Review Article

The effect of exercise training on neurotrophins in obese and overweight individuals: A systematic review and meta-analysis of randomized controlled trials

Rasoul Eslami[1], Diako Heidary[2], Serve Heidari[3], Arezoo Soleymani Fard[2*]

Abstract

The purpose of this research was to conduct a systematic review and meta-analysis on the effect of exercise training on neurotrophin levels in obese and overweight individuals. The research evaluated the effect of exercise training on neurotrophins in the databases of PubMed, Science Direct, Scopus, and Google Scholar with identified keywords among papers published from 2000 onwards. After preliminary screening, full-text studies as well as critical evaluation of the papers meeting the inclusion criteria were analyzed. Finally, 12 studies entered systematic research, and 6 studies entered meta-analysis research. The results show that exercise training has an addictive effect on neurotrophin levels in obese individuals, but this addictive effect is not significant. The present meta-analyze shows that the brain -Derived Neurotrophic Factor (BDNF) response to exercise in obese individuals is increasing, but the increase is not significant (Difference in means = -0.42 pg/ml, P = 0.460). On the other hand, the Nerve Growth Factor (NGF) response to exercise is also increasing which is significant (Z = 2.12, P = 0.034). Thus, it can be concluded that exercise cannot increase neurotrophins in obese and overweight individuals; although, further studies are needed in this area.

Key Words: **Exercise training, Physical activity, Neurotrophilic factors, Neurotrophins, BDNF**

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Introduction

Neurotrophic factors (NTFs) are secretory proteins that regulate the growth, maintenance, function, and flexibility of the vertebrate nervous system. There are four major classes of neurotropic molecules in Neurotrophins' family: Glial cell line-derived neurotrophic factor (GDNF) family, Neurotrophic cytokines (Neurokines), the new family of Cerebral dopamine neurotrophic factor (CDNF) and Mesencephalic astrocyte-derived neurotrophic factor (Aron & Klein, 2011).

The neurotropic family includes several genes, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) (Eslami et al., 2016). In the central nervous system (CNS), adult NGF has neuroprotective effects and can affect neural responses to damage in a variety of cells that exhibit NGF receptors, such as sensory neurons of joint pain (sympathetic peripheral neurons with a small diameter) and motor neurons α. Brain-derived neurotrophic factor also exerts neuroprotective and growth-promoting effects on a variety of post-injury neural populations. This issue is particularly evident in the Rubrospinal, Reticulospinal, and Vestibulospinal ducts, as well as in Clark-specific nerve cells in the gray matter of the lumbar spinal cord. The neuroprotective results may be specifically attributed to the downstream effects of TrkB receptor signaling. Studies also show that BDNF reduces glutamate-induced apoptotic cell death (Keefe et al., 2017). However, the function of BDNF goes beyond the brain, because BDNF has a role to regulate metabolic functions such as fat oxidation and glucose uptake (Marosi & Mattson, 2014).

Currently, exercise creates a set of powerful effects on the brain such as memory, learning, mood, cognitive function, formability, and learning ability. An active lifestyle is a powerful way to delay the onset of brain and nerve problems. Exercise as a low-cost treatment method has a positive effect on cognitive function, which is most likely due to neurological factors (Darvishi, 2020; Kazemi, 2017). Exercise is a model that can affect the expression of neurotrophin within the appropriate physiological range. Increased exercise stimulates sensory nerve cells and gene expression that stimulates required proteins for axon growth and regeneration after injury (Eslami et al., 2017). It is reported that scheduled exercise for at least two weeks increases peripheral BDNF levels in adults (Dinoff et al., 2017). There is also a hypothesized mechanism that exercise increases BDNF levels in the brain (Vaynman et al., 2004), and BDNF may play a role in fat oxidation in obese and overweight individuals (Jiménez-Maldonado et al., 2014).

Several stimuli can increase BDNF expression and function. Based on the findings of various studies, exercise has been widely recognized as an effective stimulant for increasing BDNF synthesis in the brain (Erickson, 2011; Gomez-Pinilla, 2003) and peripheral nerves (Dinoff et al., 2017). Considering the effect of exercise on increasing BDNF in the brain, various molecular mechanisms have been proposed to explain the increase in BDNF synthesis in neurons due to exercise (mainly moderate-intensity continuous exercise) (Fernandes et al., 2017). Exercise has been shown to increase intracellular calcium levels in nerve cells. This ion indirectly activates Ca2+/calmodulin-dependent protein kinase (CaMKII). This kinase alters the Mitogen-activated protein kinase (MAP-K) pathway to the protein bound to phosphorylate CRE-binding protein and increases CREB transcription and thus BDNF transcription (Vaynman et al., 2004). Moreover, another model shows that physical activity stimulates the synthesis of BDNF in the brain by increasing the activity of reactive oxygen species (ROS). Exercise increases the activity of mitochondria in nerve cells, and higher mitochondrial activity has been found to cause the overproduction of ROS. Thus, ROS increases the activity of CRE-binding proteins to increase CREB and BDNF transcription (Radak et al., 2016).

Up to now, numerous studies have considered the effect of exercise on neurotrophins in obese and overweight individuals. However, the results of these investigations are inconsistent (Cho & Roh, 2016). Therefore, it is necessary to have a systematic review and Meta-analysis study in this scope. Hence, this research conducted a systematic review and meta-analysis study on the effect of exercise training on neurotrophins in obese and overweight individuals.

Materials and Methods

This is a systematic review and meta-analysis randomized clinical trial. Accordingly, the papers were extracted using a systematic search strategy in Pubmed, Science Direct, and Scopus databases. The specific keywords: 'Exercise', 'Training', 'Physical Activity', 'Neurotrophic Factors', 'Neurotrophins', 'BDNF' and 'NGF' in all the papers published from 2000 onwards were extracted. The Google Scholar Database was used as a complementary search, and the number of papers was added to the research project. It should also be noted that the search process in this study was completed on April 1st, 2022.

The exclusion criteria were all of the review papers, case reports, and conference papers that were presented only with the abstract of the article, papers that had irrelevant titles or were non-sport articles, papers written other than English, and papers focued on non-obese and overweight individuals. Other papers met the inclusion criteria in this study. Complete information of the papers that were eligible for the study included the type of the study, sample size, characteristics of the subjects (age, gender, and health status), data on neurotrophins before and after exercise intervention in the experimental and control groups and specifications of exercise program (type of exercise, intensity, and duration of exercises). The information was drawn from papers after a comprehensive review, categorized and then reported. These data were analyzed by Comprehensive Meta-analysis software version 2.

In addition, the quality of the papers was assessed by using the Downs and Black checklists. This checklist consists of 27 items, of which 25 items have a score of zero or one, one item has a score of zero to two, and the last item has a score of zero to five, and the maximum score based on this checklist is 31. Meanwhile, papers that scored between 20 and 25 were rated as mediocre quality papers, and papers that scored above 25 were rated as high-quality papers. The validity and reliability of this checklist have been confirmed in previous studies (Jacket, 1998). The quality assessment of the papers and data extraction were done by two authors separately. In case of disagreement, the issue was discussed between the two authors, and the final opinion was applied. All the steps of extracting and selecting papers are shown in Fig 1.

Results

According to various databases searching, 1821 papers were found. After the initial review of the titles and abstracts of the papers and the removal of irrelevant and duplicate papers, 113 papers entered the evaluation stage. The full-text information of the remaining papers was extracted after reviewing if the article met the inclusion criteria. At this stage, 97 papers that didn't meet the inclusion criteria were removed. Altogether 12 papers were included in the systematic review, of which 6 papers were suitable for entering the meta-analysis and were evaluated by the meta-analysis (Figure 1).10 papers were related to human studies (Table 1), and 2 papers were related to animal studies (Table 2).

The meta-analysis results of studies on the effect of exercise training on BDNF in obese and overweight individuals (Figure 2) indicated that the response of BDNF to exercise is increased, although these changes are not significant (Difference in means = -0.42 pg/ml, Z = -0.73, P = 0.460).

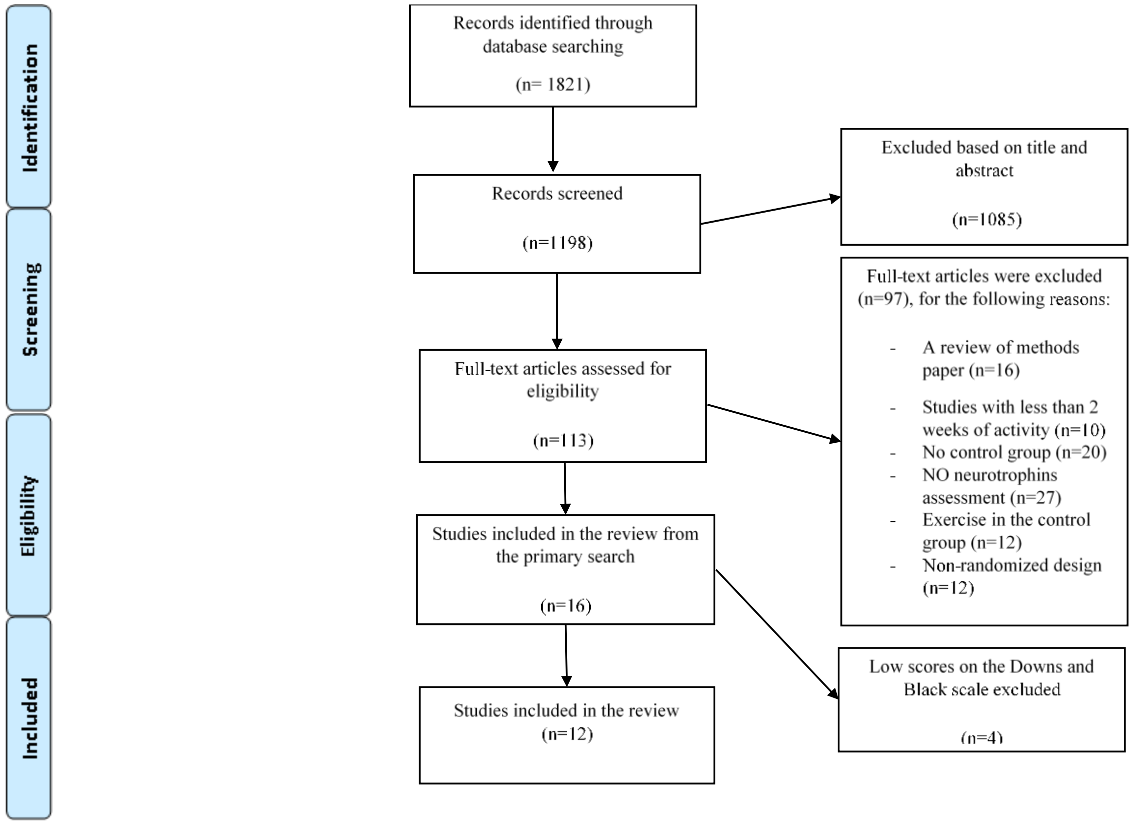

Figure 1. Flow diagram of the search process.

Table 1. Summary of studies included in the review (human studies).

Study	Country	Exercise + Control= Total sample size (Baseline)	Sex	Participants characteristics	Groups	Age (years) (Baseline)	BMI (kg/m^2) (Baseline)	d/w	W	Exercise Intervention	Results
Cho & Roh, 2016	Republic of Korea	8+8=16	Male	obese young men	Exercise Control	Exercise: 22.9±2.5 Control: 22.3±2.1	Exercise: 28.7±2.5 Control: 27.7±2.2	3	8	The exercise group performed treadmill exercise at the intensity of 70% heart rate reserve	Aerobic exercise training can induce neurogenesis in obese individuals by increasing the levels of brain-derived neurotrophic factors and reducing the levels of eotaxin-1
Cho et al., 2016	Republic of Korea	12+12=24	Female	obese middle-aged women	Exercise Control	Exercise: 54.83±2.79 Control: 54.67±3.03	Exercise: 26.87±2.15 Control: 26.28±1.67	3	8	Aerobic exercise consisted of treadmill running for 40 minutes at 70% of the subjects' heart rate reserve (HRR)	results suggest that aerobic exercise training could improve the mood state of obese middle-aged women through a decrease in serum cortisol and an increasing in serum BDNF and NGF
Glud et al., 2019-1	Denmark	9+6=15	Male	overweight and obese participants	Exercise Control	Exercise: 37.8±6.8 Control: 37.0±5.9	Exercise: 33.4±2.1 Control: 32.4±2.4	3	12	The exercise consisted of supervised aerobic exercise with a duration of 60–75 min per training session, estimated energy expenditure of 500–600 kcal per session, and an intensity of 70% of heart rate reserve	Circulating BDNF was significantly changed by diet alone or combined with exercise in women and only by exercise alone in men
Glud et al., 2019-2	Denmark	11+8=19	Female	overweight and obese participants	Exercise Control	Exercise: 38.3±8.3 Control: 34.6±7.0	Exercise: 35.1±3.9 Control: 37.2±2.7	3	12	The exercise consisted of supervised aerobic exercise with a duration of 60–75 min per training session, estimated energy	Circulating BDNF was significantly changed by diet alone or combined with exercise in women and only by exercise alone in men

Table 1 (continue). Summary of studies included in the review (human studies).

										expenditure of 500–600 kcal per session, and an intensity of 70% of heart rate reserve	
Goldfield et al., 2018-1	Canada	69+69=138	Female /Male	adolescents with obesity	Exercise (Aerobic) Control	Exercise: 15.5±1.3 Control: 15.6±1.3	Exercise: 34.6±4.2 Control: 34.3±5.0	4	22	The Aerobic group exercised on treadmills, elliptical machines, and/or bicycle ergometers. The intensity of exercise was also progressive, whereby participants began at 65% and progressed to 85%of their pre-determined maximum heart rate	No significant change
Goldfield et al., 2018-2	Canada	70+69=139	Female /Male	adolescents with obesity	Exercise (Resistance) Control	Exercise: 15.8±1.5 Control: 15.6±1.3	Exercise: 35.3±4.8 Control: 34.3±5.0	4	22	The Resistance group 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)	No significant change
Goldfield et al., 2018-3	Canada	74+69=143	Female /Male	adolescents with obesity	Exercise (Combined) Control	Exercise: 15.5±1.3 Control: 15.6±1.3	Exercise: 34.5±4.1 Control: 34.3±5.0	4	22	The Combined exercise group did the full of aerobic training program plus the resistance training program during each session	No significant change
Lee et al., 2014	Republic of Korea	8+11=19	Female /Male	Juvenile Obesity and Type 2 Diabetes Mellitus	Exercise Control	Exercise: 16.37±0.91 Control: 16.45±1.36	Exercise: 27.47±2.51 Control: 22.35±3.94	3	12	The outcome of doing aerobic exercise sessions at 40–60 minutes with maximum oxygen intake (VO2max) of 50~60% was investigated	While 12 weeks of regular aerobic exercise had a positive effect on body composition and increased BDNF levels of juveniles in the OG, it did not affect the inflammatory factor levels and did not affect the TG
Roh et al., 2020	Korea	13+13=26	Female	Elderly Women with Obesity	Exercise Control	Exercise: 70.92±6.60 Control: 70.23±6.06	Exercise: 24.67±1.55 Control: 25.72±2.32	3	12	The exercise group performed resistance training by using elastic bands	Results imply that regular resistance training in elderly women with obesity can increase muscle mass, reduce inflammation, and stimulate neurotrophic factors
Roh and So, 2017	Republic of Korea	10+10=20	Male	obese and non-obese men	Exercise (obese) Control (non-obese)	Exercise: 23.00±2.36 Control: 22.80±2.35	Exercise: 29.74±3.12 Control: 22.00±1.22	3	8	Both groups performed treadmill exercise at 40 min with 70% heart rate reserve	Results suggest that obesity can reduce serum neurotrophic factor levels. On the other hand, aerobic exercise can improve an oxidant-antioxidant imbalance in obese subjects.
Nazari et al., 2016	Iran	10+10=20	Male	Overweight Men	Exercise Control	Exercise: 22.7±1.5 Control: 22.3±1.5	Exercise: 26.9±0.7 Control: 27.1±0.8	3	8	This study involved a combined training program(strength and endurance)	It seems that brain-derived neurotrophic factor levels are affected by physical activity
Walsh et al., 2018	Canada	152+50=202	Female/ Male	Adolescents with Obesity	Exercise Control	Exercise: 15.5±1.4 Control: 15.4±1.3	Exercise: 34.5±4.1 Control: 34.3±5.1	4	4	Participants engaged in low-intensity and low-volume, resistance and aerobic training	Exercise-induced reductions in some diabetes risk factors were associated with increases in BDNF in adolescents with obesity, suggesting that exercise training may be an effective strategy to promote metabolic health and increases in BDNF, a protein favoring neuroplasticity
Woo, 2012	Korea	15+15=30	Female/ Male	Obese Children	Exercise (Obese) Control (Normal)	10-12 years	---	4	12	The aerobic exercise program of this study was performed with 40-60% heart rate reserve	BDNF and NGF expression increased significantly

Table 2. Summary of studies included in the review (animal studies).

Study	Country	Exercise + Control= Total Sample Size (Baseline)	Animals	Participants Characteristics	Groups	D/W	W	Exercise Intervention	Results
Kim et al., 2020-1	Korea	7+7=14	Mice	Obese mice maintained on high fat diet	Low-intensity exercise Control	5	8	All exercise groups were subjected to exercise on an animal treadmill	No significant change
Kim et al., 2020-2	Korea	7+7=14	Mice	Obese mice maintained on high fat diet	Moderate intensity exercise Control	5	8	All exercise groups were subjected to exercise on an animal treadmill	No significant change
Kim et al., 2020-3	Korea	7+7=14	Mice	Obese mice maintained on high fat diet	High intensity exercise Control	5	8	All exercise groups were subjected to exercise on an animal treadmill	BDNF expression increased significantly
Woo et al., 2019-1	Republic of Korea	9+9=18	Mice	Obese mice	Moderate intensity exercise Control	5	8	In both groups, the tail of the mice was attached with a pendulum weighing 75% of the body mass before climbing up the ladder. Upon successfully climbing the ladder to the top, the one repetition maximum (1RM) value was assessed through the gradual addition of weights of 15% of the body mass to the tail. A total of eight rounds of climbing were performed by mice of both groups in one set of exercises with loads equivalent to approximately 50% and 75% of 1RM	BDNF and NGF expression increased significantly
Woo et al., 2019-2	Republic of Korea	9+9=18	Mice	Obese mice	High-intensity exercise Control	5	8	In both groups, the tail of the mice was attached with a pendulum weighing 75% of the body mass before climbing up the ladder. Upon successfully climbing the ladder to the top, the one repetition maximum (1RM) value was assessed through the gradual addition of weights of 15% of the body mass to the tail. A total of eight rounds of climbing were performed by mice of both groups in one set of exercises with loads equivalent to approximately 50% and 75% of 1RM	BDNF and NGF expression increased significantly

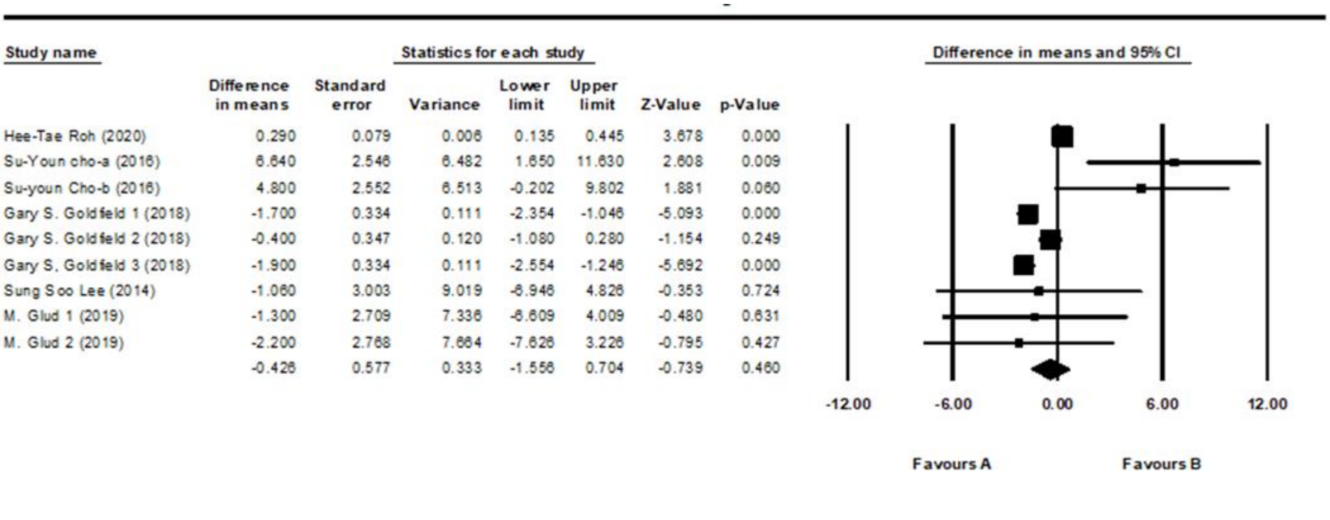

Figure 2. Meta-analysis of the effects of exercise training on BDNF in obese and overweight individuals

According to the obtained I2 score (I2 = 90.4% and P = 0.000), it is observed that the heterogeneity of different studies with each other is significant. On the other hand, Figure 3 shows the funnel plot to check the status of publication bios in the meta-analysis, which does not show significant bias. In other words, these results are almost reliable.

Also, the results of the meta-analysis of studies on the effect of exercise training on NGF in obese and overweight individuals (Figure 4) indicated that the response of NGF to exercise increased, and these changes are significant (Difference in means = 25.62 pg/ml, Z = 2.12, P = 0.034). According to the obtained I2 score (I2=0.0% and P = 0.804), it is observed that the

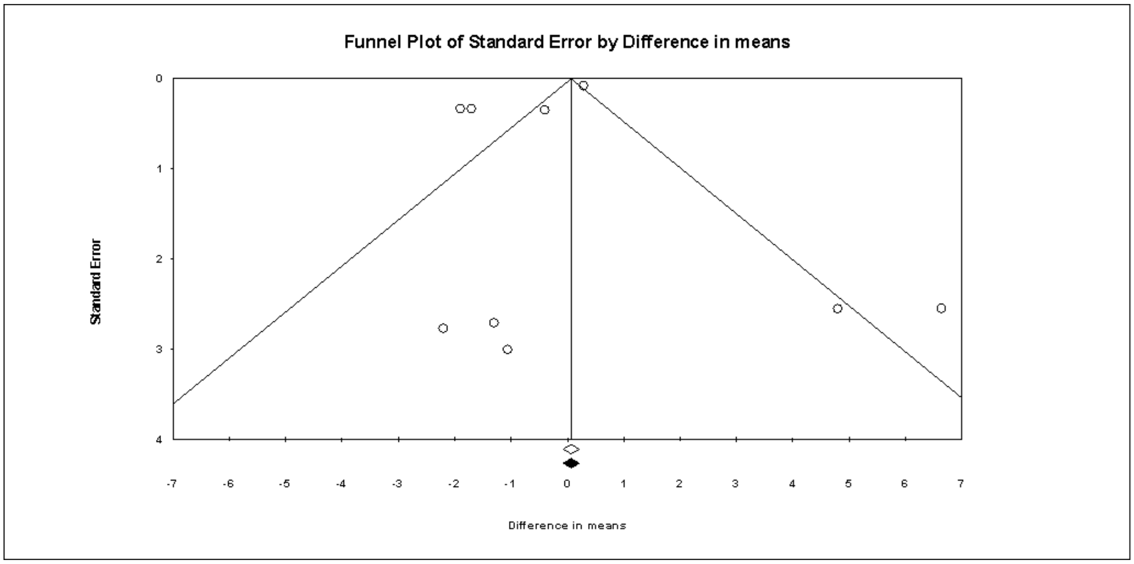

Figure 3. Funnel plot of studies on the effects of exercise training on BDNF in obese and overweight individuals.

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Su-Youn Cho (2016)	32.630	30.641	938.894	-27.426	92.686	1.065	0.287
Sung Soo Lee (2014)	24.340	13.147	172.833	-1.427	50.107	1.851	0.064
	25.629	12.082	145.964	1.949	49.308	2.121	0.034

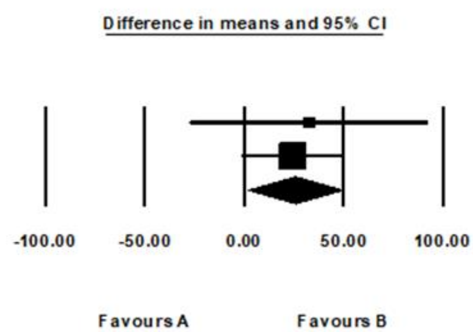

Figure 4. Meta-analysis of the effects of exercise training on NGF in obese and overweight individuals.

heterogeneity of different studies with each other is not significant.

Discussion

The purpose of this research was to investigate and identify the response of neurotrophins to exercise in obese and overweight individuals. The present meta-analysis results show that exercise training can increase the levels of some important neurotrophins in humans, including BDNF and NGF. However, it should be mentioned that while the increase in BDNF was not significant, NGF had a significant incremental response. These results are consistent with tose of Goldfield et al. (2018) who investigated the long-term effects of aerobic exercise, resistance training, and combination training on the BDNF level of a large group of overweight and obese adolescents (Goldfield et al., 2018). According to meta-analysis results, several studies such as Cho et al. (2016) and Roh et al. (2020) (19 and 23), Lee et al. (2014) and Glud et al. (2019) have shown a reduction in BDNF levels in response to exercise in obese and overweight individuals. Regar-ding NGF levels, some studies such as Lee et al. (2014) and Chou et al. (2016) have reported the increased effect of exercise on NGF levels in humans.

There are several biological mechanisms associated with neurotropic expression and obesity and overweight that are still unknown. However, there is evidence to suggest that brain-derived neurotrophic factor (BDNF) is involved in cognitive function in prescribing or reducing food intake (Szuhany et al., 2015). On the other hand, high levels of BDNF are associated with a healthy lifestyle and low levels of BDNF are associated with the risk of metabolic disorders and eating disorders (Rosas-Vargas et al., 2011). Other studies have shown conflicting data in association with low BDNF levels in overweight individuals (Sandrini et al., 2018). A meta-analytic study by Sandrini et al. (2018) showed that there is no significant relationship between BDNF levels and obesity (Sandrini et al., 2018). In this study, the effect of exercise on neurotropic levels in obese and overweight individuals was investigated in various studies and it was found that there is no significant relationship between these variables, which can be a confirmation of previous studies.

According to the results, physical activity and exercise have beneficial effects on brain health such as reducing the risk of dementia and Alzheimer's, maintaining cognitive function, and controlling metabolism (Costman, 2002; Pedersen, 2019; Santos-Lozano, 2016; Sardahaee, 2010; Williams, 2010). Physical exercise increases attention, processing speed, and executive functions, as well as improves reaction time and language learning (Smith et al., 2010). Exercise improves several basic physiological functions, such as sleep (Kelley & Kelley, 2017), appetite (Blundell et al., 2015), and mood (Crush et al., 2018), which are associated with the brain. In this regard, research has indicated that a wide network of brain areas and about 82% of the total volume of gray matter involved in learning and memory are affected by exercise (Batouli & Saba, 2017). Although the beneficial effects of exercise on the brain are evident, the mechanisms of this effect are not yet fully understood (Darvishi & Eslami, 2020).

The effects of exercise on the resting BDNF level are highly complex and variable. Studies indicate that some of these inconstancies, especially in acute periods of exercise, may be due to the potential moderating effects on the study population (healthy versus clinical specimens), age, gender (more severe effects in men), measurement method (serum versus plasma), and programmatic factors such as frequency, intensity, and duration of exercise (Dinoff, 2017; Eslami, 2015). BDNF is one of the neurotrophins and one of the most important mediators of the effects of exercise on the brain, especially cognition (Loprinzi & Frith 2019). BDNF is essential for many effects of exercise on the brain (Chambliss, 2003; Farmer, 2004; Perreau, 2005). For example, BDNF is involved in neuronal production and differentiation, nerve cell survival, hippocampal function, and learning (Wrann et al., 2013). In this regard, studies have shown that the release of BDNF in the human brain increases a period of acute exercise (Ramaussen, 2009; Seifert, 2010).

Although several studies support the idea that BDNF plays a dominant role in mediating the effects of exercise on the brain, the mechanisms involved in increasing BDNF levels induced by muscle activity during exercise are unclear. BDNF is a protein in skeletal muscle whose production is stimulated by muscle contraction (Matthews et al., 2009). There is also little evidence that muscle-derived BDNF enters the bloodstream. However, there is no evidence that BDNF mediates brain-muscle interactions (Eslami et al., 2018). Thus, exercise training is likely to increase the levels of other factors secreted by the muscle into the bloodstream and cross the blood-brain barrier, then stimulate increased BDNF production in the brain (Nourollahi & Eslami, 2019).

On the other hand, NGF plays an important role in the survival of sympathetic and sensory neurons as well as biological activities, including cell growth (Steers & Tuttle, 2006). Schules et al. examined the effects of 8 weeks of aerobic exercise using ergometers on patients with multiple sclerosis (MS) and did not report a significant difference in the NGF level of the exercise group (Schulz et al., 2004). Bansi et al. performed 3 weeks of regular exercise for middle-aged patients with MS and were unable to significantly alter resting NGF levels (Bansi et al., 2013). Lee et al. (2014) also did not show a significant difference in resting NGF levels in the obese group of trained individuals compared to the control group, although they observed an increase in NGF levels compared to the control group. Another previous study of 146 adults reported that NGF levels were higher in obese people than in normal-weight people (Bullo et al., 2007). In general, it can be claimed that exercise does not have a significant increase in resting NGF levels in obese and overweight individuals.

Conclusion

Neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) are other members of the neurotrophic factors that have similar properties to BDNF. These nutritional factors increase neuronal maturation and enhance the maintenance of adult neurons (Numakawa et al., 2010). NT-3 and NT-4 play an important role in regulating the plasticity of brain cells and their function is very important for synaptic transmission (Eslami et al., 2018). NT-3 also plays an important role in the survival and function of sensory nerve cells. NT-4 is also involved in long-term synaptic potential (Eslami et al., 2015). Studies on the effect of exercise on these neurotrophins in obese and overweight individuals are limited and it is hoped that high-quality research will be done in the future. There may be limitations to the present study, including the small number of studies that have been performed in this area and the exact amount of neurotrophins reported in them. There may also be studies published other than English that are not included in this study.

Exercise does not play a significant role in increasing neurotropic levels in obese and overweight individuals, and exercise-induced neurotropic responses are heterogeneous and very variable like most of the intervention studies. Future randomized clinical trials to confirm these initial findings and further elucidate the effects that duration, intensity, and various exercise methods have on resting neurotropic levels and can help optimize exercise prescriptions in high-risk populations such as obese and overweight individuals.

What is already known on this subject?

Up to now, numerous studies have considered the effect of exercise on neurotrophins in obese and overweight individuals. However, the results of these investigations are inconsistent.

What this study adds?

Exercise does not play a significant role in increasing neurotropic levels in obese and overweight individuals, and exercise-induced neurotropic responses are heterogeneous and very variable like most of the intervention studies.

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Compliance with ethical standards

Conflict of interest The author declare that she has no conflict of interest.

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Author contributions

Conceptualization: A.S.F., D.H.; Methodology: R.E., D.H.; Software: S.H.; Validation: A.S.F., R.E.; Formal analysis: S.H.; Investigation: A.S.F.; Resources: R.E.; Data curation: D.H.; Writing - original draft: A.S.F.; Writing - review & editing: D.H.; Visualization: S.H.; Supervision: A.S.F.; Project administration: R.E.; Funding acquisition: A.S.F.

Conflict of interest The author declare that she has no conflict of interest.

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