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Review

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Systematic Review

Exploring the Effect of Acute and Regular Physical Exercise on Brain-Derived Neurotrophic Factor Levels in Individuals with Obesity: A Comprehensive Systematic Review and Meta-Analysis

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Abstract: This investigation aimed to explore the impact of acute and regular physical exercise on Brain-Derived Neurotrophic Factor (BDNF) levels in individuals with obesity. Using the Population, Intervention, Comparator, Outcome, and Study design (PICOS) approach, the inclusion criteria were defined as follows: i) population - individuals with overweight or obesity of any age or gender; ii) intervention - acute or chronic interventions involving aerobic or anaerobic methodologies; iii) comparator - for acute effect studies, pre- and post-evaluations served as comparators, while interventions included at least one experimental group or the inclusion of a control group; iv) outcome - BDNF variability concerning the applied methodology; v) study design - restricted to experimental studies exclusively. Conducted in August 2022, the searches were carried out on PubMed, Academic Search Complete, and Web of Science. The risk of bias was assessed using the Risk of Bias in Non-randomized Studies (RoBANS) tool. Out of 98 potentially relevant articles, 16 met the eligibility criteria, encompassing 23 trials. Substantial heterogeneity was observed for both acute ($I2 = 80.4\%$) and long-term effects ($I2 = 88.7\%$). Additionally, RoBANS analysis indicated a low risk of bias for the included studies. The study's findings revealed a significant increase in the concentration of circulating BDNF in individuals with obesity compared to the control group following acute exercise. However, such an effect was not evident in the context of long-term physical exercise, with a small effect size ($ES = 0.49$) recorded in the latter scenario. The observed significant increase in BDNF levels post-acute exercise suggests a potential acute response mechanism contributing to the intricate interplay between exercise and neurotrophic factors in this population. Nevertheless, the absence of a similar effect in the context of long-term physical exercise implies a potential adaptation or ceiling effect. These findings underscore the importance of considering both the duration and nature of exercise interventions when exploring the neurobiological responses associated with obesity and exercise. The study provides valuable insights for future research and clinical implications in understanding the nuanced relationship between exercise, neurotrophic factors, and obesity.

Keywords: obesity; BDNF; physical exercise; meta-analysis

1. Background

The World Health Organization (WHO) stated that, worldwide, obesity has nearly tripled since 1975 [1]. Despite being deemed preventable, the ramifications of overweight and obesity are pervasive, impacting almost 60% of adults and nearly one in three children, with 29% of boys and 27% of girls affected, within the WHO European Region. Currently, obesity is considered as disease by several medical institutions (as The American Medical Association, WHO, Obesity Society, among others), and the World Obesity Federation see obesity from an epidemiological model, with an agent affecting the host and producing disease [2]. In fact, it is now clear from long-term follow-up studies, that obesity is related to a greater probability to develop heart diseases, type 2 diabetes mellitus, some cancers, dementia, osteoarthritis, among others [3–6]. Recently, attentions have been given to the link between obesity and neurobiological impairments, since the high levels of dysfunctional adipose tissue observed in patients with obesity population may aggravate metabolic abnormalities, which increase the risk of mood disorders as depression [7,8] and affect the balance of energy expenditure control [9,10]. Indeed, the brain-derived neurotrophic factor (BDNF), which is a protein that has a significant role in the energy homeostasis of body fluids and blood pressure in humans [11], registered significantly lower levels in the patients with obesity [7,12]. Reduced satiety and hyperphagia manifest as discerning features of BDNF deficiency, providing a plausible rationale for fat accumulation. This phenomenon is undeniably associated with the pivotal role of BDNF in the intricate regulation of dietary intake [13]. Furthermore, diminished levels of circulating BDNF have been ascertained in individuals diagnosed with type 2 diabetes [14]. Notably, an inverse correlation has been established between peripheral BDNF concentration and key anthropometric parameters, such as body mass index (BMI), in both pediatric and adult populations [15]. Additionally, in adult males, a negative relationship has been identified between peripheral BDNF levels and fat mass [16].

BDNF is a member of the neurotrophin family and exhibits abundant expression within the hippocampus and cerebral cortex [17,18]. It is mainly produced by the central nervous system, but also by peripheral tissues [19,20], in immune cells, adipocytes, endothelial cells, and monocytesand also by skeletal muslces during contraction [21]. Thus, its levels are detectable in different tissues including brain and blood (6–8 do 4). The significance of its role is intricately tied to its regulatory influence on synaptic activity, neurotransmission, and plasticity across various cohorts of mature neuron [22,23]. This impact extends to neurological development, synaptic plasticity, as well as the processes of learning and memory [17,24].

Physical exercise has been shown to be a way to improve the BDNF concentration in our body, thus inducing brain plasticity and cognitive enhancement [25,26]. In a general context, physical exercise broadly elicits the release of neurotransmitters and neurotrophins in an activity-dependent manner. This acute stimulation not only potentiates neural function but also initiates a cascade of events that actively contribute to the promotion of structural and functional plasticity within the brain. [27–29]. Empirical evidence has established that physical exercise induces an elevated rate of mitochondrial respiration and cerebral oxygen consumption[30]. This physiological response engenders several advantageous outcomes, including heightened levels of BDNF[31–33] and enhanced functionality of the prefrontal cortex in individuals without pre-existing health condition [34]. Nonetheless, the comprehensive inflationary processes associated with obesity may impede the realization of these aforementioned benefits. Consequently, the main objective of this current review, supplemented by a meta-analysis, is to investigate the influence of physical exercise on BDNF levels in people suffering from obesity. It was hypothesized that physical exercise would have the potential to increase BDNF levels in individuals with obesity, thereby potentially mitigating neurobiological impairments associated with the condition.

2. Method

The present review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [35,36], as well as the PRISMA guidelines specifically designed for scoping reviews (PRISMA-ScR) [37].

2.1. Protocol and Registration

The review protocol was meticulously formulated and pre-released to facilitate transparency in the search methodology. The comprehensive protocol is accessible on the Open Science Framework (OSF) under the registration number DOI 10.17605/OSF.IO/4UM3B, documented on the 10th of August 2022. Interested parties can review the protocol through the following web address: https://archive.org/details/osf-registrations-4um3b-v1.

2.2. Eligibility Criteria

Research articles considered for inclusion in this study must be published in peer-reviewed journals, without imposing any restrictions on the publication date. The eligibility criteria are constructed according to the Participants, Intervention, Comparators, Outcomes, and Study Design (PICOS) framework below [38,39]:

Participants (P): As a criterion for inclusion, studies involving subjects classified as overweight (Body Mass Index-BMI= 25-30 kg/m^2) or obese (BMI= 30 kg/m^2 or greater) according to the BMI have been accepted. The classification employed in the original studies will be disregarded. Studies conducted with participants of both genders and aged 18 years and older, spanning any age within this range, have been included in our meta-analysis. Contrastingly, studies involving athletes or those incorporating subjects with normal body weight have been excluded from our investigation.

Intervention (I): Both acute (single-session) and chronic interventions (multiple sessions, with no minimum session requirement) employing aerobic or anaerobic methodologies will be included. Studies lacking physical exercise programs or containing only cognitive programs will be excluded.

Comparators (C): In acute effect studies, the comparator will encompass pre- and post-evaluations. For interventions, comparators will involve at least one experimental group or the inclusion of a control group.

Outcomes (O): The primary outcome of interest is Brain-Derived Neurotrophic Factor (BDNF) variability, with a focus on the methodology applied during the session or sessions.

Study Design (S): Only experimental studies, whether acute or interventions, and whether randomized or non-randomized, will be considered for inclusion [38,39].

2.3. Information Sources

The current review involved searching the following databases on the same day (05/08/2022): (i) PubMed; (ii) Academic Search Complete; and (iii) Web of Science. The search encompassed files up to the present year, with no lower limit. Additionally, a manual search was carried out to identify potentially relevant articles not covered in the automated searches, including sources such as Google Scholar and ResearchGate. The manual search focused on: (i) scrutinizing the reference lists of included full-texts to identify potentially relevant titles; (ii) reviewing abstracts for adherence to inclusion criteria; and, if necessary, (iii) revising the full-text. Furthermore, errata/retractions were examined to ensure the accuracy of the included articles [37].

2.4. Search Strategy

The search strategy employed Boolean operators AND/OR without applying any filters or limitations (e.g., date, study design) to enhance the likelihood of identifying relevant studies [40]. The primary search strategy comprised the following terms:

"BDNF" OR "brain-derived neurotrophic factor"
AND
"aerobic*" OR "HIIT" OR "high intensity interval training" OR "anaerobic*"
AND
"obesity" OR "overweight"
The complete search strategy [40] is detailed in Table 1

Table 1. Full search strategy for each database.

Database	Specificities of the databases	Search Strategy
PubMed	None to report	("brain derived neurotrophic factor"[MeSH Terms] OR ("brain derived"[All Fields] AND "neurotrophic"[All Fields] AND "factor"[All Fields]) OR "brain derived neurotrophic factor"[All Fields] OR "bdnf"[All Fields] OR ("brain derived neurotrophic factor"[MeSH Terms] OR ("brain derived"[All Fields] AND "neurotrophic"[All Fields] AND "factor"[All Fields]) OR "brain derived neurotrophic factor"[All Fields] OR ("brain"[All Fields] AND "derived"[All Fields] AND "neurotrophic"[All Fields] AND "factor"[All Fields]) OR "brain derived neurotrophic factor"[All Fields])) AND ("aerobic*"[All Fields] OR "HIIT"[All Fields] OR ("high intensity interval training"[MeSH Terms] OR ("high intensity"[All Fields] AND "interval"[All Fields] AND "training"[All Fields]) OR "high intensity interval training"[All Fields] OR ("high"[All Fields] AND "intensity"[All Fields] AND "interval"[All Fields] AND "training"[All Fields]) OR "high intensity interval training"[All Fields]) OR "anaerobic*"[All Fields]) AND ("obeses"[All Fields] OR "obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields] OR "obesities"[All Fields] OR "obesity s"[All Fields] OR ("overweight"[MeSH Terms] OR "overweight"[All Fields] OR "overweighted"[All Fields] OR "overweightness"[All Fields] OR "overweights"[All Fields]))
Academic Search Complete	Search for title and abstract also includes keywords	"(BDNF OR brain-derived neurotrophic factor) AND (aerobic* OR HIIT OR high intensity interval training OR anaerobic*) AND (obesity OR overweight)
Web of Science	Search for title and abstract also includes keywords and its designated "topic"	BDNF OR brain-derived neurotrophic factor (All Fields) and aerobic* OR HIIT OR high intensity interval training OR anaerobic* (All Fields) and obesity OR overweight (All Fields)

2.5. Selection Process

The initial phase of the study involved a meticulous screening process conducted by two authors, namely HC and AFS, who independently evaluated the titles and abstracts of the retrieved records. Following this initial screening, the same authors independently assessed the full texts of the gathered literature. Discrepancies that arose between these two authors were subjected to thorough discussion in a collaborative reanalysis. In instances where a consensus could not be achieved, a fourth author, EMC, assumed the responsibility of making the final decision. To ensure a comprehensive and unbiased selection process, all co-authors actively participated by sharing their opinions whenever uncertainties arose. This collaborative approach aimed to facilitate a collective decision-making process and enhance the robustness of the study's methodology. Furthermore, the management of bibliographic records was executed with precision using Mendeley, version 3.2.72. This software facilitated the efficient handling of records, including the automatic or manual removal of duplicate entries. The systematic utilization of Mendeley underscored the commitment to maintaining data integrity and streamlining the organizational aspects of the research process.

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2.6. Data Collection Process

The data collection process commenced with AFS as the primary investigator (November 2022), who meticulously gathered the data. To ensure the accuracy and completeness of the collected information, a dual verification process was implemented, involving two co-authors, namely HC and EMC. This collaborative effort aimed to confirm the fidelity of the data through rigorous scrutiny. A specially designed Microsoft® Excel datasheet was employed as the tool for extracting and organizing the data, encompassing key information pertinent to the study[41]. In instances where essential data were absent from the full text of the included studies, proactive measures were taken by author HC, who initiated direct communication with the corresponding authors via email and/or ResearchGate. This communication sought to obtain the requisite information, with an anticipated response time of approximately 10 business days. The systematic extraction of pre- and post-intervention means, coupled with the standard deviation of dependent variables, from the included studies was methodically carried out using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) [41]. In situations where studies reported data in formats other than means and standard deviations—specifically, presenting values such as median, range, interquartile range, or standard error—a methodically standardized conversion procedure was systematically implemented, strictly adhering to established recommendations[42–44]. The statistical analysis of diverse data formats employed the Comprehensive Meta-Analysis Software, Version 2, developed by Biostat in Englewood, NJ, USA. This software was chosen for its versatility in handling various data structures inherent in the included studies [45]. In instances where the required data were not transparently or exhaustively reported in the literature, the authors of the respective studies were engaged through direct communication to seek clarification. This proactive approach aimed to enhance the accuracy and completeness of the dataset under consideration. Following a standard protocol, if no response was received from the authors after two attempts, with a 72-hour waiting period between attempts, or if the authors were unable to provide the requested data, the corresponding study outcome was deemed ineligible for further analysis. Moreover, when data were visually presented in figures without accompanying numerical values, a validated software tool, WebPlotDigitizer, version 4.5 (https://apps.automeris.io/wpd/), was employed. This software, validated with a correlation coefficient ($r = 0.99$, $p < 0.001$) [46], facilitated the extraction of numerical data from the graphical representations. The extraction process was spearheaded by one author, AFS, with another author, HC, responsible for confirming the accuracy of the extracted data. Any discrepancies between the two authors, such as disagreements on mean values for specific outcomes, were judiciously resolved through consensus with a third author, ensuring the reliability and consistency of the data extraction process throughout the analytical phase[47].

2.7. Data Items

The primary outcomes of interest were systematically extracted from each study, encompassing a comprehensive set of information categories:

Descriptive characteristics of study participants, including age, sex, and weight, were meticulously documented to provide a contextual understanding of the study population.

Context-related information played a pivotal role in the data extraction process and included, though was not restricted to, the presence of other clinical complications such as diabetes and hypertension, among others.

Methodological-related details were integral to the analysis and included information on the specific physical exercise protocols employed in the studies. This encompassed details such as the type of exercise (aerobic or anaerobic), as well as the number, volume, and intensity of the exercise sessions.

The main outcome of interest, namely the changes in BDNF in response to the prescribed physical exercise protocols, formed the core focus of the data extraction process. Variations in BDNF levels, whether indicative of increases or decreases, were systematically recorded to discern the effects of different exercise methodologies.

In addition to the aforementioned categories, supplementary information was gathered, including citation details, the publication year, and any potential competing interests declared by the authors.

2.8. Study Risk of Bias Assessment

The evaluation of the risk of bias within each study was a rigorous process conducted independently by two authors, namely EM and AFS. In instances where discrepancies emerged between the two assessors, a collaborative reanalysis was undertaken to resolve differences. In instances where a consensus could not be attained, a third author, RRC, assumed the responsibility of making the final decision, ensuring a robust and impartial assessment. The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) was employed as the standardized instrument for evaluating the risk of bias in the included studies [48]. This tool has demonstrated moderate reliability, as well as trustworthy feasibility and validity [48], making it a suitable choice for the present analysis. The RoBANS framework encompasses six pivotal domains: participant selection, confounding variables, exposure measurement, outcome assessment blinding, handling of incomplete outcome data, and avoidance of selective outcome reporting[48]. Each of these domains was systematically assessed, and the risk of bias within each domain was classified as low, high, or unclear. The utilization of the RoBANS tool, in conjunction with a meticulous and independent assessment by multiple authors, underscores the commitment to a robust evaluation of the risk of bias in the included non-randomized studies.

2.9. Data Management and Synthesis Methods

The analytical approach adhered to a previously established methodology, as outlined in references [49,50], wherein the analysis and interpretation of results were undertaken only when a minimum of three studies provided both baseline and follow-up data for the same outcome measure. The effect size (ES), denoted by Hedge's g, was computed for each outcome measure within the experimental groups by utilizing pre- and post-exercise mean values in conjunction with standard deviations (SD)[42,43]. Standardization of data involved the utilization of post-intervention SD values. A random-effects model was employed to accommodate variations between studies that might influence the impact of interventions on BDNF response [51,52]. Effect sizes were presented with 95% confidence intervals (CIs) and interpreted as follows: <0.2, trivial; 0.2–0.6, small; >0.6–1.2, moderate; >1.2–2.0, large; >2.0–4.0, very large; >4.0, extremely large [52]. The assessment of heterogeneity was conducted using the I^2 statistic, with low heterogeneity characterized by values <25%, moderate heterogeneity when values fell between 25% and 75%, and high heterogeneity observed with values >75% [53]. The risk of bias was evaluated utilizing the extended Egger's test [51]. In instances where bias was identified, the trim and fill method was applied, with L0 serving as the default estimator for missing studies [54,55]. All statistical analyses were performed using Comprehensive Meta-Analysis software (version 2; Biostat, Englewood, NJ, USA)[45]. Statistical significance was set at $p \leq 0.05$. Moderators associated with acute or interventional studies, physical exercise frequency, and type were considered in cases where two or more studies provided relevant data, enhancing the depth of the analysis and interpretation of results.

3. Results

3.1. Study Identification and Selection

The initial phase of the literature search yielded a total of 98 titles, which were systematically managed using the EndNote™ reference manager software (version 20.2, Clarivate Analytics, Philadelphia, PA, USA). Subsequent to the removal of duplicates, totaling 35 titles, through an automated or manual process, the dataset was refined to 63 unique titles. These were then subjected to a screening process based on their relevance, involving an assessment of the title and abstract. This screening led to the exclusion of 32 titles. The remaining 31 titles underwent a thorough evaluation in their full-text versions, resulting in the exclusion of an additional 15 studies for various reasons.

Specifically, one study focused on pregnant individuals, five studies did not incorporate physical exercise and were merely report-based, one study constituted a review paper, and eight studies were excluded due to issues related to the outcome measure. In the latter case, one study evaluated proBDNF instead of mBDNF, while in the remaining eight studies, no pertinent data were available in the manuscripts, and attempts to obtain information from the au-thors were unsuccessful. Following this meticulous selection process, 16 studies remained eligible for data extraction and subsequent analysis. This final set of studies formed the basis for the comprehensive examination and synthesis of data to address the research objectives (Figure 1)
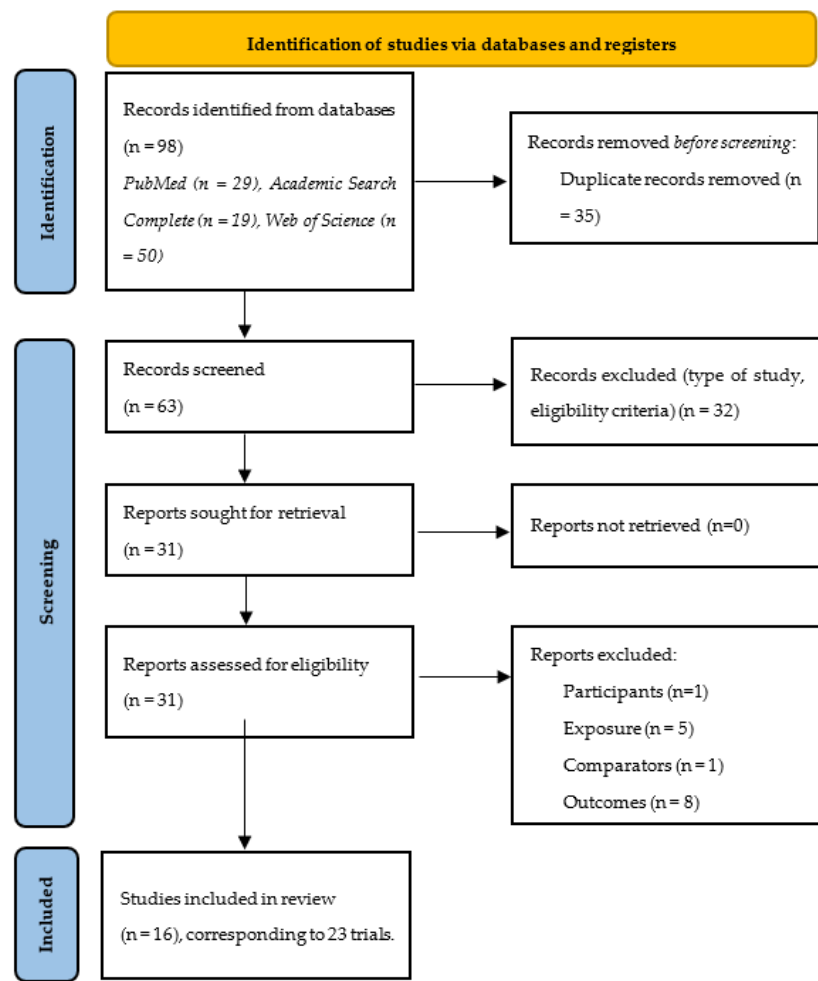
Figure 1. PRISMA 2020 flow diagram.

3.2. Study Characteristics and Context

The characteristics and contexts of studies showing the effect of acute and regular exercise on BDNF are shown in Tables 2–7.

Table 2. Characteristics of the included studies for acute effect on BDNF level (N: 3, 6 trials).

Study	Study design	Population (n)	Sex	Sample characteristics	Mean age (years)	BMI (kg/m²)	Training Status
Dominguez-Sanchez 2018a,b,c [56]	RCT (parallel-group	51 Overweight adults (BMI ≥25 and ≤30 kg/m²)	Men	-HIIT group: 14 -RT group: 12 -CT group: 12	- HIIT group: 24.5±3.7	-HITT group: 27.4±1.7	Physically inactive

Study	Design	Participants	Sex	Groups	Age	BMI	Status
Roh et al. 2017a [57]	RCT (parallel-group	24 obese and non-obese healthy	Men	-Obese group: 12 -Non-obese group: 12	-Non-exercising control: 12 - CT group: 22.2±3.4 -Non-exercising control: 24.7±3.4 -Obese group: 22.9±2.2 -Non-obese group: 22.9±2.2	- RT group: 22.8±3.1 -RT group: 27.8±1.3 -CT group: 28.1±1.2 -Non-exercising control: 28.7±2.0 -Obese group: 29.3±3.0 -Non-obese group: 21.5±1.6	Untrained
Wheeler et al. 2020 a,b [58]	RCT (parallel-group	65 overweight/obese older adults with normal cognitive function	Men and postmenopausal women (≥55 to ≤80 years; BMI ≥25 kg/m² to <45 kg/m²)	-Sitting: 22 - EX+SIT: 23 - EX+BR: 20	67±7 years	31.2±4.1	Sedentary

Abbreviations: RCT= Randomized controlled trial; BMI= Body mass index; HIIT= High intensity interval training; RT= Resistance training; CT= Combined training; EX+SIT =exercise + sitting; EX+BR= exercise + breaks.

Table 3. Characteristics of acute exercise protocols and main results.

Study	Physical Exercise protocol	Comparators	Main outcome	Brand/company name of BDNF kits	Main Results
Dominguez-Sanchez 2018a,b,c [56]	-HIIT group: 5-min warm-up and ended with a 4-min cooldown at a 65% HRmax; HIIT: four bouts of 4-min intervals at 85– 95% HRmax interspersed with 4 min of active recovery at 75–85% HRmax -RT group: initiated with ≈12–15 repetitions per set of six exercises that targeted all the major muscle groups at high intensity included both upper and lower body large-muscle exercises using weight machines (bicep screw curl, triceps extension, dumbbell side lateral raise, military press,	Non-exercising control: Without exercise training	Plasma BDNF (ng/mL)	SPR Biosensors methods, an amino-coupling chemistry kit KAN-50 Coupling Kit (GE Healthcare, Uppsala, Sweden)	-HIIT group: BDNF increased (+6.8 %, p= 0.134) -RT group: BDNF increased (+9.3 %, p= 0.066) -CT: BDNF increased +11.6 %, p=0.029) -CG: BDNF increased +0.6 %, p=0.804) -Compared to the CG, the greatest increase was as follows: CG (+20.8 %), RT (14.3 %), HIIT (9.8 %)

	dumbbell squat, and dumbbell front) CG group: underwent both the HIIT and RT protocols, as described above, in that order.			
Roh et al. 2017a [57]	Acute exercise on the treadmill was applied to both groups. Treadmill run of 20 min at an intensity of 85% of the anthropometrically measured VO2max (Bruce protocol)	-	Serum BDNF (pg/mL)	Human BDNF enzyme-linked immunosorbent assay (ELISA) kit (cat. no. DBD00; R&D Systems, Minneapolis, MN, USA)	-BDNF increased in both groups (obese and non-obese) after acute exercise. -Compared to the non-obese, BDNF increased more in the obese group after exercise.
Wheeler et al. 2020a,b [58]	-EX+SIT: sitting (1 hour), moderate-intensity walking (30 min, the speed was set at 3.2 km/hour, between 65% and 75% of age predicted HRmax), uninterrupted sitting (6.5 hours), that is, 30 min. aerobic exercise, 109±12 bpm, 71%±8% HRmax, 11±2 RPE -EX+BR: sitting (1 hour), moderate-intensity walking (30 min, the speed was set at 3.2 km/hour, HR between 65% and 75% of age predicted HRmax), sitting interrupted every 30 min with 3 min of light-intensity walking (6.5 hours), that is, 30 min. aerobic exercise 109±12 bpm, 71%±8% HRmax, 11±2 RPE.	SIT: uninterrupted sitting (8 hours, control)	Serum BDNF (ng/mL)	Human BDNF ELISA Kits (R&D Systems, Wiesbaden, Germany)	-Serum BDNF was increased in both EX+SIT, +171 (−449 to +791, p=0.03 vs SIT), and EX+BR, +139 (−481 to +759, p=0.045 vs SIT), relative to SIT, −227 (−851 to +396). -No significant differeence was observed between EX+SIT and EX+BR

Abbreviations: RCT= Randomized controlled trial; BDNF= Brain-derived neurotrophic factor; BMI= Body mass index; HIIT= High intensity interval training; RT= Resistance training; CT= Combined Training; CG= Control group; HRmax= maximum heart rate; HRR= Heart rate reserve; VO2max= Maximum oxygen intake; RPE= Rate of perceived exertion; EX+SIT =exercise + sitting; EX+BR= exercise + breaks; SIT= Sitting; bpm= beat per minute; SPR: Surface Plasmon Resonance, Elisa: Enzyme-linked immunosorbent assay.

Table 4. Characteristics of the included studies for exercise intervention on BDNF level (N: 13, 17 trials).

Study	Study design	Population (n)	Sex	Sample characteristics	Mean age (years)	BMI (kg/m²)	Training Status
Cho et al. 2016a [59]	RCT (parallel-group)	16 obese young men with a BMI greater than 25 kg/m².	Men	-EG: 8 -CG: 8	-EG: 22.9±2.5 -CG: 22.3±2.1	-EG: 28.7±2.5 -CG: 27.7±2.2	No participation in regular physical activity programs
Cho et al. 2016b [60]	RCT (parallel-group)	36 obese middle-aged Korean women	Women	-AE group: 12 -AE+CES group: 12 -CG: 12	-AE group: 54.83± 2.79 -AE+CES group : 54.75±2.45 -CG: 54.67±3.03	-AE group: 26.87±2.15 -AE+CES group: 26.90±2.82 -CG: 26.28±1.67	No participation in regular physical activity programs
Damirchi et al. 2014 [61]	RCT (parallel-group)	21 middle-aged men diagnosed with MetS	Men	-EG: 11 -CG: 10	-EG: 54.12±2.77 -CG: 55.57±3.45	-EG: 29.8±3.75 -CG: 27.04±2.89	None of the subjects followed a training program within the past 2 year
Glud et al. 2019ab [62]	RCT (parallel-group)	50 overweight or obese (26 women, 24 men) but healthy individuals	Men and Women	-EXO: 7 women, 9 men -DIO: 8 women, 6 men -DEX: 11 women, 9 men	-EXO: 31.2±2.9-35±1.3 -DIO: 32.4±2.4-37.2±2.7 -DEX: 33.4±2.1-35.1 ± 3.9	-EXO: 31.2±2.9-35±1.3 -DIO: 32.4±2.4-37.2±2.7 -DEX: 33.4±2.1-35.1 ±3.9	Physically inactive
Goldfield et al. a,b,c 2018 [63]	RCT (parallel-group)	282 adolescents with overweight and obesity (84 boys, 198 girls)	Boys and girls	-AE group: n=69 -RT group: n=70 -CT group: n=74 -CG: n=69	-AE group: 15.5±1.3 -RT group: 15.8±1.5 -CT group: 15.5±1.3 -CG: 15.6±1.3	-AE group= 34.6±4.2 -RT group= 35.3±4.8 -CT group= 34.5±4.1 -CG= 34.3±5.0	Irregularly active
Gyorkos et al. 2019 [64]	RCT (parallel-group)	12 obese with MetS	Free-Living Individuals	-CRPD-Sed: 5 -CRPD-Ex: 7	40.9±20.2 years of age	-	Sedentary (defined as not engaged in physical activity at least 3 days/week for three months)

Abbreviations: RCT= Randomized controlled trial; BDNF= Brain-derived neurotrophic factor; BMI= Body mass index; MetS=Metabolic syndrome; EG= Exercise Group; RT= Resistance training; CT= Combined Training; CG= Control group; EXO= Exercise-only; DIO= Diet-only; DEX= Diet and exercise; AE= Aerobic exercise; CES=Cranial electrotherapy stimulation; CRPD-Sed= Carbohydrate-restricted paleolithic-based diet with sedentary behavior; CRPD-Ex= Carbohydrate-restricted Paleolithic-based diet with high intensity interval training.

Table 5. Characteristics of the included studies for exercise intervention on BDNF level (N: 13, 17 trials) (Continuation of Table 4).

Study	Study design	Population (n)	Sex	Sample characteristics	Mean age (years)	BMI (kg/m²)	Training Status
Lee et al. 2014 [65]	RCT (parallel-group)	26 juveniles (boys = 15, girls = 9)	Boys and girls	-Obesity group (OG, n= 8) -T2DM group (TG, n=7) -CG (CG, n = 11)	-Obesity group= 16.37±0.91 -T2DM group= 15.57±2.14 -CG= 16.45±1.36	-Obesity group= 27.47±2.51 -T2DM group= 23.72±4.47 -CG= 22.35±3.94	Physically inactive
Levinger et al. 2008a [66]	RCT (parallel-group)	49 men (N = 25) and women (N = 24)	Men and women	-HiMF training: 15 -HiMF control: 14 -LoMF training: 10 -LoMF control: 10	-HiMF training: 51.0±7.0 -HiMF control: 51.9±5.8 -LoMF training: 50.3±4.1 -LoMF control : 48.9±7.4	-HiMF training: 31.6±4.6 -HiMF control: 30.3±3.7 -LoMF training: 23.9±3.4 -LoMF control: 23.8±3.0	Physically inactive
Li et al. 2021a,b [67]	RCT (parallel-group)	29 (18 males and 11 females) older adults	Male and female	-HIIT (group: 10 -VICT group: 10 -CG: 9	-HIIT group: 64.9±3.45 -VICT group: 66.4±4.50 -CG: 63.9±3.95	-HIIT group: 27.8±1.04 -VICT group: 27.7±2.84 -CG: 27.1±1.50	Physically inactive
Osali et al. 2020 [68]	RCT (parallel-group)	44 women with Mets	Women	-MetS exercise+Nano-Curcumin: 11 -MetS exercise: 11 -MetS Nano-Curcumin: 11 -MetS control: 11	62.3±1.23 years	MetS exercise+Nano-Curcumin: 31.24±3.12 MetS exercise: 32.22±2.46 MetS Nano-Curcumin: 29.54±2.67 MetS control: 29.02±1.56	Pysically inactive (<30 min of physical activity or exercise training per day)
Roh et al. 2017b [69]	RCT (parallel-group)	20 healthy	Men	-Obese group:10 -Non-obese group: 10	-Obese group: 23.00±2.36 -Non-obese group: 22.80±2.35	-Obese group: 29.74±3.12 -Non-obese group: 22.00±1.22	Physically inactive
Saleh et al. 2020 [70]	RCT (parallel-group)	60 subjects with age range of 8 to 12 years old		-Obese experimental group: 15 -Obese control group: 15 -Normal weight experimental group: 15 -Normal weight control group: 15	-Obese experimental group: 10.13±1.35 -Obese control group: 9.80±1.32 -Normal weight experimental group: 9.80±1.47 -Normal weight control group: 9.86±1.30	Body fat (%) -Obese experimental group: 27.33±0.67 -Obese control group: 27.03±0.69 -Normal weight experimental group: 6.74±0.35 -Normal weight control group: 6.79±0.45	Participants who enrolled in the elementary level of gymnastics

Zibinaite et al. 2019 [71]	RCT (parallel-group)	26 overweight and obese participants	Women	EG: 13 CG: 13	EG: 44.2±8.7 CG: 44.1±5.8	EG: 31.9±3.4 CG: 32.5±3.6	Women with a sedentary lifestyle (regular exercise ≤1 h/week)

Abbreviations: RCT= Randomized controlled trial; BDNF= Brain-derived neurotrophic factor; MetS=Metabolic syndrome; T2DM= Type 2 diabetes mellitus; HiMF= number of metabolic risk factors ≥2; LoMF= number of metabolic risk factors ≤1; HIIT= High intensity interval training; VICT = Vigorous-intensity continuous training; EG= Exercise group; CG= Control Group.

Table 6. Characteristics of exercise intervention and main results.

Study	Physical Exercise protocol	Comparators	Main outcome	Brand/company name of BDNF kits	Main Results
Cho et al. 2016a [59]	EG had undergone the supervised treadmill running exercise [70% of the HRR, 40 min each] sessions 3 times a week for 8 weeks	CG just maintained their usual lifestyles	Serum BDNF (ng/mL)	A human BDNF ELISA Kit (R&D Systems, Minneapolis, MN, USA).	After intervention, BDNF increased significantly only in EG (20.56 %)
Cho et al. 2016b [60]	The AE group was subjected to three sessions of 40-minute treadmill running a week for 8 weeks. The program consisted of 10-minutes of warm-up stretching before the exercise and 10-minutes of cool-down stretching after the exercise. Exercise intensity of treadmill running was set at 70% of HRR determined using Karvonen's formula.	CG maintained their own lifestyles with no intervention.	Serum BDNF (pg/mL)	A human BDNF ELISA Kit (Cat. no. DBD00; R&D Systems, Minneapolis, MN, USA)	Serum BDNF levels were significantly increased in the AE group compared to CG (p <.05).
Damirchi et al. 2014 [61]	The participants followed a 6-week aerobic training Programs (3 sessions per week; 25-40 minutes walking, running by 50%-60% of VO₂peak adjusted by heart rate determined by a graded exercise test. There were 20 minutes for warm-up and calisthenics at the beginning of each session and also a 10-	The CG was asked not to change their sedentary lifestyle during the study	Serum BDNF (pg/mL)	A human BDNF ELISA Kit (R&D Systems, Minneapolis, MN, USA)	High BDNF level in patients with MetS decreased significantly after AE.

Glud et al. 2019ab [62]	minute cool down period at the end. -EXO; 12 weeks of aerobic exercise and isocaloric diet= The exercise consisted of supervised aerobic exercise three times per week with a duration of 60–75 min per training session, an estimated energy expenditure of 500–600 kcal per session, and an intensity of 70% of HRR -DEX; 12 weeks of aerobic exercise in parallel with 8 weeks of VLED (800 kcal/day) followed by a 4-week weight maintenance diet)	DIO; 8 weeks of VLED 600 kcal/day followed by a 4-week weight maintenance diet	Serum BDNF (ng/mL)	Quantikine ELISA Human Free BDNF immunoassay (DBD00, R&D Systems, Abingdon OX14, UK)	EXO: BDNF decreased significantly 22.4% in women, and 22.1% in men DIO: BDNF decreased significantly 29.9% in women, and 4.2% in men DEX: BDNF decreased significantly 32.5% in women.
Goldfield et al. a,b,c 2018 [63]	-AE group: Aerobic group exercised on treadmills, elliptical machines and/or bicycle ergometers (6 months intervention, twice a week, 20–45 min, 65–85% HRmax) -RT group: 6 months intervention, twice a week, RT group also progressed from 20 to 45 min per session, performing 7 exercises using weight machines or free weights, and progressing from 2 sets of 15 repetitions at moderate intensity to 3 sets of 8 repetitions at the maximum resistance that could be moved 8 times (8-RM)) -CT group: aerobic+resistance	The CG received only dietary counselling with no exercise prescription	Serum BDNF (ng/mL)	Human Free BDNF Quantikine ELISA kit, R&D systems, Cat# DBD00)	No significant within- or between-group changes in BDNF level. Although not significant, after 6 months intervention; AE group: (+1.80) RT group: (−2.00) CT group: (−1.70)

Abbreviations: RCT= Randomized controlled trial; BDNF= Brain-derived neurotrophic factor; MetS=Metabolic syndrome; HRR= Heart rate reserve; EG= Exercise Group; AE= Aerobic exercise; CT= Combined Training; CG= Control group HRmax= maximum heart rate; VO_2peak= Highest oxygen uptake; 1RM=1 repetition maximum; EXO= Exercise-only; DIO= Diet-only; DEX= Diet and exercise; VLED= very low energy diet; Elisa: Enzyme-linked immunosorbent assay.

Table 7. Characteristics of exercise intervention and main results (Continuation of Table 6).

Study	Physical Exercise protocol	Comparators	Main outcome	Brand/company name of BDNF kits	Main Results
Gyorkos et al. 2019 [64]	Each session consisted of HIIT on a cycle ergometer, including a 3-min warm-up, 10 x 60s cycling intervals interspersed with 60s of active recovery, ~90% HRmax, and a 3-min cool down, 3 day/week for four-week.	-CRPD-Sed: (<50gCHO)	Serum BDNF (ng/mL)	Human BDNF Elisa Kit (#DBD00, Thermo Fisher Scientific)	-Basal BDNF protein content was significantly increased following CRPD-Sed (+20%; P < 0.05) and CRPD-Ex (+38%; p< 0.05) when compared to baseline. -The addition of HIIT exercise to the diet resulted in a significant increase in circulating serum BDNF when compared to CRPD-Sed.
Lee et al. 2014 [65]	Aerobic exercise was conducted for a total of 40–60 minutes per session at a VO2max of 50~60%, 3 sessions a week, for 12 weeks.	-CG maintained their own lifestyles with no intervention.	Serum BDNF (pg/mL)	A human BDNF Elisa Kit (R&D Systems, Minneapolis, MN, USA)	-There was an increase in BDNF level after 12 weeks of regular aerobic exercise program, only in the obese group.
Levinger et al. 2008a [66]	10 weeks, two sets of 15–20 repetitions at 40–50% 1RM. From weeks 2–10, participants performed each exercise for three sets, 8–20 repetitions, at 50–85% 1RM.	CG: did not perform regular exercise during the study period.	Serum BDNF (pg/mL)	Human BDNF Elisa Kit (Catalog number: DY248; Minneapolis, MN)	-Resistance training had no effect on BDNF levels or other risk factors for MetS.
Li et al. 2021a,b [67]	HIIT: 4 × 3 min at 90% VO2max interspersed with 3 min at 60% VO2max, about 45 min., 3 training sessions per week for 12 week, VICT: 25 min at 70% VO2max, about 45 min.,3 training sessions per week for 12 week	The subjects in the CG lived normally and did not participate in any training	Serum BDNF (pg/mL)	Human BDNF Elisa Kit (Abcam Inc., Cambridge, UK)	-BDNF increased significantly in both HIIT and VICT group. -There was no significant difference between HIIT and VICT in terms of BDNF.
Osali et al. 2020 [68]	Exercise with moderate intensity: Each subject walked or ran at 65–75% HRR on a treadmill for 3×12–17 min, 6 weeks.	continued the regular daily life	Serum BDNF (pg/mL)	Human BDNF Elisa Kits (Adipo Bioscience, USA)	BDNF increased significantly in EG

Roh et al. 2017b [69]	Subjects performed treadmill exercise for 40 min 3 times weekly for 8 weeks at 70% HRR, totally 60 min.exercise program	Non-obese	Serum BDNF (pg/mL)	Human BDNF ELISA Kit (#DBD00; R&D Systems, Minneapolis, MN, USA)	BDNF increased significantly only in obese group, not non-obese group.
Saleh et al. 2020 [70]	45 minutes anaerobic gymnastics exercise including 10-minute warm up, 30- minutes of main exercises, and 5 minutes cool down, 3 times per week for 8 weeks.	Normal weight and obese control groups continued the regular daily life	Saliva BDNF (pg/mL)	Human BDNF PicoKine™ ELISA Kit (Catalog No. EK0307; R&D Systems, Austria)	BDNF increased in obese group (+33.80%, p=0.002), and normal-weight group (+31.36%, p=0.003).
Zibinaite et al. 2019 [71]	Participants underwent 72 supervised aerobic exercise training sessions on cycle ergometers during 6 months, including 3 sessions of training per week. A 50 min aerobic training 80 at an intensity between 60% and 70% of the HRmax was performed.	CG did not undergo any intervention and were instructed to maintain their regular physical activity and diet regime for 6 months	Serum BDNF (pg/mL)	Human BDNF Elisa Kits (Gemini; Stratec Biomedical, Birkenfeld, Germany).	BDNF level remained unchanged (p>0.05)

Abbreviations: BDNF= Brain-derived neurotrophic factor; CG= Control group; HIIT= High intensity interval training; VICT = Vigorous-intensity continuous training; 1RM=1 repetition maximum; HRmax= maximum heart rate; HRR= Heart rate reserve; VO2max= Maximum oxygen intake; CRPD-Sed=carbohydrate-restricted Paleolithic-based diet with sedentary behavior; CRPD-Ex= Carbohydrate-restricted Paleolithic-based diet with exercise. Elisa: enzyme-linked immunosorbent assay; MetS=Metabolic syndrome **Risk of bias in individual studies.**

The Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS) was diligently applied by two independent authors to evaluate potential biases in six distinct do-mains. Notably, the selection of participants posed challenges in several studies, as the recruitment methods were not consistently explained, raising concerns about potential convenience sampling without clear contextual information. However, given that the ma-jority of studies adhered to clinical trial assumptions, the domains of confounding varia-bles, exposure measurements, and blinding of outcome assessments exhibited a low risk of bias. The comprehensiveness of protocols was generally high, with 16 studies provid-ing detailed explanations, while a few studies lacked minor protocol characteristics. One study, in particular, lacked information regarding training load characteristics. Regarding outcome data, biases were identified in some studies (3 at high risk), where explanations for discrepancies in sample sizes from the beginning to the end of the study were not provided. In the overall analysis, the included studies appeared to have a low risk of bias, with none exhibiting a high risk in more than three domains. Despite uncertainties in par-ticipant selection methodologies in some studies, the majority adhered to rigorous clinical trial principles in other key domains, contributing to the overall robustness of the studies. These findings underscore the methodological quality of the included studies in this assessment of bias risk.

3.3. Synthesis of Results

This systematic review with meta-analysis synthesized findings from three studies encompassing a total of six trials, involving 104 participants, to assess the impact of acute exercise on BDNF levels (see Figure 2). The meta-analysis revealed a statistically significant increase in

circulating BDNF levels in individuals with obesity compared to controls (Effect Size, ES: 1.25, indicating a large effect, p < 0.05). However, it is important to note that there were indications of heterogeneity in the results, as evidenced by an I² statistic of 80.4%.

The current study provides a comprehensive summary of findings from 13 studies, encompassing 17 trials and involving a total of 571 participants, to investigate the impact of exercise intervention on circulating BDNF levels (see Figure 3). Contrary to initial expectations, the results revealed that exercise interventions did not yield a statistically significant change in BDNF levels when compared to control groups (p > 0.05). Despite the lack of statistical significance, a small positive effect on BDNF levels was observed in the exercise intervention group (Effect Size, ES: 0.49, indicating a small effect). This suggests a potential trend toward a positive influence of exercise on BDNF levels, even though the effect size is considered small. It is noteworthy that the analysis identified high heterogeneity among the studies investigating the impact of exercise intervention on BDNF levels (I² = 88.7%).

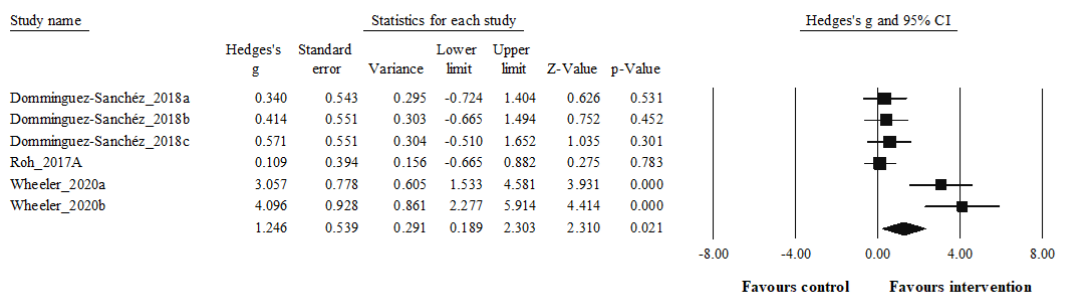| Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI
Domminguez-Sanchéz_2018a	0.340	0.543	0.295	-0.724	1.404	0.626	0.531	
Domminguez-Sanchéz_2018b	0.414	0.551	0.303	-0.665	1.494	0.752	0.452	
Domminguez-Sanchéz_2018c	0.571	0.551	0.304	-0.510	1.652	1.035	0.301	
Roh_2017A	0.109	0.394	0.156	-0.665	0.882	0.275	0.783	
Wheeler_2020a	3.057	0.778	0.605	1.533	4.581	3.931	0.000	
Wheeler_2020b	4.096	0.928	0.861	2.277	5.914	4.414	0.000	
	1.246	0.539	0.291	0.189	2.303	2.310	0.021	

Figure 2. Forest plot illustrating acute exercise-related improvements in BDNF levels in comparison to controls. Forest plot values are shown as effect sizes (Hedges' g) with 95% confidence intervals (CI). Black squares: individual studies. The size represents the relative weight. Black rhomboid: summary value. Mean results: ES = 1.25, 95% CI = 0.19 to 2.30, p=0.021, I2 = 80.4%, N total participants = 104.

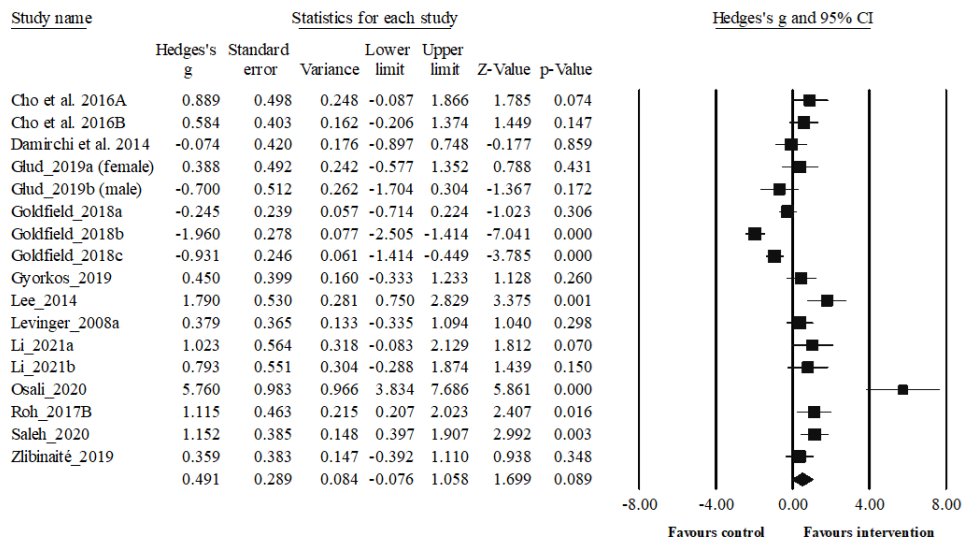| Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI
Cho et al. 2016A	0.889	0.498	0.248	-0.087	1.866	1.785	0.074	
Cho et al. 2016B	0.584	0.403	0.162	-0.206	1.374	1.449	0.147	
Damirchi et al. 2014	-0.074	0.420	0.176	-0.897	0.748	-0.177	0.859	
Glud_2019a (female)	0.388	0.492	0.242	-0.577	1.352	0.788	0.431	
Glud_2019b (male)	-0.700	0.512	0.262	-1.704	0.304	-1.367	0.172	
Goldfield_2018a	-0.245	0.239	0.057	-0.714	0.224	-1.023	0.306	
Goldfield_2018b	-1.960	0.278	0.077	-2.505	-1.414	-7.041	0.000	
Goldfield_2018c	-0.931	0.246	0.061	-1.414	-0.449	-3.785	0.000	
Gyorkos_2019	0.450	0.399	0.160	-0.333	1.233	1.128	0.260	
Lee_2014	1.790	0.530	0.281	0.750	2.829	3.375	0.001	
Levinger_2008a	0.379	0.365	0.133	-0.335	1.094	1.040	0.298	
Li_2021a	1.023	0.564	0.318	-0.083	2.129	1.812	0.070	
Li_2021b	0.793	0.551	0.304	-0.288	1.874	1.439	0.150	
Osali_2020	5.760	0.983	0.966	3.834	7.686	5.861	0.000	
Roh_2017B	1.115	0.463	0.215	0.207	2.023	2.407	0.016	
Saleh_2020	1.152	0.385	0.148	0.397	1.907	2.992	0.003	
Zlibinaité_2019	0.359	0.383	0.147	-0.392	1.110	0.938	0.348	
	0.491	0.289	0.084	-0.076	1.058	1.699	0.089	

Figure 3. Forest plot illustrating exercise intervention-related improvements in BDNF lev-els in comparison to controls. Forest plot values are shown as effect sizes (Hedges' g) with 95% confidence intervals (CI). Black squares: individual studies. The size represents the relative weight. Black rhomboid: summary value. Mean results: ES = 0.49, 95% CI = -0.08 to 1.06, p=0.089, I2 = 88.7%, N total participants = 571.

4. Discussion

The objective of this systematic review with meta-analysis is to understand the short-term and long-term effects of physical activity on BDNF levels in patients with obesity. Our results showed that acute exercise led to a significant increase in the concentration of circulating BDNF patients with obesity compared to the control group. Despite long-term physical exercise, there was no significant increase in BDNF levels when compared to the control group. Although the results were not statistically significant, it was revealed a small effect size of long-term physical exercise interventions on BDNF levels. (ES = 0.49). Our study also found high levels of heterogeneity in both acute effects (I^2 = 80.4%) and long-term effects (I^2 = 88.7%). Finally, the quality of the methodologies used in the included studies was determined to be low risk of bias, with none of the studies exhibiting high risk in more than three of the six evaluated domains.

Acute physical exercise has been shown to be an effective stimulant that arise peripheral BDNF levels [72]. The present study found that acute exercise led to a statistically significant augment in BDNF level compared to the control group (ES: 1.25). This review synthesized the findings of three studies involving 104 participants to specify the impact of acute physical exercise on BDNF levels. This result confirms previous systematic reviews nd meta-analysis studies showing that acute exercise increases BDNF levels in healthy adults [72–75], and older adults [76]. Regarding the included studies, Dominguez-Sanchéz et al. [56] found that acute combine exercise (high-intensity interval exercise and resistance) led to a greater increases (+11.6%, p=0.029) in BDNF levels compared with acute resistance (+9.3%, p= 0.066), and high intensity interval exercises (+6.8%, p= 0.134) in overweight men adults. Likewise, another study notified that acute high-intensity exercise (20 minutes at 85% of VO2max) triggered a rise in serum BDNF levels in inactive adult patients with obesity [57].Additionally, Wheeler et al.[58] (2020) observed that 30 minutes of aerobic exercise (65% and 75% HRmax) performed in the morning hours elevated BDNF levels in inactive elderly men patients with obesity and postmenopausal women. Based on the studies mentioned (3 studies, 6 trials), regardless of the type of exercise, it has been shown that BDNF levels increase in patients with obesity after both acute moderate (1 trial) and high-intensity exercises (5 trials)

Considering the studies mentioned above (3 studies, 6 studies), regardless of the type of exercise (aerobic, resistance and high intensity exercise), it is seen that the BDNF levels of patients with obesity increase after both acute moderate (1 trials), and high-intensity exercise (5 trials). Regarding the studies analyzed, it was concluded that high-intensity exercise protocols were commonly used in patients with obesity, resulting in elevated BDNF levels. The elevation in BDNF levels after acute exercise can be linked to intensity of the exercise. For instance; previous systematic review studies indicated that BDNF levels augmented in a manner dependent on both intensity [74,77], and duration (lasting more than 30 minutes) of the exercise [73]. Furthermore, a recent meta-analysis of 22 studies in healthy adults (aged 20-31 years) with a total of 552 participants noted that greater BDNF levels were observed after acute high-intensity exercise compared to light and moderate-intensity exercise conditions [78].

In literature and our study, several potential mechanisms behind the elevation of BDNF after acute exercise have been proposed, one of which is exercise-induced thrombocytosis. Due to the fact that the most of peripheral BDNF is found in thrombocytes, exercise can lead to a rise in BDNF levels through exercise-induced thrombocytosis, which is thought to occur due to splenic contractions releasing BDNF-rich platelets [79,80]. However, the increase in platelets and peripheral blood BDNF after exercise was reported to be temporary and returned to pre-exercise levels within 15-30 minutes of ceasing physical activity [81]. Despite its temporary nature, it was stated that the increased BDNF response to acute exercise could have the potential to enhance cognitive function by triggering various neuronal processes [82]. Second, the contraction of skeletal muscle during physical activity boosts the manufacture and activity of certain proteins involved in mitochondrial biogenesis, such as PGC-1α, Erra, and FNDC5/irisin. These factors regulate BDNF transcription in the brain and energy metabolism in skeletal and fat tissue [83]. Third, exercise elevates insulin-like growth factor-1 (IGF-1). This hormone has been shown to have a close relationship with an increase in BDNF level in the hippocampus, playing a role in mediating exercise-induced changes in synaptic function and

cognitive plasticity [84]. Lastly, a single high-intensity exercise has been linked to higher levels of brain hydrogen peroxide (H2O2) and Tumor Necrosis Factor -α (TNF-α). These molecules are among the many stimulators of PGC-1α signaling, which in turn increases BDNF synthesis in neurons [85].

Furthermore, BDNF, like leptin, promotes feelings of satiety. Recent studies has shown that it actively controls food intake, regulates body weight, and balances energy at the hypothalamic level [86,87]. According to these studies, the BDNF-producing neurons in the paraventricular hypothalamus were found to limit food intake and serve as an anorexigenic factor, resulting in feelings of satiety. These neurons also improve energy consumption by the way of excitement of thermogenesis in brown adipose tissue. Also, research revealed that mutations in the BDNF gene and its receptor TrkB in mice and humans caused an increase in food consumption, and contributed to the onset of severe obesity [88,89]. Based on these studies, the rise of BDNF levels, which are lower baseline in patients with obesity compared to normal-weight individuals[89–91], following high-intensity exercise may be related to decreased hunger and an increased sense of fullness. This can minimize the likelihood of obesity developing arising from excessive appetite sensation or appetite signal disorder, and in addition, it can make an additional contribution to the treatment of various neuropsychological diseases (especially brain health) accompanying obesity. More mechanisms of neuropsychological disturbance, especially related to the depression state has been summarised by Murawska-Cialowicz et. al.[92]. Moreover, a previous study noted that administering BDNF to mice increased the levels of glucose transporter 4 (GLUT4) in skeletal muscle[93]. This suggests that the possible impact of increased BDNF levels following acute high-intensity exercise on substrate utilization may enhance the management of metabolic disorders related to obesity [94].

Numerous studies indicate that there is communication between organs and that substances in the nature of growth factors, including BDNF, which is one of the most important factors communicating skeletal muscle with brain and adipose tissue, among others, are involved in this communication. Therefore, the term, metabolokine, is used in relation to BDNF, which is a neurokinin, adipokine and myokine [95]. We can think that one of the main mechanisms of BDNF synthesis during very intense exercise, is the production of lactate [La-]. High-intensity exercise is an effort that stimulates anaerobic energy processes, the product of which is a very large increase in the concentration of lactate [La-] that exceeds the anaerobic threshold. Not so long ago it was thought that [La-] was an unnecessary product of anaerobic metabolism. Nowadays, it is known to be a very important substance acting as a transmitter involved in various metabolic processes [96–98]. In the brain [La-] W mediated by monocarboxylate transporters (MCT) [99,100] enters neurons (via MCT2) and astrocytes (via MCT4) supporting, among other things, glucose transport into neurons, their energy metabolism and ion [101].

Current studies indicate that [La-] transport from astrocytes to neurons plays a key role in memory formation [102,103] and may represent a link between exercise and neuroplasticity and BDNF synthesis [97], although the mutual mechanisms are not fully understood. One of them may be the activation by [La-] of various G protein-related receptors, as well as the silent information regulator 1 (SIRT1). With relation to adipose tissue, activation of the PGC1α/FNDC5/BDNF pathway seems to be a convincing one [104]. Lactate can induce the PGC1α/FNDC5/BDNF pathway through activation of SIRT1. Intraperitoneal infusion of lactate in mice was shown to induce SIRT1 activity, thereby enhancing the PGC1α/FNDC5/BDNF pathway, resulting in improved spatial learning and memory retention [105].

FNDC5 (Fibronectin type III domain-containing protein 5) is a precursor protein called irisin, which is an exercise hormone involved in carbohydrate and fat utilization and fat reduction. Expression/secretion of irisin promotes the conversion of white adipose tissue (WAT) into brown adipose tissue (BAT) (browning) as a result of increased expression of UCP-1 (uncoupling protein 1). WAT browning was found to be induced by irisin through p38MAPK and ERK MAPK signaling [106]. A recent study found that lack of irisin is associated with poor adipocyte browning and impaired glucose/lipid levels [107]. The another study shows that irisin concentrations are increased after intense exercise in healthy men [108] as well as in obese subjects in whom aerobic exercise

showed no change in irisin levels [109] which given the common mechanism of action of irisin with BDNF, may potentiate BDNF secretion during exercise.

Chronic physical activity increases BDNF in answer to an acute exercise [75]. Regarding the relationship between long-term exercise intervention and BDNF, this systematic review and meta-analysis summarized the findings of 13 studies comprising a total of 571 participants, regarding the impact of exercise intervention on BDNF levels. The associations between chronic exercise interventions and BDNF is complicated [80]. In the literature, recent meta-analysis studies indicated that peripheral BDNF concentrations significantly increased after exercise intervention in healthy individuals [74,110], older adults [76], individuals with multiple sclerosis [111], and neurodegenerative disorders [112]. Contrary to the studies mentioned, the present study observed that long term exercise did not significantly augment BDNF levels compared to the control group. Although not statistically significant, it was found a small effect size of long-term physical exercise on BDNF levels (ES = 0.49; trivial, p=0.089). Consistent with our study, previous meta-analysis studies demonstrated that chronic exercise had a minimal impact on BDNF level in healthy [73,75] and elderly individuals [113]. The current meta-analysis of included studies showed inconsistent findings considering the effect of chronic physical activity on BDNF level. According to this, it was notified that BDNF level significantly increased [59,60,64,65,67–70], decreased [61,62], and remained unchanged [63,66,71] after exercise intervention in patients with obesity. However, the lack of significant changes in BDNF levels following regular exercise in our meta-analysis could be due to the high heterogeneity in the studies included, which explains the inconsistent results. Moreover, the high heterogeneity could be attributed to differences in the methodology of the included studies, including the characteristics of participants, exercise applications (frequency, intensity, type, time, volume), measurement methods, methodological quality of studies, and type of Elisa kits used. Also, the absence of a significant difference in exercise intervention compared to acute exercise may be related to difficulties in controlling too many variables that may affect the results depending on the duration of the program. In this sense, Fleitas et al. [113] emphasized that some factors should be considered in the lack of significant effects of chronic physical exercise on peripheral BDNF levels. Failure to control participants' nutritional status or energy intake during the study and before blood samples are collected may have a negative impact on BDNF results. When the included studies were examined, it was observed that the energy intake of the participants during the exercise program was not considered in many studies. Conducting more controlled studies in the laboratory environment by applying standardized nutrition programs to the participants during the study may contribute to obtaining more accurate results. Additionally, BDNF levels fluctuate throughout the day due to the diurnal variations of the cortisol and various hormonal fluctuations [114]. Thus, time of the day on both exercise interventions and data collection (blood collection time), and non-standardization of the collection may have a negative impact on BDNF-related measurements [113]. In this context, it is important to conduct quality and randomized controlled studies with larger sample groups, taking into account the energy intake of the participants in order to elevate BDNF in response to exercise intervention in patients with obesity.

The important seems to be also the analytical material type-serum/plasma, sample storage time and centrifugation [115]. The different levels of BDNF are reported in serum and plasma. This can be connected with thrombocytosis mechanism and utilization of BDNF after chronic, intensive or long-lasting exercise. Higher production of growth factors in platelates and utilization of BDNF for reparation and regeneratin of skeletal muscle and nerve fibers at the muscle levels is quite possible mechanism of BDNF reduction in serum and plasma [16,116].

Moreover, in our study, it was revealed that the BDNF level did not differ significantly following the six months of high-intensity [63], and ten weeks of moderate-intensity [66] regular resistance exercises, and 6 months of moderate-intensity aerobic exercise [71]. In literature, studies have shown that resistance exercise had no significant effect on BDNF concentration in both healthy [72,74,110], and elderly [113] individuals. Nevertheless, despite all these, it was seen that the BDNF level increased after regular exercise in many studies included in present study. Regarding the studies in which the BDNF level increased (1 study: moderate aerobic exercise, the other 7 studies: high-

intensity aerobic exercise, a total of 8 studies), it was observed that high-intensity aerobic exercise programs performed for approximately 8-12 weeks were more likely to trigger the increase in BDNF levels. In the light of this information, recent meta-analysis study suggested that moderate and high-intensity aerobic exercise programs (3-5 times a week and 20-60 minutes, 12 weeks) were an effective strategy to increase BDNF levels in adolescents [117]. Considering the all studies mentioned above, it can be said that aerobic exercises are effective in increasing BNDF level compared to resistance exercises. Consistent with this finding, previous studies indicated that regular exercise augmented circulating BDNF, while resistance exercise did not [72,110,113]. This is due to the fact that aerobic exercise is linked to physiological processes that enhance BDNF, including improved endothelial function, insulin sensitivity, and cerebral blood flow [72,80]. The another study by Walsh et al. [80] suggested that high-intensity short-duration physical activities might increase BDNF levels and improve brain health. Subsequently, the same researchers stated that combining aerobic and anaerobic exercise at approximately 60% of VO_2max may have the greatest effect on BDNF elevation due to mechanisms such as cardiovascular changes and lactate release.

The present meta-analysis study has several limitations. One such limitation is the potential confounding effect of age among participants included in the studies analyzed. Unfortunately, due to the small number of studies analyzing exercise-induced changes in BDNF concentrations in obese subjects, subjects of different ages were included in the analysis. Moreover, age-related differences in physiological responses to exercise could impact the magnitude of BDNF upregulation, thereby influencing the overall effect size observed in our meta-analysis. Therefore, future studies with age-stratified analyses could provide more nuanced insights into the relationship between exercise, BDNF, and obesity. Another limitation may be the gender of the subjects. Changes were not differentiated separately for male and female subjects. Older patients may exhibit differential responses to exercise interventions compared to younger individuals, which could influence the observed effects on BDNF levels. Future investigations should consider stratified analyses based on gender, allowing for a more nuanced understanding of how exercise-induced changes in BDNF levels may differ between male and female participants, especially in the context of obesity. Lastly, previous studies on different populations showed that duration of the exercise intervention (weeks) [78,111–113], intensity of exercise [72,80], the weekly volume of the exercise [112] did not significantly affect the circulating BDNF level. Although the studies above do not show a significant effect, the last limitation in our study is that, due to the small number of studies in obese individuals, separate submodular analyzes were not performed to examine the effects of individual components of exercise prescription such as time, intensity, type and frequency on BDNF responses. These components are critical determinants of the physiological responses to exercise, and their nuanced exploration could provide valuable insights into the specific parameters influencing BDNF levels in individuals with obesity. For instance; diverse exercise modalities, such as aerobic, resistance, or combined training may elicit distinct molecular responses, and the variability in exercise interventions could introduce heterogeneity into our meta-analysis. Recognizing this limitation is essential for interpreting our findings and emphasizing the need for more focused investigations into the specific effects of different exercise regimens on BDNF in the context of obesity. Thus, more studies are needed to provide a clearer understanding of which type of physical activity has the greatest impact on BDNF in patients with obesity. By acknowledging these limitations, we aim to provide a comprehensive and transparent assessment of the findings while highlighting areas for future research to address these potential sources of bias and variability. Well designed and quality randomized controlled studies with greater populations are recommended to determine how different exercise configurations may affect BDNF levels in patients with obesity [112].

5. Conclusion

The present meta-analysis represents a pioneering effort in investigating the impact of acute and regular physical activity on BDNF levels, focusing exclusively on individuals afflicted by obesity. This study distinguishes itself by synthesizing findings exclusively from randomized control group studies, thereby contributing a specialized perspective to the existing literature. The principal

objective was to discern whether a single session of exercise or a more sustained physical activity intervention could elicit alterations in BDNF levels in comparison to a control group within the context of obesity. The meta-analysis reveals that a singular episode of exercise induces a noteworthy elevation in BDNF levels among individuals with obesity when juxtaposed with the control group. However, intriguingly, interventions involving sustained physical exercise did not yield a statistically significant alteration in BDNF levels when compared to the control group. Although the observed effect of exercise interventions on circulating BDNF did not attain statistical significance, there was a discernible small-scale impact, underscoring the nuanced nature of the relationship. This investigation underscores the potential utility of both acute and regular exercise regimens in positively modulating BDNF levels in the context of obesity. Given the intricate interplay of BDNF with appetite regulation, neuroplasticity, and cognitive functions, augmenting the diminished basal levels inherent in obesity through non-pharmacological means, such as physical exercise, emerges as a promising avenue for mitigating the condition. Moreover, the potential ancillary benefits extend beyond mere weight management, encompassing the amelioration of psychological comorbidities associated with obesity, including cognitive disorders and depression. Additionally, given the complex processes regulating BDNF levels in tissues, it is challenging to explain the relationship between BDNF and obesity. Therefore, further research is needed to understand the mechanisms of exercise and BDNF regulation in order to develop more effective therapies for obesity and optimize exercise-based treatments. Consequently, the findings of this meta-analysis contribute valuable insights that may inform the development of comprehensive and multifaceted interventions for individuals grappling with obesity, addressing both the physiological and psychological dimensions of the condition.

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