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The Association between Macronutrient Intake and the Metabolic Syndrome in Yazdian Adult Population

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ABSTRACT

Background: Metabolic syndrome (MetS) is a collection of metabolic disorders including abdominal obesity, dyslipidemia, high glucose levels, and high blood pressure. The macronutrients such as carbohydrates, proteins, and fats are the effective factors in the occurrence of MetS. This study aimed to determine the association between the macronutrients intake and MetS in 20-69 year-old adult population of Yazd Greater Area, Iran**. Methods:** This study used Yazd Health Study (YaHS) recruitment phase data. The YaHS was a prospective cohort conducted on a random sample of 10,000 Yazdian adults aged 20-69 years. To conduct this study data from TaMeZ (Taghzieh Mardom-e-Yazd) or Yazd Nutrition Study, which was a nutrition study associated with YaHS were also used. MetS was defined according to the ATP III criteria. Dietary intake was evaluated using Food Frequency Questionnaire (FFQ). To evaluate the relationship between macronutrients and MetS, multivariate logistic regression analysis was used. **Results:** The odds ratio for the incidence of MetS was significantly higher in individuals who consumed higher amounts of carbohydrates. However, fat and protein intake did not have any significant relationship with odds of the developing MetS. Individuals with higher intake of carbohydrates had significantly higher odds of abdominal obesity (OR: 1.89, CI: 1.06-3.34); whereas, the probability of abdominal obesity decreased significantly in the highest quintile of protein intake (OR: 0.45, CI: 0.25-0.79). **Conclusion:** High intakes of carbohydrate increased the odds of getting to MetS and abdominal obesity. However, high levels of protein reduced the odds of abdominal obesity. No association was found between fat intake and the odds of the MetS. More prospective studies are needed to determine the role of macronutrients in MetS.

Keywords: *Metabolic syndrome (MetS); Macronutrien;, Carbohydrate; Protein; Fat*

Introduction

Metabolic syndrome (MetS) is a combination of metabolic disorders such as abdominal obesity, dyslipidemia, high glucose levels, and high blood pressure (Linardakis *et al.*, 2008). These factors increase the risk of cardiovascular disease, arthritis, chronic kidney disease, and type 2 diabetes directly and indirectly (Lakka *et al.*, 2002). The high prevalence of MetS in developed and developing countries has been investigated by

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many researchers (Kolovou *et al.*, 2007). MetS has an incidence rate of about 34 and 35 percent among the adults of US (Esposito and Giugliano, 2010) and Iran (Delavari *et al.*, 2009), respectively. In addition, MetS is more prevalent among the Iranian women than other women in the world (Dalvand *et al.*, 2017).

Among various factors including race, family history of chronic diseases, age, and gender, diet plays an important role in the development and control of MetS and its components (Kaur, 2014, Povel *et al.*, 2012). No specific diet has been introduced to treat MetS. Some studies have shown the beneficial effects of Mediterranean (Esposito and Giugliano, 2010) and DASH diets (Azadbakht *et al.*, 2005) on improving components of the MetS. Consumption of some nutrients and food groups (Casas-Agustench *et al.*, 2011, Esmaillzadeh *et al.*, 2005) was also reported to reduce the risk factors of this syndrome. In recent years, the combination of macronutrients in the diet of patients with MetS has attracted extensive attention. Since fats have the highest energy density among macronutrients, dietitians recommend individuals to reduce its consumption (Johnson *et al.*, 2007). However, we should note that a reduction in the percentage of calorie received from the fats is associated with increased calorie intake from carbohydrates. High intake of carbohydrate increases serum triglycerides, decreases serum HDL-C, and impairs glucose metabolism as components of the MetS (McKeown *et al.*, 2004, Mittendorfer and Sidossis, 2001). Considering the effect of consuming macronutrients such as lipids, proteins, and carbohydrates on the MetS, the findings of different studies are inconsistent (Carnethon *et al.*, 2004).

For example, a cross-sectional study on Framingham research found no significant relationship between carbohydrate intake and MetS (McKeown *et al.*, 2004). Similarly, the results of another study on men and women did not show any association between macronutrients' intake and MetS (Eilat-Adar *et al.*, 2008). However, the results of a cross-sectional study on 1626 patients with history of cardiovascular diseases showed that high consumption of carbohydrates decreased the prevalence of MetS (Skilton *et al.*, 2008). Furthermore, the results of a prospective study in this area indicated that high intake of fat was associated with increased risk of MetS (Skilton *et al.*, 2008).

In this area, the results are controversial and the distribution of macronutrients in diets can determine the successful prevention and treatment of MetS. Moreover, no recommendation has ever been made to set up an appropriate diet for treatment of MetS. So, the current study was conducted to evaluate the effect of macronutrients on MetS and its components in adult population of Yazd city.

Materials and Methods

Participants and design: This cross-sectional study was carried on the data collected by two prospective studies; Yazd Health Study (YaHS) and TAghzieh Mardom-e-YaZd (TAMEZ) or Yazd Nutrition Study. The study population included people who lived in Yazd city and were in the age range of 20-69 years. The study design, sampling method, participants' characteristics, and data collection method were published elsewhere (Mirzaei *et al.*, 2017).

Initially, we studied the data of TAMEZ and YaHS to extract the required information on participants' dietary intake, anthropometric indices measurement, blood factors, blood pressure measurement, and confounding factors including socioeconomic status, history of chronic diseases, and physical activity status. Later, we merged the data of the above mentioned research projects.

Finally, of 3826 available profiles, 383 were excluded due to lack of specific codes (n = 2), lack of nutrition information (n = 332), repeated codes (n = 49), and lack of information on metabolic syndrome (n = 105). Finally, 3338 participants entered the study. In the next stage, we excluded people with a history of cardiovascular disease, stroke, diabetes, and cancer as well as individuals with higher or lower

energy intakes (more than 6500 kcal and less than 600 kcal, respectively). Finally, the analysis was conducted on 2221 individuals.

Diet evaluation: Participants' dietary information was collected by completing a semi-quantitative FFQ consisting of 178 food items and 551 questions. The validity and reliability of this questionnaire was measured and confirmed in TAMEZ project (Mirzaei *et al.*, 2017). In order to complete this questionnaire, we explained the average size of each food item for the participants and asked them to report the amount and frequency of that food. Later, the values related to each food item were determined in grams using guidelines of household scales (Ghaffarpour *et al.*, 1999). The amount of energy, protein, carbohydrate, and fat intake was also determined.

Diagnosis of MetS*:* MetS was diagnosed in accordance with National cholesterol education program adult panel III (ATP III) (Alberti *et al.*, 2009). Accordingly, the MetS was defined as having at least 3 cases of metabolic sub-syndrome factors: 1) Triglyceride above 150 mg/dl; 2) HDL cholesterol level of less than 40 mg/dl in men and less than 50 mg/dl in women; 3) Systolic blood pressure above 130 mmHg and diastolic blood pressure above 850 mmHg; 4) Fasting blood glucose above 110 mg/dl; and 5) waist circumference (WC) above 102 cm in men and 88 cm in women**.**

Evaluation of anthropometric indices: The participants' weights were measured using a digital scale (Omron BF511 Inc. Nagoya, Japan) with an accuracy of 0.1 kg. The height was also measured in standing position using the tape meter with an accuracy of 0.1 cm while the participants were leaning against a smooth wall without shoes. Waist circumference was measured with an accuracy of 0.5 cm using a tape measure in the horizontal plane midway between the lowest ribs and the iliac crest. The hip circumference was also measured at the largest part of the hips with an accuracy of 0.5 cm. All measurements were performed three times (before the interview, after completing one third of the questionnaire, after completing two third of the questionnaire). Later, we calculated the body mass index (BMI) by dividing the weight in kilograms by height in meters squared.

Blood pressure measurement: Systolic and diastolic blood pressures were measured in the sitting position after completing two-thirds of the questionnaire, which was after about 40 minutes of rest. The measurements were repeated three times with five-minute intervals using the Richter pressure gauge. Next, average of the second and the third measures was calculated and recorded as the blood pressure.

Laboratory data: Later, we measured the fasting blood glucose (FBG) (mg/dl), high density lipoprotein-cholesterol (HDL-C), and triglycerides (TG). An auto-analyzer device and kits related to each test (Pars Azmoon) were used for this purpose.

Other variables: Physical activity information was collected using a standard questionnaire (Mirzaei *et al.*, 2017). Then, the amount of physical activity was calculated in metabolic equivalent of an hour per week. Furthermore, the participants' socioeconomic status and smoking status were collected using questionnaires and interviews (Mirzaei *et al.*, 2017).

*Data analysis***:** In order to carry out the analyses, we used the IBM SPSS version 22. For quantitative variables, the values were reported in mean and standard deviations and percentages were applied to report the classified variables. Student t-test and chi-square tests were also used to compare the quantitative and qualitative variables, respectively. The intake of macronutrients (grams per day) was adjusted based on the total energy intake and participants were divided into quantiles according to their consumption of macronutrients. These quantiles were then used as qualitative variables in the next statistical analyses. Finally, to evaluate the association of macronutrients' intake with the risk of metabolic syndrome and its components, we run multivariate regression after adjusting for the

confounding variables such as age, education, gender, physical activity, smoking status, BMI, and family history of Chronic diseases.

Ethical considerations: both YaHS and TAMEZ studies have ethical approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences. Informed consents were also obtained from all participants.

Results

A cross-sectional study was carried out on 2221 individuals; 529 were afflicted with the MetS and 1692 did not have it. The general characteristics of the study participants are shown in **Table 1**. The BMI, WC, hip circumference, blood pressure, TG, and FBG were significantly higher in people with MetS. Moreover, 71 percent of the individual with MetS were women over 40 years of age.

A significant difference was observed between individuals with and without metabolic syndrome in terms of physical activity, education, marital status, occupational status, home ownership, and the number of family members. However, no significant difference was observed between the two groups regarding smoking status, ethnicity, house in meters, and the history of chronic diseases.

Table 2 shows the odds ratio of MetS and 95 percent confidence interval for intake of macronutrients in the crude model and after adjusting for the confounding factors in three models.

We adjusted for the confounding variables such as age, education, gender, physical activity, smoking status, BMI, and family history of chronic diseases and found that the odds ratio of MetS was significantly higher in individuals with more intake of carbohydrates (OR: 1.67, CI: 1.01-2.75). However, intake of fat and protein did not have any significant association with the probability of developing MetS (OR: 0.97, CI: 0.59-1.60, OR: 0.90, CI: 0.54-1.49).

Furthermore, individuals with higher intake of carbohydrates had more probability of abdominal obesity (OR: 1.89, CI: 1.06-3.34); whereas, higher consumption of proteins reduced the probability of abdominal obesity (OR: 0.45, CI: 0.25-0.79).

Table 1. General Characteristics of study participants according to metabolic syndrome

Variables	Metabolic syndrome		
	YES	**NO**	**P-value**
Quantitative variables	Mean ± SD	Mean ± SD	
Body mass index (kg/m^2)	29.99 ± 4.45	26.21 ± 4.82	< 0.001
Waist circumference (cm)	101 ± 10.94	90.58 ± 12.66	< 0.001
Hip circumference (cm)	107 ± 10.41	100 ± 11.34	< 0.001
Qualitative variables	% (N)	%(N)	
Age **(y)**			
20-40	23.44 (124)	46.15 (781)	< 0.001
40-60	52.55 (278)	41.60 (704)	
≥60	24 (127)	11.8 (199)	
Sex			
Male	28.2 (149)	53.1 (898)	< 0.001
Female	71.8 (380)	46.9 (794)	
Physical activity			
Sedentary	36.3 (192)	28.5 (482)	< 0.001
Moderate	38.9 (206)	33.3 (563)	
Active	20.8 (110)	34.5 (583)	
Education			
Lower than high school diploma	68.76 (361)	48.80 (819)	< 0.001
High school or college	21 (111)	32.9 (556)	
University	10 (53)	17.9 (303)	
Marital status			
Married	89.4 (473)	85.3 (1443)	< 0.001
Single	3.6 (19)	11.8 (199)	
Divorce or widowed	6.6 (35)	2.7 (45)	
Smoking			
Never and former	92.78 (476)	91.45 (1509)	0.46
Current	7 (37)	8.3 (141)	
Job status			
Not employed	74.3 (393)	54.9 (929)	< 0.001
Employed	24.4 (129)	44.1 (746)	
House status			
Owner	83.7 (443)	76.4 (1292)	< 0.001
Not owner	14.4 (76)	22.5 (380)	
House in meters (m^3)			
Less than 100	20.2 (107)	20.3 (343)	0.66
100-200	52.9 (280)	53.7 (908)	
More than 300	24.6 (130)	24.3 (411)	
Family size			
4≥	72.27 (378)	71.57 (1211)	0.001
5≤	27.4 (145)	27.6 (467)	
Ethnicity			
Yazdian	88.1 (466)	85.9 (1453)	0.75
Not from Yazd	10.45 (55)	12.4 (210)	
Chronic diseases history			
No	89 (16.8)	339 (20)	0.06
Yes	40.26 (213)	30.85 (522)	
Features of metabolic syndrome			
Abdominal obesity	67 (460)	31 (525)	< 0.001
Elevated blood pressure	63.5 (336)	260 (15.4)	< 0.001
High serum triacylglycerol	72 (381)	58 (982)	< 0.001
Low serum HDL-C	66 (349)	25.2 (426)	< 0.001
Abnormal glucose homeostasis	35.3 (187)	6.1 (103)	< 0.001

Table 2. Multivariate adjusted odds ratios and 95%confidence intervals for metabolic syndrome and its components based on quintile of macronutrients intake.

	Quintiles of carbohydrate intake[a]				Quintiles of protein intake[a]				Quintiles of fat intake[a]			
	Q1	**Q3**	**Q5**	**P-for trend**	**Q1**	**Q3**	**Q5**	**P-for trend**	**Q1**	**Q3**	**Q5**	**P-for trend**
Metabolic syndrome												
Crude	1.00	1.28(.94-1.74)	1.28(.94-1.75)	0.32	1.00	1.08(0.79-1.47)	0.92(0.67-1.26)	0.98	1.00	0.86(0.63-1.17)	0.90(0.66-1.24)	0.56
Model 1[b]	1.00	1.23(0.89-1.70)	1.37_0.99-1.90)	0.17	1.00	1.11(0.80-1.54)	0.93(0.67-1.30)	0.81	1.00	0.78(0.56-1.09)	0.89(0.64-1.24)	0.45
Model 2[c]	1.00	1.47(0.90-2.40)	1.68(1.03-2.73)	0.06	1.00	1.02(0.63-1.65)	0.80(0.50-1.28)	0.25	1.00	0.66(0.40-1.09)	0.88(0.54-1.44)	0.61
Model 3d	1.00	1.54(0.93-2.54)	1.67(1.01-2.75)	0.04	1.00	0.97(0.59-1.60)	0.75(0.46-1.22)	0.22	1.00	0.72(0.43-1.20)	0.90(0.54-1.49)	0.73
Component of metabolic syndrome												
Abdominal obesity												
Crude	1.00	1.17(0.90-1.52)	1.31(1.01-1.70)	0.06	1.00	0.87(0.67-1.13)	0.82(0.63-1.06)	0.46	1.00	0.91(0.70-1.18)	0.97(0.74-1.25)	0.38
Model 1[b]	1.00	1.15(0.85-1.56)	1.58(1.17-2.13)	0.002	1.00	0.85(0.63-1.15)	0.77(0.57-1.04)	0.23	1.00	0.79(0.58-1.07)	0.89(0.65-1.20)	0.09
Model 2[c]	1.00	1.27(0.79-2.03)	1.97(1.24-3.13)	0.002	1.00	0.76(0.48-1.22)	0.62(0.40-0.98)	0.07	1.00	0.85(0.53-1.38)	1.12(0.69-1.81)	0.42
Model 3[d]	1.00	1.17(0.65-2.08)	1.89(1.06-3.34)	0.007	1.00	0.83(0.46-1.49)	0.45(0.25-0.79)	0.02	1.00	1.03(0.57-1.86)	1.27(0.69-2.31)	0.67
Elevated blood pressure												
Crude	1.00	1.41(1.05-1.90)	1.13(0.83-1.53)	0.79	1.00	1.24(0.91-1.68)	1.26(0.93-1.71)	0.05	1.00	0.96(0.72-1.29)	0.75(0.56-1.02)	0.03
Model 1[b]	1.00	1.38(1.01-1.88)	1.16(0.84-1.60)	0.91	1.00	1.27(0.92-1.76)	1.27(0.92-1.75)	0.13	1.00	0.89(0.65-1.21)	0.80(0.58-1.10)	0.17
Model 2[c]	1.00	1.45(0.90-2.33)	1.38(0.86-2.22)	0.52	1.00	1.17(0.72-1.89)	1.20(0.76-1.88)	0.28	1.00	0.73(0.46-1.17)	0.65(0.41-1.06)	0.02
Model 3[d]	1.00	1.47(0.91-2.38)	1.37(0.85-2.20)	0.54	1.00	1.13(0.7-1.83)	1.14(0.72-1.81)	0.34	1.00	0.75(0.47-1.21)	0.65-0.40-1.05)	0.02
High serum triacylglycerol												
Crude	1.00	1.09(0.84-1.43)	0.97(0.74-1.26)	0.88	1.00	0.93(0.71-1.21)	0.91(0.70-1.18)	0.43	1.00	0.90(0.69-1.17)	1.24(0.95-1.62)	0.16
Model 1[b]	1.00	1.15(0.87-1.51)	0.99(0.75-.29)	0.94	1.00	1.05(0.80-1.38)	1.10(0.84-1.45)	0.63	1.00	0.91(0.70-1.19)	1.15(0.87-1.5)	0.34
Model 2[c]	1.00	1.26(0.82-1.92)	103(0.68-1.56)	0.58	1.00	0.82(0.54-1.24)	0.75(0.50-1.12)	0.26	1.00	0.73(0.47-1.12)	0.93(0.61-1.44)	0.74
Model 3[d]	1.00	1.26(0.82-1.94)	1.08(0.71-1.64)	0.48	1.00	0.82(0.53-1.25)	0.78(0.52-1.17)	0.28	1.00	0.70(0.45-1.08)	0.97(0.62-1.5)	0.67
Low serum HDL-C												
Crude	1.00	1.06(0.81-1.38)	1.03(0.79-1.35)	0.80	1.00	0.99(0.75-1.30)	98(0.75-1.29)	0.65	1.00	1.16(0.89-1.52)	1.04(0.79-1.36)	0.69
Model 1[b]	1.00	1.07(0.81-1.41)	1.07(0.81-1.41)	0.99	1.00	1.00(0.76-1.31)	0.98(0.74-1.29)	0.69	1.00	1.18(0.90-1.55)	1.0(0.75-1.32)	0.93
Model 2[c]	1.00	1.65(1.08-2.53)	1.26(0.82-1.93)	0.49	1.00	1.36(0.90-2.07)	0.82(0.54-1.24)	0.27	1.00	1.24(0.80-1.94)	0.96(0.61-1.5)	0.58
Model 3[d]	1.00	1.66(1.09-2.54)	1.22(0.79-1.87)	0.59	1.00	1.40(0.92-2.12)	0.83(0.55-1.26)	0.31	1.00	1.28(0.82-2.00)	0.96(0.61-1.05)	0.57
Abnormal glucose homeostasis												
Crude	1.00	0.91(0.63-1.32)	0.78(0.53-1.14)	0.04	1.00	1.35(0.92-1.98)	1.35(0.92-1.98)	0.08	1.00	1.16(0.79-1.71)	1.04(0.70-1.54)	0.22
Model 1[b]	1.00	0.82(0.55-1.21)	0.77(0.52-1.15)	0.05	1.00	1.10(0.72-1.68)	1.40(0.94-2.08)	0.13	1.00	0.88(0.58-1.34)	1.10(0.73-1.66)	0.16
Model 2[c]	1.00	0.70(0.40-1.22)	0.60(0.34-1.06)	0.01	1.00	1.53(0.86-2.73)	1.55(0.89-2.71)	0.15	1.00	1.33(0.72-2.44)	1.33(0.72-2.47)	0.04
Model 3[d]	1.00	0.69(0.39-1.22)	0.57(0.32-1.02)	0.009	1.00	1.51(0.84-2.71)	1.53(0.87-2.7)	0.15	1.00	1.48(0.79-2.78)	1.45(0.77-2.74)	0.02

[a] : Values are reported as odds ratio and 95% confidence interval; [b] : Adjusted for age, sex; [c]: Adjusted for marriage status (married/single/divorce or widowed), physical activity (sedentary/moderate/active), education level (less than high school diploma/college/ university), Smoking (never or former, current), job status (Not employed, employed), house status (owner, not owner), family size(less than 4, more than five),house in meters (less than 100 meters, between 100 to 200 meters, more than 200 metres), ethnicity(yazdi or not from yazd), disease history (yes/ no) plus variables in model 1.; [d] : Additionally adjusted for BMI (kg/m^2)

Discussion

Our results showed that the probability of developing MetS in individual with high intake of carbohydrates was 67 percent more than others. Furthermore, high levels of carbohydrate and protein increased and decreased abdominal obesity up to 89 and 55 percent, respectively. To the best of our knowledge, this study was the first research on the association between macronutrients and metabolic syndrome using this number of participants (n = 2221) in Yazd Greater Area. Previous studies in this area presented contradictory results. Similarly, a prospective study on 4152 adult population of China showed that increase in the total intake of carbohydrates, especially starchy foods, could increase the risk of developing MetS significantly (Feng *et al.*, 2015). Moreover, results of cross-sectional studies showed that high intake of carbohydrates and low intake of fats could increase the risk of MetS in women and men (Kwon *et al.*, 2018). In fact, high intake of carbohydrates can inhibit the lipoprotein lipase activity, increase the production of fatty acids in liver cells, increase the levels of triglycerides, and decrease HDL-C levels (Grundy *et al.*, 2002, Nordmann *et al.*, 2006, Song *et al.*, 2012). As a result, it increases the risk of developing MetS.

In addition, the results of a study on the association of high-carbohydrate diet and physical inactivity with abdominal obesity among housewives before their menopause showed a positive correlation between high intake of carbohydrate and WC (Rathnayake *et al.*, 2014). Furthermore, a study on a multi-ethnic population indicated that higher intake of proteins was associated with lower abdominal obesity and WHR (Merchant *et al.*, 2005).

The possible mechanisms for these results may be attributed to the replacement of protein with carbohydrates, which reduces the abdominal obesity in several ways: 1) Postprandial thermogenesis is higher after consuming proteins than carbohydrates (Halton and Hu, 2004); 2) Conjugated linoleic acid, which is abundant in beef and dairy products increases the feeling of satiety in individuals (Kamphuis *et al.*, 2003); 3) Intake of proteins in comparison with carbohydrates improves insulin sensitivity (McAuley *et al.*, 2005) and increases the energy consumption in resting position (Pereira *et al.*, 2004).

However, our results are different from some previous studies. For example, a study on adults population showed that high intake of dietary fat could increase the odds of developing metabolic syndrome. However, no significant relationship was observed between carbohydrate intake and metabolic syndrome (Freire *et al.*, 2005). In a similar study, no correlation was reported between carbohydrate intake and MetS; whereas, intake of whole grains decreased the incidence of MetS (McKeown *et al.*, 2004).

These controversies can be justified by the fact that in the current study, we initially adjusted the amount of macronutrients based on the energy consumption and then conducted the analyses. On the contrary, in other studies energy adjustment was carried out in the final analyses (Kwon *et al.*, 2018, McKeown *et al.*, 2004). Furthermore, individuals' diets and types of consumed carbohydrates are different in various countries. Type and amount of the consumed carbohydrates can play an important role in developing metabolic syndrome. Consequently, these contradictions can be attributed to the difference in intake of refined carbohydrates such as bread without bran, white rice, biscuits, and cakes compared to the whole grains.

The current study has several strong points: the data were collected from the first and largest prospective study in Yazd, which covered a wide range of health-related data, including the urban and rural areas. Furthermore, we used the valid FFQ and evaluated the confounding variables as much as possible. However, some limitations exist in the current study: cross-sectional design that makes us unable to extract the causal inferences. In this regard, we need prospective studies for comprehensive investigations. Despite use of valid FFQ, the measurement error and misclassification of participants may exist.

Ultimately, the data on alcohol consumption were not collected according to the religious sensitivities.

Conclusion

In this cross-sectional study, we concluded that large quantities of carbohydrates increased the risk of getting to MetS and abdominal obesity, while high levels of protein intake reduced the risk. We did not find an association between fat intake and the risk of MetS; so, prospective studies are suggested in this field.

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Authors' contributions

Hasanizadeh S and Hosseinzadeh M designed this study. Hasanizadeh S, Hosseinzadeh M, and Salehi Abarghouei A cooperated in statistical analysis of this study. Hasanizadeh S wrote the initial draft of this manuscript. Other authors edited the draft and all the authors approved the final version for submit.

Conflict of interests

The authors declare no conflict of interest regarding this study.

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