE, +11%; CON, −2%	The change in BDNF mediated the relationship between exercise group and executive function, specifically for participants aged 71 years and older
Ledreux et al., 2019a (United States) [58]	RP	Healthy older adults AE, N = 14; CON, N = 19 Age approx. 75 and 25 are female in all group	--- AE routines with 11–13 of RPE --- Length: 35 min/session, 5 sessions/wk for 5 wks	Serum BDNF AE, −5%; CON, −0.8%	N/A
Ledreux et al., 2019b (Sweden) [58]	RP	Healthy older adults AE, N = 15; CON, N = 20 Age approx. 71 and 26 are female in all group	--- AE routines with 11–13 of RPE --- Length: 35 min/session, 5 sessions/wk for 5 wks	Serum BDNF AE, +10%; CON, −9%	N/A

Table 1. *Cont.*

Author, Year, and Country	Design	Participant *N* (Female), Mean Age ± SD	Intervention Components	Exerkines (The Change Between Pre- and Post-Exercise)	Brain-Related Outcomes
Maass et al., 2016 (Germany) [59]	RP	Healthy older adults AE: 21 (11), 69 ± 5 CON: 19 (11), 68 ± 4	--- Running interval training on a treadmill with 70% of HR_{max} --- Length: 40 min/session, 3 sessions/wk for 3 months	--- Serum BDNF AE, −4%; CON, 0% --- Plasma BDNF AE, +31%; CON, +9% --- Serum VEGF AE, 0%; CON, −7% --- Serum IGF-1 AE, −2%; CON, −3%	Positive correlation between the change in IGF-1 with hippocampal volume and memory
Matura et al. 2017 (German) [60]	RP	Cognitively healthy older adults AE: 29 (12), 73 ± 6 CON: 24 (12), 77 ± 8	--- Cycle ergometer with 64 ± 9% of VO_{2max} --- Length: 30 min/session, 3 sessions/wk for 3 months	Serum BDNF AE, +2%; CON, −7%	--- CON increased whereas AE remained stable in cerebral choline concentration --- No change in Cortical gray matter volume after AE
Moon et al., 2016 (Germany) [61]	RP	Healthy young adults AE, N = 20; CON, N = 23 Age approx. 19–34 and 24 are female in all group	--- Running interval training on a treadmill with 70–90% of HR_{max} --- Length: 45–75 min/session, 3 sessions/wk for 4 months	Plasma CTSB AE, +22%; CON, −4%	Positive correlation between the change in CTSB with memory
Rodriguez-Ayllon et al. 2023 (Spain) [71]	RP	Children without neurological and attention deficit/hyperactivity disorder CE: 42 (15), 10 ± 1 CON: 39 (18), 10 ± 1	--- CE with an average of 38 min above 80% of HR_{max} --- Length: 90 min/session, 3 sessions/wk for 5 months	--- Plasma BDNF CE, −20%; CON, −40% --- Plasma CTSB CE, −5%; CON, +5% --- Plasma FGF21 CE, −12%; CON, +11% --- Plasma kynurenine CE, 0.29 z-score; CON, 0.22 z-score	CE improved total intelligence and cognitive flexibility but no difference in working memory and hippocampal volume
Rodziewicz-Flis et al. 2023 (Poland) [62]	RP	Older adults without cognitive impairment AE, N = 14; CON, N = 12 Age 71 ± 6 and 6 are female in all group	--- Folk-dance training with 60–80% HR_{max} --- Length: 50 min/session, 3 sessions/wk for 3 months	--- Serum BDNF AE, −66%; CON, −33% --- Serum Irisin AE, +13%; CON, 0%	N/A
Ruscheweyh et al. 2011 (German) [65]	RP	Healthy older adults AE: 20 (14), 60 ± 6 CON: 21 (14), 58 ± 7	--- Nordic walking with lactate between 1.5 and 2.0 mmol/L --- Length: 50 min/session, 3 sessions/wk for 6 months	Trend to increase serum BDNF after AE	--- AE improved memory --- Positive correlation between the increases in local gray matter volume in prefrontal and cingulate cortex, and BDNF levels
Schiffer et al., 2009 (Germany) [63]	RP	Healthy sports young adults RT: 10, 22 ± 2 AE: 8, 23 ± 2 CON: 9, 22 ± 2 No gender reported	--- RT: 70–80% of 1 RM --- AE: Running on a treadmill with 70–80% of HR_{max} for 45 min --- Length: 3 sessions/wk for 3 months	--- Plasma BDNF RT, −14%; AE, −20%; CON, −3% --- Plasma IGF-1 RT, −9%; AE, −6%; CON, −6%	N/A

Table 1. *Cont.*

Author, Year, and Country	Design	Participant *N* (Female), Mean Age ± SD	Intervention Components	Exerkines (The Change Between Pre- and Post-Exercise)	Brain-Related Outcomes
Seo et al., 2010 (Korea) [64]	RP	Healthy postmenopausal women AE: 7 (7), 55 ± 5 CE: 8 (8), 54 ± 4 CON: 7 (7), 58 ± 4	--- AE: 60–80% of HRR --- CE: Walking and resistance exercise with 50–70% of 1 RM --- Length: 60 min/session, 3 sessions/wk for 3 months	--- Serum IGF-1 AE, +12%; CE, +9%; CON, −2% --- Serum GH AE, +45%, CE, +88%; CON, +7%	N/A
Solianik et al. 2021 (Lithuania) [74]	RP	Healthy older adults Tai Chi, 15 (13); CON, 15 (13) 67 ± 6 years old in both group	--- 8-form Yang-style Tai Chi practice --- Length: 60 min/session, 2 sessions/wk for 10 wks	Serum BDNF Tai Chi, +99%; CON, −8%	--- In Tai Chi, correlation between the change in BDNF and the change in reaction time --- Tai Chi improved cognitive function
Tsai et al., 2015 (Taiwan, China) [69]	RP	Healthy older adults RT: 24 (0), 71 ± 3 CON: 24 (0), 72 ± 4	--- 75–80% of 1 RM --- Length: 60 min/session, 3 sessions/wk for 1 year	--- Serum GH RT, +22%; CON, −9% --- Serum IGF-1 RT, +12%; CON, −2%	--- RT improved reaction time --- Negative correlation between the change in IGF-1 with neurocognitive decline
Vaughan et al. 2014 (Australia) [72]	RP	Older adults without cognitive impairment CE: 25 (25), 69 ± 3 CON: 23 (23), 69 ± 4	--- Each session includes aerobic, resistance and motor fitness (balance, co-ordination, flexibility and agility), with the intensity of 3–6/10 RPE --- Length: 60 min/session, 2 sessions/wk for 4 months	Significantly increased in plasma BDNF after CE	CE improved cognitive function
Vints et al., 2024 (Lithuania) [70]	RP	MoCA score > 25 older adults RT: 27 (15), 71 ± 6 CON: 25 (13), 69 ± 6	--- RT: 70–85% of 1 RM --- Length: 2 sessions/wk for 3 months	--- Serum IGF-1 RT, +17%; CON, +21% --- Serum IL-6 RT, +44%; CON, −7% --- Serum kynurenine RT, −18%; CON, −8%	In RT, negative correlation between the increases in IGF-1 with the improvements in response time on a mathematical processing test

1 RM, 1 repetition maximum; AE, aerobic exercise; BDNF, brain-derived neurotrophic factor; CE, combined exercise; CON, control group; CTSB, cathepsin-B; FGF21, fibroblast growth factor 21; GH, growth hormone; H, high-intensity; HIIT, high-intensity interval training; HR, heart rate; HR_{max}, maximal heart rate; HRR, heart rate reserve; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; L, low-intensity; M, moderate intensity; Min, minute; N/A, not applicable; RC, randomized crossover design; RP, randomized parallel design; RPE, rating of perceived exertion; RPM, revolutions per minute; RT, resistance training; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; VO_{2max}, maximal oxygen uptake; Wk, week.

Table 2. Responses of exerkines to voluntary aerobic exercise on the brain and blood in healthy animals.

Exerkines	Ages		Detected Regions	Levels	Significance or Tendency	Refs.
BDNF	Adolescence	Short-term	Hippocampus	Protein	↑ *	[91,92]
					↓ *	[89]
		Short-term	Perirhinal cortex	Protein	↑	[89]
		Long-term	Hippocampus	Protein	↑	[108]
	Adults	Acute	Hippocampus	Protein	↑ *	[77]
				mRNA	↑ *	[77,78]
		Short-term	Hippocampus	mRNA	↑	[85]
					↑ *	[82,88]
			Cerebral cortex	Protein	↑ *	[101]
			Hippocampus		↑	[81]
					↑ *	[82]
			Perirhinal cortex		↑	[89]
			Striatum		↔	[102]
		Long-term	Basolateral amygdala	mRNA	↑ *	[105]
			Hippocampus	mRNA	↑ *	[104,105]
				Protein	↑ *	[103]
	Old-aged	Short-term	Hippocampus	mRNA	↔	[85]
pro-BDNF	Adults	Short-term	Hippocampus	mRNA	↑ *	[82]
				Protein	↑ *	[82]
Mature BDNF	Adults	Short-term	Hippocampus	Protein	↑ *	[83]
		Long-term			↑ *	[107]
CTSB	Adolescence	Short-term	Blood	Plasma	↑ *	[61]
FNDC5	Adults	Short-term	Hippocampus	mRNA	↑	[97]

Table 2. *Cont.*

Exerkines	Ages		Detected Regions	Levels	Significance or Tendency	Refs.
IGF-1	Adults	Short-term	Blood	Serum	↑	[84]
			Hippocampus	mRNA	↑ *	[82]
				Protein	↓	[84]
VEGF	Adults	Short-term	Blood	Plasma	↑	[102]
			Hippocampus	Protein	↔	[102]
			Striatum		↔	[102]

Note: Preclinical evidence, reported for mechanistic context only. Not combined with human analyses; no clinical inference is drawn from these data. Aerobic exercises were classified according to length as acute (one single session or a bout of PE), short-term (≤4 weeks) and long-term (>4 weeks). *BDNF*, brain-derived neurotrophic factor; *CTSB*, cathepsin-B; *FNDC5*, fibronectin type III domain-containing protein 5; *IGF-1*, insulin-like growth factor 1; *Mature BDNF*, formed by pro-BDNF after specific protease trimming; *pro-BDNF* is the precursor form of BDNF when it is initially synthesized by cells; *Refs.*, references; *VEGF*, vascular endothelial growth factor; ↑ up-regulation; ↓ down-regulation; ↔ unchanged or nearly; * $p < 0.05$.

Table 3. Subgroup analysis of BDNF according to different characteristics of the programs.

Acute Exercises	*N* = Trails	Cohen's d (95% CI)	I^2 (%)	P^1	P^2	Chronic Exercises	*N* = Trails	Cohen's d (95% CI)	I^2 (%)	P^1	P^2
Gender					-	*Gender*					**0.01**
Male	24	2.09 (1.54, 2.63)	92.9	**<0.01**		Male	4	1.52 (−0.04, 3.07)	87.9	0.06	
Female	-	-	-	-		Female	4	6.99 (3.13, 10.85)	96.8	**<0.01**	
Age (years old)					0.06	*Age* (years old)					0.99
<18	-	-	-	-		<18	6	1.29 (0.39, 2.18)	85.1	**<0.01**	
18–30	19	1.77 (1.23, 2.32)	86.1	**<0.01**		18–30	3	1.16 (−1.58, 3.89)	93.3	0.41	
30–60	-	-	-	-		30–60	-	-	-	-	
>60	5	3.02 (1.84, 4.21)	84.6	**<0.01**		>60	13	1.18 (0.24, 2.11)	94.9	**0.01**	
Baseline BMI (>18 y/o)					0.42	*Baseline BMI (>18 y/o)*					0.23
<25	12	1.92 (1.24, 2.60)	85.1	**<0.01**		<25	7	2.05 (0.42, 3.67)	94.3	**0.01**	
≥25	3	3.75 (−0.6, 8.09)	95.5	0.09		≥25	12	0.95 (0.17, 1.73)	92.8	**0.02**	
Physical activity levels					-	*Physical activity levels*					0.07
Low	-	-	-			Low	9	1.36 (−0.15, 2.87)	97.0	0.08	
Moderate	-	-	-			Moderate	-	-	-		
High	18	1.84 (1.26, 2.42)	86.9	**<0.01**		High	4	−0.18 (−0.93, 0.58)	71.1	0.64	
Blood composition					0.62	*Blood composition*					**<0.01**
Serum	20	2.13 (1.51, 2.76)	90.1	**<0.01**		Serum	17	1.76 (1.00, 2.53)	93.1	**<0.01**	
Plasma	4	1.88 (1.10, 2.66)	49.4	**<0.01**		Plasma	6	−0.98 (−2.23, 0.28)	91.9	0.13	
Types of exercise					**0.01**	*Types of exercise*					**0.01**
Aerobic	19	1.80 (1.25, 2.34)	87.0	**<0.01**		Aerobic	17	0.70 (−0.05, 1.44)	93.6	0.07	
Resistance	-	-	-	-		Resistance	3	0.62 (−0.64, 1.88)	83.4	0.33	
Concurrent	-	-	-	-		Concurrent	3	7.74 (3.10, 12.39)	97.7	**<0.01**	
HIIT	3	4.50 (1.84, 7.16)	89.5	**<0.01**		HIIT	-	-	-	-	

Table 3. *Cont.*

Acute Exercises	*N* = Trails	Cohen's d (95% CI)	I^2 (%)	P^1	P^2	Chronic Exercises	*N* = Trails	Cohen's d (95% CI)	I^2 (%)	P^1	P^2
Intensity					0.36	*Intensity*					0.60
Light	3	3.57 (0.69, 6.45)	96.6	**0.02**		Light	2	0.46 (−0.59, 1.50)	67.2	0.39	
Moderate	10	1.69 (0.89, 2.48)	86.8	**<0.01**		Moderate	15	1.11 (0.31, 1.90)	93.9	**0.01**	
Vigorous	11	2.22 (1.49, 2.95)	84.9	**<0.01**		vigorous	4	1.08 (−0.29, 2.45)	89.2	0.12	
Length (wks)					-	*Length* (wks)					0.26
≤12	-	-	-	-		≤12	15	0.76 (0.01, 1.51)	91.3	0.05	
>12	-	-	-	-		>12	8	1.60 (0.35, 2.84)	95.4	**0.01**	
Frequency (sessions/wk)					-	*Frequency* (sessions/wk)					0.41
≤3	-	-	-	-		≤3	14	0.84 (0.04, 1.64)	93.0	**0.04**	
>3	-	-	-	-		>3	8	1.55 (0.09, 3.00)	94.8	**0.04**	
Duration (min/session)					0.37	*Duration* (min/session)					0.67
≤30	16	1.91 (1.26, 2.56)	88.6	**<0.01**		≤30	2	0.92 (0.13, 1.71)	55.9	**0.02**	
30–60	8	2.45 (1.46, 3.45)	88.1	**<0.01**		30–60	18	1.17 (0.31, 2.04)	94.8	**<0.01**	

Results from random-effects meta-analysis shown as BDNF changes (expressed as Cohen's d) along with 95% confidence interval (CI). P^1, value for net change; P^2, difference between groups, analyzed by categorical variables; *BMI*, body mass index; *HIIT*, high-intensity interval training; *wk*, week; *y/o*, years old; significant *p*-values of <0.05 are highlighted in bold prints.

3.3.2. IGF-1

As we can see in Figure 3, studies analyzed on acute exercise were conducted only in the adult population, all reporting an association with a pooled increase in IGF-1 levels after the intervention. Similar results were observed in chronic exercise interventions with increased IGF-1 levels, although only in older adults (SMD = 3.62, 95% CI = 1.53 to 5.71).

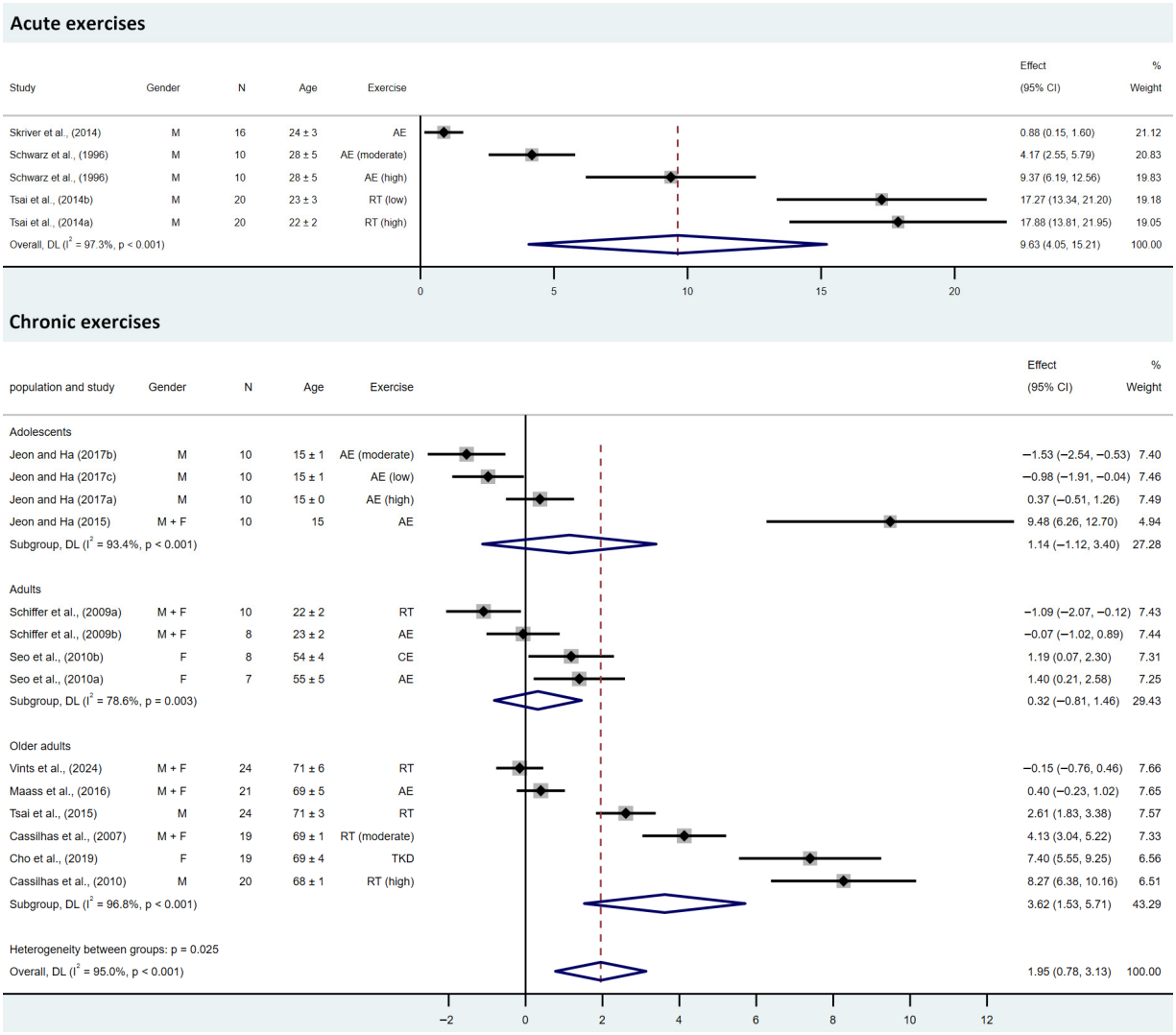


Figure 3. Acute and chronic physical exercise responses on circulating IGF-1 among healthy people of various ages (results shown as standardized mean differences, weights and between-subgroup heterogeneity test are from random-effects DerSimonian–Laird model). *AE*, aerobic exercise; *CE*, combined exercise; *CI*, confidence interval; *F*, female; *high*, high-intensity; *low*, low-intensity; *M*, male; *moderate*, moderate-intensity; *RT*, resistance training; effect (95% CI) represents the standardized mean difference calculated as Hedges' g. Black dots, effect size; horizontal short lines, 95 CI; Blue diamonds, pooled effect size; solid vertical line, line of no effect [41,42,48,55,56,59,63,64,66,67,69,70,75].

3.3.3. Other Exerkines

Quantitative data of the changes in exerkine levels before and after PE view Table 1.

3.4. Quality Assessment, Risk of Publication Bias, Sensitivity Analysis, and Heterogeneity

Supplementary Materials S3 summarizes the methodological quality according to the PEDroScale. The mean score of the methodological quality assessment was 7.1 and all studies were classified as good quality or above. The deduction of scores was mostly because of lacking blindness, among others, as shown in Supplementary Materials, S3.

Additionally, in 54% of the included chronic-exercise studies, the need to maintain a normal lifestyle (physical activity and/or dietary habits) throughout the experimental cycle was addressed to participants in the intervention and/or control groups. Moreover, most studies did not report sports injuries or any adverse events except for two studies reporting injuries that occurred during the non-intervention period, and then injured participants were excluded from analysis [44,65]. The publication bias risk and sensitivity analysis results for the BDNF and IGF-1 are available in Supplementary Materials, S4 and S5. In addition to the nature of the human experiment, we explored other factors that may contribute to the heterogeneity of the BDNF and IGF-1. By means of meta-regression analysis, Supplementary Materials S6 illustrates participant characteristics, experimental methods, and exercise protocols which are the factors comprising heterogeneity. As a result, the quality of evidence (GRADE system) for evaluating the response of exerkines after PE was classified as moderate quality (Supplementary Materials, S7).

4. Discussion

The present review was designed to synthesize randomized controlled evidence on how structured physical exercise alters circulating exerkines in healthy individuals. Rather than examining clinical populations or disease outcomes, our objective is to characterize the physiological signaling environment elicited by exercise under normal conditions. The pooled findings indicate that exercise induces measurable changes in several circulating factors, and most consistently in the BDNF and IGF-1, although the magnitude and direction of responses vary across studies. These observations support the view that exercise functions as a systemic biological stimulus capable of modulating inter-organ communication pathways that are relevant to brain physiology [11]. Given study heterogeneity and, for some biomarkers, indirectness, interpretations should remain cautious and be viewed as suggestive rather than conclusive.

The confidence we place in these pooled estimates reflects the methodological quality of the included studies, as summarized by PEDro and GRADE assessments, which identify where certainty is stronger and where evidence remains limited.

It is important to note that exercise did not always demonstrate superiority over all control conditions. Studies employing passive controls (e.g., sedentary behavior or maintenance of habitual lifestyle) tended to report clearer between-group differences, whereas trials using active comparators or low-intensity movement often showed attenuated effects. This pattern suggests that exerkine responses are sensitive to the relative physiological load imposed by the intervention, consistent with the dose–response relationship described in exercise endocrinology [109,110]. Therefore, the findings should be interpreted as reflecting differences in metabolic and mechanical stimulus rather than a contrast between “exercise” and “no exercise.”

The increase in circulating BDNF following exercise is well documented and has been linked to synaptic plasticity and cognitive support mechanisms [111]. The contribution of the present review lies not in reestablishing this association, but in evaluating the BDNF alongside other exercise-responsive mediators within the same analytical framework. Emerging research emphasizes that exercise induces a coordinated network of signaling molecules, including myokines, hepatokines, and neurotrophic factors that act collectively rather than independently [10,11]. By examining multiple candidates simultaneously in healthy populations, this study provides a more integrated perspective on how exercise may shape the biochemical environment that supports brain function.

The divergent findings across acute, short-duration, and longer interventions likely reflect different layers of physiological adaptation. Acute exercise is characterized by rapid, transient elevations in circulating signaling molecules driven by metabolic stress,

calcium flux, and muscle contraction-induced secretion [112]. With repeated exposure over weeks, these responses become part of an adaptive process involving mitochondrial biogenesis, altered substrate utilization, and endocrine recalibration [109]. Over longer periods, baseline regulation may stabilize as tissues adapt structurally, resulting in smaller circulating fluctuations despite meaningful functional adaptation. Such temporal dynamics are consistent with general models of training adaptation, in which early signaling events trigger downstream remodeling rather than remaining chronically elevated [113].

4.1. Cerebral Responses to Physical Exercise and the Link Between Exerkines and Brain Health

In acute experiments, PE significantly improved cognitive function [13,37,43,45,46,48,49] and neuroplasticity [47]. Specifically, participants with increased levels of the BDNF induced by PE had a higher working memory [50]. Moreover, correlations were found between BDNF levels and cognitive functions following one session of PE [13,42,44,45]. Furthermore, significant negative correlations were also found between the changes in irisin and reaction time [43,73].

Of the studies that carried out long-term interventions, aerobic exercise increased hippocampal volume [12], while resistance training improved mood and anxiety [66,74,114]. Moreover, chronic interventions with PE improved cognitive functions from the following testing: global cognitive function, including short-term memory and dual-task performance [68], memory [65], reaction time and accuracy rate [69,74], Stroop and Trail-making tests [72,75,76], total intelligence and cognitive flexibility [71], and working memory [55].

In an exercise protocol that involved walking for 40 min per session for one year, it was observed that the changes in the BDNF mediated improvements in executive function, specifically for participants over 70 years old [57]. The increase in BDNF level after PE was also found to correlate with the increase in local gray matter volume [65], changes in hippocampal volume [12], and changes in reaction time [74]. IGF-1 exhibits parallel roles in structural changes in the brain and cognitive functions, and it was demonstrated to correlate with hippocampal volume [59] and neurocognitive performance [59,69,70]. Furthermore, CTSB was also identified to be positively correlated with cognitive functioning [54,61], while an increase in irisin has recently been detected to be relevant to certain memory tests [73].

4.2. Acute and Chronic Effects of PE on Exerkine Levels in Healthy Humans and Animals (The Reporting Sequence of Exerkines According to Initial A–Z)

Our meta-analysis results reveal that both acute and chronic exercise increased the levels of the BDNF in older adults (Figure 2). Again, other studies in healthy adults investigating acute response [45,49] and chronic response [65,72,75] also report a consistent result of exercise increasing the BDNF. However, a research team recruited physically active adults, but no difference was found in serum BDNF following moderate-intensity cycling [46]. Additionally, another team conducted a single session of exercise protocol with low-intensity cycling for 30 min and middle-intensity cycling for 15 min, and a trend with a decrease in the BDNF was observed in both [47].

From the perspective of animal experimentation performing acute PE, as shown in Table 2, a significant elevation of the BDNF was found in the hippocampus at both mRNA and protein levels. Fourteen studies in rodents analyzed the changes in mRNA level of the BDNF in the hippocampus by short-term voluntary exercise (Table 2). Of these, twelve studies performed aerobic exercise, and one study was resistance training [96]; all reported upregulation of the BDNF in adult rats, while one study found no significant change in the BDNF in Fischer 344 old-aged rats [85]. At the protein level of the BDNF in the hippocampus during short-term exercise, all exercise protocols used aerobics except one that was resistance training [96]; they all reported upregulation in BDNF except for

one experiment that showed a different result in adolescent rats [89]. Five of the studies in Table 2 consistently showed that long-term voluntary exercise upregulated the mRNA and protein levels of the BDNF in the hippocampus among adolescent and adult rats. Furthermore, other trials found consistency on ≥4 weeks of voluntary exercise, reporting a significant increase in the mature BDNF and pro-BDNF in adult rats, as shown in Table 2.

CTSB and FGF21 levels among young adults were both significantly increased by a single session of HIIT and high-intensity aerobic exercise [38]. Likewise, 4 weeks or more of aerobic exercise led to a significant elevation of CTSB in adolescents (animal trail, [61]), young adults [61], and older adults [54]. However, no difference was seen in either CTSB or FGF21 among children after conducting a 90 min combined exercise [71]. GH was one of the exerkines examined in this review. All included trials consistently reported increased GH levels following both acute and chronic exercise [41,48,64,69].

As with the BDNF, IGF-1 levels were observed to be elevated in older adults after both acute and chronic exercise. Moreover, in a study that was excluded from the present meta-analysis because of a low weighting, a significant boost of IGF-1 was detected in children after 16 weeks of taekwondo training [76]. Likewise, an upregulation of serum IGF-1 by voluntary exercise was discovered in an animal experiment [84]. Furthermore, although short-term voluntary exercise significantly increased the mRNA level of IGF-1 in the hippocampus in adult rats [82], it downregulated the protein level of IGF-1 [84].

As for myokine IL-6, a recent study has demonstrated that performing resistance training twice a week for three months led to a significant rise in IL-6 among active older adults [70]. Irisin is another member of the myokines family; among acute exercises, no significant changes in irisin were found in young adults after performing HIIT or aerobic exercise [14], but irisin was found to be significantly higher compared to baseline in older adults following HIIT exercise [43]. Also, among older adult participants, Tai Chi practice, combined exercise, and folk-dance training over three months significantly elevated irisin [62,73]. Moreover, at the mRNA level in the hippocampus of rodents, two weeks of voluntary exercise conducted an upregulation of FNDC5 (irisin) in C57BL/6 rats [97]. The review also included klotho, kynurenine, and TNF-α as exerkines, but PE did not significantly affect their levels [52,54,70]. Lastly, a study reported an increase in VEGF levels in young adults after a single session of aerobic exercise [42]. Similar findings were observed in both children [76] and older adults [75] after four months of a taekwondo program intervention. Nevertheless, three months of moderate-intensity interval running did not change VEGF levels in older adults [59]. In animal models, plasma VEGF was upregulated in Wistar rats after two weeks of voluntary exercise [102]. However, no changes in VEGF protein levels were observed in brain regions such as the hippocampus or striatum [102].

4.3. Subgroup Analysis

We executed subgroup analysis for the BDNF and found subgroup effects for age and type of exercise, indicating that the BDNF has a higher effect size in combined exercise. A prior meta-analysis reported that exercise-induced elevations in circulating BDNF are influenced by exercise modality and participant characteristics, with aerobic-based protocols generally producing more consistent increases than other forms of training [115]. Our results align with these observations, as exercise type emerged as a significant moderator, particularly in acute interventions, suggesting that the metabolic and neuromuscular demands of the activity are key determinants of BDNF release.

4.4. Exploring the Contributions of Exercise-Induced Changes in Exerkines to Brain Structure and Function

We systematically reviewed and analyzed the response of exerkines to PE in healthy brains (Figure 4). Recent evidence reveals that exerkines can be useful tools for identifying individuals at a high risk of developing diseases [11,116,117], enabling timely interventions. The most reported exerkine among selected studies was the BDNF, followed by IGF-1. IGF-1 plays a crucial role in vascular maintenance and remodeling, and evidence suggests that IGF-1 along with VEGF contribute to the induction of the hippocampal BDNF [118]. Evidence indicates that IGF-1 and VEGF interact with each other to collectively regulate cognitive improvement induced by exercise [111]. Although reductions in the levels of the BDNF and IGF-1 were found to associate with age-related hippocampal dysfunction, memory impairment, and decreased cerebral vascular density and blood flow [119–121], raising the BDNF by exercise seems to alleviate hippocampal deterioration and improve memory [9,120]. Moreover, elevated levels of the BDNF, IGF-1, and VEGF were positively associated with enhanced hippocampal volume, neurogenesis and angiogenesis, which contributes to an increase in cognitive performance among older adults [12,19]. Together, the BDNF, IGF-1, and VEGF are considered key factors in the effects of exercise on learning and memory [119,120,122].

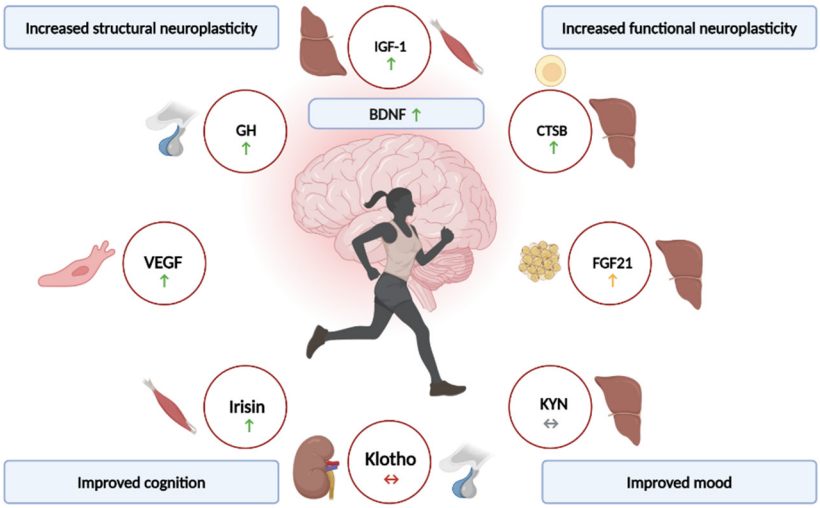


Figure 4. The responses of exerkines to physical exercise in healthy populations and its potential to promote brain health. *BDNF*, brain-derived neurotrophic factor; *CTSB*, cathepsin B; *FGF21*, fibroblast growth factor 21; *GH*, growth hormone; IGF-1, insulin-like growth factor 1; KYN, kynurenine; VEGF, vascular endothelial growth factor. ↑ Strong evidence of increased exerkine after physical exercise; ↑ a likely increase in exerkine after physical exercise; ↔ novel exerkine but limited study finds no post-physical-exercise changes; ↔ potential exerkine but limited study finds no post-physical-exercise changes.

GH, mostly secreted during sleep, is also released from the pituitary gland in response to PE [123]. Decreased levels of GH were found to be associated with age-related sarcopenia [124]. Moreover, it was reported that all effects of GH on cognition are mediated by the induction of IGF-1 synthesis [117], and some studies even indicate GH has a direct effect on cognition [117,123]. It is noteworthy that GH appears highly sensitive to the response to PE, as post-exercise increases in GH were reported in all included studies, regardless of whether the exercise was of low intensity, such as resistance exercise.

FGF21 has been identified as a liver-produced hormone secreted by adipose tissue and skeletal muscle and has received widespread attention for its multifaceted role in metabolic regulation. Evidence for a mediated effect of FGF21 on inducing brain plasticity is unclear, but a study reported a direct neuroprotective effect on neurons [21]. In addition, an animal

experiment found that peripheral FGF21 could cross BBB, suggesting a potential central action of FGF21 [21], which was also detected in human cerebrospinal fluid [125]. Notably, the exercise-induced increase in FGF21 may be regulated by exercise intensity [38]. Irisin (also known as FNDC5) is a hormone generated during PE, contributing to thermogenesis and energy expenditure. Beyond its metabolic effect as FGF21, irisin plays a significant role in brain health [126]. For instance, short-term voluntary endurance exercise increased hippocampal BDNF gene expression by increasing intrinsic irisin expression in mice neurons or plasma irisin [97,127]. Moreover, in a mouse model of Alzheimer's disease (AD), the administration of irisin improved synaptic plasticity and memory function [128,129]. The human experiments of these studies also demonstrate a significant elevation of irisin following long-term physical exercises among older adults [62,73]. Another exerkine, CTSB, was evidenced by traversing through BBB to augment BDNF production, enhancing neurogenesis, memory and learning [20]. Additionally, running led to a significantly upregulated muscular expression of the CTSB gene in mice, coinciding with increased plasma CTSB [61]. These findings in rodents are corroborated by evidence of increased levels of CTSB in rhesus macaques (performing five sessions per week) and in humans (performing three sessions per week) after over 4 months of running [54,61].

In this review, IL-6, klotho, kynurenine, and TNF-α were each reported in only one study. IL-6 and TNF-α are cytokines involved in inflammation, metabolism and immune responses. In AD transgenic mice, inhibited glial cell activation and down-regulated IL-1β, IL-6, and TNF-α caused by the BDNF/NF-κB pathway reduced neuro-inflammation, ultimately protecting memory function [130]. Despite IL-6 being the first myokine to be discovered [11], there is a dearth of research concerning its link with brain mitochondria. Given the demonstrated direct control impact of IL-6 treatment on the mitochondrial dynamics of skeletal muscle [131], further research is essential to investigate its potential effects on the mitochondrial bioenergetics and other functional controls in the brain [132]. Regarding klotho, it is an anti-aging protein associated with resilience to neurodegenerative disease [133], and it has recently been demonstrated that it may be a novel exerkine [134]. Although emerging research suggests that physical exercises lead to upregulation of klotho [134,135], it lacks examination in conjunction with exercise interventions [54], especially in healthy populations. Lastly, kynurenine was mentioned in our included studies, which is one of the products of tryptophan metabolism and is generally secreted in the liver [20]. Its metabolism is known to produce either neuroprotective or neurotoxic substances in the brain [20]. Kynurenine can cross the BBB [22] and high levels of kynurenine were observed in people with depression [136]. Evidence suggests that physical exercises increase muscle expression in kynurenine aminotransferase, which converts neurotoxic kynurenine in the bloodstream to neuroprotective kynurenic acid, thereby reducing depressive symptoms [20]. A recent study suggests that kynurenine may be a surrogate biomarker for neurodegeneration and cognitive decline, and it was found that serum kynurenine decreased not only in the performing 12 weeks of resistance training group but also in the control group [70]. Nonetheless, kynurenine is at least starting to be noticed more in sports science.

4.5. Strengths and Limitations

Mechanistic insights derived from animal models should be regarded as hypothesis-generating and require confirmation in humans; accordingly, these findings are kept separate from the quantitative analysis and are not used to draw clinical inferences.

To our knowledge, this is the first meta-analysis of PE on IGF-1 response in healthy populations. Further, we systematically reviewed the effects of exercise-induced exerkine changes on brain health. This review comprises healthy populations of all ages, involving

both humans and animals, and discusses the contributions of exerkines and exercise-induced changes to brain structure and function to make these findings more generalizable. However, this review has limitations. For instance, in our meta-analysis, while ELISA was used in more than 90% of trials for testing the BDNF, IGF-I was determined by various techniques. This may lead to bias in the effect size of IGF-1. In addition, the age subgroup definitions were constrained by the available study populations, the findings may not be generalizable across all age groups, and the sample sizes for gender-specific subgroup analysis were insufficient, particularly for acute intervention studies. Moreover, the current evidence is the reliance on peripheral exerkine levels as biological proxies for brain health. While these markers provide insight into the molecular response to exercise, they do not inherently reflect direct functional or clinical brain outcomes. Furthermore, the translational gap between rodent models and human physiology represents a significant limitation. While animal studies provide direct access to brain tissue, the biological response to exercise may differ significantly in humans due to genetic and lifestyle complexities. Future research should integrate neuroimaging or cognitive assessments to better bridge the gap between systemic molecular changes and actual brain health improvements.

5. Conclusions

In summary, we systematically reviewed and analyzed the response of exerkines across healthy populations of all ages. The present meta-analysis reveals that along with the BDNF, IGF-1 levels also increase after both acute and chronic exercise in older adults. These findings suggest that exercise-induced exerkine fluctuations may serve as valuable biological proxies for monitoring the systemic physiological environment associated with brain health. Beyond the BDNF, it may be beneficial for future research to consider integrated panels of exerkines (such as IGF-1, CTSB, or VEGF) to characterize the molecular response during PE. Future studies are warranted to explore the impact of various exercise modalities, such as resistance training and HIIT, given the preliminary evidence of exerkine responses observed in this review. In addition, these findings should not be interpreted as universal exercise prescriptions. Especially in older populations, exercise intensity and modality must be individualized based on functional status, clinical screening, and supervision to ensure safety and tolerability.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/sci8040084/s1, S1 = Full search strategy; S2 = Complete reasons for exclusion from each study; S3 = summarizes the methodological quality according to the PEDroScale; S4 = The publication bias risk and sensitivity analysis results for the BDNF; S5 = The publication bias risk and sensitivity analysis results for the IGF-1; S6 = By means of meta-regression analysis, Supplementary Materials S6 illustrates participant characteristics, experimental methods, and exercise protocols which are the factors comprising heterogeneity; S7 = Includes the quality of evidence (GRADE system) for evaluating the response of exerkines after PE which was classified as moderate quality.

Author Contributions: S.T., R.P.-C. and M.G.-G. were responsible for the conception of the study. S.T. wrote the initial version of the manuscript, participated in the literature search, study selection, data extraction, and analysis, and created the figures and tables. C.Q.-G. and M.P.-R. interpreted the data. R.P.-C. resolved any disagreements. R.P.-C., E.G. and M.G.-G., participated in the review and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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