MOLECULAR MECHANISMS OF THE PHYSICAL EXERCISE-INDUCED INCREASE OF BRAIN-DERIVED NEUROTROPHIC FACTOR LEVELS: A SYSTEMATIC REVIEW

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Physical inactivity triggers several metabolic syndromes and influences cognitive function, including the development of dementia. Exercise can help to prevent these negative effects. However, there is currently limited research examining how exercise affects cognitive function through brain-derived neurotrophic factor (BDNF) levels, and the underlying mechanisms remain unclear. The aim of this study was to analyze existing literature on the effect of physical exercise on brain-derived neurotrophic factor (BDNF) levels as a biomarker of cognitive function. Several journal databases, including Scopus, Web of Science, PubMed, and Science Direct, were searched for this study. The study considered several variables, including studies on BDNF, high-intensity exercise, and moderate-intensity exercise published within the last ten years. Articles that did not meet the inclusion criteria (e.g. animal studies) were excluded from this systematic review. Using databases from PubMed, Science Direct, Web of Science, and Scopus, a total of 152 publications were identified. Ten carefully selected, peer-reviewed articles addressed the need for this systemic change. Standard operating procedures for this study were established using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Based on the results of this comprehensive study, it is evident that exercise increases BDNF levels in humans. Although high-intensity exercise is more effective in increasing BDNF levels in humans than moderate-intensity exercise, further research is needed for selection of the optimal physical load required for BDNF expression. Physical exercise is recommended to improve brain development and memory ability.

Keywords: physical exercise; BDNF; health; dementia

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INTRODUCTION

One of the most pressing health problems in the world is Alzheimer's disease which is a serious threat to public health [1]. In 2020, there were about 50 million dementia sufferers globally. Every 20 years, this number will almost double, rising to 82 million in 2030 and 152 million in 2050. The majority of the growth will take place in developing nations [2]. According to the latest World Health Organization statistics 39 million deaths, or 57% of the 68 million deaths globally, were caused by the top 10 causes of death. With 1.8 million deaths, Alzheimer's disease ranks seventh as the leading cause of death [3]. About 25% of dementia sufferers worldwide reside in China, making it the country with the highest number of dementia patients worldwide. This has a significant negative impact on both health and the economy [4].

Dementia shortens life expectancy [3]. The majority of deaths among dementia patients in nursing homes occurs in the advanced stages of the disease before the end stage, with eating and/or drinking issues and pneumonia being the most frequent reasons for death [5]. Issues with respiration or circulation are frequently cited reasons of death in dementia patients [6]. Advanced age, male gender, chronic physical illnesses, increasing drug use, dementia type, more severe stages of dementia, delirium, and psychiatric history are the factors that contribute to dementia patients' death [7]. Interestingly, when evaluated using a neuropsychiatric checklist, difficult conduct was also linked to increased fatality rates [8]. Previous studies have shown a strong link between dementia and a sedentary lifestyle or lack of physical activity. If left untreated the latter can worsen and negatively impact health [9]. Frequent exercise has numerous health

advantages, such as enhancing physical fitness and preventing or reducing a number of mental and physical illnesses [10, 11]. Physical exercise is the best non-pharmacological therapy in improving public health and it also has an effect on increasing bone metabolism [12]. In addition, exercise also maintains balance and walking ability, motor skills, and non-motor symptoms including preventing cognitive deficits, sleep disturbances, and improving mood [13]. Previous research has shown that resistance training significantly increases human BDNF levels [14]. In addition, aerobic exercise also has an impact on increasing BDNF levels [15].

One of the most prevalent neurotrophic factors in the central nervous system, brain-derived neurotrophic factor (BDNF) is essential for both neuronal plasticity and synaptic homeostasis [16]. BDNF simultaneously activates the PI3K/Akt, MAPK/ERK, and PLC-γ signaling cascades upon binding to its cognate high-affinity receptor, tropomyosin receptor kinase B (TrkB). These cascades collectively control cell survival, neurogenesis, synaptogenesis, and long-term potentiation, processes that underlie memory consolidation and learning [16]. BDNF protects the brain dopaminergic neurons from damage and acts as a dopaminergic neuron growth factor in the *substantia nigra pars compacta* [17]. BDNF synthesis is dynamic and extremely responsive to environmental cues, including stress and physical activity [18]. A meta-analysis of exercise programs in older adults showed that strength training significantly increased BDNF concentrations, while aerobic exercise did not have such an effect [19]. Another systematic review reported that the increase in BDNF concentration was greater after aerobic exercise compared to resistance exercise [20]. BDNF levels in humans are affected by exercise routine [21]. However, the mechanisms and stages by which exercise increases BDNF levels have not been widely discussed, and information is still limited. This has created confusion and debate among researchers. Further exploration of the mechanisms underlying the increase in both types of exercise is needed to provide a deeper understanding of the beneficial effects of physical exercise on BDNF levels. BDNF expression has a vital role in the developing and functional brain [22]. Strength training and endurance training can increase BDNF expression of in humans, thus having a positive effect on brain development [23]. Physical exercise has been shown to increase BDNF levels in humans, but the underlying mechanisms are still debated. Therefore, this systematic review will discuss how humans who exercise can have higher BDNF expression levels and explain the mechanisms and stages underlying the increase in BDNF during physical exercise.

METHODS

Study Design

The effect of physical exercise on human BDNF levels has analyzed by reviewing the scientific literature. The following search engines were used to locate scientific literature: Web of Science, PubMed, Science Direct, and Scopus. The search keywords used are physical exercise, BDNF, health, dementia. Publications were selected based on the following inclusion criteria: year of publication, experimental study, and articles related to humans (Table 1).

Eligibility Criteria

The inclusion criteria for this study were established by searching pre-defined databases for materials published between 2019 and 2025. Experimental studies on increased BDNF levels after exercise were also included in these publications. The search terms used included BDNF levels. Furthermore, our study excluded papers that did not meet scientific validity standards or were not included in the leading search indexes such as Scopus, Web of Science, PubMed, or Science Direct. Therefore, we screened the selected papers using the pre-defined inclusion criteria.

Procedure

The full text, abstract, and title of each publication were added to the Mendeley database after review and confirmation (Fig. 1). Using Scopus, Science Direct, PubMed, and Web of Science, 152 publications were identified during the initial screening phase. Sixty-five eligible papers were selected for the second screening phase after identifying duplicate articles and the reasons behind title discrepancies. In the next stage, 27 papers were identified based on title relevance, specifically related to the impact of exercise on increasing BDNF levels in humans, abstracts

Table 1. Inclusion criteria

Web search engines	PubMed, Science Direct, Scopus, and Web of Science
Publishing period	2019–2025
Keyword	Cognitive function, BDNF, and physical exercise
Language	English
Type of article	Original research article
Full Text	Articles matched the purpose and/or topic of the research

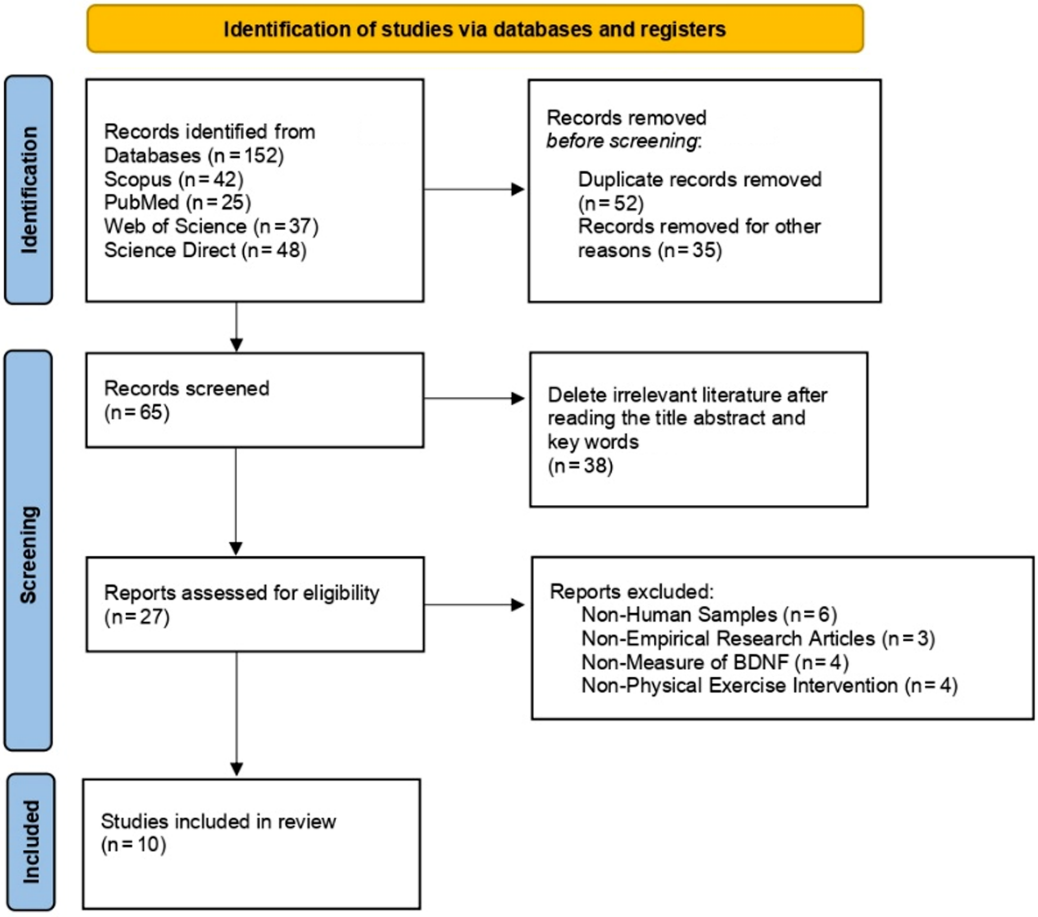

Figure 1. PRISMA flowchart of the article selection process.

that matched experimental studies, and pre-determined keywords such as BDNF and exercise. After reviewing each paper, we determined whether the study was experimental. The parameters used included cognitive function (due to the role of BDNF, as a potential marker for neurodegenerative diseases). In this context changes in BDNF levels can reflect changes in cognitive function and therefore the intervention must be exercise in human. This was the final step in the process. We screened these publications to identify those that met our predetermined inclusion criteria. After a rigorous review and observation process, ten papers that met the inclusion criteria were selected for analysis. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria were used in this study.

RESULTS AND DISCUSSIONS

The purpose of this study was to investigate how physical activity could increase BDNF levels in humans (Table 2). We also wanted to explore in depth the underlying mechanisms. It is known that physical exercise has an effect on increasing the expression of BDNF in humans. Data from the study showed that physical exercise with moderate intensity using a treadmill for 30 min had an effect on human BDNF levels [24]. Another study also showed that high-intensity physical exercise had a significant effect on increasing serum BDNF levels [25]. So it can be understood that physical exercise has a positive effect on improving health status by increasing BDNF levels. The comparative study of the effects of high-intensity physical exercise and moderate-intensity physical exercise has shown that high-intensity exercise had the highest effect on serum BDNF levels than moderate-intensity exercise [26].

There is still a need for many references related to how the mechanism that occurs during high-intensity exercise on increasing BDNF expression and why high-intensity physical exercise has higher BDNF expression than moderate-intensity exercise. The underlying mechanisms are complex. High intensity interval training (HIIT) is known to have many beneficial effects on humans. One study showed that 20 min of HIIT produced better cognitive function responses and BDNF levels than 30 min of HIIT in healthy young men [34]. The duration of HIIT training affects BDNF expression. This is a matter of debate and certainly requires further research and special experimental testing. Further exploration is important to provide

Table 2. The effect of physical exercise on serum BDNF levels in humans

Author	Sample Characteristics	Intervention*	Results
(Wheeler et al., 2020) [24]	67 subjects were divided into three groups: exercise + sitting (n = 23), activity + rest (n = 21), and sitting (n = 23)	Moderate intensity exercise using a treadmill for 30 min at 65%–75% of maximum HR	In the EX + SIT group, there was a notable rise in BDNF levels ($p = 0.03$)
(Gyorkos et al., 2019) [25]	12 subjects were divided into 2 groups: a carbohydrate-restricted Paleolithic-based diet + inactivity (n = 5), and a carbohydrate-restricted Paleolithic-based diet + exercise (n = 7)	HIIT workout 3 days/week for four weeks	Diet and exercise increased serum BDNF protein levels from 15.4±3.5 ng/ml to 18.5±4.6 ng/ml (CRPD-Sed group) or from 15.2±4.3 ng/ml to 21.2±6.4 ng/ml (CRPD-Ex group)
(Li et al., 2021) [26]	29 subjects were divided into 3 groups: control (n = 9), HIIT (n = 10), and high-intensity continuous exercise VICT (n = 10)	HIIT and VICT were performed three times a week for 12 weeks with 45 min per training session	There was a significant increase in BDNF levels in the HIIT group from 1036.60±265.03 pg/ml to 1412.10±345.64 pg/ml ($p < 0.05$) and in the VICT group from 1045.4±256.04 pg/ml to 1322.40±319.60 pg/ml ($p < 0.05$)
(Osali, 2020) [27]	44 women were divided into 4 groups: MetS exercise (ME), MetS exercise + Nano-Curcumin (MENC), MetS Nano-Curcumin (MNC), and MetS control (MC)	Moderate intensity exercise on a treadmill every week for 6 weeks	The group receiving curcumin + exercise intervention experienced a significant increase in BDNF levels from 115.33±15.31 pg/ml to 273.50±15.86 pg/ml ($p = 0.001$)
(Saleh et al., 2020) [28]	60 subjects were divided into four groups: experimental obesity (n = 15), control obesity (n = 15), normal weight (n = 15), and normal weight control (n = 15)	For eight weeks, the experimental group engaged in three sessions of 45 min of anaerobic exercise training, which included a 10-min warm-up, a 30-min main exercise, and a 5-min cool-down	In obese subjects + exercise, there was a significant increase in BDNF levels from 0.059±0.006 pg/ml to 0.078±0.019 pg/ml ($p = 0.002$) and the normal weight + exercise group also experienced a significant increase in BDNF levels from 0.061±0.014 pg/ml to 0.078±0.022 pg/ml ($p = 0.003$)
(Kambestad et al., 2023) [29]	23 healthy subjects participated in this study with a pre-test and post-test design	Total 28 min of aerobic activity using a stationary bike	After physical activity intervention, there was a significant increase in BDNF levels from 16.03 ng/ml to 16.81 ng/ml ($p = 0.023$)
(Arazi et al., 2021) [30]	30 subjects were divided into three groups: strength training (n = 10), endurance training (n = 10), and control (n = 10)	Resistance training 65–70% HRMax and endurance training 65–70% HRMax	In both therapy groups, BDNF levels increased significantly. In the strength training group, BDNF levels increased from 3.58±1.05 ng/ml to 4.16±1.82 ng/ml ($p < 0.05$), and in the endurance group, BDNF levels increased from 4.13±3.65 ng/ml to 4.68±3.90 ng/ml ($p < 0.05$)
(Devenney et al., 2019) [31]	64 patients were divided into two groups: control (n = 29) and physical exercise (n = 35)	Use of an ergometer for high-intensity aerobic workout till exhaustion	The high-intensity physical exercise intervention group showed a significant increase in BDNF levels from 4564.61 pg/ml to 5173.27 pg/ml ($p = 0.024$)
(Gumelar et al., 2024) [32]	16 women were divided into two groups: aerobic exercise (n = 8) and control (n = 8)	Moderate intensity aerobic exercise for 40 min at an intensity between 60 and 70 HRmax five times a week for two weeks	The group receiving aerobic exercise intervention experienced a significant increase in BDNF levels from 2173.81±705.89 pg/ml to 3635.01±699.71 pg/ml ($p = 0.013$)
(Kujach et al., 2020) [33]	36 men were divided into two groups: control (n = 16) and treatment group (n = 20)	Sprint interval training (SIE) includes six sets of 30-s cycling activity after a 5-min warm-up, and then a 4.5-min ergometer rest	The group receiving sprint interval exercise intervention had a significant rise in BDNF levels ($p < 0.01$)

* – Randomized controlled trial. HIIT – high intensity interval training; HRmax – maximal heart rate.

an explanation regarding how the optimal duration increases the BDNF levels. Another research included 60 children who were grouped and divided into 4 groups: obese children doing gymnastics, obese control group children, normal weight children doing gymnastics, and normal weight control group children. The data showed that BDNF levels increased both obese and normal weight children exposed to physical exercise intervention for 8 weeks of treatment [28].

Other data also showed an increase in BDNF expression, namely subjects who had undergone pretest and posttest research given submaximal aerobic physical exercise interventions with a total time of 28 min of intervention showed an increase in BDNF levels after the intervention [29]. Comparison of several types of physical exercises between endurance training and strength training on BDNF levels showed that strength training resulted in higher BDNF levels than endurance training [23]. This strengthens the data that strength training has a better effect on increasing BDNF levels. A previous study has demonstrated that moderate-intensity physical activity can raise circulating BDNF [35]. The mechanism underlying physical exercise in increasing the expression of BDNF still needs further elucidation.

BDNF is a member of the neurotrophin family of proteins, which the brain produces; they support the survival, growth, and maintenance of neurons as well as a number of learning and memory-related processes. Neurotrophins also play a significant role in the regulation of neuronal plasticity, which is dependent on human activity [36]. Physical exercise can affect epigenetic regulation of the *BDNF* gene in neurons [37]. Exercise activates N-methyl-D-aspartate (NMDA) receptors, this is accompanied by calcium influx into neurons via a cascade of molecular processes that activate BDNF transcription and cAMP response elements (CREs) binding proteins [38]. Exercise promotes generation of some byproducts, such as reactive oxygen species (ROS) due to increased mitochondrial activity, that control other molecular pathways and events [39]. In addition, exercise causes the blood to circulate with more lactate [40]. Exercise increases the levels of TNF-α and HIF-1 [41]. They all may be considered as mediators of the exercise impact on BDNF transcription and translation.

The human skeletal muscles, produce more ROS during physical activity [42], which also results in a shortage of oxygen supply and makes it impossible for the body to fulfill the quickly rising oxygen demand [43]. Other signal transduction pathways will be influenced by ROS. As a physiological response to physical activity, the rise in ROS during exercise is entirely normal and antioxidants become more abundant in the body when ROS levels increased [44].

Physical exercise is accompanied by a tremendous increase in skeletal muscle contraction [45], acetylcholine release from the presynaptic motor neuron to the postsynaptic muscle end plates [46]. Skeletal muscles secrete hormones known as myokines, making it the biggest endocrine organ. In both humans and animals, skeletal muscles secrete the myokine irisin, which enters the bloodstream during or right after physical activity [47]. Skeletal muscles may therefore both directly and indirectly raise BDNF levels in the bloodstream (Fig. 2). Certain evidence exists that increased peripheral irisin concentrations precede the expression of BDNF in rat hippocampal neurons [48]. Skeletal muscles are an important source of lactate, which can pass through the blood-brain barrier and affect BDNF synthesis of [49]. PGC-1α (peroxisome proliferator-activated gamma cofactor) is thought to be able to raise BDNF levels by inducing irisin expression or by producing it locally [50].

The signal transduction pathway that stimulates PGC-1α production includes adenosine monophosphate-activated protein kinase (AMPK) influenced by ROS [51]. PGC-1α is thought to be able to raise BDNF levels by inducing irisin expression or by producing it locally [50]. Analysis of accumulated knowledge shows that physical exercise enhances PGC-1α expression. Exercise intensity, duration, and type all affect expression levels of PGC-1α. Interval training and resistance training had a positive impact on PGC-1α expression, and the interventions were often moderate to high intensity [43]. Based on the reviewed literature, each study demonstrated an increase in PGC-1α following physical exercise [52, 53]. So there is a close link between PGC-1α and increased BDNF.

Irisin release and muscle-specific expression of PGC-1α and FNDC5 are both increased during contractions of large muscle groups [54]. After 12 weeks of consistent aerobic activity, blood irisin levels in humans reach about 3.6 ng/ml in sedentary people and 4.3 ng/ml in active people [55].

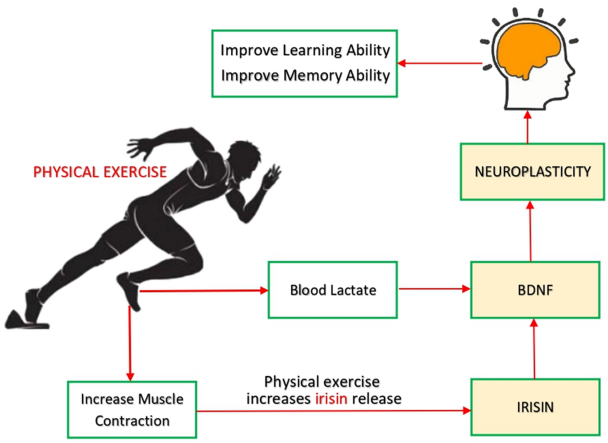

Figure 2. The mechanisms underlying increased serum BDNF levels induced by physical exercise.

Irisin helps the immunological, digestive, adipose, and cardiovascular systems adjust physiologically to exercise [54, 56, 57]. For obese people, exercise combined with calorie-restricted exercise improves health [58] and raises the levels of circulating irisin [59]. Even though the primary source of exercise-induced irisin released into plasma is skeletal muscle [60], whether neural irisin is made inside neurons or comes from muscle still remains unknown. PGC-1α controls FNDC5 expression in neurons via interacting with estrogen-related receptor alpha (ERRα) [61]. Enhanced FNDC5 expression promotes growth and differentiation of neurons [62, 63]. FNDC5 is present in astrocytes and microglia in brain tissue, cerebrospinal fluid, cortical neurons, paraventricular neurons in the hippocampus, Purkinje cells in the cerebellum, hypothalamus, and multipolar neurons in the anterior spinal cord [64].

Previous research has demonstrated that after two weeks of jogging on an exercise wheel, mouse hippocampus neurons express more PGC-1α and FNDC5 [61]. FNDC5 has a positive impact on the neural activity-induced genes (*BDNF*, *Arc*, *cFos*, and *Zif268*). Regular exercise is necessary to sustain the neurological benefits of this feedback loop, which most likely represents a CNS detraining mechanism. According to these data, the transcriptional response to exercise in the central nervous system, which includes neuroplasticity and neuroprotection, also includes FNDC5 upregulation [65]. Irisin may be important for neuronal survival following cerebral ischemia since BDNF is a crucial regulator of neuronal plasticity. Even in female mice aged 20 months, physical exercise (wheel running, 12 weeks) raised blood levels of BDNF and irisin [66], improved motor and cognitive function, increased BDNF expression, and reduced neuroinflammation in the hippocampal regions of elderly rats and mice [67].

Results of experiential research show that high-intensity physical exercise increases BDNF levels in humans [68]. Another study also confirmed that high-intensity physical exercise could also effectively increase BDNF levels [69]. Obese patients who were given aerobic exercise interventions were characterized by a significant increase in BDNF expression [70]. So it can be concluded that the increase in BDNF that occurs in exercise has an advantageous impact on the development of human memory and besides that, exercise is also the best effort in keeping the body healthy.

In conclusion, even if the brain continues to be the primary source of BDNF during exercise, it is critical to acknowledge the role that peripheral sources play in influencing the rise in BDNF levels. It is yet unclear how BDNF contributes to exercise-induced plasticity in humans. In this systematic review of research, of course, the authors have limitations in conducting the analysis and in presenting the discussion. Researchers only focused on the increase in BDNF expression during exercise. There is still confusion regarding the optimal dose during exercise in increasing the expression of BDNF. Many opinions state that high-intensity physical exercise, strength training or weight lifting has a better effect in increasing BDNF expression, but this still needs to be explored further related to mechanism(s) and stages. For future research, it is necessary to further explore the relationship between physical exercise and other biomarkers that affect BDNF levels such as irisin. In addition, future research is also needed to discuss the right and optimal dose, intensity and duration of exercise in increasing BDNF expression.

Strengths and Limitations

This systematic review has the advantage of focusing only on randomized controlled trials, the most reliable form of scientific evidence, and eliminating the potential for ambiguous causal relationships. Furthermore, the collected samples focused on humans, provided consistent data, and were not mixed with samples from other categories, including animal samples.

One limitation we identified was the lack of information on how exercise could increase BDNF levels. Therefore, this study is considered significant in increasing our understanding of how physical exercise affects BDNF levels and improves cognitive function. The general population, especially the elderly, may benefit from physical exercise to prevent cognitive decline. However, this may be related to its effective duration and intensity, which remain unclear. Therefore, further experimental studies are needed to determine the optimal timing and intensity for increasing BDNF levels in humans.

CONCLUSIONS

Exercise has been shown to significantly increase BDNF expression. The type of physical exercise also has a different effect on increasing BDNF expression. Physical exercise with high intensity is highly recommended in increasing BDNF expression, but it should be noted that duration also affects. Therefore, there is still a need for further research that is related to how much the optimal dose is good in increasing BDNF expression. So that it has a positive effect on memory and human health.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ УВЕЛИЧЕНИЯ УРОВНЯ НЕЙРОТРОФИЧЕСКОГО ФАКТОРА МОЗГА, ИНДУЦИРОВАННОГО ФИЗИЧЕСКИМИ УПРАЖНЕНИЯМИ

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Физическая пассивность провоцирует развитие ряда метаболических синдромов, влияет на когнитивные функции и способствует деменции. Физические упражнения могут помочь предотвратить эти негативные эффекты. Однако в настоящее время существует ограниченное количество исследований, ориентированных на изучении основных механизмов, ответственных за влияние физических упражнений на когнитивные функции путём изменения уровня нейротрофического фактора головного мозга (BDNF). Целью данного исследования был анализ существующих литературных данных о влиянии физических упражнений на уровни нейротрофического фактора головного мозга (BDNF) как биомаркера когнитивных функций. Для данного исследования был проведён поиск в нескольких базах данных научных журналов, включая Scopus, Web of Science, PubMed и Science Direct. В исследовании учитывали различные переменные, в том числе результаты исследований BDNF, высокоинтенсивных и умеренно интенсивных физических упражнений, опубликованные за последние десять лет. Статьи, не соответствующие критериям включения (например, исследования на животных), были исключены из данного систематического обзора. С помощью баз данных PubMed, Science Direct, Web of Science и Scopus было выявлено в общей сложности 152 публикации. Десять тщательно отобранных рецензируемых статей соответствовали сформулированным критериям отбора. Стандартные рабочие процедуры для данного исследования были установлены в соответствии с рекомендациями PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses). Приведённые результаты свидетельствуют о том, что физические упражнения повышают уровень BDNF у людей. Хотя высокоинтенсивные упражнения более эффективны в повышении уровня BDNF у людей, чем умеренно интенсивные, необходимы дальнейшие исследования для выбора оптимальной физической нагрузки, необходимой для экспрессии BDNF. Физические упражнения рекомендуются для улучшения развития мозга и памяти.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: физические упражнения; BDNF; здоровье; деменция

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