



# The Effect of Short-Term Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet on Hunger Hormones, Anthropometric Parameters, and Brain Structures in Middle-Aged Overweight and Obese Women: A Randomized Controlled Trial

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## What's Known

- Research suggests that a higher body mass index (BMI) is associated with changes in hormone circulation and brain structure, in addition to the known metabolic and physiological concomitant medical risks.
- In 2015, Morris and colleagues developed the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) pattern, which provides brain protection. This diet was inspired by the Mediterranean and DASH diets to improve some of their dietary factors, while also having the greatest impact on brain health.

## What's New

- There has been no randomized controlled trial to investigate this relationship.
- The results revealed that MIND hypocaloric diet intervention could improve anthropometric and metabolic profiles more than the control hypocaloric standard diet. However, our results findings were insufficient to find any differences in the whole and regional brain structures between the two groups. This study demonstrated for the first time that strict adherence to the MIND diet, as well as calorie restriction, could reverse the destructive effect of obesity.

## Abstract

**Background:** The rising prevalence of obesity, as well as its detrimental effects on the brain, has drawn attention to specific dietary patterns. This study aimed to examine the effect of the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) pattern on anthropometric parameters, hunger hormones, and brain structures in overweight and obese women.

**Methods:** This randomized trial was conducted in Shiraz between October 2018 and March 2019. We analyzed 37 healthy women with a mean age of  $48 \pm 5.38$  years and a Body Mass Index (BMI) of  $32 \pm 0.69$  Kg/m<sup>2</sup>. Participants were randomly allocated to a hypocaloric modified MIND diet or a hypocaloric control diet. Differences in anthropometric, laboratory analysis, and brain structure, were determined at baseline and three-month follow-up. Data were analyzed using SPSS 22.0. Independent and paired sample *t* test were used to determine between and within differences. We also used mixed-model ANOVA to compare the mean differences between two-factor groups.

**Results:** A more significant weight reduction ( $P < 0.0001$ ), BMI ( $P < 0.0001$ ), percentage of body fat ( $P = 0.03$ ), waist circumference ( $P = 0.01$ ), and Leptin concentration ( $P = 0.03$ ) were found in the MIND diet group. The results also showed a significant increase in Ghrelin ( $P = 0.002$ ) and GLP-1 ( $P = 0.01$ ) levels in the MIND diet group. The findings revealed no differences in the whole and regional brain structures between the two groups.

**Conclusion:** For the first time, this study showed that the MIND diet intervention could improve the devastating effect of obesity on metabolic profiles and anthropometric parameters. However, we could not find its effect on brain structures.

**Trial registration number:** IRCT20190427043387N1.

A preprint of this study was published at <https://www.medrxiv.org/content/10.1101/2020.06.28.20142018v1>.

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**Keywords** • Obesity • Gray matter • White matter • Peptide hormones • MIND diet

## Introduction

Obesity and overweight are associated with changes in body composition, hormonal secretion impairment, and inefficiency in the endocrine-nervous system network.<sup>1</sup> In addition to these deleterious effects, neuroimaging studies demonstrated that obesity causes neurophysiological changes in the brain.<sup>2</sup> Most of these changes and side effects will occur in middle-aged adults.<sup>3</sup>

Some hunger hormones, such as Leptin, Ghrelin, and glucagon-like peptide-1 (GLP-1), play an important role in transmitting information about energy storage to the hypothalamus centers. Some evidence supports the idea that Leptin resistance, which occurs in obesity, reduces the impact of Leptin in the hypothalamus and leads to weight gain. Obesity also desensitizes Ghrelin cells to signals of calorie restriction and food intake, which can attenuate weight gain and the development of glucose intolerance.<sup>4</sup> Besides, recent studies have shown that in morbid obesity diurnal secretion of GLP-1 was significantly decreased.<sup>5</sup> This indicates that unique dietary patterns and weight loss can improve its secretions.<sup>6</sup>

Clinical studies supported the pathophysiology of the brain in obese and overweight individuals.<sup>7,8</sup> According to a meta-analysis of 10 studies, body mass index is consistently associated with reduced the volume of subcortical regions.<sup>9</sup> In this regard, studies have shown that metabolically active central adipose tissue is more strongly associated with structural changes in the brain. These changes are also expressed by a reduction in whole brain and gray matter volume, regardless of insulin resistance or other complications of obesity.<sup>10</sup> In this line, diffusion-based spectrum imaging has shown that neuroinflammation in the hippocampus is one of the most critical mechanisms of this disorder in obese individuals.<sup>11</sup>

In this regard, evidence suggests that dietary-induced weight loss improves the metabolic profile and brain structures in obese patients.<sup>12</sup> This statement is supported by published studies, which show that improvement occurs before a significant amount of weight is lost.<sup>13, 14</sup> Previous research on the effect of healthy eating patterns on obesity, such as the dietary approach to stop hypertension (DASH) diet and the Mediterranean diet, have yielded inconclusive results.<sup>15, 16</sup> Morris and her colleagues designed a new dietary MIND pattern. Comprehensive epidemiologic studies have identified the MIND diet as one of the healthiest diets. The MIND pattern, on the other hand, is based on the Mediterranean

and the DASH diet and shares many of the same food groups for neuronal protection. It differs by allocating separate categories for the consumption of brain-healthy foods such as green leafy vegetables, berries, and olive oil as well as unhealthy brain foods such as red meat, sweets, and fast foods, all of which have been linked to neuroprotective features.<sup>17</sup>

Given the rising prevalence of obesity and its detrimental effects on both general and brain health, there is a greater demand for interventions that can break this vicious cycle. Since the MIND dietary pattern was based on the Mediterranean and DASH diets, it can be assumed that, in addition to brain health benefits, the MIND diet might also be beneficial for weight loss and general health. In addition, obesity in middle age can also be considered as a chronic and significant risk factor for global death in the future. There was no Randomized Controlled Trial (RCT) to investigate the effect of the MIND diet on obesity. As a result, we designed a randomized controlled trial in middle-aged women to investigate the effect of the short-term MIND dietary pattern intervention on anthropometric parameters and hunger hormones in healthy overweight and obese women, as well as brain structure investigation.

## Patients and Methods

A randomized, single-blind clinical trial was conducted at Imam Reza Specialty and Subspecialty Complex affiliated with Shiraz University of Medical Sciences (Shiraz, Iran) from October 2018 to March 2019. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1397.759) and registered in the Iranian Registry of Clinical Trials (IRCT20190427043387N1). The participants were informed about the goals of the research and written informed consent was obtained from the patients before participation. The study was carried out in agreement with the principles of the Helsinki Declaration.

Forty healthy overweight and obese middle-aged (40-60 years) women with BMI 30-35 Kg/m<sup>2</sup> have entered the study. The sample size was calculated using the below formula.<sup>18</sup>

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

Where  $Z_{1-\frac{\alpha}{2}}$  is corresponding to different desired levels of significance and is equal to 1.96 for  $\alpha=0.05$ ,  $Z_{1-\beta}$  different values of power and is equal to 1.28 for power=90%,  $\mu_1$  is mean of the outcome variable in group 1,  $\mu_2$  is mean

of the outcome variable in group 2,  $S_1$  is SD of the outcome variable in group 1, and  $S_2$  is SD in group 2.

We used data related to cognitive performance from Laura McMillan and others to calculate the sample size in which term of  $\mu_1, \mu_2$  was equal to 6.99,  $S_1$  and  $S_2$  were equivalent to 5.6 and 4.21, respectively.<sup>18</sup> The sample size was expanded to account for an estimated drop-out rate. As a result, each group's sample size was increased to 11 women.

Mini-Mental State Examination survey (MMSE)  $\geq 24$ ,<sup>19</sup> no history of severe medical problems (psychosis, bipolar disorder, depression or psychiatric disorder, unstable cardiovascular disease or myocardial infarction in last six months, stroke, history of brain injury, liver disease or hepatitis C and HIV), participation in weight loss programs, or consumption of weight loss drugs in the last three months were the inclusion criteria. During a telephone screening, participants were first asked about their eligibility. We also excluded people, if they did not entirely follow study protocols, or if they became pregnant.

Following admission, the participants were randomly assigned to the calorie-restricted MIND diet and calorie-restricted waiting list control diet. The allocation sequence was generated by a computerized software (Random allocation software) as simple randomization. The individuals, who randomized participants to the study groups and measured outcomes were blinded. Since our intervention is a dietary intervention, the study groups could not be blinded. These groups, however, had no communication with one another. Besides, there is no emphasis on the superiority of any diet in either group, because the control group was active and had a calorie-restricted diet. To avoid bias in the study, the individuals, who collected the study output were separated from those, who gave the intervention.

Individuals' dietary histories were assessed at the first visit using a 168-item semi-quantitative food frequency questionnaire (FFQ).<sup>20</sup> To estimate the basal metabolic rate, energy demands were calculated using World Health Organization equations.<sup>21</sup> Meals in both calorie-restricted diet groups included a balanced mix of 50-55% carbohydrates, 30% fat, and 15-20% proteins, and the calorie intake was restricted to at least 1500 Kcal/day. In the MIND diet group, the participants were trained to adjust their dietary patterns in accordance with the MIND diet instruction during the three months of the trial. The mentioned diet was developed to promote the consumption of additional green leafy

vegetables, berries, nuts, fruits, and legumes (especially beans). The diet also emphasized olive oil as the primary source of fat in the diet. In the MIND diet, it is also recommended that fish and poultry should be consumed more than one meal and more than two meals per week, respectively. In addition, in the current diet, for improving brain function and general wellness, the consumption of red meat, butter, and all types of margarine, as well as processed foods and sweets, has been restricted. All of the recommended components were chosen based on the energy requirements of each individual. The use of calorie restriction in both groups was justified in order to examine the effect of the only MIND diet as the major intervention as well as ethical concerns. The control group was urged not to change their typical eating habits for three months and to adhere to a calorie-restricted diet alone. Additionally, the MIND dietary recommendation was given to the waiting list control group at the end of the study. The participants received a menu based on the group's recommendation weekly. The adherence to the MIND diet was tracked using the MIND diet score questionnaire (table 1), a shopping list, and a three-day food diary.

#### *Blood Sampling, Clinical and Anthropometric Data*

The participants fasted for 24 hours, and then the blood samples were collected at the baseline and the end of the three-month period of the trial. The blood samples were centrifuged for five minutes at 5,000 rpm, and the isolated serums were deposited in microtubes. The collected samples were then stored at  $-80^\circ\text{C}$  for further analysis. To determine the plasma levels of Leptin, Ghrelin, and Glucagon-like peptide-1 (GLP-1), we used Enzyme-linked Immunosorbent Assay (ELISA) specialized kits (Bioassay Technology Laboratory, USA) before and after three months according to the manufacturer's instructions. All of the laboratory measurements were done in the same laboratory.

Weight, height, waist circumference, and the percentage of body fat were also measured at each of the two-time points of the study. Body weight (Kg) and height (m) were measured using standard scales, based on which the BMI ( $\text{Kg}/\text{m}^2$ ) of each participant was calculated. Body composition was obtained with a Bioelectrical Impedance Analysis device (BIA) closest to a standardized protocol (In Body S-10, USA). Hip circumference was measured using a plastic fiber tape placed directly on the skin at the Iliac crest and the widest diameter of the buttocks. Participants were asked not to engage in strenuous physical activity or drink alcohol or

**Table 1:** Changes in food intake from baseline to follow-up in the MIND diet group vs. control group

Foods	MIND diet group (n=22)			Control group (n=15)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Green leafy vegetables (serving/week) <sup>□</sup>	3.72±0.55	5.50±0.51	<0.001	3.60±0.50	3.93±0.25	<0.019
Other vegetables (serving/week) <sup>□</sup>	3.86±0.63	6.90±0.52	<0.001	3.93±0.25	4.00±0.65	<0.670
Berries (serving/week)	0.90±0.42	2.00±0.00	<0.001	0.93±0.25	0.73±0.59	<0.189
Nuts (serving/month)	4.45±1.01	4.63±0.49	0.478	4.53±0.63	3.73±0.59	<0.001
Olive oil (primary oil)*	0	1	<0.001	0	0	1
Butter, margarine (Table spoon/day)	1.50±0.59	0.63±0.49	<0.001	1.20±0.41	0.46±0.51	<0.001
Cheese (servings/week)	6.40±0.50	1.68±0.56	<0.001	6.33±0.48	6.33±0.48	<0.001
Whole grains (serving/day)	1.00±0.00	2.18±0.39	<0.001	1.00±0.00	0.33±0.48	<0.001
Fish (not fried) (meals/month)	1.22±0.42	2.45±0.50	<0.001	1.33±0.48	1.00±0.00	<0.019
Beans (meal/week) <sup>□</sup>	1.36±0.49	2.92±0.52	<0.001	1.46±0.51	1.60±0.50	<0.164
Poultry (not fried) (meal/week)	2.09±0.29	2.86±0.35	<0.001	2.13±0.35	2.00±0.37	<0.164
Red meat and products (meals/week)	2.36±0.49	2.00±0.00	0.002	2.46±0.51	2.40±0.50	0.334
Fast fried foods (times/week)	1.18±0.39	0.45±0.50	<0.001	1.26±0.45	0.93±0.23	0.019
Pastries and sweets (servings/week)	4.77±0.68	2.50±0.51	<0.001	4.73±0.79	2.60±0.50	<0.001

<sup>□</sup>Kale, collards, greens; spinach; lettuce/tossed salad. <sup>□</sup>Green/red peppers, squash, cooked carrots, raw carrots, broccoli, celery, potatoes, peas or lima beans, tomatoes, tomato sauce, string beans, beets, corn, zucchini/summer squash/eggplant, coleslaw, potato salad. <sup>□</sup>Beans, lentils, soybeans. Calculated using MIND diet score questionnaire and three-day food recall, using pair sample *t* test and \*using Man-Whitney *t* test.

caffeinated beverages for 24 hours prior to the measurements. Finally, the waist circumference was measured between the costal margin and the Iliac crest, which is the narrowest part of the torso.

#### Magnetic Resonance Imaging (MRI) Acquisition

MRI scans were performed on a subgroup of 11 patients in each group at Abu Ali Sina Hospital, Shiraz University of Medical Sciences (Shiraz, Iran, using a 12-channel head coil 3T system (Siemens Skyra, Germany). T1-weighted images were prepared using 192 slices in the sagittal plane, and a gradient-echo sequence (repetition time=1900 ms, echo time=2.52 ms, flip angle=9°, voxel size=1×1×mm). Image preprocessing was performed using the Freesurfer, stable version 5.1, (<http://surfer.nmr.mgh.harvard.edu>). This procedure included motion correction, intensity normalization, Talairach registration, skull stripping, segmentation of the subcortical white matter, tessellation of the gray matter (G.M)/white matter (W.M) boundary, automated topology correction, and surface deformation. We employed Freesurfer's longitudinal processing method to reduce biased analysis, measure the noise, and record changes in the brain structure in response to MIND dietary intervention in study groups. The cortical volume was estimated by multiplying the cortical thickness by the surface area of each vertex. Furthermore, based on previous studies some anatomic parcellation of the cortex, conducted by Freesurfer, was selected as a Region of Interest (ROI) for region analysis.<sup>22</sup>

#### Statistical Analysis

Data were analyzed using SPSS 22.0 (SPSS, Chicago, IL), and all data were expressed as Mean±SEM. The normality of the data was confirmed using one-sample Kolmogorov-Smirnov test. We also used the Mann-Whitney U test to compare the brain structure changes in the whole brain and ROI analyses between the two groups. Mixed Model two-way repeated-measures analysis of variance (ANOVA) was used to show the effect of three months of MIND diet intervention on the variables, with time (baseline, three months) as a within-subject factor, and treatment (MIND diet group, control group) as a between-subject factor.

For all analyses, a P value<0.05 was considered significant. To evaluate the magnitude of all hypotheses, the corresponding effect sizes in partial Eta square were calculated.

## Results

#### Baseline Characteristics

According to the CONSORT flowchart diagram (figure 1), 37 healthy overweight and obese women with a mean age of 48±5.3 years strictly adhered to the study protocols. There were no significant differences in baseline characteristics between the two groups, and no participant reported any negative effects of interventions. Descriptive results showed that at baseline, the mean BMI of participants was 32.01±4.21, and their mean weight was 82.10±12.71. The majority of the participants were married (83.80%), and the mean years of education were 16.4±1.03 years.

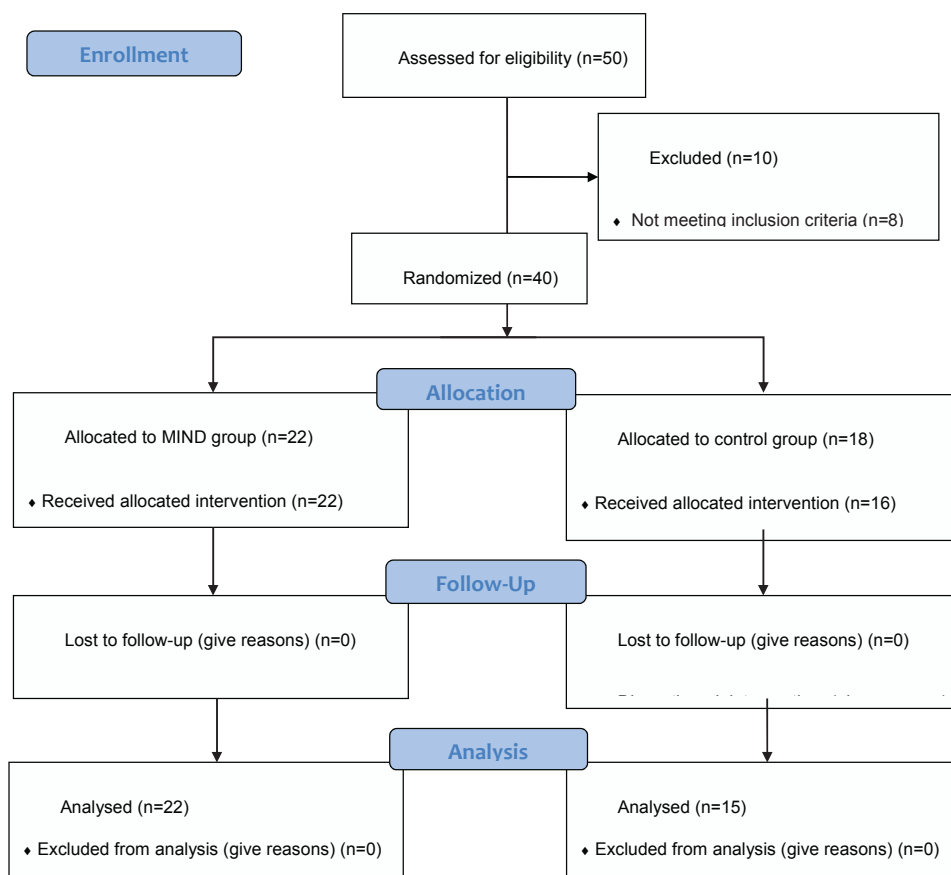


Figure 1: This figure represents the CONSORT flow diagram of the study

In terms of the baseline plasma Leptin levels, the two groups were comparable. The baseline characteristic is summarized in table 2.

*Changes in Food Intake From Baseline to Follow-up*

As shown in table 1, participants in the MIND diet group consumed significantly more green leafy vegetables, other vegetables, berries, olive oil, fish, beans, and chicken. The MIND diet

group also reduced their intake of butter, cheese, red meat, fast food, and sweets. In the MIND diet group, there were no significant differences in nut consumption before and after three months.

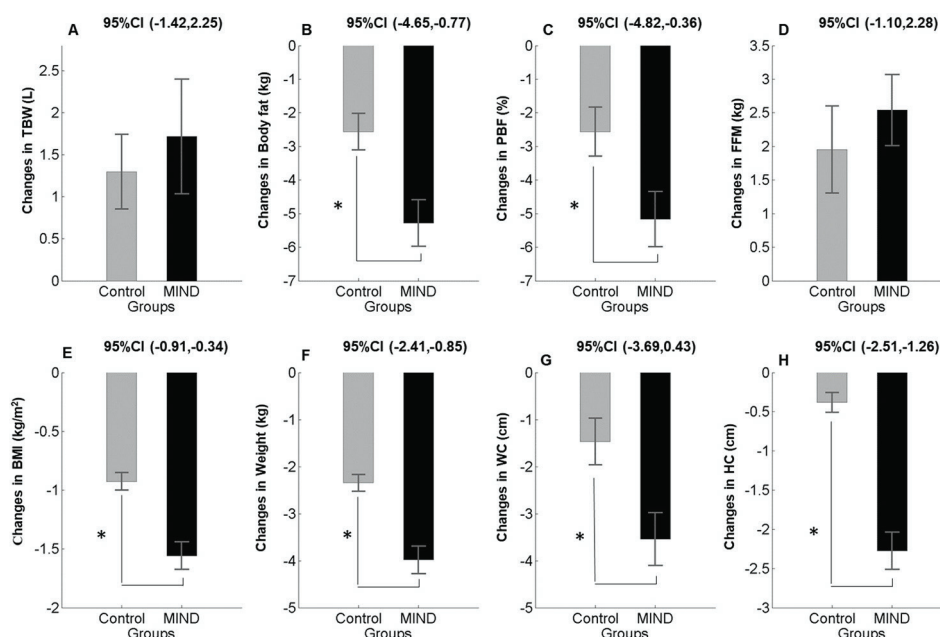
*Changes in Anthropometric Parameters*

The mean changes in anthropometric data at baseline and three months of follow-up are summarized in figure 2. The linear mixed model revealed a significant group×time interaction for

Table 2: Baseline characteristics of participants in the MIND diet vs. control group

Variables	MIND diet (n=22) Mean±SEM	Control group (n=15) Mean±SEM	P value
Age (year)	48.95±1.07	48.86±1.56	0.96
Education (year)	16.40±0.22	16.40±0.27	0.98
Weight (Kg)	81.95±2.33	82.33±3.96	0.93
Height (cm)	160.18±0.99	159.60±1.42	0.73
Percent of body fat (%)	40.84±1.13	41.05±1.63	0.91
Fat Free Mass (Kg)	48.05±1.09	47.66±1.37	0.82
BMI (Kg/m <sup>2</sup> )	31.90±0.79	32.19±1.28	0.83
WC (cm)	99.75±2.08	103.69±3.25	0.29
MMSE (score)	26.22 (0.34)	26.73 (0.45)	0.37
Leptin (ng/mL)	57.90 (6.00)	39.13 (5.93)	0.04
Ghrelin (pg/mL)	2.33 (0.65)	3.18 (1.00)	0.46
GLP-1 (pg/mL)	42.31 (8.49)	28.94 (6.49)	0.25

\*Baseline differences between groups used t test analysis. BMI: Body mass index; WC: Waist circumference; MMSE: Mini-mental state examination survey; GLP-1: Glucagon-like peptide 1.



**Figure 2:** Anthropometric changes were determined (Mean±SEM) in the MIND diet group (black color) and control group (gray color) at baseline and follow-up. Note that  $P < 0.05$  in a repeated measure ANOVA test indicating significant improvement in Body Mass Index, weight, waist circumference (2E, 2F, and 2G) and percent of body fat (2C), as well as hip circumference (2H) in the MIND diet group, in comparison with the control group. TBW: Total body water; PBF: Percent of body fat; FFM: Fat-free mass; BMI: Body mass index; WC: Waist circumferences; HC: Hip circumferences

**Table 3:** Changes in anthropometric parameters after three months follow-up in the MIND diet group vs. the control group

Anthropometric parameters	MIND group		Control group		F <sup>α</sup> (1,35)	Eta <sup>β</sup>	P value <sup>ε</sup>
	Mean±SEM	P value <sup>ε</sup>	Mean±SEM	P value			
TBW (L)	1.71±0.68	0.02	1.30±0.44	0.011	0.21	0.006	0.64
PBF (%)	-5.16±0.82	<0.001	-2.56±0.72	0.003	4.96	0.124	0.03
FFM (Kg)	2.54±0.52	<0.001	1.95±0.64	0.009	0.49	0.014	0.48
BMI (Kg/m <sup>2</sup> )	-1.55±0.11	<0.001	-0.92±0.07	<0.001	16.86	0.325	<0.001
Weight (Kg)	-3.98±0.29	<0.001	-2.34±0.17	<0.001	18.21	0.342	<0.001
WC (cm)	-3.54±0.56	<0.001	-1.46±0.49	0.011	6.74	0.162	0.01
HC (cm)	-2.27±0.23	<0.001	-0.30±0.12	0.009	37.66	0.518	<0.001

The repeated measure ANOVA for group×time interaction for anthropometrics data after three months follow-up. MIND: Mediterranean-DASH intervention for neurodegenerative delay, TBW: Total body water; PBF: Percent of body fat; FFM: Fat-free mass; BMI: Body mass index; WC: Waist circumferences; HC: Hip circumferences; <sup>α</sup>F value ( $df_1$  for the numerator,  $df_2$  for the denominator); <sup>β</sup>Partial eta squared for the ratio of variance associated with an effect; <sup>ε</sup>P value for differences between groups; <sup>ε</sup>P value for differences within groups.

body mass index and weight, indicating that the MIND diet group lost more weight after three months of intervention than the control group (table 3). The three-month MIND diet intervention had statistically significant effects on the percentage of body fat ( $P=0.032$ , figure 2C) and waist circumference ( $P=0.014$ , figure 2G), but time had no significant effect on total body water ( $P=0.647$ , figure 2A) or fat-free mass ( $P=0.486$ , figure 2D).

Finally, the MIND diet was found to reduce body fat percentage while retaining whole-body water and fat-free mass. However, the MIND diet could improve the anthropometric parameters more than the control group. According to the within-group comparison analysis, the MIND and control groups both improved over time (table 3), which expressed the effect of hypocaloric dietary

patterns on anthropometric indices.

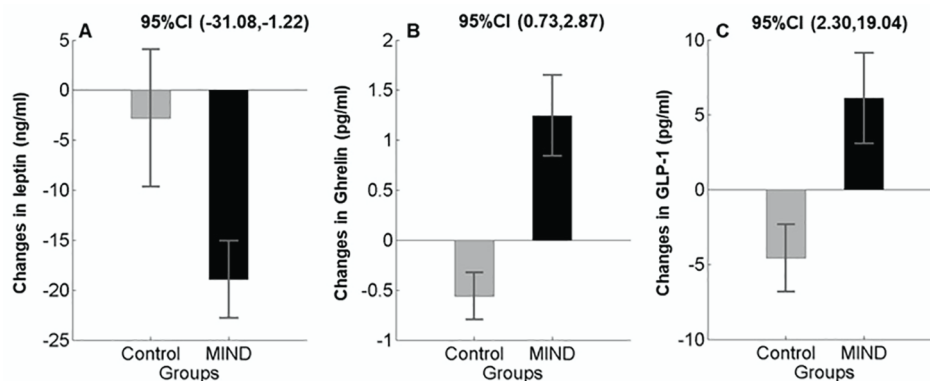
#### Changes in Metabolic Profiles

As shown in table 4, the repeated measure ANOVA for group × time interaction revealed a significant interaction effect for plasma levels of Leptin ( $P=0.035$ , figure 3A) and Ghrelin ( $P=0.02$ , figure 3B). This effect was also observed for plasma levels of GLP-1 ( $P=0.014$ , figure 3C), indicating that MIND diet intervention can improve plasma levels of these hunger hormones more than the control group. Except for Leptin, the within-group comparison showed no statistically significant difference in the primary endpoint after three months. Mean differences in each group at each time point are presented in figure 3.

**Table 4:** Changes in hunger hormones after three months follow-up in the MIND diet group vs. the control group

Hunger hormones	MIND group		Control group		F <sup>□</sup> (1,35)	Eta <sup>β</sup>	P value <sup>ε</sup>
	Mean±SEM	P value <sup>ε</sup>	Mean±SEM	P value			
Leptin (ng/mL)	-18.94±3.87	<0.001	-2.79±6.88	0.691	4.82	0.121	0.03
Ghrelin (pg/mL)	1.24±0.40	0.006	-0.56±0.23	0.032	11.74	0.251	0.002
GLP-1 (pg/mL)	6.10±3.02	0.05	-4.56±2.25	0.062	2.048	0.161	0.01

The repeated measure ANOVA for group × time interaction for metabolic profiles after three months follow-up. MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay, GLP-1: Glucagon-Like Peptide 1. <sup>□</sup>F value (df<sub>1</sub> for the numerator, df<sub>2</sub> for the denominator); <sup>β</sup>Partial eta squared for the ratio of variance associated with an effect; <sup>ε</sup>P value for differences between groups; <sup>ε</sup>P value for differences within groups.



**Figure 3:** Changes in metabolic profile were determined (Mean±SEM) in the MIND diet group (black color) and control group (gray color) at baseline and follow-up. Note that the MIND diet group indicated improvement in plasma levels of Leptin, Ghrelin, and GLP-1 (3A, 3B, 3D, and 3C) than the control group in a repeated measure group×time interaction ANOVA. MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay, GLP-1: Glucagon-Like Peptide 1.

### Changes in Brain Structures

In the current study, we first used whole-brain analysis to investigate the changes in the brain structures, so the results did not show significant differences in any of the brain areas between the two groups. This might be due to the limited sample size for this analysis. To address this issue, we anatomically selected brain areas that have previously responded to the special dietary pattern. These areas included the fusiform, parahippocampal, medial, superior, and temporal gyrus.

Our results diminished to find any interaction effects for brain structures. After three months, there were no statistically significant differences in brain structures between the MIND diet and control groups. Furthermore, there were no statistically significant between-group mean differences in brain structure between individuals assigned to the MIND diet group and those in the control group.

### Discussion

Our findings revealed that in the MIND diet group, mean changes in the weight, percentage of body fat, and waist circumference were decreased more than in the control group. In comparison to the control group, three months of MIND diet intervention improved metabolic profiles. There were no significant differences in

the brain structure of the two study groups.

Our findings also revealed a more significant effect of the MIND diet on weight, independent of energy intake, demonstrating the synergistic effect of the elements that make up the MIND diet along with the calorie restriction. In the present study, BMI in line with body fat percentage decreased significantly more in the MIND diet group than in the control group. Additionally, our findings showed that adherence to the MIND diet guidelines could help to maintain the total body water and fat-free mass. According to the Mediterranean cohort study, the highest quartile of the adherence to the Mediterranean diet as a whole dietary pattern was less likely to be associated with obesity.<sup>23</sup> The three-month parallel study on high-risk cardiovascular patients, on the other hand, found no significant relationship between the Mediterranean diet and changes in anthropometric indices.<sup>24</sup> In addition, in line with our results, a random-effects meta-analysis of 19 arms showed a greater effect of the Mediterranean diet on weight regardless of calorie consumption.<sup>25</sup> A study on the DASH diet found that when combined with energy-restricted diets for short periods of time, the DASH diet had a stronger impact on body weight (-2.27Kg) when accompanied with energy-restricted diets for short-term periods.<sup>26</sup> A possible correlation has been suggested: the MIND diet is based on the Mediterranean and DASH dietary patterns.

Therefore, the impact of the aforementioned patterns on weight loss contributes to part of its positive effects on anthropometric parameters.

In this line, an observational study reported that a high monounsaturated fatty acid olive oil content in a diet was associated with a decreasing obesity rate.<sup>27</sup> One of the possible mechanisms is that the oleic acid in olive oil triggers oleoylethanolamide, which is one of the intestinal satiety messengers in the brain.<sup>28</sup> On the other hand, berries, and anthocyanins were found to have preventive properties against body fat accumulation and were first reported in 2003.<sup>29</sup> The researchers found that berries extract could significantly suppress obesity induced by a high-fat diet by C57BL/6J mice.

In terms of inflammation markers, our findings showed that adherence to the MIND diet was associated with lower levels of Leptin. Previous studies demonstrated that these changes in the plasma levels of Leptin are only noticeable, when it is associated with weight loss.<sup>30, 31</sup> This finding is consistent with those of some studies, which show that higher adherence to the Mediterranean dietary pattern is directly associated with a significant reduction in the plasma levels of Leptin.<sup>32</sup> The MIND diet, combined with weight loss, significantly reduced the plasma Leptin levels. Leptin is well known as one of the adipokines synthesized by adipocytes in relation to fat volume, and it plays an essential role in regulating appetite. Leptin, in addition to its role as a satiety factor, is also called a considerable molecule at the cornerstone of metabolism, inflammation, and neurodegeneration.<sup>33</sup> Ghrelin is a peptide hormone that is primarily produced by specialized stomach cells, and similar to Leptin plays a vital role in regulating metabolism.<sup>34</sup> Plasma Ghrelin levels are negatively related to BMI. As a result, obese persons have lower ghrelin levels than people, who have a controlled weight. Ghrelin levels are negatively correlated with obesity-increasing factors, such as body fat percentage, insulin, and Leptin levels. In a study of non-obese and obese adults, the MRI reports indicated that Ghrelin was negatively associated with visceral obesity, fasting insulin, and insulin resistance index. On the other hand, weight loss is accompanied by a simultaneous increase in plasma Ghrelin levels, making it more difficult to maintain weight loss.<sup>35</sup> From this, it can be concluded that in our study, considering that the rate of weight loss due to decreased body fat percentage and also the decrease in plasma Leptin levels in the intervention group with MIND diet is higher than the control group, a greater increase in Ghrelin levels can be expected in the intervention group than the control group.

Our result demonstrated that a three-month MIND diet intervention could increase the mean change of GLP-1 secretion. The control group, on the other hand, indicated a decrease in secretion. The role of GLP-1 in the progression of obesity has been suggested in part because of the physiological effects of the hormone on appetite and food intake; some studies have declared that GLP-1 secretion may be reduced in obesity. BMI was found to have a significant negative relationship with GLP-1 secretion in several studies on diabetes and non-diabetic participants.<sup>36</sup> Another study found that the secretion of incretin, which stimulates insulin secretion, is inversely related to glucose tolerance and BMI.<sup>37</sup> This association is independent and developing. According to our findings, there might be other factors, such as dietary pattern components, other than calorie restriction alone, which could affect the plasma levels of GLP-1.

Additionally, consumption of green leafy vegetables and whole grains offer anti-inflammatory and anti-oxidative effects of the MIND diet, which can negatively impact the serum levels of pro-inflammatory markers such as Leptin and Ghrelin.<sup>38</sup> Finally, low amounts of red meat and saturated fatty acid content of the MIND diet improve body weight, glucose metabolism, and cardiovascular risk factors.<sup>39</sup> In this regard, the MIND diet promotes weight loss due to high dietary fiber contents, low energy density, low glycemic load, and high-water content. Therefore, the synergistic effect of MIND diet components might have a pivotal effect on the anthropometric parameters and metabolic profile of overweight and obese participants.

The results of the present study indicated that after three months, participants in the MIND diet group did not differ in some brain regions from those in the control group. Our findings are not in the same line as those of Lauri and others. In this study, calorie restriction was shown to partially reverse the white matter expansion in obese participants. However, their results could not significantly differ in the regional gray matter volume after dieting.<sup>40</sup> This RCT was performed on 16 obese subjects, who followed a very low-calorie diet for six weeks. Calorie restriction is one of the mechanisms that could be used. In the current trial, we used at least 1500 Kcal/d compared to the very low-calorie diet in the Lauri study I. One of the limitations of the present study is that the majority of studies with significant effects were conducted over a longer period of time.

Our trial had several strengths. First, as far as



we know, it was the first randomized trial, which investigated the effect of MIND intervention in healthy overweight and obese women. Second, the present study was a well-controlled dietary intervention trial with extremely high compliance. Third, both study groups were instructed to follow a calorie-restricted diet to compare the MIND diet and calorie restriction diet separately.

Our study, however, had several limitations. The current trial was a single-center, controlled recruitment study, which examined a sample of well-educated healthy volunteers. Therefore, we cannot generalize our findings to the larger society. Besides, the short length of our trial, as well as the small sample size, could be the other limitations.

### Conclusion

In summary, the result of our trial for the first time indicated that the MIND diet intervention can improve anthropometric parameters and metabolic profiles in healthy overweight and obese women. Calorie restriction could also enhance this effect. However, The findings of the current study did not reveal a relationship between brain structure and MIND dietary patterns. It is recommended to investigate the validity of these findings by conducting multicenter studies with larger sample sizes and longer durations in the future.

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### Author Contribution

Golnaz Arjmand: Conceptualization, Methodology, Data curation, Writing, Formal analysis. Mohammad Hassan Eftekhari: Conceptualization, Methodology, Review, and editing Supervising. Mojtaba Abbas-Zadeh: Methodology, Data curation, Review and editing, Formal analysis. Majid Fardaei: Conceptualization, Methodology, Design of the work. All of the authors read the final draft for important intellectual content, approve it to be published, and agree with all aspects of the work for integrity and accuracy.

### Conflict of Interest

Dr. Majid Fardaei, as the Editorial Board Member,

was not involved in any stage of handling this manuscript. A team of independent experts was formed by the Editorial Board to review the editor's article without his knowledge.

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