Title: The Association between Dietary Antioxidants, Superoxide Dismutase Activity, and serum levels of inflammatory factors in Children with ADHD

Running Title: Antioxidants and Inflammation in ADHD

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To appear in: Basic and Clinical Neuroscience

Received date: 2018/09/14

Revised date: 2019/09/18

Accepted date: 2020/05/9

Please cite this article as:

Namjoo, I., Alavi Naeini A., M., Najafi, M., Aghaye Ghazvini, R., Hasanzadeh, A. (In Press). The Association between Dietary Antioxidants, Superoxide Dismutase Activity, and serum levels of inflammatory factors in Children with ADHD. *Basic and Clinical Neuroscience*. Just Accepted publication Des. 12, 2019. Doi: http://dx.doi.org/10.32598/bcn.2021.1489.2

DOI: http://dx.doi.org/10.32598/bcn.2021.1489.2

Highlights

- Superoxide dismutase activity, an antioxidant enzyme, reduced with elevated CRP in ADHD children.
- The levels of CRP associated with homocysteine and interleukin-6 in children with ADHD.
- Homocysteine and physical activity can predict the inflammatory status induced by CRP in ADHD children.

Plain Language Summary

Attention Deficit Hyperactivity Disorder (ADHD) is a common disease in children. Children with ADHD have some impairment academic, social and occupational activities. Researchers have always attempted to find solutions to these problems and reduce the complications of the disease. Recent studies have shown that ADHD is an inflammatory condition and is associated with oxidative stress. There are different types of biological markers for assessing the status of inflammation and oxidative stress, but the researchers and physicians always have interested in choosing the best marker for assessment of the status of oxidative stress and inflammation in patients, as well as the relationship between them.

We tried to investigate the relationship between the dietary intakes of antioxidants, superoxide dismutase (an antioxidant enzyme), and the serum levels of some inflammatory markers (C-reactive protein, homocysteine, and Interleukin-6) in children aged 6 to 13 years with ADHD. For this purpose, 64 ADHD children were divided into two groups based on C-reactive protein (CRP) serum levels, 32 patients were included in the case group (with CRP equal or higher than 1 mg/L) and 32 patients in the control group with CRP (with CRP lower than 1 mg/L). CRP is one of the most important biological markers of inflammatory conditions. The finding of the study indicates that the superoxide dismutase activity decreases with elevated CRP. The levels of CRP associated with homocysteine and interleukin-6. Homocysteine and physical activity

can predict the inflammatory status associated with CRP. Also, this finding might be useful for assessing oxidative stress and inflammation status in children with ADHD.

Abstract

Introduction: Recent studies have identified ADHD as an inflammatory condition with immunological and oxidative responses. Therefore, it is necessary to examine these factors in the patients. This study aimed to investigate the relationship between the dietary intakes of antioxidants, SOD activity and the serum levels of inflammatory factors in children with ADHD.

Materials and methods: This study was a retrospective case-control study with 64 ADHD children aged 6 to 13 years. The demographic questionnaire, FFQ, and Baecke physical activity questionnaire were used. SOD activity and the serum level of inflammatory factors (homocysteine, IL-6, and CRP) were measured in all patients. Based on the values obtained from CRP, 32 patients were included in the case group (CRP≥1 mg/L) and 32 patients in the control group (0≤CRP<1 mg/L).

Results: There was no significant difference between the two groups as regards age, sex, weight, height, body mass index (BMI). In the case group, the mean SOD activity score (P=0.034), the physical activity score (P=0.04) and the zinc intake (P=0.02) and homocysteine levels were higher than they were in the control group (P=0.001). Among the variables in the presence of each other, the best predictors were homocysteine (OR: 1.34, 95% CI: 1.082-1.670, P=0.029) and physical activity (OR: 0.85, 95% CI: 0.761-0.952, P=0.022) respectively, and in the presence of these two variables, other variables were not significant predictors.

Conclusion: The present study showed that the level of inflammatory factors in the case group was significantly higher than the control group. Homocysteine and physical activity can predict the inflammatory status induced by CRP. Decreasing the antioxidant activity of SOD with increasing CRP levels, indicates oxidative stress associated with inflammation in these patients.

Key-words: Antioxidants, Inflammation, C-Reactive Protein, ADHD, Child

1. Introduction:

The most common neurodevelopmental disorder in children is attention deficit hyperactivity disorder (ADHD), which is associated with inattention, hyperactivity, impulsivity and distraction, and often continues until adolescence and adulthood (Anney et al., 2008). These patients are faced with academic, social and occupational problems; therefore, the high costs and side effects of this disorder have directed researchers towards exploring strategies for preventing, controlling and treating it (Anney et al., 2008; Stoltz, 2004). Although what causes the incidence of this disorder is still not clear, genetic and environmental factors and their interactions have been investigated in various researches (Crosbie & Schachar, 2001).

Recent studies have reported that ADHD is an inflammatory condition with immunological responses and oxidative stress. The ability to pass inflammatory mediators from the blood-brain barrier and its effect on the metabolism of some amino acids (such as tryptophan), dopaminergic and noradrenergic systems, and on the function of neurons and synapses, has led to the proposal of hypotheses regarding the role of inflammatory mediators in ADHD pathology (Oades, Dauvermann, Schimmelmann, Schwarz, & Myint, 2010). Stressful life events experienced during and after pregnancy and subsequent immunological responses may interfere with the balance of pro-inflammatory/anti-inflammatory mediators and ultimately lead to further increase in inflammatory factors such as the tumor necrosis factor (TNF) and pro-inflammatory interleukins. These inflammatory mediators can lead to neuronal degeneration and behavioral problems (Ma, Chen, Chen, Liu, & Wang, 2011; Martino, Rocchi, Escelsior, & Fornaro, 2012). Recently, several study highlighted the relationship between inflammatory markers and the consequences of neurodevelopmental growth among children. One cohort study introduces inflammation as an independent risk factor which may disrupt the neuronal development of children, and serum levels of C-reactive protein (CRP) as one of the most critical inflammatory biomarkers (Jiang et al., 2017). Although evidence has introduced CRP as a risk factor for

cardiovascular diseases, increased levels of CRP have been seen in neuropsychiatric disorders, such as chronic depression (Miller, Freedland, Carney, Stetler, & Banks, 2003; Ridker, Hennekens, Buring, & Rifai, 2000). There are limited and contradictory studies regarding the role of inflammatory factors in ADHD. According to epidemiological studies, there is a significant and direct correlation between homocysteine levels and cognitive disorders (bipolar disorder, autism, and Alzheimer disease), but one study has shown that these levels decrease in ADHD (Karababa et al., 2017; Refsum et al., 2004).

In addition to inflammatory and immunologic factors, researchers suggested that oxidative metabolism may be involved in the development of ADHD. Some cross-sectional studies have found that oxidative balance is impaired in patients with ADHD (Selek, Bulut, Ocak, Kalenderoglu, & Savas, 2012), while one study of children with ADHD indicated no relationship between oxidative stress and the disorder (Oztop, Altun, Baskol, & Ozsoy, 2012). According to the results of the meta-analysis, the relationship between antioxidant status and ADHD was not significant; but, responses to oxidative stress were inadequate (Joseph, Zhang-James, Perl, & Faraone, 2015).

The relationship between nutrients (macronutrients and micronutrients) and the immune system has always been relevant; some nutrients are known as immune system regulators and others as pro-inflammatory or anti-inflammatory agents (Thaler & Schwartz, 2010). Some studies have highlighted high dietary fat intakes and obesity as inflammatory factors in the nervous system (Yi, Tschop, Woods, & Hofmann, 2012). However, other studies have shown that the intake of sufficient amounts of omega-3 fatty acids can play a significant role in preventing neuroinflammatory diseases. Fat-soluble vitamins, mainly vitamin A, vitamin D, and vitamin E, play a potential role in regulating the production of immune cells and reducing inflammation (Cha et al., 2010). Few studies have been carried out on the role of food antioxidants in ADHD. The plasma levels of micronutrients like zinc and copper, which play an essential role in the

antioxidant defense mechanism, are lower in ADHD children than in healthy people (Yorbık, Olgun, Kırmızıgül, & Akman, 2004). Besides, ADHD patients demonstrated a lower activity of SOD, which is the first and most important antioxidant defense enzyme (Selek, Savas, Gergerlioglu, Bulut, & Yilmaz, 2008). On the other hand, vitamin E, which has antioxidant effects by reducing lipid peroxidation, has beneficial effects on ADHD treatment (Tsaluchidu, Cocchi, Tonello, & Puri, 2008).

There are different types of biomarkers for assessing inflammation and oxidative stress status, but the researchers and physicians always have interested in identifying the best indicator of inflammation and oxidative stress status in patients, as well as the relationship between them (Scassellati, Bonvicini, Faraone, & Gennarelli, 2012). Due to the limited evidence and the importance of inflammation and oxidative stress in the pathogenesis and treatment of ADHD, this study was aimed to elucidate the relationship between dietary intakes of antioxidants, superoxide dismutase (SOD) enzyme activity, and serum levels of inflammatory factors in ADHD children. To our knowledge, this is the first study using CRP levels of ADHD patients for grouping them and they were divided into case (CRP≥1mg/L) and control (0≤CRP<1 mg/L) groups.

2. Materials and methods

2.1. Study design and participants

This retrospective case-control study was conducted in Isfahan, Iran, from November to March 2016. A total of 98 ADHD children who had been referred to the psychiatric clinic of Isfahan University of Medical Sciences (Isfahan Behavioral Sciences Research Center at Noor Hospital) recruited in the study. Participants inclusion criteria included the ADHD diagnosis based on DSM-IV criteria by a child and adolescent psychiatrist, age 6–13 years, using similar dosages of the standard drug i.e. methylphenidate, and having a BMI within the normal range.

The exclusion criteria were as follows: presence of any other chronic diseases, taking dietary supplements or other medicines, treated with medications and/or psychotherapy for ADHD and following a particular diet. Out of 98 individuals, 64 children were included in the study based on inclusion criteria and an informed consent form was obtained from their parents. The other patients (n=34) were excluded from the study because of obesity, presence of chronic diseases, taking dietary supplements and other medicines except methylphenidate).

2.2. Data collection

A general questionnaire including personal information, medical history, and medications was completed. The body weight and height of the children were measured without shoes and with light indoor clothing.

The usual dietary intakes of antioxidants (vitamin E, vitamin C, alpha-tocopherol, beta-carotene, selenium and zinc) were assessed by a validated and reliable 168-item food frequency questionnaire (FFQ) (Mirmiran, Esfahani, Mehrabi, Hedayati, & Azizi, 2010). Dietary data were analyzed using the Nutritionist-4 software (First Databank Inc., Hearst Corp., San Bruno, CA, USA). The physical activity of the patients was measured by using Baecke's 16-item questionnaire (Baecke, Burema, & Frijters, 1982; Maddah, Eshraghian, Djazayery, & Mirdamadi, 2003).

Blood sampling was performed by a qualified expert and SOD activity and the serum levels of inflammatory factors (CRP, IL-6, and homocysteine) were measured. Regarding to the classification of CRP levels proposed by the American Heart Association, an individual with a CRP higher than 1 mg/L compared to a CRP of less than 1 mg/L is exposed to inflammation and an increased risk of chronic diseases, such as coronary artery diseases (Pearson et al., 2003). Based on the obtained results, 32 patients with CRP≥1 mg/L were chosen for the case group and 32 patients with 0≤CRP<1 mg/L for the control group that matched by gender and age.

2.3. Laboratory Procedures

SOD activity was measured by spectrophotometry using the ZellBio GmbH GmbH kit, Germany with Intra/Inter-assay coefficients of variations; 5.8/7.2%. The serum levels of IL-6 and homocysteine were measured by the ELISA method and measured by kits from the DIACLON Company, France (Intra/Inter-assay CV; 4.1/6.2%) and Axis-Shield Diagnostic Ltd, UK (Inter-assay CV; 7.2%), respectively. CRP was measured by ELISA using Pars Azmoon kit (Tehran, Iran) with an inter-assay CV of 1.7%. All biochemical parameters were evaluated in Hasht-Behesht laboratory, Isfahan, under the direct supervision of the relevant specialist.

2.4. Statistical analysis

The normality of data was checked by the Shapiro-Wilk test. Chi-squared test and independent samples t-tests were used to analyze qualitative and quantitative data, respectively. The logistic regression model was used to predict who each patient is in each of the two groups (CRP≥1 mg/L or 0≤CRP<1 mg/L). The statistical analysis was done using SPSS 22 software (IBM Corporation, Armonk, NY, USA) and the *P*-value <0.05 was statistically significant.

3. Results

Based on Table 1, there was no significant difference in age, sex, weight, height, body mass index (BMI) between the two groups (CRP≥1mg/L and with 0≤CRP<1 mg/L). The mean ± standard deviation (mean ± SD) of the physical activity score in the case group was significantly lower than that of the control group.

The mean ± SD for CRP, IL-6, homocysteine, SOD, and dietary intake of antioxidants are presented in Table 2. The mean ± SD of IL-6 in the case group was significantly more than it was in the control group (*P*=0.06). ADHD patients had significantly higher homocysteine levels in the case group (*P*=0.001). The mean ± SD for SOD activity (*P*=0.03) and zinc intake (*P*=0.02) in the case group were significantly lower in comparison with the control group. There

was no significant difference in the dietary intake of vitamin E, vitamin C, beta-carotene, alpha-tocopherol, and selenium between the two groups.

The variables that had a significant relationship with CRP in the independent t-test were entered into a logistic regression model (Table 3) to predict who each patient is in each of the two groups (CRP≥1 mg/L or 0≤CRP<1 mg/L). This model showed that these variables can accurately predict 82.1% of patients in which group they are. The sensitivity (the proportion of true high levels of CRP) and specificity (the proportion of true low levels of CRP) of this model were 81.8% and 82.4%, respectively. Among the variables in the presence of each other, the best predictors were homocysteine (OR: 1.34, 95% CI: 1.08-1.67, P=0.03) and physical activity (OR: 0.85, 95% CI: 0.76-0.95, P=0.02) respectively, and in the presence of these two variables, other variables were not significant predictors.

4. Discussion

The present study was conducted with the aim of determining the relationship between dietary antioxidants and SOD activity and the serum levels of inflammatory mediators in children with ADHD. According to the result of the study, the levels of interleukin-6 and homocysteine, as inflammatory factors, were significantly higher in the case, as compared to the control group. Among the variables in the presence of each other, the best predictors were homocysteine and physical activity, respectively, and in the presence of these two variables, other variables were not significant predictors.

Researchers have recently given special attention to the relationship between inflammatory factors and neurodevelopmental growth (Leviton et al., 2016). Jiang et al. found that high levels of CRP and IL-6 lead to impaired neurodevelopmental growth in children (Jiang et al., 2017). There has been considerable attention to CRP, as a systemic inflammatory biomarker, in neuropsychiatric disorders such as chronic depression as well as cardiovascular diseases (Jiang

et al., 2017; Penninx et al., 2003). The results of the current study revealed that this biomarker could also be important in ADHD patients. The findings of a systematic review published in 2014 suggested the primary evidence for the claim that inflammation plays an important role in children and adolescents with psychiatric disorders (Mitchell & Goldstein, 2014). Nonetheless, studies regarding the relationship between inflammatory factors and ADHD are limited. High levels of inflammatory cytokines have been observed in the brain of patients with Alzheimer disease, depression, and bipolar disorders. The results of two study on ADHD have shown that cytokines increase in the cerebrospinal fluid and plasma (Oades, Myint, Dauvermann, Schimmelmann, & Schwarz, 2010). IL-6 is produced by stimulating TNF-α and enhances the synthesis of CRP in the liver (Laimer et al., 2002). IL-1 and IL-6 change the metabolism of neurotransmitters such as norepinephrine and dopamine (Anisman, Kokkinidis, & Merali, 1996; Dunn, Wang, & Ando, 1999) which are involved in the development of ADHD symptoms (Martino, Rocchi, Escelsior, & Fornaro, 2012). Inflammation might play a role in ADHD pathogeneses based on these mechanisms.

Homocysteine is considered a probable cause of some diseases such as strokes, depression, cognitive disorders, bipolar disorder and Alzheimer disease (McCully, 2009; Stanger et al., 2009). It has been shown that homocysteine can be involved in functional and cognitive disorders in youth with schizophrenia and bipolar disorder (Dittmann et al., 2008). The level of homocysteine increases in cognitive disorders such as Alzheimer disease, bipolar disorder, and autism. However, in a study conducted by Karababa et al. in 2017 with the aim of comparing the level of homocysteine and antioxidant indices in two groups of healthy and ADHD adults, it was shown that the level of homocysteine in ADHD patients was lower than that in the control group. The low plasma homocysteine in ADHD adults could be due to increased metabolism by hormones, as seen in hyperthyroidism, and therefore increasing glomerular filtration rate thus speeding up homocysteine elimination. Moreover, no significant difference was observed

in the level of antioxidant indices in the two groups (Karababa et al., 2017). However, SOD activity in the case group was significantly lower than that of the control group in the present study. A contradiction in the results of the two studies can be explained by different study design and control group. Also, adult patients were included in the Karababa study, while in current study patients were children.

Numerous studies have shown that free radicals play a crucial role in the pathology of depression, bipolar disorder and other psychological disorders (Papas, 1996; Stadtman, 2006). About 75% of hyperactive adults suffer from other mental disorders such as anxiety, depression and bipolar disorder (Tarazi, Zhang, & Baldessarini, 2002). Based on such evidence, researchers have suggested that oxidative stress might be important in the pathophysiology of ADHD. The findings of some studies showed that elevated oxidative stress increases the release of dopamine, a crucial neurotransmitter in ADHD, by increasing in membrane permeability to calcium ions (Selek et al., 2008). Kul et al. showed that oxidative stress is significantly higher in ADHD children (Kul et al., 2015). Other studies are also consistent with this finding (Guney et al., 2015; Sezen et al., 2016). Selek et al. found that SOD activities in adults with ADHD were lower in comparison with the control group. There was an oxidative imbalance in these patients as shown by high levels of nitric oxide and low SOD activities (Selek et al., 2008). Increasing the oxidant parameters indicates the role of inflammation in ADHD because excessive production of oxidants can lead to inflammatory responses in the body. (Vida, Gonzalez, & De la Fuente, 2014).

In the study of Naghashpour et al., there is no significant relationship between the food intake of B vitamins (folate, riboflavin, thiamine and cobalamin), Vitamins D and C, Magnesium, zinc and total daily calories in healthy and depressed groups and hs-CRP serum levels (Naghashpour, Amani, Nutr, Nematpour, & Haghighizadeh, 2011). These results are similar to the findings of previous studies (Bertran et al., 2005; Ghayour-Mobarhan, Yaghootkar,

Lanham-New, Lamb, & Ferns, 2007). However, the correlation between the food intake of vitamins E, C, beta-carotene, alpha-tocopherol, zinc and selenium with CRP levels was inverse and insignificant in the present study (Naghashpour et al., 2011). Bertran et al. indicated that less intake of food (e.g., lower carbohydrate, protein, lipid, thiamine, alpha-tocopherol, and folate quantities) is related to higher concentrations of CRP plasma (Bertran et al., 2005). Nonetheless, most of these relationships were not observed in the multi-variant analysis. Furthermore, the study of Naghashpour et al. showed a significant difference in the intake of vitamin E in various quartiles of hs-CRP serum levels in depressed individuals. Patients in the second quartile had significantly less vitamin E intake than those in the fourth quartile (Naghashpour et al., 2011). Another study showed an inverse relationship between vitamin E and CRP serum (Seddon, Gensler, Klein, & Milton, 2006). However, Fredrikson et al. found no significant association between CRP serum and vitamin E and Beta-carotene intake (Fredrikson et al., 2004). It can be suggested that further research needed to explain these relationships.

Zinc plays a pivotal role in the cell growth and cognitive evolution of children and its levels are high in sections of the brain responsible for structural and functional duties (Benton, 2010; Black, 1998). Zinc deficiency in children is associated with reducing cognitive and motor function (Bryan et al., 2004) and a higher prevalence of depression and ADHD (DiGirolamo & Ramirez-Zea, 2009). Zinc is necessary for neuropsychological functioning, neurogenesis, neural migration and synaptogenesis. Zinc deficiency may block neural transmission and stop children from achieving the full growth and development potential (Bhatnagar & Taneja, 2001). Yorbık et al. were found that plasma levels of zinc, which play an essential role in the antioxidant defense mechanism, were lower in ADHD children compared to the control group (Yorbık et al., 2004). Furthermore, cross-sectional studies show the shortage of zinc in children with ADHD. Additionally, serum zinc levels are closely related to inattention scores (Arnold et

al., 2005). Nonetheless, it is not clear whether the differences in diet were related to the period before the emergence of behavioral problems or that the behavioral changes had influenced food intake.

Various studies show that exercise reduces inflammation, particularly CRP (Balagopal et al., 2005; Tsang, Kohn, Chow, & Singh, 2009). The studies show an inverse relationship between physical activity (PA) and levels of inflammatory markers in older adults (Ertek & Cicero, 2012; Hamer et al., 2012) and in children and young adults (Isasi et al., 2003), in agreement with our findings, while other studies in children show no association (Carson et al., 2013). On the other hand, The evidence suggests a positive association between increased PA and decreases in ADHD symptoms, particularly the cognitive and behavioral outcomes (Song, Lauseng, Lee, Nordstrom, & Katch, 2016). Based on the present study findings, physical activity predicts serum levels of CRP and inflammation status in these patients. According to being hyperactivity in most ADHD children and the role of physical activity in reducing inflammation, more studies are needed to determine the effect of increased physical activity and regular exercise on symptoms and inflammatory status in these patients.

The present case-control study was a first attempt with the aim of investigating dietary antioxidants, SOD activities and serum levels of inflammatory mediators in children with ADHD conducted in a case-control study on two groups of CRP≥1 mg/L and 0≤CRP<1 mg/L. One of the most important strengths of the present study was subject grouping based on CRP levels, as one of the most important inflammatory markers of chronic diseases, as well as assessing dietary intakes of antioxidants besides SOD. The weak point of this study was its small sample size and its lack of investigation of mental functions, disease severity and psychometric test.

Finally, this research results showed that the level of inflammatory factors in case group was significantly higher than the control group. Homocysteine and physical activity can predict the

inflammation status induced by CRP. Further studies with bigger sample sizes should be carried out to confirm these results.

Ethical Considerations

The Ethics Committee of Isfahan University of Medical Sciences approved the present study (Ethics code: IR.MUI.REC.1395.3.370). Written informed consent was gained from parents of the participants before taking part in the study. All participants could have been voluntarily discontinued the study. All data obtained from individuals is kept confidential and is used only for research purposes, and the patient's identity remains confidential within the framework of the rules.

Funding

This study extracted from MSc dissertation, which was approved and granted by the School of Nutrition & Food Sciences, Isfahan University of medical sciences (Project No. 395370)

Conflict of interest

The authors declared no financial or personal conflicts of interest regarding the submission and publication of the manuscript.

Acknowledgments

The authors would like to thank the school of Nutrition & Food Sciences, Isfahan University of medical sciences for their financial support. Moreover, many thanks go to all the participated children, their parents, physicians, laboratory staffs and officials.

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Tables:

Table 1: General characteristics of the study population[1]

Variables		ADHD with CRP≥1 (case group) N=32	ADHD with 0≤CRP<1 (control group) N=32	*P*-value[2]
Age (year)		9.2 ± 1.6	9.0 ± 1.5	0.80
Gender	Male	26 (%40.6)	26 (%40.6)	0.96
	Female	6 (%9.4)	6 (%9.4)	
Weight (kg)		31.1 ± 9.1	31.2 ± 9.5	0.97
Height (cm)		134.3 ± 10.1	135.4 ± 12.8	0.72
BMI (kg/m^2)		16.9 ± 2.9	16.78 ± 3.4	0.82
Physical activity (score)		18.9 ± 3.9	20.30 ± 4.7	0.04*

[1] All values are presented as mean ± standard deviation or percentage (%)
[2] *P*-values is obtained from Independent sample t-test
* indicates significance at *P*-value <0.05 level.

Table 2: Comparison of serum inflammatory mediators (CRP, IL-6 and Hcy), SOD activity and dietary intake of antioxidants between ADHD patients with CRP≥1 and 0≤CRP<1 groups[1]

Variables	ADHD with CRP≥1 (case group) N=32	ADHD with 0≤CRP<1 (control group) N=32	*P*-value[2]
CRP (mg/L)	1.4 ± 0.4	0.6 ± 0.2	<0.001*
Interleukin-6 (pg/L)	9.3 ± 1.2	8.2 ± 2.6	0.06
Homocysteine (µmol/L)	6.7 ± 3.3	3.5 ± 4.2	0.001*
SOD activity (U/ml)	4.5 ± 0.1	5.1 ± 2.6	0.03*
Vitamin E intake (mg/day)	16.6 ± 13.1	18.5 ± 13.3	0.55
Vitamin C intake (mg/day)	65.8 ± 35.8	76.2 ± 61.6	0.38
Beta-carotene intake (µg/day)	406.5 ± 415.6	508.6 ± 745.9	0.47
Alpha-tocopherol intake (mg/day)	12.4 ± 8.1	13.9 ± 8.9	0.46
Zinc intake (mg/day)	7.2 ± 1.7	8.6 ± 3.1	0.02*
Selenium intake (µg/day)	61.6 ± 7.1	66.7 ± 5.3	0.59

[1] All values are presented as mean ± standard deviation

[2] P-values are obtained from Independent sample t-test

* indicates significance at *P*-value <0.05 level.

Table 3: Results of logistic regression analysis of variables to predict who each patient is in each of the two groups.

Variables	Coefficient (ß)	Standard error (SE)	Wald	*P*-value[1]	Odds ratio (OR)	95% CI for OR	
						Lower	Upper
Interleukin-6	0.26	0.27	0.92	0.38	1.29	0.76	2.20
Homocysteine	0.29	0.14	4.48	0.03*	1.34	1.08	1.67
SOD activity	- 0.05	0.11	0.20	0.65	0.95	0.79	1.14
Zinc intake	- 0.73	0.41	3.15	0.08	0.48	0.21	1.08
Physical activity	- 0.16	0.07	5.25	0.02*	0.85	0.76	0.95

[1] P-values are obtained from Pearson correlation.

* indicates significance at *P*-value <0.05 level.