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The effect of four-weeks combined exercise improves cognitive functions in obese women
El efecto del ejercicio combinado durante cuatro semanas mejora las funciones cognitivas en mujeres obesas

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Abstract. This study investigated the effects of a four-week combined exercise program on brain-derived neurotrophic factor (BDNF) levels in obese women. Obesity has been associated with reduced BDNF levels, which can negatively impact cognitive function. Although previous research has shown that obesity affects BDNF levels in both men and women, this study focused on female participants to examine gender-specific responses. Twenty obese females (mean age: 21.85±1.43 years, body mass index [BMI]: 31.61±2.87 kg/m²) participated in the program, which involved moderate-intensity exercises performed three times per week. Blood samples were collected before and after the intervention to measure brain-derived neurotrophic factor (BDNF) levels using Enzyme-linked Immunosorbent Assay (ELISA) kits. Paired sample t-tests were conducted with a significance level of 5%. Results indicated that BDNF levels in the control group (COG) increased from 614.49±34.86 to 626.74±34.13 pg/mL (p=0.399), while the treatment group (TRG) showed a significant increase from 619.14±69.96 to 716.41±21.92 pg/mL (p=0.001). These findings suggest that a four-week combined exercise program effectively increases BDNF levels and may be a physical therapy option for improving cognitive function in obese individuals.
Keywords: BDNF, Cognitive function, combined exercise, obesity, women

Resumen. Este estudio investigó los efectos de un programa de ejercicio combinado de cuatro semanas sobre los niveles del factor neurotrófico derivado del cerebro (BDNF) en mujeres obesas. La obesidad se ha asociado con niveles reducidos de BDNF, lo que puede afectar negativamente la función cognitiva. Aunque investigaciones anteriores han demostrado que la obesidad afecta los niveles de BDNF tanto en hombres como en mujeres, este estudio se centró en participantes femeninas para examinar las respuestas específicas de género. Veinte mujeres obesas (edad media: 21,85 ± 1,43 años, índice de masa corporal [IMC]: 31,61 ± 2,87 kg/m²) participaron en el programa, que incluía ejercicios de intensidad moderada realizados tres veces por semana. Se recolectaron muestras de sangre antes y después de la intervención para medir los niveles del factor neurotrófico derivado del cerebro (BDNF) utilizando kits de ensayo inmunoabsorbente ligado a enzimas (ELISA). Se realizaron pruebas t para muestras pareadas con un nivel de significancia del 5%. Los resultados indicaron que los niveles de BDNF en el grupo control (COG) aumentaron de 614,49±34,86 a 626,74±34,13 pg/mL (p=0,399), mientras que el grupo de tratamiento (TRG) mostró un aumento significativo de 619,14±69,96 a 716,41±21,92 pg. /ml (p=0,001). Estos hallazgos sugieren que un programa de ejercicio combinado de cuatro semanas aumenta efectivamente los niveles de BDNF y puede ser una opción de fisioterapia para mejorar la función cognitiva en personas obesas.
Palabras clave: BDNF, Función cognitiva, ejercicio combinado, obesidad, mujeres

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Introduction

Globally, the prevalence of obesity in women has increased across all ages and ethnicities, negatively impacting not only physical and cardiometabolic health but also cognitive performance (Keawtep et al., 2024; Boutari et al., 2022; Whitmer et al., 2005). In 2022, more than 2.5 billion adults worldwide were overweight, with 1 in 8 living with obesity, and of that number, 890 million suffered from obesity, indicating more than a twofold increase in adult obesity and a fourfold increase in adolescent obesity since 1990 (WHO, 2024). Obesity has been linked to cognitive deficits, which involve impairments in mental and intellectual functions (Sui & Pasco, 2020). Additionally, neuroimaging studies have demonstrated that obesity contributes to structural and functional brain changes, increasing the risk of Alzheimer's disease (AD) (Livingston et al., 2020). These associations underline the need for further research into the mechanisms underlying the relationship between obesity and cognitive decline.

Emerging evidence in neuroscience and endocrinology suggests that obesity affects brain-derived neurotrophic factor (BDNF) levels, a neurotrophic protein that plays a crucial role in neuronal growth, differentiation, and maintenance (Lister et al., 2023). BDNF is also critical for synaptic plasticity, a key factor in learning and memory processes (Wang et al., 2022). Several studies have demonstrated that reduced BDNF levels are present in both men and women with obesity (Bacopoulou et al., 2023), though some gender-specific differences have been observed. For instance, research has shown that obese female adolescents are particularly vulnerable to significant reductions in BDNF concentrations (Bacopoulou et al., 2023). This decrease in BDNF raises concerns about its long-term impact on cognitive function, particularly in obese individuals (Sui & Pasco, 2020). Further investigation into gender differences in BDNF expression and their implications for cognitive health is necessary. Moreover, a multidisciplinary approach that considers both physical and neurobiological consequences of obesity is essential to support the long-term quality of life and potential of affected individuals (Beltrán-Garrayo et al., 2024). Regular physical exercise has been identified as a key intervention for enhancing cognitive function in obese individuals by

increasing BDNF levels in the brain (Keawtep et al., 2024; Dadkhah et al., 2023). Physical activity facilitates increased blood flow to the brain, which enhances the transport of BDNF, and activates gene expression related to BDNF production (Ribeiro et al., 2021). This process is reinforced by the activation of intracellular signaling pathways, including NMDA receptors that trigger the transcription of BDNF exon IV through a protein signaling cascade involving ERK, CaMK II/IV, PI3K, and PLC (Kiss Bimbova et al., 2021; Colucci-D'Amato et al., 2020). These pathways contribute to neuroregeneration, neuro synaptic plasticity, memory formation, and the regulation of cognitive functions (Sama Jaberi & Fahnestock, 2023). Furthermore, physical exercise triggers the release of exerkines from peripheral tissues, which stimulate BDNF production in the brain, indirectly supporting brain health and cognitive function (Cefis et al., 2023). Therefore, a combined exercise program, which includes aerobic and strength exercises, provides benefits not only for cardiometabolic health but also for brain health by increasing BDNF levels (Migueles et al., 2023).

Given the critical role of BDNF in cognitive function, this study aims to investigate the effects of a four-week combined exercise regimen on BDNF levels in obese women. By focusing on BDNF as a biomarker, this study emphasizes the importance of physical exercise as an intervention strategy to mitigate the neurobiological impacts of obesity, particularly in women. Future research should also consider examining similar effects in men to provide a more comprehensive understanding of the gender-specific impacts of obesity on brain health.

Materials and Methods

This study employed a true-experimental approach with a pretest-posttest control group design. A total of 20 obese women with an average age of (21.85 ± 1.43) years, body mass index (BMI) of (31.61 ± 2.87) kg/m^2, blood pressure (systolic: (111.90 ± 8.79) mmHg and diastolic: (77.95 ± 6.39) mmHg), heart rate ((72.60 ± 5.46) bpm), oxygen saturation ((97.60 ± 1.19) %), and body temperature ((36.09 ± 0.29) °C) were selected to participate in the study and randomly divided into two research groups: the control group (COG), and the treadmill-resistance group (TRG), each consisting of (n=10). Informed consent was obtained before the subjects participated in the study. All research procedures followed the WMA Helsinki Declaration and were approved by the Health Research Ethics Commission (KEPK), Faculty of Medicine, Ciputra University (Indonesia) (No:103/EC/KEPK-FKUC/II/2024).

The combined exercise intervention program was implemented and supervised by a personal trainer from the Faculty of Sports and Health Science, Universitas Negeri Surabaya (Indonesia). The combined exercise was applied by combining aerobic exercise (treadmill exercise) and resistance training (leg presses, leg curls, leg extensions, pull-downs, shoulder presses, and chest presses) performed with moderate-intensity, frequency of three times/week for four weeks (Pranoto et al., 2024.

Data collection was carried out by taking blood samples pre- and post-treatment of 3mL from the cubital vein, followed by centrifugation to separate the blood serum for 15 minutes at a speed of 3000 rpm. Subsequently, BDNF levels were observed using Human BDNF (Brain Derived Neurotrophic Factor) ELISA Kits (Cat.No.:E-EL-H0010; Elabscience Bionovation Inc., USA).

Statistical analysis techniques were applied using IBM SPSS 26 for Windows. Descriptive statistical analysis was presented with mean ± standard deviation (SD). Normality testing was applied with the Shapiro–Wilk test. Data that were normally distributed were further analyzed statistically using the paired sample t-test to determine the difference in BDNF levels between pre- and post-treatment in each group. Meanwhile, the independent sample t-test was used to determine the difference in BDNF levels between the intervention group and the control group. Effect size evaluation was applied with Cohen's d. Data were declared to have a significant difference if ($p \leq 0.05$).

Results

The descriptive analysis and difference test on the characteristics of the research subjects showed no differences found in each parameter, which can be seen in Table 1. Therefore, we assume that the increase in BDNF levels is likely due to the effect of the intervention applied. The results of the BDNF level analysis between pre- and post-treatment for the control group (COG) and the treadmill-resistance group (TRG) can be seen in Figure 1.

Table 1.
Characteristics of the research subject population

Parameters	Units	COG (n = 10)	TRG (n = 10)	p-Value
Age	yrs	21.80±1.39	21.90±1.52	0.880
Body weight	kg	78.11±9.77	76.75±8.17	0.741
Body height	m	1.57±0.07	1.55±0.06	0.500
Body mass index	kg/m^2	31.22±3.04	32.01±2.78	0.554
Systolic blood pressure	mmHg	109.80±8.69	114.00±8.83	0.298
Diastolic blood pressure	mmHg	76.00±6.22	79.90±6.24	0.179
Heart rate	bpm	72.00±5.48	73.20±5.67	0.636
Oxygen saturation	%	97.70±1.34	97.50±1.08	0.717
Body temperature	°C	36.09±0.36	36.10±0.23	0.942

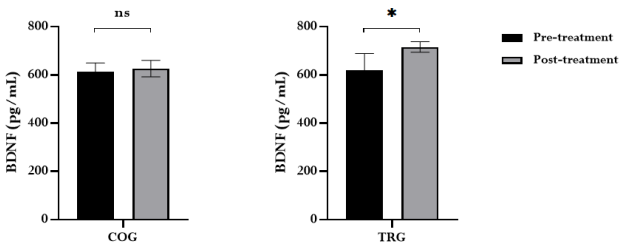

Figure 1. Kadar BDNF (pg/mL) pre-treatment and post-treatment pada masing-masing kelompok. Description: (ns): Not significant in COG ($p \geq 0.05$); (*): Significant at pre-treatment in TRG ($p \leq 0.001$)

The paired sample t-test results shown in Figure 1 indicate that the average BDNF levels between pre-

treatment and post-treatment for the COG changed from (614.49 ± 34.86) to (626.74 ± 34.13) pg/mL with a p-value of 0.399 and for the TRG from (619.14 ± 69.96) to (716.41 ± 21.92) pg/mL with a p-value of 0.001. The comparison of BDNF levels between COG with TRG was presented in Table 2.

Table 2.
Comparison of BDNF level observation points (pg/mL) between COG and TRG.

Parameters	COG (n = 10)	TRG (n = 10)	p-Value	Mean (95% CI)	Effect size
Pre-BDNF (pg/mL)	614.49±34.86	619.14±69.96	0.853	-4.66 (-57.97 to 48.66)	-
Post-BDNF (pg/mL)	626.74±34.13	716.41±21.92*	0.001	-89.67 (-116.62 to -62.73)	3.127
Δ-BDNF (pg/mL)	12.25±43.79	97.26±61.46*	0.002	-85.01 (-135.15 to -34.87)	2.509
Change-BDNF (%)	2.23±7.01	17.18±15.01*	0.011	-14.95 (-25.96 to -3.95)	1.277

Description: (*): Significant at COG ($p \leq 0.05$).

Discussion

The main finding of this study is that levels of Brain-Derived Neurotrophic Factor (BDNF) significantly increased in the intervention group compared to the control group, consistent with previous research (Goldfield et al., 2018). This result highlights the potential of combined aerobic and resistance exercises as effective interventions for enhancing BDNF levels in obese adolescent girls (Loprinzi et al., 2020; Azevedo et al., 2020; Church et al., 2016). BDNF has been consistently identified as a crucial biomarker correlated with cognitive function, particularly in its role as a mediator of neuroplasticity, which is fundamental for learning and memory (Azman & Zakaria, 2022; Ismail et al., 2020). Higher BDNF levels are associated with improvements in cognitive domains, including working memory, processing speed, and executive function (Sharma et al., 2022; Wang et al., 2022), and interventions that elevate BDNF, such as physical exercise, have proven effective in enhancing cognitive performance (Ribeiro et al., 2021).

Adolescence presents a critical period for addressing obesity and its long-term complications, as early-life environments significantly influence the development of obesity and related health outcomes later in life (Lister et al., 2023; Nicolucci et al., 2022). The Developmental Origins of Health and Disease framework supports this perspective, emphasizing the importance of early intervention strategies. A deeper understanding of BDNF's role in cognitive function can inform the development of more effective interventions, particularly in addressing obesity-related cognitive impairment in adolescents (Mudjihartini, 2021; Pisani et al., 2023; Li et al., 2022; Hildreth et al., 2023).

Physical exercise, particularly when combining aerobic and resistance training, has been shown to effectively increase BDNF levels and improve cognitive function (Lee et al., 2024; Schroeder et al., 2019; Keawtep et al., 2024; Xiang et al., 2019). Aerobic exercise enhances cerebral blood flow, stimulating BDNF synthesis, which is essential for neurogenesis and synaptic differentiation (Azman & Zakaria, 2022; Moriarty et al., 2019; Kowiański et al., 2017). Resistance training contributes further by promoting muscle hypertrophy and releasing growth factors, including BDNF, which supports neuroplasticity and overall brain health (Iván Rentería et al., 2022; Patroklos et al., 2023). The synergistic effects of combined aerobic and resistance exercises maximize BDNF production, improving neurogenesis and cognitive functions, including memory, attention, and executive function (Ploughman et al., 2019; Amorós-Aguilar et al., 2021).

Recent research further elucidates the molecular mechanisms by which physical exercise influences BDNF levels. Activation of intracellular signaling pathways, such as NMDA receptors, triggers the transcription of BDNF exon IV through signaling cascades involving ERK, CaMK II/IV, PI3K, and PLC (Kiss Bimbova et al., 2021; Colucci-D'Amato et al., 2020). Additionally, exercise induces the release of exerkines from peripheral tissues, which stimulate BDNF production in the brain, supporting cognitive function (Cefis et al., 2023; Sama Jaberi & Fahnestock, 2023). This holistic approach addresses both the physical and mental aspects of obesity, offering significant potential in combating cognitive decline associated with obesity in young women (Migueles et al., 2023; Massimo Fioranelli et al., 2023).

However, this study also has limitations due to the relatively short duration of the intervention. While a significant increase in BDNF levels was observed, a longer intervention period may be necessary to achieve more substantial and long-term cognitive benefits. Additionally, the focus on adolescent girls limits the generalization of findings to other populations, such as males or adults of different age groups. Future research should extend the duration of the intervention, diversify the study population, and conduct comparative analyses of aerobic and resistance exercises, both separately and in combination, to better assess their relative contributions to BDNF enhancement and cognitive function. Other outcomes, such as quality of life and physical fitness, should also be considered, and further exploration of the molecular mechanisms underlying the relationship between BDNF and cognitive function, including the role of exerkines and intracellular signaling pathways, is needed.

In summary, this study highlights the positive impact of a four-week combined exercise regimen on BDNF levels in individuals with obesity. The significant increase in BDNF observed supports the potential of combined exercise programs as a viable strategy for improving cognitive function in this population. These findings emphasize the importance of incorporating regular, moderate-intensity

exercise into obesity management plans to address both cardiometabolic and neurobiological health. Future research should explore the long-term effects of such exercise regimens and assess their efficacy across different demographics, including men and various age groups.

Conclusion

This study demonstrates that a four-week regimen of moderate-intensity combined exercise significantly increases BDNF levels in individuals with obesity. Consequently, a combined exercise program performed at least three times per week over four weeks can be recommended as an effective intervention for enhancing cognitive function in obese individuals, as indicated by elevated BDNF levels as a key biomarker.

Conflict of interest

This study has no conflict of interest.

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