



## The Association between Metabolic Syndrome and the Consumption of some Supplements

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### ABSTRACT

**Background:** Beneficial effects of vitamins and dietary supplements in the prevention and treatment of metabolic syndrome (MS) are controversial. This study aims to evaluate the association between dietary supplements intake and MS. **Methods:** This analytical cross-sectional analysis was conducted on 9539 people aged 35-70 years who participated in the recruitment phase of Shahedieh Cohort Study in Yazd-Iran (May 2015 to September 2017). The consumption of supplements, such as multivitamin-mineral, multivitamin, calcium-D, calcium, vitamin D, folic acid, omega 3, iron, and zinc were asked in the study. the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria used for defining MS. **Results:** 4785 (50.2%) men and 4754 (49.8%) women with mean age of  $47.64 \pm 9.60$  years participated in this study. The prevalence of MS was 2901 (30.41%). The participants with MS were significantly different in consuming supplements, such as Calcium-D ( $P < 0.001$ ), Calcium ( $P < 0.001$ ), Calcium-D or Calcium products ( $P = 0.001$ ), vitamin D; injection ( $P = 0.017$ ) and vitamin D orally or injection ( $P = 0.005$ ), Omega 3, fish oil ( $P = 0.001$ ), and at least one supplement intake ( $P = 0.001$ ). However, the relationship between MS and supplement consumption was not significant after adjusting for covariates in the multivariate regression model. **Conclusion:** Multiple factors may be responsible for the high prevalence of MS. It seems that a known supplement may not be the pathologic factor in the MS.

**Keywords:** Metabolic syndrome; Oxidative stress; Vitamins

### Introduction

The metabolic syndrome (MS) defined as a combination of numerous factors increasing the

risks of cardiovascular diseases, such as dyslipidemia, abdominal obesity, hypertension, and

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hyperglycemia (Takahashi *et al.*, 2011). The prevalence of MS by the the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria was  $21.3 \pm .017\%$ , ( $27.3 \pm .019\%$  in women and  $12.5 \pm .015\%$ , in men) in Yazd during 2004-2005 (Rezaianzadeh *et al.*, 2012). The prevalence of MS has increased significantly over the last years, and the etiology includes genetic, metabolic, and environmental factors (Mirmiran *et al.*, 2008). Among environmental factors, diet and low physical activity are the main factors related to the high prevalence of MS (Buckland *et al.*, 2008). High levels of oxidative stress decrease endogenous and exogenous pools of antioxidants in human (Ford *et al.*, 2003). Adults with the MS have sub-optimal concentrations of several antioxidants, such as retinyl esters, vitamin C, vitamin E, and several carotenoids, which may partially explain their increased risk for diabetes and cardiovascular disease in this group (Ford *et al.*, 2003). Also obesity, hyperglycemia, hypertension, and hypertriglyceridemia, as the components of the MS, are characterized by high oxidative stress (Bae *et al.*, 2001, Dandona *et al.*, 2001, Redón *et al.*, 2003). Some studies have shown beneficial effect of omega-3 and Calcium intake in the subjects with MS (de Camargo Talon *et al.*, 2015, Han *et al.*, 2019). The benefits of vitamin D supplementation on MS and related components are not clear (Kern and Mitmesser, 2018). Piazzolla *et al.* revealed that early correction of folic acid levels may prevent cardiovascular complications in MS patients (Piazzolla *et al.*, 2019). Ghamarchehreh *et al.* showed no relationship between iron status and the MS among patients with non-alcoholic fatty liver disease (Ghamarchehreh *et al.*, 2016). Moreover, there was no relationship between any type of dietary iron and red meat intake, and the incidence of MS in the Tehran Lipid and Glucose Study (Esfandiari *et al.*, 2019). Observational and interventional study in the relationship between dietary zinc intake and MS prevalence is controversial. Some studies have reported an inverse relationship and others have found a direct relationship between zinc status and prevalence of MS (Ruz *et al.*, 2019).

Currently, there are concerns to find effective strategies to detect, treat, and control MS. Also it is unclear to what extent some supplements could be beneficial to MS. The present study was conducted due to high prevalence of MS in Yazd city and controversy about the association between supplements and MS.

### Materials and Methods

*Study population and data collection:* This analytical cross-sectional study was conducted on 9539 people aged 35-70 years living in Shahedieh, Zarch, and Ashkezar cities of Yazd province. This study is a subset of the PERSIAN Cohort Study; a prospective cohort study aiming to include 180,000 Iranians aged 35–70 years from 18 geographically distinct areas of Iran. While the Ministry of Health and Medical Education have monitored the project, investigators at local universities carried it out. The universities of medical sciences in 18 cities and regions of Iran were included. The protocol of this study was published elsewhere (Poustchi *et al.*, 2018).

Men and women aged 35–70 years living in Shahedieh, Zarch, and Ashkezar cities were invited to participate in the study. The inclusion criteria were being indigenous and living in designated area for at least 9 months of the year. The subjects with physical or psychological disabilities that render them unable to complete the recruitment process were excluded from the study. The participants were invited to the Cohort office face-to-face and door-to-door by trained research staffs. This approach was consistent with the indigenous culture. After completing the informed consent form, anthropometric measurements and data collection were conducted by the researchers in an interview. Age, sex, body mass index (BMI), physical activity, tobacco smoking, and consumption of supplements, such as multivitamin-mineral, multivitamin, Calcium-D, Calcium, vitamin D injection or orally intake, folic acid, omega 3, iron, and zinc were asked and recorded by a trained interviewer.

The revised criteria of the NCEP-ATP III was used to define MS (Grundy *et al.*, 2005). The

NCEP-ATP III criteria define MS as the presence of any of three or more of the following five MS components: waist circumference  $\geq 102$  cm for men and  $\geq 88$  cm for women according to the Iranian society for the study of obesity cut-off point for abdominal obesity (Rashidy-Pour *et al.*, 2009); triglyceride levels  $\geq 150$  mg/dl or taking medication for elevated triglycerides; high-density lipoprotein (HDLc) cholesterol levels  $< 40$  mg/dl ( $< 50$  mg/dl for women) or taking medication to decrease HDLc; systolic blood pressure  $> 130$  mmHg or diastolic blood pressure  $> 85$  mmHg or taking antihypertensive medication; fasting blood glucose (FBS)  $> 100$  mg/dl or taking medication for elevated glucose levels. The MS phenotypes represented any three or more combinations of the five MS components.

**Measurements:** The consumption of supplements is defined positive if each supplement is taken at the current time or during past 12 months. The International Physical Activity Questionnaire (IPAQ) was used to calculate physical activity levels. The amount of each activity in hours and min was determined. The MET-value of each activity was multiplied by its duration, and total MET score was calculated. So physical activity is divided into three categories with low physical activity (less than 30 min of physical activity per week), moderate physical activity (30 min to 2 hours of physical activity per week), and high physical activity (more than 2 hours of physical activity per week). Blood pressure was measured from each right and left hand, and finally the mean was recorded.

Blood chemistry tests, such as FBS, triglycerides (TG), and HDLc were analyzed using an auto analyzer BA-400 (Bio systems, European). Commercially available kits were used according to the manufacturer's instructions.

Weight was measured without shoes and wearing only light clothing using an electronic weighing scale (SECA, Model Country: Germany) and recorded to the nearest 100 g. Height was measured once at baseline without shoes with the subject stretching to the maximum height and the head positioned in the plane using a portable

stadiometer and was recorded to the nearest 0.1 cm. BMI was also calculated ( $\text{kg}/\text{m}^2$ ). Waist circumference (WC) was measured midway between the lowest border of rib cage and the upper border of iliac crest, at the end of normal expiration. For all measurements the tape was positioned at a level parallel to the floor.

**Ethical consideration:** This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran with the reference number IR.SSU.REC.1399.064 and informed consent was obtained from all the participants.

**Data analyses:** SPSS version 20 software was used for statistical analysis. The results were expressed as mean  $\pm$  standard deviation for quantitative and percentage for qualitative variables. The relationship between MS and each supplement was assessed by chi-square test. Then Logistic regression analysis was performed to identify mentioned relationship after adjustment for some variables. Four models were used and the variables entered the models as follows: Model 1: Adjustment for age and sex; Model 2: Adjustment for age, sex, and BMI; Model 3: Adjustment for age, sex, BMI, and physical activity; Model 4: Adjustment for age, sex, BMI, physical activity, and smoking. P-value of less than 0.05 was considered to be statistically significant.

## Results

Among 9539 participants, 4785 (50.2%) were men and 4754 (49.8%) were women. The mean age of participants was  $47.64 \pm 9.60$  years (range 35-70 years). Demographics of the participants' supplements consumption are summarized in **Table 1**. The prevalence of MS was 2901 (30.41%).

Comparison of supplements intake in the subjects with and without MS in the study population is shown in **Table 2**. The participants with MS differ from healthy subjects in consuming supplements, such as Calcium-D ( $P < 0.001$ ), Calcium ( $P < 0.001$ ), Calcium-D or Calcium products ( $P = 0.001$ ), vitamin D, injection ( $P = 0.017$ ), vitamin D oral or injection ( $P = 0.005$ ),

Omega 3, fish oil ( $P = 0.001$ ), and at least one supplement ( $P = 0.001$ ).

**Table 3** reveals the results using the multivariate

regression model. In all models, the relationship between MS and supplement intake was not significant after adjusting for covariates.

**Table 1.** Demographics and frequency of supplement consumption from recruitment phase of Shahedieh Cohort study.

Variables	n (%) or mean $\pm$ SD
Age (year)	47.64 $\pm$ 9.60
Body mass index (kg/m <sup>2</sup> )	28.42 $\pm$ 4.80
Sex	
Male	4785 (50.2)
Female	4754 (49.8)
Physical activity	
Low	4917 (51.6)
Moderate	3568 (37.4)
High	1054 (11.0)
Smoking	2115 (22.5)
Multivitamin-mineral	315 (3.3)
Multivitamin	257 (2.7)
Multivitamin-mineral or multivitamin	572 (5.9)
Calcium-D	1441 (15.1)
Calcium	599 (6.3)
Calcium-D or Calcium	2040 (21.3)
Vitamin D (Oral)	1121 (11.8)
Vitamin D (injection)	485 (5.1)
Vitamin D (oral or injection)	1606 (16.8)
Folic acid	1187 (12.4)
Omega 3, fish oil	778 (8.1)
Iron	1597 (16.7)
Zinc	105 (1.1)
At least one supplement consumption	4152 (43.5)

**Table 2.** Comparison of supplements consumption in the subjects with and without metabolic syndrome in the study population from recruitment phase of Shahedieh Cohort study.

Supplements consumption	Metabolic syndrome		P-value <sup>a</sup>
	No (6638)	Yes (2901)	
Multivitamin-mineral	230 (3.5)	85 (2.9)	0.179
Multivitamin	186 (2.8)	71 (2.4)	0.325
Multivitamin-mineral or Multivitamin	416 (6.2)	156 (5.3)	0.090
Calcium-D	934 (14.1)	507 (17.5)	<0.001
Calcium	365 (5.5)	234 (8.1)	<0.001
Calcium (Total)	1299 (19.5)	741 (25.5)	<0.001
Vitamin D (Oral)	755 (11.4)	366 (12.6)	0.083
Vitamin D (Injection)	314 (4.7)	171 (5.9)	0.017
Vitamin D (oral or injection)	1069 (16.1)	537 (18.5)	0.005
Folic acid	825 (12.4)	362 (12.5)	0.946
Omega 3 (fish oil)	481 (7.2)	297 (10.2)	<0.001
Iron	1115 (16.8)	482 (16.6)	0.826
Zinc	82 (1.2)	23 (0.8)	0.057
At least one supplement consumption	2762 (41.6)	1390 (47.9)	<0.001

<sup>a</sup>:chi-square test

**Table 3.** The relationship between supplement consumption and metabolic syndrome in the study population from recruitment phase of Shahedieh Cohort study.

	Model 1	Model 2	Model 3	Model 4
Multivitamin-mineral	0.83 (0.64-1.09) <sup>a</sup>	0.85 (0.64-1.11)	0.85 (0.63-1.13)	0.863 (0.64-1.15)
P-value <sup>b</sup>	0.18	0.29	0.27	0.32
Multivitamin	0.88 (0.72-1.07)	0.93 (0.75-1.15)	0.92 (0.74-1.15)	0.96 (0.77-1.19)
P-value	0.22	0.51	0.50	0.71
Multivitamin, total	0.90 (0.79-1.02)	0.87 (0.76-1.00)	0.87 (0.76-1.00)	0.87 (0.76-1.00)
P-value	0.12	0.06	0.05	0.05
Calcium-D	1.12 (0.94-1.35)	1.09 (0.89-1.32)	1.09 (0.89-1.32)	1.08 (0.89-1.31)
P-value	0.18	0.37	0.38	0.41
Calcium, total	0.96 (0.86-1.08)	0.93 (0.82-1.05)	0.92 (0.82-1.04)	0.92 (0.82-1.04)
P-value	0.55	0.24	0.22	0.22
Vitamin D, tablet	0.92 (0.80-1.06)	0.87 (0.74-1.01)	0.87 (0.74-1.01)	0.87 (0.75-1.02)
P-value	0.28	0.07	0.07	0.09
Vitamin D, injection	0.90 (0.74-1.11)	0.82 (0.66-1.03)	0.82 (0.65-1.02)	0.82 (0.65-1.02)
P-value	0.34	0.09	0.07	0.08
Vitamin D, total	0.93 (0.82-1.06)	0.87 (0.76-1.00)	0.87 (0.76-1.00)	0.87 (0.76-1.01)
P-value	0.31	0.06	0.05	0.07
Omega 3, fish oil	1.08 (0.92-1.27)	0.95 (0.79-1.13)	0.94 (0.79-1.12)	0.93 (0.78-1.11)
P-value	0.30	0.56	0.51	0.43
Zinc	0.65 (0.40-1.05)	0.70 (0.42-1.17)	0.69 (0.41-1.16)	0.70 (0.42-1.18)
P-value	0.08	0.18	0.17	0.19
At least one supplement	0.97 (0.87-1.07)	0.95 (0.85-1.06)	0.94 (0.85-1.05)	0.94 (0.85-1.05)
P-value	0.54	0.37	0.32	0.30

Model 1: Adjustment for age and sex; Model 2: Adjustment for age, sex, and BMI; Model 3: Adjustment for age, sex, BMI, and physical activity; Model 4: Adjustment for age, sex, BMI, physical activity, and smoking; <sup>a</sup>: OR (95% CI); <sup>b</sup>: Logistic regression statistical test

## Discussion

In this study, the subjects with and without MS differ in the consumption of some supplements, such as Calcium products, vitamin D products, omega 3, fish oil, and at least one supplement. However, using multivariate regression model, the relationship between MS and supplements consumption was not significant after adjusting for age, sex, BMI, physical activity, and smoking.

Pathogenesis of MS includes genetic, metabolic, and environmental factors (Mirmiran *et al.*, 2008). Diet and low physical activity are environmental factors related to the high prevalence of MS (Buckland *et al.*, 2008). Adults with MS have low plasma level of several antioxidants, such as retinyl esters, vitamin C, vitamin E, and several carotenoids (Ford *et al.*, 2003). Oxidative stress and low grade inflammation are two important mechanisms implicated in the pathogenesis, and developing MS and atherosclerosis (McGrowder *et al.*, 2011, Parthasarathy *et al.*, 2008). Therefore,

dietary supplements may reduce the prevalence of MS.

After adjusting for age, sex, BMI, physical activity, and smoking, there is not any difference in supplements consumption in the subjects with and without MS. This result emphasizes that these confounding factors may be important in the development and progression of MS compared to supplement consumption.

The role of antioxidants consumption (single or in combination) in the metabolic health is controversial according to randomized clinical trials (Davì *et al.*, 2010, Xu *et al.*, 2014).

MS has an important role in the development of diabetes and CVD. Obesity has a major effect in the development of other features of MS. Therefore, prevention of obesity by managing an appropriate balance of energy intake is crucial for controlling MS and its consequences in the future (Xu *et al.*, 2019). Limitation of food intake and quality selection of nutritional components affect

insulin secretion, insulin sensitivity, oxidative system, and inflammatory states (Xu *et al.*, 2019).

Positive effect of omega-3 and Calcium intake in the subjects with MS has been discussed in some studies (de Camargo Talon *et al.*, 2015, Han *et al.*, 2019). However, controversy regarding the effects of vitamin D supplementation on MS and related components are present (Kern and Mitmesser, 2018). The data about the relationship between dietary zinc intake and frequency of MS is controversial (Ruz *et al.*, 2019). The underlying mechanism of vitamins and minerals effects on MS include modulation of systemic inflammation, oxidative stress, impacts on insulin secretion, and insulin sensitivity (Kern and Mitmesser, 2018).

In a prospective cohort study, a significant inverse association was found between higher healthy lifestyle scores and the incident of MS. This healthy lifestyle includes combination of less intake of alcohol, no depression, following Mediterranean diet pattern, and a slightly higher total energy intake per day. In this study, the participants with high healthy lifestyle scores had 34% lower risk of developing MS than those who had lower healthy lifestyle scores. These results emphasize the importance of healthy lifestyle (multiple factors but no single factor) as a tool for preventing MS (Garralda-Del-Villar *et al.*, 2019).

One of the limitations of this study is ignorance of dietary intake of these vitamins/minerals in the food. Future studies with focus on the association between micro nutrient intake from both food and supplements and MS would be useful. The other limitation was the cross-sectional design and loss of its ability to conclude a cause and effect relationship.

MS is a complex research topic with multi-factorial etiology and it is not clear whether a specific supplement may be responsible for all of the etiology of MS. The present study confirms that multiple factors may be responsible in the prevalence of MS. However, consuming any supplement for treatment or prevention of metabolic diseases requires evidence derived from randomized controlled trials.

### Conflict of interest

The authors declare no conflict of interest.

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### Authors' contributions

Ghadiri-Anari A designed this study. Gholami S wrote this manuscript. Hazar N and Bagheri-Fahraji B helped in analyzing the data. Azizi R, Nadjarzadeh A and Ghelmani SY reviewed the manuscript. Mirzaei M and Khayyatzadeh SS were involved in supervising Shahedieh Cohort. Also Mirzaei M revised the manuscript. Ghadiri-Anari A was the main editor and correspondent of the written manuscript. All authors read and approved the final draft of the study.

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