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Body fat, cognitive performance and inflammatory cytokines in healthy, young women

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ABSTRACT

Introduction: There is growing evidence indicating that being overweight and obese has a negative impact on the central nervous system. It was also demonstrated that excessive body fat coincides with lower levels of cognitive functions. The potential mechanism by which the excessive adipose tissue can negatively influence cognitive performance is unclear. However, it is generally accepted that the negative impact of body fat on cognitive function may be mediated by inflammatory cytokines. The current study examines the impact of body fat on cognitive performance in young, healthy people. The authors also attempt to determine the potential mechanism of such an impact.

Material and methods: 38 women, age 21.65 ± 1.45 took part in this study. To evaluate the cognitive performance of the present subjects, standard cognitive tests were used: the Face/name Association Test, Stroop Test, and Trail Making Test. The level of fat tissue was determined by a body composition analyzer (Tanita, type BC-418MA). The levels of IL-6 and TNF-alpha were determined in serum using an enzyme-linked immunosorbent assay (ELISA) kit (LDN GmbH & Co., Nordhorn, Germany).

Results: A statistically significant relationship was observed between the percentage of body fat tissue and the level of TNF-α as well as waist-hip ratio and IL-6. A negative correlation was demonstrated between the level of IL-6 and cognitive performance. A statistically significant correlation between the level of TNF-α and the results of cognitive tests was not observed.

Conclusions: This study confirms that an increase in body fat content leads to a decreasing level of cognitive performance. Also, demonstrated was a negative correlation between the level of IL-6 and the results of cognitive tests in young people.

Keywords: fat tissue, cognitive function, young people, Interleukin-6, TNF-α, inflammation

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Introduction

It is well known that adipose tissue plays an important role in energy storage, glucose metabolism, and inflammatory processes [1, 2]. An adequate level of adipose tissue is critical for metabolic health. Above normal body fat content may result in many pathological states such as obesity, cardiovascular diseases, and different stages of insulin resistance including type 2 diabetes [3, 4]. The negative influence of excessive fatty tissue may also manifest itself in altered functions of the central nervous system, e.g. cognitive performance [5, 6]. It was observed that overweight or obesity is associated with atrophy in many areas of the human brain, especially the temporal and frontal lobes, parietal cortex, hippocampus, cerebellum as well as midbrain [7, 8]. At the same time, reduction in body mass was reported to correlate with beneficial effects on cognitive functioning [9, 10]. A potential mechanism by which adipose tissue affects the nervous system is unclear. Firstly, adipose tissue is a source of many pro-inflammatory cytokines such as leptin, tumor necrosis factor

(TNF-α), interleukins 6 (IL-6), and interleukin 1 β (IL-1β), all of them involved in promoting chronic inflammation [11, 12]. Pro-inflammatory cytokines are also contributing to the development of neuroinflammation in the Central Nervous System [13, 14]. Many studies have shown that chronic inflammation is linked to cognitive decline and cognitive impairment, including memory loss and difficulty with problem-solving and decision-making [15, 16]. Secondly, body fat can negatively influence the condition of the vascular endothelium, which contributes to the impairment of the blood-brain barrier and consequently, to the impairment of cognitive functions [17]. The latest reports also show significant differences in the composition of the gut microbiota in obese and non-obese people. Such an alteration of intestinal microflora — in turn — may affect the level of cognitive functions [18].

So far, most research has focused on the negative effects of excess body fat mass on the level of cognitive functions in the elderly. A relatively limited number of studies address the problem of cognitive changes resulting from body fat mass in younger subjects. The purpose of this study was to assess the impact of body fat on cognitive performance in young, healthy people. The authors also attempted to evaluate the potential role of inflammatory cytokines in this interaction.

Material and methods

The study was conducted by the Declaration of Helsinki for Human Studies. The study protocol was approved by a local Ethics Committee.

Volunteers (50 people, age 21.55 ± 1.33) were recruited from the Collegium Medicum in Bydgoszcz. Participants were qualified based on a questionnaire. Exclusion criteria included a history of medications and dietary supplement use, a history of sleeping disorders, and a history of alcohol dependence. In addition, volunteers assessed their mood, level of physical activity, eating habits, and sleep quality. Only healthy women were qualified to participate in the study (38 women, age 21.65 ± 1.45).

The levels of cognitive skills were evaluated with the following tests: the Face/Name association test, the Trial Making Test, and the Stroop Test. The face/name association test consists of two stages. In the first stage (acquisition phase), volunteers were exposed to 100 faces associated with a single name each on a computer screen. In the second phase (retrieval phase), volunteers were presented with the same faces, but each face had two names associated with it. One of those names was the same as those presented during the first stage. The test result is a percentage of correctly answered names and the duration of the retrieval phase [19]. The Trial Making Test consisted of two pages. The first page contained numbers from 1 to 25, which were randomly arranged on a piece of paper. The task of the subject is to connect numbers of a continuous line (without revealing a paper pencil). The second page contained numbers (from 1 to 13) and letters (from A to L), which were randomly arranged on paper. The task of the subject was to connect numbers and letters alternately (without revealing a paper pencil). The result of the test is the time it took to complete part A and part B, respectively [20]. The Stroop test consisted of four pages. The first test page contained the names of colors written in two columns in black ink (20 words in each column). The task was to read the names of colors. The second page contained the rows of cross marks in two columns (20 rows in each column). The rows of cross marks were displayed in different colors. Each participant recognized and pronounced the color of each row. The third and fourth pages contained the names of colors written in two 20-word columns. An ink color was different than the name of a color. The written name of the color (third page) or the color of the ink (fourth page) was recognized and pronounced by each subject. For each page, the time of reading duration was recorded. In the statistical analysis, the authors used the reading time of the last page expressed as a percentage of the first page's reading time [21].

All participants underwent anthropometric measurements (weight, height, waist, and hip circumference) and determined body fat content using a body composition analyzer (TANITA, type BC-418MA).

The serum levels were determined of IL-6 and TNF-α. IL-6 concentration in serum was determined using an enzyme-linked immunosorbent assay (ELISA) kit (LDN GmbH & Co., Nordhorn, Germany). The assay uses monoclonal antibodies directed against distinct epitopes of IL-6. Reference range (according to manufacturer's manual) < 50 pg/mL. TNF-α concentration in serum was determined using an enzyme-linked immunosorbent assay (ELISA) kit (LDN GmbH & Co., Nordhorn, Germany). The assay uses monoclonal antibodies directed against distinct epitopes of TNF-α. Reference range (according to manufacturer's manual) 4.6–12.4 pg/mL.

The results are presented as means with standard deviation. The relationship between anthropometric measurements and concentration of IL-6 and TNF-α concentration and between cognitive test results and IL-6 and TNF-α are presented as a correlation. The statistical significance of the results was assessed using a T-test. P < 0.005 was considered statistically significant.

Results

Cognitive test results

The average score on the Face/Name Association Test was 66.97% ± 6.92. The mean retrieval phase duration equaled 316.23 ± 84.95 seconds. In the Stroop test, volunteers reached the mean score of 208.02 ± 31.37%. In the Trial Making Test, the average score was 81.09 ± 15 seconds and 93.51 ± 21.69, respectively, in parts A and B.

Anthropometric analysis

The average value of the body mass was 62.90 ± 12.72 kilograms (from 45.9 to 99.8). The average height was 167 ± 5.3 centimeters (from 158 to 175). The average fat content was 25.08% ± 8.47 (from 14 to 44.9). The average waist-hip ratio was 0.73 ± 0.004 (from 0.67 to 0.87).

Cytokine analysis

In 38 samples tested, the concentration of TNF-α ranged from 3.20 to 17.04 pg/mL. Concertation of IL-6 in 25 samples was below the detection level (< 2), in the other 13 samples concentration was from 8.52 to 58.66 pg/mL.

Observed was a statistically significant positive relationship between bodily fat content and TNF-α level ($p < 0.05$; $r = 0.14$) (Fig. 1). Not observed was a statistically significant correlation between bodily fat content and IL-6 level ($p > 0.5$; $r = 0.24$). However, a statistically significant positive relationship was observed between the waist-hip ratio and level of IL-6 level ($p < 0.005$; $r = 0.28$) (Fig. 2). A correlation between the waist-hip ratio and level of TNF-α ($r = 0.01$) was not observed.

The present study observed a negative correlation between of percentage fat tissue and the results of the Face/Name Association Test (recognition face/name) ($p < 0.05$; $r = 0.25$) (Fig. 3). The authors did not observe the influence of percentage body fat on results of Stroop test, Trial Making Test (part A and B) and time of recognition phase of Face/Name Association Test.

The authors observed a negative, statistically significant correlation between waist-hip ratio (WHR) and results of the Face/Name Association Test (percentage of recognition face) ($p < 0.05$; $r = 0.22$) (Fig. 4). The authors did not observe a negative correlation between time of recognition in Face/Name Test, results of Stroop Test and results of Trial Making Test.

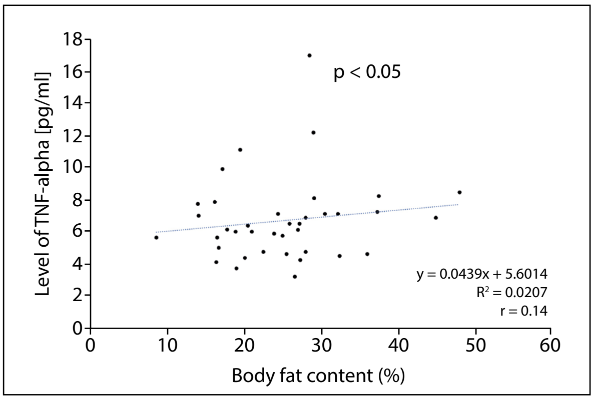

Figure 1. Correlation between the percentage of body fat and the level of TNF-alpha

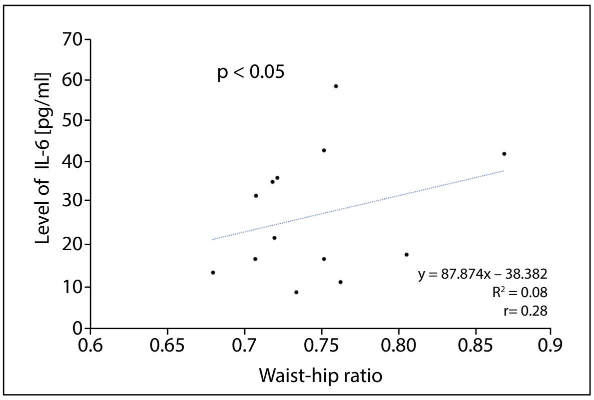

Figure 2. Correlation between waist-hip ratio and the level of IL-6

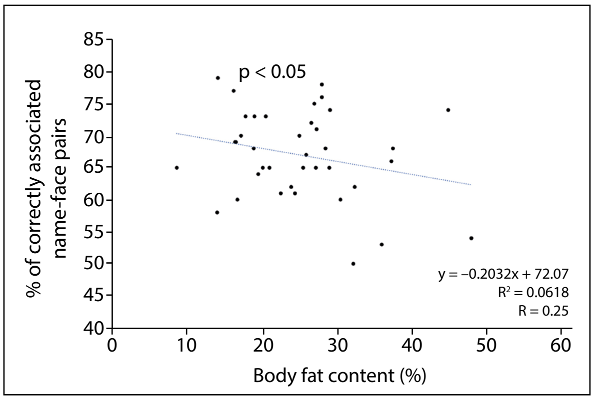

Figure 3. Correlation between the percentage of body fat and the % of correctly associated face/name pairs in the retrieval phase

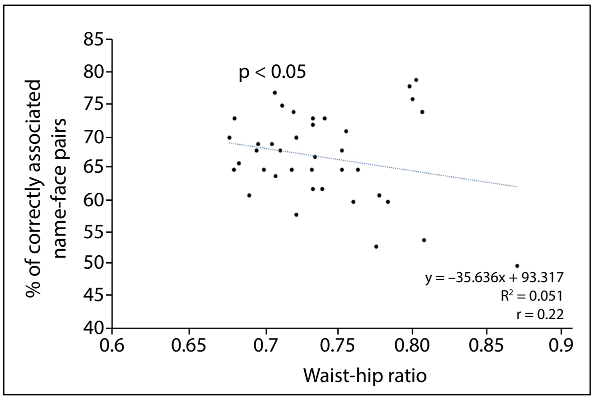

Figure 4. Correlation between waist-hip ratio and the % of correctly associated face/name pairs in the retrieval phase

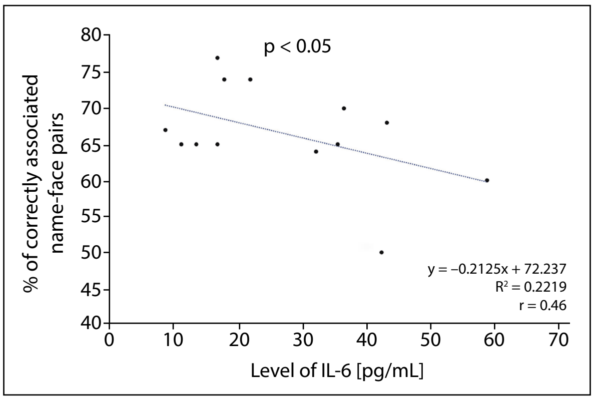

Figure 5. Correlation between the level of IL-6 and the % of correctly associated face/name pairs in the retrieval phase

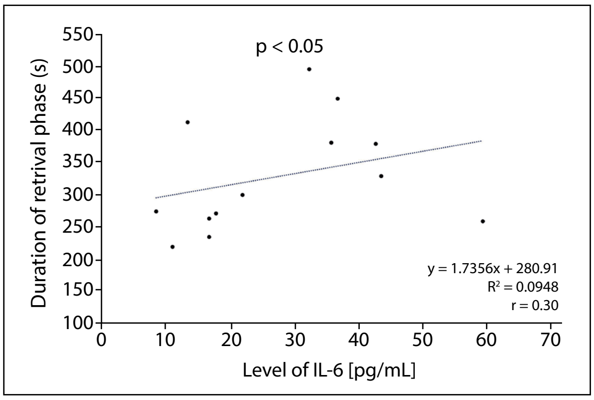

Figure 6. Correlation between the level of IL-6 and the duration of the retrieval phase

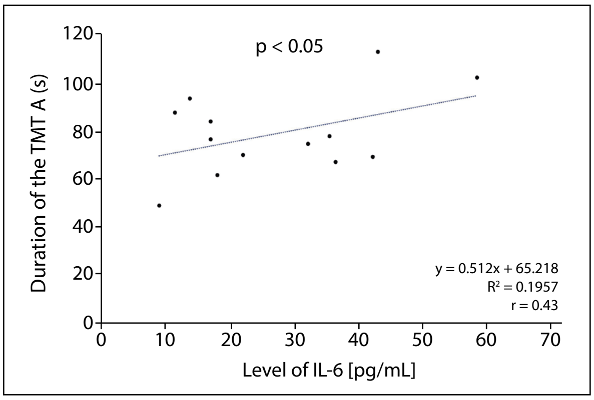

Figure 7. Correlation between the level of IL-6 and the duration of the TMT A

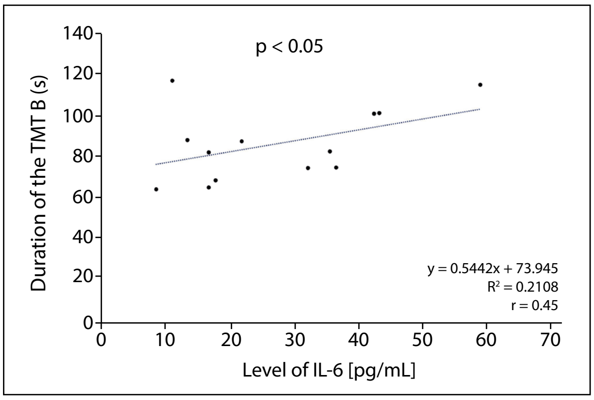

Figure 8. Correlation between the level of IL-6 and the duration of the TMT B

The authors did not observe a correlation between the level of TNF-α and the results of the Face/Name Association Test, Stroop Test, and Trial Making Test. Whereas they observed a negative, statistically significant correlation between the level of IL-6 and the results of the Face/Name Association Test, both in recognition of face ($p < 0.05$; $r = 0.46$) (Fig. 5) and in time duration ($p < 0.05$; $r = 0.30$) (Fig. 6), results of Stroop Test ($p < 0.05$; $r = 0.18$) and also results of Trial Making Test part A ($p < 0.05$; $r = 0.43$) and part B ($p < 0.05$; $r = 0.45$) (Fig. 7 and 8, respectively).

Discussion

Interleukin-6 (IL-6) is a cytokine that plays an important role in the immune system's response to inflammation and infection. Stimulation of B lymphocytes, enhanced synthesis of hepatic acute phase proteins, and regulation of metabolic and neurotrophic activities are the main functions of this cytokine. IL-6 is produced by various cells in the body, including immune cells, muscle cells, and adipose fat tissue. The receptors for IL-6 are expressed in the central nervous system [22]. Under normal physiological conditions, the concentration of IL-6in the human body remains relatively low [23].

However, elevated levels of IL-6 significantly contribute to inflammatory processes and have been linked to various health problems, such as chronic inflammation, autoimmune diseases, cancer, neurological disease, and a decline in long-term potentiation and learning [24, 25]. Increased level of Il-6 is associated with adipocyte hypertrophy in obesity [26]. Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine mainly produced by microglial cells and astrocytes [27]. Previous studies revealed that TNF-α has been linked to changes in body fat composition, especially among older adults, and plays a role in promoting inflammation and insulin resistance in the context of obesity-related metabolic complications. Furthermore, TNF-α at chronically high levels has been implicated in synaptic dysfunction, neuronal cell death, and cognitive impairment [28, 29].

The main result of the present study shows that: 1) an increase in the percentage of body fat tissue is associated with the increase of serum level of TNF-α. 2) An increase in the waist-hip ratio is associated with an increase in IL-6. 3) An increase in body fat content leads to a decreased level of cognitive performance dependent on the hippocampus, 4) there is a negative correlation between the level of Il-6 and the results of cognitive tests and 5) there is no statistically significant correlation between level of TNF-α and results of cognitive tests. The present findings are concordant with the results of several lines of evidence, which indicate that an increase in body mass negatively impacts cognitive performance [6, 30, 31]. Higher WHR is associated with elevated levels of IL-6 [32]. Studies demonstrated that individuals with higher levels of adipose tissue have increased levels of pro-inflammatory markers and worse cognitive functioning [33, 34]. Additionally, some research suggests that reducing body fat through exercise and weight loss can lower IL-6 levels [35]. The results from this study suggest a negative effect of IL-6 on cognitive performance. In the present study, an increased level of IL-6 was associated with a decline in cognitive function. The negative influence of IL-6 on cognitive performance is unclear, but previous research conducted on mice suggests that it disrupts neural circuitry involved in cognitive performance, inhibits neurogenesis, and decreases synaptic plasticity [36]. The authors did not observe a statistically significant correlation between the level of TNF-α and the results of cognitive tests (Face/Name Association Test, Stroop Test, Trail Making Test), but it has been shown that the level of TNF- can influence cognitive performance. Increased TNF level was observed to be associated with cognitive decline. One of the reports described the negative effect of overexpressing TNF-α on learning and memory but only in adult mice [37]. Similarly, adult rats with increased levels of TNF-α have impairment in spatial memory. Further, in mice, the cognitive deficit is reduced by pharmacological inhibition of TNF-α. Animal studies have shown that elevated levels of TNF-α are observed in mice with cognitive diseases (such as Alzheimer's disease) and have been linked to cognitive impairments [38]. Moreover, TNF-α has been implicated in neuroinflammatory processes that contribute to neuronal necroptosis, a mechanism associated with cognitive decline in AD [8]. Research studies on elderly people conducted by Alzamir [39] demonstrated that serum TNF levels in patients with diabetes and obesity were significantly higher than in non-obese counterparts. However, reports by Miyazaki et al. [40] did not confirm such association.

The hippocampus is one of the brain structures that is influenced by the bodily content of adipose tissue [41]. Brain scanning techniques showed that a greater BMI is related to reduced hippocampal volume [42]. Furthermore, the hippocampus is sensitive to fat tissue-derived inflammatory cytokines impairing synaptic plasticity in the dentate gyrus and CA regions of the hippocampus [43]. The present study observed the influence of the level of adipose tissue and the level of Il-6 on the results of The Face/Name Association test, which evaluates short-term declarative memory associated with hippocampal activity. Furthermore, a correlation was observed between the level of IL-6 and the results of the Trial Making Test, which measures prefrontal cortex-dependent attention and cognitive flexibility. No correlation was observed between the percentage of body fat, level of IL-6, and TNF-α, and the results of the Stroop Test, which is strongly associated with the activity of prefrontal and anterior cingulate cortical areas [44].

Conclusions

The current study demonstrated that in young women the increased body fat content is associated with decreased levels of cognitive performance. Furthermore, there was a positive correlation between the waist-hip ratio and the level of inflammatory cytokine Il-6, and a correlation between the higher level of IL-6 and lower cognitive test results. These observations together with the known negative impact of chronic IL-6 increase on CNS neurons, suggest that IL-6 may be a part of the mechanism responsible for the negative influence of excess adipose tissue on cognitive performance.

Article information

Data availability statement: *The data are available at the Department of Human Physiology CM UMK.*
Ethics statement: *The study was reviewed and approved by the Bioethics Committee of the Medical University in Bydgoszcz.*
Author contributions: *Study design: Blanka Dwojaczny, Piotr Złomańczuk; Data collection: Blanka Dwojaczny, Katarzyna Bergmann, Patrycja Czaj; Manuscript preparation: Blanka Dwojaczny, Patrycja Czaj, Kacper Denisiuk; Approval of final manuscript version: Piotr Złomańczuk.*
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