

# Dietary Inflammatory Index and Cognitive Function: Findings from a Cross-Sectional Study in Obese Chinese Township Population from 45 to 75 Years

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**Background and Objective:** Cognitive dysfunction is highly prevalent in obese people, and food is a key factor in obesity, and dietary inflammatory index (DII) can reflect whether diet has anti-inflammatory or pro-inflammatory potential. In addition, dietary fatty acid consumption is linked to inflammation, obesity, and cognitive impairment. Erythrocyte membrane fatty acids can reflect dietary fatty acid intake. Our hypothesis was that erythrocyte membrane fatty acids might have a significant impact on the relationship between DII and cognition in obese individuals, and we designed experiments to test the hypothesis.

**Methods:** In three villages in Beijing, we collected 579 respondents from individuals 45 to 75 years old and categorized them by body mass index. The Montreal Cognitive Assessment (MoCA) score and DII score was calculated and gas chromatography was used to measure the proportion of erythrocyte membrane fatty acids. The relationship between the DII score and cognition was examined using multiple linear regression and binary logistic regression. Mediation analysis can help to understand the causal chain between variables, deeply explore the internal relationship and mechanism of action between variables. So a multiple chain mediation model was developed to investigate the mediating factors between the DII score and cognitive association.

**Results:** According to adjusted linear regression, higher DII scores were linked to lower MoCA scores in the obese group. The negative correlation between DII score and cognitive function score remains in binary linear regression. We discovered through mediation analysis that erythrocyte membrane fatty acids mediate the detrimental link between DII and cognitive function in obese individuals.

**Conclusion:** We propose that higher DII scores in obese people are associated with a decline in cognitive function. In addition, this effect might be mediated via the fatty acids in the erythrocyte membrane.

**Keywords:** mild cognitive impairment, dietary inflammatory index, obesity, fatty acids, chain mediation effect

## Introduction

Dementia has emerged as one of the most ominous medical challenges of the 21st century, affecting over 1.5 million individuals aged 60 years in China.<sup>1,2</sup> In addition, mild cognitive impairment (MCI) affected 38.77 million people over the age of 60, with a prevalence of 15.5%.<sup>2,3</sup> With the acceleration of the aging process of Chinese society, it is expected that by 2030, the proportion of elderly people aged 60 years and older in China will expand from the current 15% to 25%,<sup>4</sup> which revealed that the harm of cognitive dysfunction is increasing year by year. Evidence indicates that obesity is associated with the development of the cognitive impairment and has a higher potential for acquiring dementia in the mild and later life of individuals.<sup>5-8</sup> As is reported by a system review, the prevalence of MCI in obese persons in China and Egypt was 18.5% and 42.9%, respectively.<sup>8</sup>

Dietary intake has a significant impact on obesity induced cognitive impairment.<sup>9,10</sup> Ozawa et al, discovered that an inflammatory dietary pattern strong in red and processed meat, peas, legumes, and fried food and deficient in whole grains was linked to higher levels of interleukin-6 (IL-6) and hastened cognitive impairment in later age.<sup>11</sup> Contrarily, the Mediterranean diet is mostly made up of fruits and vegetables, fish, grains, legumes, and olive oil, which has anti-inflammatory and antioxidant

characteristics that can reduce the incidence of obesity and cognitive dysfunction.<sup>12,13</sup> A systematic review examined the correlation between elevated levels of circulating IL-6 and overall cognitive decline, finding a positive relationship between the two variables.<sup>14</sup> Additionally, a large neuroimaging study revealed a relationship between reduced hippocampal and increased ventricular volumes in late life and increased mid-life inflammatory marker expression in plasma.<sup>15</sup> These results suggest that inflammation may be associated with obesity-related cognitive dysfunction. Dietary inflammatory index (DII) is a literature-derived and population-based indicator, designed and developed by Shivappa et al, is used to evaluate the potential for dietary inflammation.<sup>16,17</sup> According to reports, DII may be utilized to investigate the links between dietary inflammation potential and illnesses including obesity and cognitive dysfunction.<sup>18,19</sup> Diets with the most pro-inflammatory potential were linked to a higher incidence of MCI or dementia in older women, according to Hayden et al.<sup>20</sup> According to Frith et al, there is a continuous negative correlation between DII and many types of memory, such as episodic memory, working memory, and semantic memory.<sup>21</sup> However, less frequently are such investigations conducted in obese individuals, despite obesity plays important roles in cognitive decline.

Dietary fatty acids can be determined by serum, plasma, and erythrocyte membrane fatty acids, erythrocyte membrane fatty acids represent a comprehensive measure of the interaction between dietary fatty acid intake, other dietary factors, and fatty acid metabolism patterns, and reflect several months of dietary intake,<sup>22,23</sup> with sensitive and accurate characteristics, can be used as biomarkers for a variety of metabolic diseases, including obesity, diabetes, metabolic syndrome, etc.<sup>24</sup> In our previous study, it was found that there was an association between erythrocyte membrane fatty acids and cognitive function in obese patients.<sup>25,26</sup>

Given the current research progress, we hypothesized that DII may be associated with cognitive dysfunction and that erythrocyte membrane fatty acids may play a mediating role in it. Therefore, we performed a cross-sectional study to assess the association between dietary inflammatory potential and cognitive function in normal and obese population. In determining if dietary inflammation worsens the negative effects of obesity on cognitive function, we looked at the relationships between DII and Montreal cognitive assessment (MoCA) by regression analysis in normal and obese individuals. Finally, mediation analysis was carried out to explore the mediating factors of this association.

## Methods

### Study Design

Participants (aged from 45 to 75) was recruited from November to December in 2020 in three townships of Beijing (Caiyu town, Weishanzhuang town and Lixian town). Subsequently, the basic information, diet and cognitive function of the subjects were collected through questionnaires, physical examination was performed and blood was collected for testing.

### Participants and Groups

Similar to previous studies,<sup>25</sup> the inclusion and exclusion criteria for this study were: subjects who volunteered were excluded if they were thin, had severe thyroid and renal dysfunction, had a history of central nervous system disease such as cancer, encephalitis, head trauma, or had a clear history of mental illness, had reading, hearing, or visual impairment, or lost self-care, or had missing or mandatory suspicious data. We further excluded the people with  $24 \text{ kg/m}^2 \leq \text{body mass index (BMI)} < 28 \text{ kg/m}^2$ . A total of 1282 participants volunteered to participate in this investigation. After screening, 579 participants were subsequently included in this study and split into normal weight group (NM;  $18.5 \text{ kg/m}^2 \leq \text{BMI} < 24 \text{ kg/m}^2$ ) and obese group (OB;  $\text{BMI} \geq 28 \text{ kg/m}^2$ ) based on BMI, according to the Chinese Obesity Working Group<sup>27</sup> (Figure 1).

### Informed Consent

Before formal signing, we submitted the informed consent form template to the ethics committee for review and obtained approval from the Ethics Review Committee of Capital Medical University (Z2019SY011). We performed the trial in strict accordance with the approved version of the ethical review and ensured that the informed consent was clear to the subject by reading the informed consent form to the subject before the trial and by carefully reading the informed consent form and signing the agreement entirely voluntary. During the conduct of the trial, any subject may ask the investigator

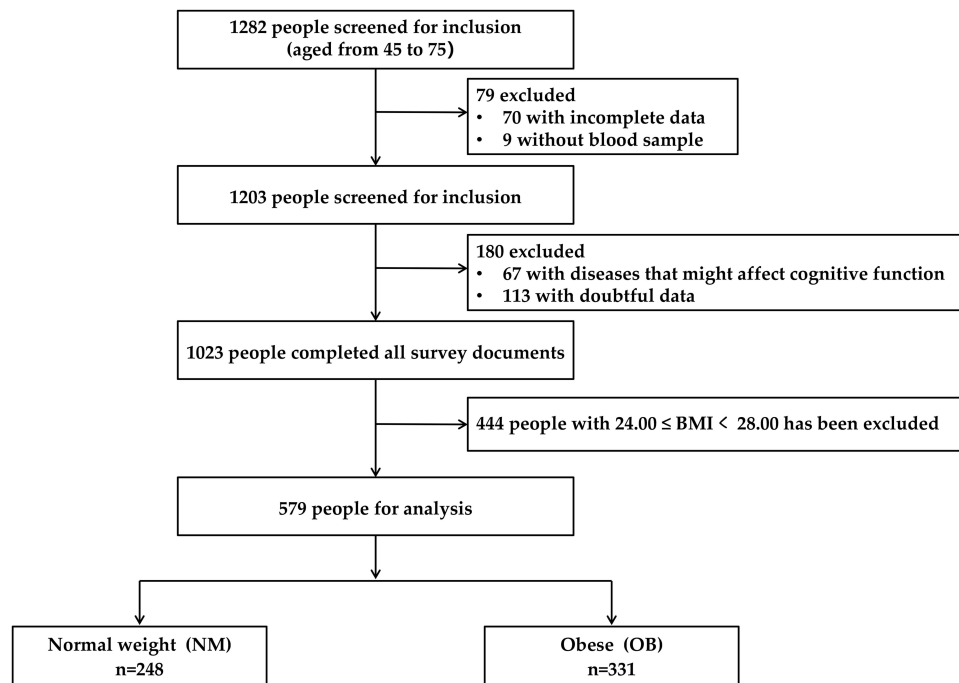


Figure 1 Study flowchart.

any questions, and may withdraw from the study at any time without being influenced by the outside world, and we shall properly handle the subsequent work.

## Baseline Data Collection

A face-to-face questionnaire survey were used to gather data on dietary intake, cognitive performance, and sociodemographic factors. To guarantee the caliber of the questionnaires, the investigators received specialized training. Name, age, gender, smoking, drinking, exercising, employment status, past medical history, and family history of possible Alzheimer's diseases (AD) or dementia were collected as sociodemographic factors for this study. As in our earlier study, we assessed cognitive function and overall cognitive status using the Chinese translations of the MoCA scale.<sup>25,28,29</sup> The study's definition of the MCI group included people with no more than six years of education and a MoCA score  $\leq 19$ , those with seven to twelve years of education and a MoCA score  $\leq 22$ , and people with more than twelve years of education and a MoCA score  $\leq 24$ .<sup>30</sup> Later, a second examination by neurologists was performed to validate the clinical diagnosis. The 34 items of the food frequency questionnaire (FFQ) were used to obtain information on dietary intake during interviews. The questionnaire employed for the Dietary Investigation of Chinese Residents served as the basis for the FFQ.<sup>31</sup> The "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China" released by the Diabetes Society of Chinese Medical Association in 2017<sup>32</sup> states that diabetes mellitus is diagnosed by fasting blood glucose (FBG)  $\geq 7.0$  mmol/L. Triglyceride levels in serum  $\geq 1.7$  mmol/L were used to define hypertriglyceridemia.<sup>33</sup>

## Physical Examination, Blood Sample Collection and Detection

As was mentioned in our previous study,<sup>25</sup> briefly, measurements of height (m), weight (kg), waist circumference (cm), hip circumference (cm) were taken. BMI and waist-hip ratios (WHR) were calculated according to the following formula: BMI = weight (kg)/ height (m)<sup>2</sup>; WHR = waist circumference (cm)/ hip circumference (cm).

The fasting peripheral blood samples were collected (10mL), of which 6 mL were used for biochemical analysis, and the test items included: total cholesterol (TC), total triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), FBG, apolipoprotein E (ApoE), serotonin (5-HT) and inflammatory cytokines, including toll-like receptor 4 (TLR4), lipopolysaccharide (LPS), TLR1, TLR2, IL-3, IL-12 and interferon gamma (IFN- $\gamma$ ). An additional

4 mL blood sample was used for measurement of erythrocyte membrane fatty acid content. As mentioned earlier by us,<sup>25</sup> after detection, erythrocyte membrane fatty acid content was represented as a percentage.

## Dietary Inflammatory Index (DII)

The DII scores were calculated according to the research of Shivappa et al.<sup>16</sup> In a nutshell, the dietary data is transformed into the food ingredient content found in the DII scale, per the food ingredient database (the Chinese food ingredient table). The Z-score for each nutrient was derived based on the mean and standard deviation of each participant's dietary intake data by comparing to the worldwide standard dietary intake database.  $Z\text{-score} = (\text{actual intake of food components} - \text{average intake level}) / \text{standard deviation}$ . Z-scores were converted to a percentile approach to minimize the impact of "right bias". Each percentile was multiplied by two and then "1" was subtracted to produce a symmetrical distribution. The distribution that results has a center point of 0 and upper and lower limits of -1 and +1. The "Food Parameter Specific DII Score" is then calculated by multiplying the center percentile value (ie, median) of each nutrient or food parameter by the corresponding "Overall Inflammatory Response Score". The final step is to calculate the person's "Overall DII score" by adding up all their "food-specific DII scores". We ranked DII scores in order from small to large and divided them equally into three groups: tertile 1 (most anti-inflammatory potential), tertile 2 (neutral diet) and tertile 3 (most pro-inflammatory potential).

In this analysis, 20 kinds of food parameters were available from the FFQ, including energy (kcal), protein (g), carbohydrate (g), total fat (g), fiber (g), cholesterol (mg), vitamin A (RE),  $\beta$ -carotene ( $\mu\text{g}$ ), thiamin (mg), riboflavin (mg), niacin (mg), vitamin C (mg), vitamin E (mg), saturated fatty acids (SFA; g), monounsaturated fatty acids (MUFA; g), polyunsaturated fatty acids (PUFA; g), magnesium (Mg; mg), ferrum (Fe; mg), zinc (Zn; mg), selenium (Se;  $\mu\text{g}$ ).

## Tool Validity and Reliability

We gave participants a quick physical check and a health assessment in an effort to boost patient cooperation. Every day once the survey is finished, its correctness and completeness are verified. Information that was inaccurate or lacking was quickly updated. To guarantee accuracy and completeness, two investigators were chosen to enter the data independently throughout the data entry stage.

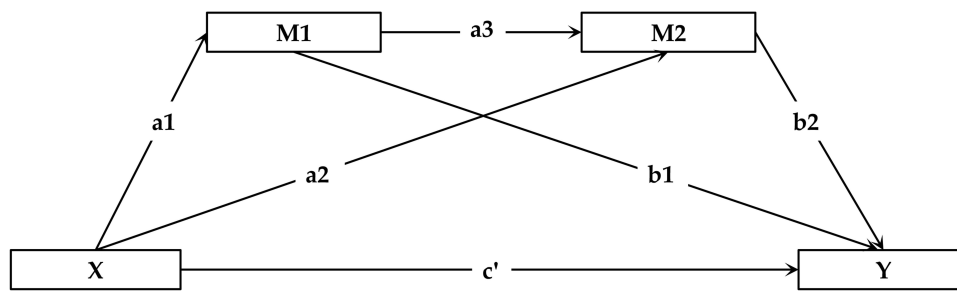
## Covariates

The covariates that adjusted in multivariable models were summarized as follows: age, gender, WHR, culture, energy intake, lifestyles (smoking, drinking and exercise) and diseases (history of hypertension, diabetes mellitus and hypertriglyceridemia).

## Statistical Analysis

The data entry was done using the Epidata 3.1 software (The Epi Data Association, Odense, Denmark). To verify accuracy, every piece of data was checked twice, and a consistency test was run. In our study, SPSS 26.0 was used for all statistical analysis. The categorical variables were reported as n (%), while the continuous variables were shown with their mean values and standard deviation (Mean and SD). Continuous data were tested for normality. The DII scores were divided into tertiles. Using the one-way ANOVA test, Mann-Whitney *U*-test, Kruskal-Wallis test, Chi-squared test and Fisher's exact test to detect the significance among continuous and categorical variables between the DII tertile groups in different groups.

The association between DII scores and MoCA scores was estimated using multivariable linear regression adjusted for three models, including the Model 1 (adjusted for age, gender, WHR, energy intake and culture), the Model 2 (adjusted for the covariates in Model 1 plus lifestyles), the Model 3 (adjusted for the covariates in Model 2 plus diseases). The association between DII tertiles and incidence of MCI was further analyzed using binary logistics regression, using the same adjusted model as multivariable linear regression. Finally, multiple mediation analysis model was used to investigate the relationship between DII score, erythrocyte membrane fatty acids and cognitive function (MoCA score) (Figure 2).  $P < 0.05$  representing statistically significant differences.



**Figure 2** Schematic Diagram of Multiple Chain Mediation Effect Model. (X) Independent variable; (Y) Dependent variable; M1: Mediator 1; M2: Mediator 2; a1: Effect coefficient of X on M1; a2: Effect coefficient of X on M2; b1: Effect coefficient of M1 on Y; b2: Effect coefficient of M2 on Y; c': Effect coefficient of X on Y.

## Results

### Demographic Sociology

A final total of 579 participants were included in the current study, with 248 in the NM group and 331 in the OB group (Figure 1). Results of Table 1 provided an overview of the demographic and sociological features of the NM and OB participants based on DII tertiles. The participants, who was in tertile3 group were more prone to have lower energy intake, either in NM or in OB group ( $P<0.01$ ). In NM group, tertile 3 had the largest percentage of people who never drank, followed by tertile 2 and then tertile 1 ( $P<0.05$ ).

### The Compositions of Dietary Inflammatory Index in Different BMI Based Groups

In the OB group, tertile3 (most pro-inflammatory potential) was more prevalent and tertile1 (most anti-inflammatory potential) was less than it was in the NM group, but the difference was not statistically significant ( $P=0.623$ ) (Figure 3). The components of food intake and the mean values of the total DII scores were compared between the NM and OB groups (Figure 4). The OB group has a lower intake in protein, vitamin A, riboflavin, Mg and Se than the NM group ( $P<0.05$ ), despite the fact that the difference in overall DII scores between the two groups was not significant.

### Cognitive Scores for Comparison Among the DII Tertiles

The MoCA scales was employed in this investigation to evaluate cognitive function. No significant difference in any of the scores between the normal and obese groups could be found in our earlier investigation.<sup>25</sup> Following DII stratification, MoCA scores in the NM group revealed disparities in DII tertiles. Tertile3 (most pro-inflammatory potential) has worse MoCA visuospatial function score ( $P<0.05$ ) and better MoCA language skills score ( $P<0.01$ ) (Table 2).

### Comparison of the Blood Biochemistry Parameters and Inflammatory Related Cytokines Among the DII Tertiles

As shown in [Supplementary Material Tables S1](#) and Table 3, after stratification according to DII, there was no discernible difference in the blood biochemistry parameters whatever in NM or OB group. Participants adhering to the tertile 2 diet tended to have higher IFN- $\gamma$  level and greater levels of IL-12 in NM and OB groups, respectively ( $P<0.05$ ).

### Comparison of the Erythrocyte Membrane Fatty Acid Among the DII Tertiles

In the NM group, participants in the highest DII group were more likely to have larger proportions of 1-tricosanoic acid (C23:0) and lower proportions of ginkgolic acid (C15:1) ( $P<0.05$ ). Additionally, tertile2 has a higher proportion of C15:1 than tertile1 ( $P<0.05$ ). In the OB group, participants in tertile3 revealed relatively lower proportion of C15:1 compared with tertile1 ( $P<0.05$ ) (Table 4).

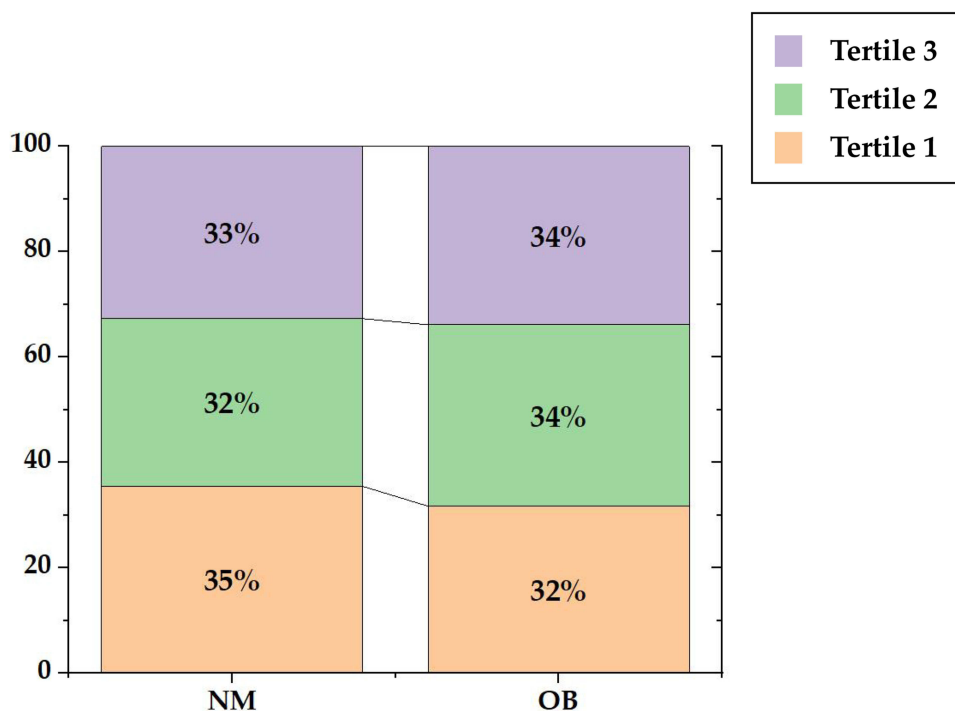
**Table 1** Demographic Sociology of Study Population

Variables		NM (N=248)				OB (N=331)			
		Tertile 1 (-3.24 ~ -0.79) (N=88)	Tertile 2 (-0.78 ~ 0.77) (N=79)	Tertile 3 (0.79 ~ 2.97) (N=81)	P	Tertile 1 (-3.46 ~ -0.81) (N=105)	Tertile 2 (-0.77 ~ 0.77) (N=114)	Tertile 3 (0.80 ~ 3.58) (N=112)	P
		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
DII scores		-1.68±0.64	0.01±0.45	1.66±0.63	<0.001 <sup>abc</sup>	-1.71±0.62	0.02±0.46	1.69±0.60	<0.001 <sup>abc</sup>
BMI (kg/m <sup>2</sup> )		22.20±1.36	22.05±1.44	22.23±1.28	0.797	30.43±2.25	30.83±2.37	30.96±2.49	0.274
Age		61.63±7.34	61.69±7.38	62.68±7.48	0.472	59.85±7.42	58.66±6.30	59.91±6.78	0.156
Waist-hip ratio		0.90±0.06	0.91±0.06	0.91±0.07	0.719	0.92±0.06	0.92±0.08	0.93±0.06	0.576
Energy intake (kcal)		2601.40±980.77	1783.63±575.55	1480.55±610.24	<0.001 <sup>abc</sup>	2669.471±1105.495	1785.175±576.269	1332.85±400.82	<0.001 <sup>abc</sup>
Gender	Male	37(42.05)	23(29.11)	22(27.16)	0.080	41(39.05)	29(25.44)	33(29.46)	0.085
	Female	51(57.95)	56(70.89)	59(72.84)		64(60.95)	85(74.56)	79(70.54)	
Central obesity	No	24(27.27)	13(16.67)	14(17.28)	0.160	12(11.88)	8(7.27)	7(6.36)	0.307
	Yes	64(72.73)	65(83.33)	67(82.72)		89(88.12)	102(92.73)	103(93.64)	
Culture	≤6 years	25(28.41)	22(28.57)	31(38.27)	0.267	27(25.71)	30(26.79)	38(33.93)	0.213
	7~12 years	63(71.59)	54(70.13)	48(59.26)		76(72.38)	78(69.64)	74(66.07)	
	>12 years	0(0.00)	1(1.30)	2(2.47)		2(1.90)	4(3.57)	0(0.00)	
MCI	No	40(45.45)	32(40.51)	42(51.85)	0.352	57(54.29)	58(50.88)	54(48.21)	0.670
	Yes	48(54.55)	47(59.49)	39(48.15)		48(45.71)	56(49.12)	58(51.79)	
Smoking	Never	57(67.86)	58(77.33)	62(76.54)	0.641	84(81.55)	93(81.58)	86(77.48)	0.218
	Continuous smoking for at least 6 months	25(29.76)	16(21.33)	17(20.99)		16(15.53)	21(18.42)	20(18.02)	
	Smoking for at least 6 months but not continuous	2(2.38)	1(1.33)	2(2.47)		3(2.91)	0(0.00)	5(4.50)	
Drinking	Never	54(63.53)	53(69.74)	67(82.72)	0.026*	63(61.76)	82(72.57)	84(76.36)	0.138
	Former	3(3.53)	3(3.95)	4(4.94)		6(5.88)	7(6.19)	3(2.73)	
	Current	28(32.94)	20(26.32)	10(12.35)		33(32.35)	24(21.24)	33(20.91)	
Exercise	No	11(12.64)	10(12.66)	11(13.58)	0.979	15(14.42)	10(9.01)	18(16.36)	0.248
	Yes	76(87.36)	69(87.34)	70(86.42)		89(85.58)	101(90.99)	92(83.64)	

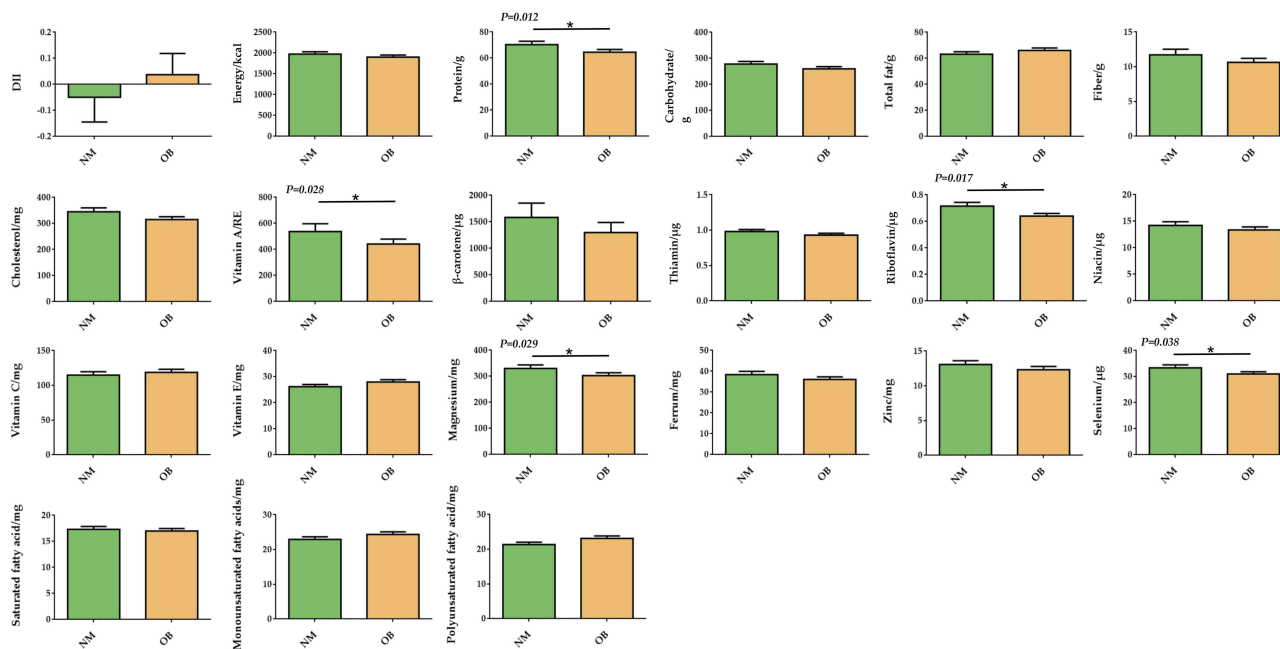
History of hypertension	No	56(63.64)	49(62.03)	53(65.43)	0.623	52(49.52)	50(43.86)	49(43.75)	0.800
	Yes	29(32.95)	29(36.71)	28(34.57)		53(50.48)	63(55.26)	62(55.36)	
	Unknow	3(3.41)	1(1.27)	0(0.00)		0(0.00)	1(0.88)	1(0.89)	
Diabetes mellitus	No	70(79.55)	61(77.22)	73(90.12)	0.072	80(76.19)	92(80.7)	86(76.79)	0.677
	Yes	18(20.45)	18(22.78)	8(9.88)		25(23.81)	22(19.3)	26(23.21)	
Hypertriglyceridemia	No	51(57.95)	51(64.56)	50(61.73)	0.679	72(68.57)	78(68.42)	75(66.96)	0.961
	Yes	37(42.05)	28(35.44)	31(38.27)		33(31.43)	36(31.58)	37(33.04)	

**Notes:** Frequency (n) and percentage (%) were used to describe enumeration data; mean and standard deviation (SD) were used to express measurement data that followed a normal distribution. Multiple sample means were compared using the Kruskal–Wallis H-test in a non-parametric test, and Bonferroni correction was used for statistically significant variables for post-hoc pairwise comparisons. Univariate analysis was carried out using the chi-square test and Fisher exact test. <sup>a</sup>Indicates a significant different between tertiel1 and tertiel2; <sup>b</sup>Indicates a significant different between tertiel1 and tertiel3; <sup>c</sup>Indicates a significant different between tertiel2 and tertiel3; \*P<0.05.

**Abbreviations:** BMI, body mass index; NM, normal weight group; OB, obese group; SD, standard deviation.



**Figure 3** The proportions of DII tertiles in NM and OB groups. Univariate analysis was carried out using the chi-square test. **Abbreviations:** NM, normal weight group; OB, obese group.



**Figure 4** Comparison of food compositions and the DII scores in NM and OB group. Data were tested for normality and comparisons between groups were performed using the Mann–Whitney U-test \* $P < 0.05$ . **Abbreviations:** NM, normal weight group; OB, obese group.

### Association Between the DII Scores and MCI: Results of Regression Analysis

No matter the adjustments, there was no linear correlation between DII scores and MoCA scores in the NM group that was statistically significant. Participants in the OB group who scored higher on DII significantly scored lower on MoCA in all adjusted models ( $P < 0.05$ ) (Table 5).

**Table 2** Cognitive Score of the Study Population in the NM and OB Groups

Variables	NM (N=248)				OB (N=331)			
	Tertile1 (-3.24 ~ -0.79) (N=88)	Tertile2 (-0.78 ~ 0.77) (N=79)	Tertile3 (0.79 ~ 2.97) (N=81)	P	Tertile1 (-3.46 ~ -0.81) (N=105)	Tertile2 (-0.77 ~ 0.77) (N=114)	Tertile3 (0.80 ~ 3.58) (N=112)	P
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
MoCA	21.28±3.75	20.78±4.25	21.10±4.29	0.835	21.79±4.22	21.31±3.78	21.23±4.29	0.480
MoCA visuospatial function	3.27±1.20	2.84±1.13	2.79±1.48	0.030 <sup>ab</sup>	3.29±1.19	2.95±1.18	2.82±1.36	0.075
MoCA naming	2.75±0.51	2.66±0.71	2.75±0.54	0.841	2.72±0.57	2.78±0.50	2.64±0.70	0.409
MoCA attention	5.00±1.10	5.03±1.13	5.04±1.16	0.911	5.23±1.09	5.21±0.91	5.06±1.00	0.167
MoCA language skills	1.78±0.89	1.67±0.90	2.17±0.96	0.001 <sup>bc</sup>	1.88±0.90	1.94±0.89	2.05±1.01	0.453
MoCA abstracting	0.98±0.84	0.82±0.81	0.90±0.88	0.506	0.97±0.84	0.84±0.80	0.96±0.92	0.552
MoCA memory	1.97±1.50	2.28±1.81	1.85±1.49	0.270	2.22±1.53	2.02±1.66	2.05±1.55	0.454
MoCA orientation	5.53±0.83	5.49±0.71	5.59±0.88	0.191	5.49±0.83	5.57±0.70	5.65±0.71	0.308
MoCA	21.28±3.75	20.78±4.25	21.10±4.29	0.835	21.79±4.22	21.31±3.78	21.23±4.29	0.480

**Notes:** Data were tested for normality and expressed as mean ± standard deviation (SD). The comparisons among three groups were performed using the Kruskal–Wallis H-test, and Bonferroni correction was used for statistically significant variables for post-hoc pairwise comparisons.; <sup>a</sup>Indicates a significant different between tertile1 and tertile2; <sup>b</sup>Indicates a significant different between tertile1 and tertile3; <sup>c</sup>Indicates a significant different between tertile2 and tertile3.

**Abbreviations:** MoCA, Montreal cognitive assessment; NM, normal weight group; OB, obese group; SD, standard deviation.

**Table 3** Inflammatory Related Cytokines of the Study Population in the NM and OB Groups

Variables	NM (N=248)				OB (N=331)			
	Tertile1 (-3.24 ~ -0.79) (N=88)	Tertile2 (-0.78 ~ 0.77) (N=79)	Tertile3 (0.79 ~ 2.97) (N=81)	P	Tertile1 (-3.46 ~ -0.81) (N=105)	Tertile2 (-0.77 ~ 0.77) (N=114)	Tertile3 (0.80 ~ 3.58) (N=112)	P
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
5-HT (pg/mL)	1759.57±380.55	1816.29±407.44	1770.52±350.29	0.600	1684.90±392.20	1683.78±399.77	1685.47±378.70	0.981
TLR4 (ng/mL)	7.69±1.15	7.70±1.23	8.01±1.37	0.173	7.57±1.37	7.55±1.30	7.59±1.28	0.958
LPS (pg/mL)	3.51±0.75	3.61±0.77	3.33±0.77	0.060	3.50±0.75	3.34±0.76	3.28±0.75	0.168
TLR1 (ng/mL)	4.90±0.85	4.85±0.79	4.88±0.97	0.915	4.81±0.83	4.77±0.85	4.77±0.75	0.733
TLR2 (ng/mL)	23.29±9.62	25.82±9.95	23.27±9.57	0.162	22.97±10.47	24.60±10.08	23.09±9.77	0.412
IL-3 (pg/mL)	76.72±38.97	78.92±37.85	75.72±39.40	0.867	76.02±33.44	81.12±34.76	73.78±34.74	0.328
IL-12 (pg/mL)	52.41±21.81	53.60±21.25	57.41±24.09	0.325	48.42±21.88	54.42±21.12	52.06±22.70	0.045 <sup>a</sup>
IFN-γ (pg/mL)	831.78±347.41	953.43±348.77	844.66±314.60	0.043 <sup>ac</sup>	844.59±316.24	845.31±333.61	857.37±357.00	0.877
5-HT (pg/mL)	1759.57±380.55	1816.29±407.44	1770.52±350.29	0.600	1684.90±392.20	1683.78±399.77	1685.47±378.70	0.981

**Notes:** Data were tested for normality and expressed as mean ± standard deviation (SD). The comparisons among three groups were performed using the Kruskal–Wallis H-test, and Bonferroni correction was used for statistically significant variables for post-hoc pairwise comparisons. <sup>a</sup>Indicates a significant different between tertile1 and tertile2; <sup>b</sup>Indicates a significant different between tertile2 and tertile3.

**Abbreviations:** 5-HT, serotonin; IL-3, interleukin-3; IL-12, interleukin-12; IFN-γ, interferon gamma; LPS, lipopolysaccharide; NM, normal weight group; OB, obese group; TLR1, toll-like receptor 1; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; SD, standard deviation.

There was a negative relationship between DII score and MoCA visuospatial function ( $P<0.01$ ) in NM group, meanwhile a positive relationship between DII score and MoCA language ( $P<0.01$ ) was found in NM group. Among OB group, significant negative associations were also observed for DII scores and MoCA visuospatial function, MoCA naming, MoCA attention and MoCA memory ( $P<0.05$ ) in each adjusted model.

DII score was divided into tertiles of categorical variables, the lowest DII score considered the anti-inflammatory diet (tertile1), tertile2 considered the neutral diet, and tertile with the highest DII score considered the pro-inflammatory diet (tertile3). We performed binary logistic regression with setting the tertile1 as reference (Figure 5). In NM group, there was no significance between DII tertiles and the occurrence of MCI, whatever the adjustments. In OB group, DII was positively associated with the risk of MCI in all models. The significantly increased Odds Ratio (95% Confidence

**Table 4** The Fatty Acid Composition of the Erythrocyte Membranes of Study Population

Variables	NM (N=248)				OB (N=331)			
	Tertile1 (-3.24 ~ -0.79) (N=88)	Tertile2 (-0.78 ~ 0.77) (N=79)	Tertile3 (0.79 ~ 2.97) (N=81)	P	Tertile1 (-3.46 ~ -0.81) (N=105)	Tertile2 (-0.77 ~ 0.77) (N=114)	Tertile3 (0.80 ~ 3.58) (N=112)	P
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)		Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
C23:0%	0.00±0.00	0.00±0.00	0.04±0.19	0.044 <sup>bc</sup>	0.00±0.04	0.01±0.08	0.01±0.08	0.805
SFA %	47.15±8.14	46.37±8.83	47.21±8.35	0.518	50.39±9.65	50.29±9.91	49.68±9.76	0.519
C15:1%	0.00±0.00	0.04±0.24	0.00±0.00	0.039 <sup>ac</sup>	0.08±0.32	0.05±0.29	0.00±0.00	0.037 <sup>b</sup>
MUFA %	12.15±1.90	12.40±2.28	12.32±2.43	0.793	11.94±3.60	11.69±2.60	12.13±2.65	0.297
n-6%	35.86±6.05	35.98±7.35	35.38±5.99	0.449	32.43±7.49	32.34±8.35	33.35±7.97	0.448
n-3%	4.80±1.39	5.20±3.12	5.05±1.45	0.528	5.20±4.05	5.65±4.84	4.82±1.79	0.862
PUFA %	40.70±6.91	41.23±7.72	40.47±6.85	0.597	37.67±8.24	38.02±8.64	38.20±8.54	0.851
n6/n3	7.90±2.00	7.75±2.48	7.44±2.00	0.275	7.25±1.95	6.93±2.04	7.40±1.92	0.223

**Notes:** Data were tested for normality and expressed as mean ± standard deviation (SD). The comparisons among three groups were performed using the Kruskal–Wallis H-test, and Bonferroni correction was used for statistically significant variables for post-hoc pairwise comparisons. <sup>a</sup>Indicates a significant different between tertiel1 and tertiel2; <sup>b</sup>Indicates a significant different between tertiel1 and tertiel3; <sup>c</sup>Indicates a significant different between tertiel2 and tertiel3.

**Abbreviations:** MUFA, Monounsaturated fatty acids; NM, normal weight group; n-3, omega-3 fatty acids; n-6, omega-6 fatty acids; OB, obese group; PUFA, Polyunsaturated fatty acids; SFA, Saturated fatty acids; SD, standard deviation.

**Table 5** β Values of DII in Linear Regression Models Between DII and Cognitive Scores After Adjusting for Different Covariates

Variables	NM		OB	
	β (95% CI)	P-value	β (95% CI)	P-value
MoCA				
Model 1	0.115 (-0.266, 0.496)	0.553	-0.374 (-0.714, -0.033)	0.032*
Model 2	0.100 (-0.289, 0.490)	0.612	-0.382 (-0.725, -0.040)	0.029*
Model 3	0.107 (-0.282, 0.497)	0.588	-0.389 (-0.733, -0.044)	0.027*
MoCA visuospatial function				
Model 1	-0.193 (-0.318, -0.067)	0.003**	-0.140 (-0.252, -0.029)	0.014*
Model 2	-0.179 (-0.307, -0.052)	0.006**	-0.137 (-0.250, -0.024)	0.017*
Model 3	-0.177 (-0.306, -0.049)	0.007**	-0.142 (-0.255, -0.029)	0.014*
MoCA naming				
Model 1	0.009 (-0.051, 0.070)	0.768	-0.069 (-0.123, -0.015)	0.013*
Model 2	0.007 (-0.054, 0.069)	0.813	-0.070 (-0.124, -0.016)	0.012*
Model 3	0.008 (-0.055, 0.070)	0.810	-0.072 (-0.126, -0.017)	0.011*
MoCA attention				
Model 1	0.018 (-0.094, 0.130)	0.746	-0.097 (-0.186, -0.009)	0.032*
Model 2	0.023 (-0.090, 0.137)	0.686	-0.101 (-0.190, -0.012)	0.026*
Model 3	0.025 (-0.089, 0.139)	0.669	-0.102 (-0.191, -0.012)	0.026*
MoCA language skills				
Model 1	0.190 (0.098, 0.283)	<0.001**	0.036 (-0.051, 0.124)	0.415
Model 2	0.171 (0.078, 0.264)	<0.001**	0.033 (-0.055, 0.122)	0.457
Model 3	0.168 (0.074, 0.261)	<0.001**	0.033 (-0.056, 0.121)	0.471
MoCA abstracting				
Model 1	0.068 (-0.019, 0.154)	0.126	0.017 (-0.059, 0.092)	0.665
Model 2	0.043 (-0.044, 0.131)	0.328	0.016 (-0.060, 0.092)	0.684
Model 3	0.045 (-0.041, 0.132)	0.304	0.008 (-0.068, 0.084)	0.842

(Continued)

Table 5 (Continued).

Variables	NM		OB	
	$\beta$ (95% CI)	P-value	$\beta$ (95% CI)	P-value
MoCA memory				
Model 1	-0.005 (-0.162, 0.152)	0.952	-0.161 (-0.307, -0.016)	0.030*
Model 2	0.002 (-0.158, 0.162)	0.982	-0.166 (-0.313, -0.020)	0.026*
Model 3	0.008 (-0.151, 0.167)	0.920	-0.156 (-0.303, -0.009)	0.037*
MoCA orientation				
Model 1	0.027 (-0.058, 0.111)	0.534	0.041 (-0.026, 0.109)	0.231
Model 2	0.033 (-0.053, 0.118)	0.452	0.043 (-0.023, 0.109)	0.200
Model 3	0.031 (-0.056, 0.118)	0.486	0.042 (-0.024, 0.109)	0.210

**Notes:** Model 1: adjusted for age, gender, waist-hip ratio, energy intake, culture; Model 2: adjusted for the variables in Model 1 plus lifestyle (smoking, drinking and exercise); Model 3: adjusted for the variables in Model 2 plus disease (history of hypertension, diabetes mellitus, hypertriglyceridemia). \*\* $P < 0.01$ , \* $P < 0.05$ .

**Abbreviations:** 95% CI, 95% confidence interval; MoCA, Montreal cognitive assessment; NM, normal weight group; OB, obese group; SD, standard deviation.

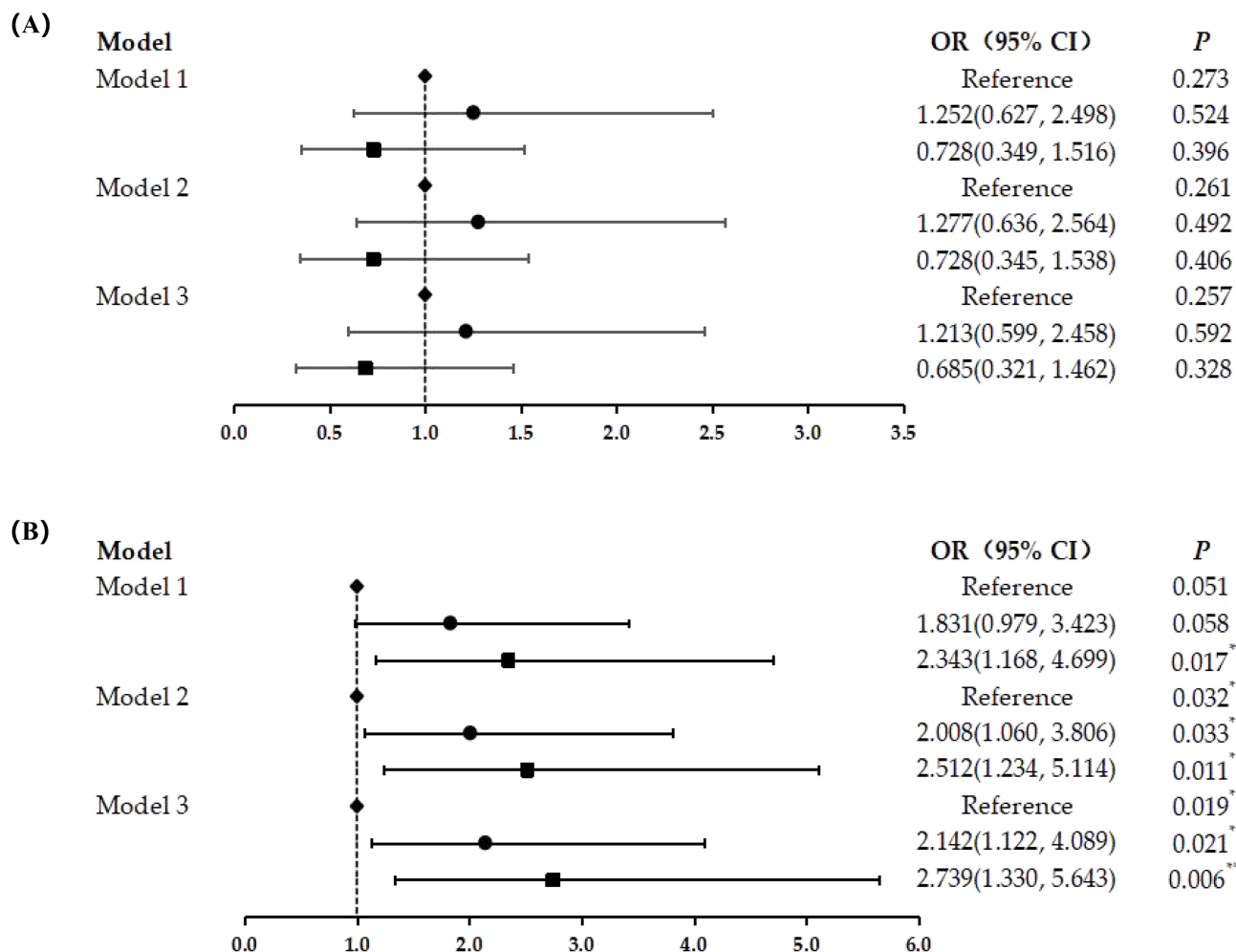
Intervals) (ORs (95% CI)) of model 1 between the risk of MCI and DII score across tertile 3 compared with tertile1 was 2.343 (1.168, 4.699). In model 2, a 1-unit increase in DII was significantly associated with higher MCI occurrence by 2.008 and 2.512-fold in tertile2 and tertile3, respectively ( $P < 0.05$ ). Additionally, in Model 3, DII tertiles revealed a 2.142 or 2.739-fold (Tertile2: OR=2.142, 95% CI: 1.122, 4.089,  $P < 0.05$ ; Tertile3: OR=2.739, 95% CI: 1.330, 5.643,  $P < 0.01$ ) in the incidence of MCI for each tertile growth of the DII score.

## Association between the DII scores and the fatty acid compositions of the erythrocyte membrane: Results of regression analysis

The  $\beta$  value of DII in linear regression models between DII and the fatty acid composition of the erythrocyte membranes after adjusting for different covariates was summarized on [Supplementary Material Table S2](#). In NM group, there was a positive relationship between the proportions of lignoceric acid (C24:0) of the erythrocyte membranes and DII scores in Model 1, and this correlation persisted in Model 2 and Model 3 ( $P < 0.01$ ). A positive association between the proportions of C23:0 and pentadecanoic acid (C15:0) of the erythrocyte membrane and DII score was observed only in Model 3 and Model 1, respectively ( $P < 0.05$ ). In the OB group, there was a negative and positive relationship between the proportion of palmitic acid (C16:0) and arachidonic acid (C20:4n-6) in the erythrocyte membrane and DII score in Model 1, respectively, and this relationship persisted in Model 2 and Model 3 ( $P < 0.05$ ). The proportions of the ratio of omega-6 fatty acids (n-6) to omega-3 fatty acids (n-3) in the erythrocyte membranes was favorably correlated with DII score in three Models ( $P < 0.05$ ). A positive correlation between the proportion of MUFA, n-6 in the erythrocyte membrane and DII score was observed only in Model 2 ( $P < 0.05$ ).

## The Erythrocyte Membrane Fatty Acids Mediate the Effect of DII on Cognition: Mediation Analysis

We investigated the association of DII score, erythrocyte membrane fatty acids, and MoCA score using a multiple mediation model in OB group. The adjustment variables of Model 3 that were previously discussed were utilized as covariates in this section. According to the findings, several erythrocyte membrane fatty acids function as mediators and form diverse chain mediation models. Regardless of the mediation paradigm, there were substantial total and direct effects between DII score and MoCA score ([Supplementary Material Table S3](#)) ( $P < 0.05$ ). While simple indirect effects mediated by single erythrocyte membrane fatty acids were not significant in these models ([Supplementary Material Table S4](#)), chain-mediated effects were substantial in each of these models ([Table 6](#)). The chain mediation effects were negative for models 1 (C16:0% for mediator 1, C11:0% for mediator 2), 5 (MUFA% for mediator 1, C11:0% for mediator 2), 8 (n-6% for mediator 1, C20:1% for mediator 2), 12 (n-3% for mediator 1, C11:0% for mediator 2), 14 (C18:1n-9% for mediator 1, C13:0% for mediator 2), and 15 (n-6/n-3%



**Figure 5** Forest plot of binary logistic analysis of the association between Dietary inflammatory index and MoCA scores in normal participants. Tertiel 1 (◆), Tertiel 2 (●), Tertiel 3 (■). (A): the association between DII and MoCA scores in NM group; (B): the association between DII and MoCA scores in OB group. 95% CI: 95% Confidence interval; \*\*P<0.01, \*P<0.05. Model 1: adjusted for age, gender, waist-Hip ratio, energy intake, culture. Model 2: adjusted for the variables in Model 1 plus lifestyle (smoking, drinking and exercise). Model 3: adjusted for the variables in Model 2 plus disease (history of hypertension, diabetes mellitus, hypertriglyceridemia). **Abbreviations:** NM, normal weight group; OB, obese group.

for mediator 1, C18:3n-3% for mediator 2) among them, whereas others showed positive chained mediation effects. These findings reveal a negative association between DII score and MoCA score that can be mediated by erythrocyte membrane fatty acids, while there is also a positive and negative chained indirect impact when various fatty acids function as mediating effects.

**Table 6** Chain Mediation Effect of Chain Mediation Effect Model

Model	Effect	Effect Value	Bootstrap SE	Boot CI Lower	Boot CI Upper
Model 1	DII→C16: 0%→C11: 0%→MoCA	-0.0035	0.0030	-0.0143	-0.0001
Model 2	DII→C20: 0%→C14: 1%→MoCA	0.0000	0.0001	0.0000	0.0004
Model 3	DII→SFA%→C11: 0%→MoCA	0.0035	0.0031	0.0001	0.0159
Model 4	DII→MUFA%→C11: 0%→MoCA	0.0033	0.0025	0.0004	0.0122
Model 5	DII→MUFA%→C13: 0%→MoCA	-0.0054	0.0044	-0.0204	-0.0003
Model 6	DII→MUFA%→C20: 1%→MoCA	0.0122	0.0091	0.0010	0.0389
Model 7	DII→C18: 2n-6%→C20: 5n-3%→MoCA	0.0001	0.0003	0.0000	0.0015
Model 8	DII→n-6%→C20: 1%→MoCA	-0.0053	0.0045	-0.0226	-0.0004

(Continued)

**Table 6** (Continued).

Model	Effect	Effect Value	Bootstrap SE	Boot CI Lower	Boot CI Upper
Model 9	DII→n-6%→C20: 5n-3%→MoCA	0.0002	0.0003	0.0000	0.0019
Model 10	DII→C20: 3n-3%→C13: 0%→MoCA	0.0018	0.0018	0.0001	0.0098
Model 11	DII→C20: 3n-3%→C18: 3n-3%→MoCA	0.0009	0.0008	0.0000	0.0036
Model 12	DII→n-3%→C11: 0%→MoCA	-0.0020	0.0019	-0.0099	-0.0001
Model 13	DII→C18: 1n-9c%→C11: 0%→MoCA	0.0033	0.0027	0.0005	0.0134
Model 14	DII→C18: 1n-9c%→C13: 0%→MoCA	-0.0047	0.0038	-0.0183	-0.0004
Model 15	DII→n-6/n-3%→C18: 3n-3%→MoCA	-0.0063	0.0043	-0.0195	-0.0009

**Notes:** Model 1: the proportion of C16:0 and C11:0 on erythrocyte membrane was used as Mediator 1 (M1) and Mediator 2 (M2); Model 2: the proportion of C20:0 and C14:1 on erythrocyte membrane was used as M1 and M2; Model 3: the proportion of SFA and C11:0 on erythrocyte membrane was used as M1 and M2; Model 4: the proportion of MUFA and C11:0 on erythrocyte membrane was used as M1 and M2; Model 5: the proportion of MUFA and C13:0 on erythrocyte membrane was used as M1 and M2; Model 6: the proportion of MUFA and C20:1 on erythrocyte membrane was used as M1 and M2; Model 7: the proportion of C18:2n-6 and C20:5n-3 on erythrocyte membrane was used as M1 and M2; Model 8: the proportion of n-6 and C20:1 on erythrocyte membrane was used as M1 and M2; Model 9: the proportion of n-6 and C20:5n-3 on erythrocyte membrane was used as M1 and M2; Model 10: the proportion of C20:3n-3 and C13:0 on erythrocyte membrane was used as M1 and M2; Model 11: the proportion of C20:3n-3 and C18:3n-3 on erythrocyte membrane was used as M1 and M2; Model 12: the proportion of n-3 and C11:0 on erythrocyte membrane was used as M1 and M2; Model 13: the proportion of C18:1n-9c and C11:0 on erythrocyte membrane was used as M1 and M2; Model 14: the proportion of C18:1n-9c and C13:0 on erythrocyte membrane was used as M1 and M2; Model 15: the proportion of n-6/n-3 and C18:3n-3 on erythrocyte membrane was used as M1 and M2.

## Discussion

This study demonstrated that in the obese population, there was a negative correlation between DII scores and MoCA scores. Furthermore, even after the DII scores were separated into tertiles, this negative relationship remained consistent. Additionally, erythrocyte membrane fatty acids may be mediators of this negative connection.

Obesity was considered to be a major risk factor for cognitive dysfunction. Substantial evidence points to the link between obesity and cognitive decline, which is reflected in a number of cognitive function domains,<sup>34,35</sup> including executive function,<sup>34–36</sup> memory,<sup>34,37</sup> attention<sup>34,35</sup>, and language.<sup>34,37</sup> Evaluating cognitive function in middle-aged and elderly normal and obese participants using the MoCA test revealed that not only the total MoCA score differed, but also differed in eight cognitive domains. For instance, in our previous research, which reported the discrimination of the normal, overweight and obese groups for the scores of total MoCA,<sup>25,38</sup> MoCA attention and MoCA memory.<sup>25</sup> Therefore, in this study, we divided the study subjects into NM and OB groups according to BMI for subsequent studies. We also took into account the following variables as adjusted covariates: age,<sup>39</sup> gender,<sup>39</sup> WHR,<sup>40</sup> energy intake,<sup>41</sup> culture,<sup>42</sup> lifestyle (ie, smoking,<sup>43</sup> drinking<sup>43</sup> and exercise<sup>43</sup>), and chronic illnesses that may lead to cognitive impairment (ie, history of hypertension,<sup>44</sup> diabetes mellitus,<sup>45</sup> hypertriglyceridemia).<sup>46</sup>

A growing body of research indicates that food (especially inflammatory diets) and nutrition are key factors in the emergence of obesity,<sup>47</sup> giving rise to the concern about inflammatory food. The DII score, which is calculated by summing the special DII scores for each food item, can reflect whether a diet has an anti- or pro-inflammatory potential. Studies in different populations have shown that DII score affects the levels of inflammatory factors such as IL-6 and TNF- $\alpha$ ,<sup>48,49</sup> and the studies on these inflammatory factors have been relatively thorough, and we no longer repeat the study. In our study, DII score affects the levels of IFN- $\gamma$  in normal patients and IL-12 in obese patients, but the significance of this effect is slight, and we believe that it may be related to the fact that the contents of these inflammatory factors themselves are not high enough. In addition, while high circulating cytokine levels are associated with poor cognitive performance, these are relatively nonspecific measures of disease, as circulating cytokines may arise from any vascularized tissue and may not be particularly related to diet- and obesity-related cognitive impairment.<sup>47</sup> Therefore, more experiments are needed to demonstrate whether and how DII affects the level of inflammation in vivo. A large number of cross-sectional surveys have shown a positive association between DII and obesity,<sup>50–53</sup> while few studies have shown no association or negative association between DII and obesity.<sup>54–56</sup> In this study, although the difference in total DII scores between the two groups was not significant, the OB group consumed less protein, vitamin A, riboflavin, Mg and Se than the NM group ( $P < 0.05$ ) (Figure 4). This finding, like a large number of previous studies, implies that protein,<sup>57</sup> vitamin A,<sup>58</sup> riboflavin,<sup>59</sup> Mg<sup>60</sup> and Se<sup>57</sup> are all food components that can play an anti-inflammatory role.

In the present study, the relationship between DII and cognitive function was explored in NM and OB populations. By grouped the DII scores into tertiles, the differences in MoCA scores among different tertile groups in NM and OB groups were compared respectively. As a result, only in the NM group, MoCA visual space capability scores decreased for Tertile 2 and Tertile 3 compared to Tertile 1 and MoCA language increased for Tertile 3 compared to Tertile 1 and Tertile 2 (Table 2). We performed multiple linear regression found that higher DII scores were negatively correlated with MoCA visuospatial function scores and positively related to higher MoCA language skills scores in the NM group in all three adjusted models; There was a negative association between DII scores and total MoCA, MoCA visuospatial function, MoCA naming, MoCA attention and MoCA memory in OB group in all three adjusted model (Table 5). Using tertile1 as a control, we conducted binary logistics regression analysis, and the outcomes showed that DII was associated with the incidence of MCI in the OB group in any adjusted model. However, MCI incidence did not differ among NM group in any adjusted model (Figure 5). Wang et al<sup>18</sup> indicated that, after adjustment, the findings of multiple linear regression among Chinese residents aged 65 to 85 years revealed that DII score was inversely connected with MoCA score. Subsequently, the higher risk of MCI was then linked to high DII scores, according to the findings of generalized linear regression analysis. Higher energy-adjusted dietary inflammatory index (E-DII) scores were specifically linked to a higher risk of MCI in the elderly Chinese population, according to Zhang et al.<sup>61</sup> In a study by Liu et al<sup>62</sup> it was discovered that MCI frequency in an older Chinese population was positively correlated with high DII scores. Song et al<sup>63</sup> found that older persons with higher DII scores had lower digit symbol substitution test (DSST) and animal fluency (AF) scores, which implies a negative correlation between cognitive performance and DII score. According to Hayden et al<sup>20</sup> higher DII scores were linked to faster cognitive impairment onset and more severe cognitive decline. Higher E-DII scores were linked to a higher incidence of cognitive impairment, according to a Korean study.<sup>64</sup> Kesse-Guyot et al<sup>65</sup> evaluated respondents' cognitive abilities and found that higher DII was linked to worse performance and lower overall cognitive function. The results of these studies are consistent with our findings in obese individuals.

Fatty acids in erythrocyte membrane can reflect the intake level of dietary fatty acids. Meanwhile, inflammation is tightly correlated with the kind and quantity of dietary fatty acids. Study showed that high SFA levels in the diet can be considered a pro-inflammatory factor.<sup>66</sup> Additionally, it has been proposed that C24:0 may increase fibroblast lipid peroxidation by promoting NADPH oxidase (NOX) activity,<sup>67</sup> which was consistent with our findings that DII scores and the proportion of C24:0 in erythrocyte membrane were positively correlated in the three adjustment modes in this study, although this link was only observed in the normal population ( $P<0.01$ ). Odd-chain saturated fatty acids (OCFAs), such as 15:0, have been linked to a lower prevalence of disorders, including type 2 diabetes, according to research.<sup>68–70</sup> Contrarily, even-chain saturated fatty acids (ECFAs), including C16:0 and C24:0, potentially detrimental to health. Intriguingly, however, we discovered that the DII score in this study was negatively connected with the proportion of erythrocyte membranes C16:0 in the obese group and favorably correlated with the proportion of erythrocyte membranes C15:0 and C23:0 in the normal population. This may be due to the obese group consuming insufficient amounts of C16:0, while the normal population drank excessive amounts of C15:0 and C23:0.

There are few studies on the role of MUFA in inflammation, and some studies suggest that MUFAs have anti-inflammatory effects,<sup>71</sup> but studies by Mika et al<sup>72</sup> have found that elevated lipid MUFA/SFA ratios are associated with high levels of circulating C-reactive protein (CRP), suggesting that MUFAs may have pro-inflammatory effects.<sup>66</sup> In our study, there was a positive correlation between the proportion of erythrocyte membrane MUFA and DII score in the OB group in Model 2 ( $P<0.05$ ). Typically, n-6 is thought to have pro-inflammatory effects.<sup>73</sup> In our study, a positive correlation was found between DII score and the proportion of erythrocyte membrane n-6 in OB group, after adjustment for model 2 ( $P<0.05$ ). The pro-inflammatory effect of n-6 is mainly related to C20:4 n-6. C20:4 n-6 is metabolised by three enzymes (cyclooxygenase, lipoxygenase, and cytochrome P450) to elicit different inflammatory responses.<sup>74</sup> In our study, in the OB group we found higher DII score was associated with the higher proportion of erythrocyte membrane C20:4n-6 whatever the adjusted models ( $P<0.05$ ). Competitive metabolism exists between n-3 and n-6 polyunsaturated fatty acids, whereas n-3 is generally considered to have anti-inflammatory effects, and a higher n-6/n-3 ratio in the diet is related to inflammation and multiple chronic diseases.<sup>73,75</sup> Our study found that DII scores were positively correlated with the proportion of the ratio of n-6 and n-3 of the erythrocyte membranes in OB group regardless of the adjusted models ( $P<0.05$ ).

These fatty acids also have potential associations with cognitive function. In our previous study,<sup>25</sup> although the proportion of erythrocyte membrane C20:4n-6 was not associated with total MoCA score in obese subjects, it was negatively correlated with the score of MoCA Orientation ( $B = -0.016$ ,  $P < 0.05$ ). Bigornia SJ et al<sup>76</sup> conducted an observational study and found that erythrocyte C20:4n-6 concentration predicted cognitive impairment among participants aged 57 years ( $OR = 1.26$ ,  $P = 0.01$ ). In a cross-sectional study conducted by us in Chinese residents aged 35–64 years, discovered that the SFA, PUFA and MUFA were negatively correlated with cognitive functions in obese subjects.<sup>77</sup> Therefore, we speculate that the effects of DII on cognitive function may be related to the changes in erythrocyte membrane fatty acids. Subsequently, we used mediation analysis to investigate the relationship among DII scores, erythrocyte membrane and MoCA scores. The findings revealed a substantial negative association between the DII and MoCA scores, which might be attributed to erythrocyte membrane fatty acids, although distinct fatty acid-mediated chain-mediating actions had both positive or negative impacts.

Our study, to the best of our knowledge, is the first to choose to look at the relationship between the DII score and cognitive abilities in obese and normal individuals, respectively. This can effectively reduce the interference effect of BMI in the effect of the DII on cognition and also close the gap that the relationship between the DII and cognitive capabilities has not been discussed in the obese population in the previously studies. Additionally, we used mediation analysis to find the chain-mediated relationship between DII scores, erythrocyte membrane fatty acids and cognition, which offers new suggestions for consuming anti-inflammatory diets to enhance cognition. The following issues with our study, however, should be noted: (1) the sample size of this study is small; (2) the use of the FFQ to assess participants' dietary status may result in recall bias; (3) this study was only conducted in three villages in Beijing, which may only be representative of a portion of the city's population. More investigations should be performed to further clarify the association between DII scores and cognitive function.

## Conclusion

In this study, we investigated the cognitive differences between DII tertiles in obese adults aged from 45 to 75 years. Using regression analysis, we discovered a strong negative association between DII scores and cognitive scores in obese people, and the occurrence of MCI increased with increasing DII tertiles. Additionally, we discovered that in obese patients, DII had some influence over the erythrocyte membrane fatty acid ratio. By using mediation analysis, we discovered that the proportion of erythrocyte membrane fatty acid might mediate the negative connection between DII and cognitive function.

## Abbreviations

DII, dietary inflammatory index; E-DII, energy-adjusted dietary inflammatory index; MCI, mild cognitive impairment; AD, Alzheimer's diseases; MoCA, Montreal cognitive assessment; DSST, digit symbol substitution test; AF, animal fluency; OB, obese group; NM, normal weight group; BMI, body mass index; WHR, waist-hip ratios; C15:0, pentadecanoic acid; C16:0, palmitic acid; C23:0, 1-tricosanoic acid; C24:0, lignoceric acid; SFA, saturated fatty acids; OCFAs, odd-chain saturated fatty acids; ECFAs, even-chain saturated fatty acids; C15:1, ginkgolic acid; MUFA, monounsaturated fatty acids; n-6, omega-6 fatty acids; n-3, omega-3 fatty acids C20:4 n-6, arachidonic acid; PUFA, polyunsaturated fatty acids; TC, total cholesterol; TG, total triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; ApoE, apolipoprotein E; 5-HT, serotonin; TLR4, toll-like receptor 4; LPS, lipopolysaccharide; IL-6, interleukin-6; IFN- $\gamma$ , interferon gamma; CRP, C-reactive protein; FFQ, food frequency questionnaire; NOX, NADPH oxidase; ORs, odds ratio; 95% CI, 95% confidence intervals; Mg, magnesium; Fe, ferrum; Zn, zinc; Se, selenium.

## Data Sharing Statement

The research article data used to support the findings of this study are available from the corresponding author upon request.

## Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Review Board of Capital Medical University (Z2019SY011).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have read and approved the final submitted manuscript.

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## Disclosure

The authors report no conflicts of interest in this work.

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