The association between nutritional exposures and metabolic syndrome in the Tehran Lipid and Glucose Study (TLGS): a cohort study

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ABSTRACT

Objectives: This study was conducted with the goal of investigating the effect of various food consumption on the incidence of metabolic syndrome (MetS).

Study design: Prospective cohort study.

Methods: This study conducted on 3616 healthy adults aged ≥20 years, who were not affected with MetS. Nutritional intake was determined at the beginning of the study (2008–2011) by the Food Frequency Questionnaire (FFQ), and the incidence of MetS was investigated after a median of 24.6 months follow-up. Data were analyzed by multiple logistic regression, with 95% confidence interval.

Results: After adjusting the effect of other variables in the model many foods in the whole grains group such as Sangak bread (OR = 0.35, 95% CI: 0.11–1.56), multiple types of vegetables and fruits – such as peach (OR = 0.11, 95% CI: 0.01–0.75), and mushroom (OR = 0.28, 95% CI: 0.11–0.71) had protective effects against MetS. From the dairy group yoghurt (OR = 0.43, 95% CI: 0.18–1.01) and ice cream (OR = 0.35, 95% CI: 0.12–1.06) had similar such effects.

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Introduction

Metabolic syndrome (MetS) is considered one of the major predisposing factors of cardiovascular diseases and diabetes, and is regarded a public health issue throughout the world. According to the World Health Organization (WHO) and International Diabetes Federation (IDF), the metabolic syndrome is defined as the simultaneous occurrence of the following five symptoms: central/abdominal obesity; hypertension (or being treated with antihypertensive drugs); elevated blood sugar levels (or being treated with hypoglycemic drugs); elevated triglyceride levels (and/or being treated with triglyceride – lowering drugs); and reduced HDL levels (and/or being treated with HDL – raising drugs). Worldwide, this disease is on the rise, such that the prevalence of MetS in the USA rose from 6.4% in 2000 to 34% in 2006. In Iran, the Tehran Lipid and Glucose Study reported the prevalence of MetS among adult women and men to be 42% and 24%, respectively. Overall, figures point to the increased prevalence of this syndrome among the Iranian population. Furthermore, according to the nine-year cohort study in Iran, the reported overall incidence of MetS among adults aged ≥20 years was 550.9 for every 10,000 person-years; and 794.2 for every 10,000 person-years in males and 443.5 for every 10,000 person-years in females. These figures show an increasing trend when compared to earlier studies.

Based on numerous studies, multiple factors are involved in the etiology of MetS, the most important of which are; immobility, genetic factors, psychosocial stress and dietary factors. Concerning dietary factors, some dietary patterns and habits such as an overall tendency towards consumption of fast foods, fatty foods and overeating are among the factors contributing to the alarming rise in the incidence of MetS. For example, dietary habits such as the repeated consumption of fast foods have undesirable effects on the quality of dietary regimes; the excess intake of energy and fat, less intake of Vitamins A, C, calcium and other nutrients, inadequate consumption of necessary food/nutritional groups such as whole grains, dairy products, fruits and vegetables.

Although many studies have been conducted so far on the role of micro- and macro- nutrients on the occurrence of cardiovascular diseases, diabetes and MetS in Iran and other parts of the world, to our knowledge, no study has investigated the simultaneous effect of multiple food substances on the incidence of MetS. Moreover, contradicting findings have been reported on the effects of certain types of foods and nutritional groups; e.g. rice – which constitutes a major portion of the diet of Middle Eastern and South East Asian countries, wherein some have reported its protective effects and others have highlighted its harmful effects. Therefore, we aimed to examine the simultaneous effects of different food components on the incidence of MetS using multivariate models that could control the confounding effects of different variables.

Methods

This prospective study is part of a larger study titled the Tehran Lipid and Glucose Study (TLGS). It is also part of a thesis that was conducted among Tehranian adults during three years of follow-up from 2011 to 2014. In this study, we have used data from the prospective TLGS cohort, which has been conducted on 15,005 persons aged 3–63 years old, from Tehran’s district 13. The study began in 1998. We used the data collected in the fourth (2008–2011) and fifth (2011–2014) phases of the study. Data related to dietary intake and confounding variables were collected from the fourth phase, and new MetS cases were chosen from the fifth phase, which is considered as the follow-up phase.

Target population

All healthy adults aged ≥20 years not affected with MetS at the beginning of the study (fourth phase) who had dietary information were selected (see Fig. 1). The newly affected MetS cases were 590 persons. The reason for selecting the ≥20 years age group was that the MetS definition holds true for adults; it is different for persons aged <20 years.

Inclusion criteria

Those who were eligible for the study included persons aged ≥20 years who had been followed up from the fourth to the fifth phase, and who possessed the following criteria: no history of chronic diseases (diabetes, stroke, thyroid problems and cancer); not having any specific dietary regime (such as a weight loss diet and the intake of fewer than 800 kcal or greater than 4000 kcal); and not being affected with the MetS.

Measurement of outcome

In the TLGS study, persons with MetS were identified using the Adult Treatment Panel (ATP) Guidelines. The criteria included having three of the following five indicators simultaneously: (1) abdominal obesity (waist circumference > 90 cm in both genders); (2) lowered serum HDL levels (lower than...
40 mg/dl in men and 50 mg/dl in women, or the consumption of HDL-elevating drugs); (3) hypertension (a systolic BP \( \geq 130 \) mmHg or a diastolic BP \( \geq 85 \) mmHg, or the consumption of antihypertensive drugs); (4) disordered FBS level (a fasting blood glucose/FBS \( \geq 100 \) mg/dl, or the consumption of hypoglycemic drugs); (5) hypertriglyceridemia (a serum triglyceride level \( \geq 150 \) mg/dl, or the consumption of triglyceride-lowering drugs).

Among the five components of MetS, four components were measured only once (at the end of each phase, i.e. once every three years), including, waist circumference, serum HDL, blood sugar, and serum triglycerides. Only hypertension was measured twice during each phase. Each time, blood pressure was measured twice with at least a 30-second interval between the two measurements. Thereafter, the mean of the two measurements was considered as the participant’s BP for that session.\textsuperscript{30,32}

**Measurement of exposure**

Nutritional information on the participants’ dietary intake was gathered using the Food Frequency Questionnaire (FFQ), which contains 147 food items. A nutritionist who had been trained in the field completed the questionnaires through a face-to-face interview. During the interview, the average size of each of the FFQ food items was explained to the participant, and then she/he was asked about the number of times each item was taken in the past year. The validity and reliability of this questionnaire has already been assessed during a pilot study on 133 samples, wherein Pearson’s correlation coefficient was acceptable.\textsuperscript{33} The consumption frequency of each food item in the past year was assessed in the form of days, weeks, months and/or years, and then, using home scale guides, the amount consumed of each item was transformed into grams per day.

The amount of intake of energy and macronutrients and micronutrients were determined using the food composition table. The data related to food intake in the fourth phase were considered as the exposure.

**Other measured variables**

Here, we measured the physical activity during the past year with the standard physical activity questionnaire. The frequency and duration of each physical activity in the past 12 months was asked, and was then calculated as Metabolic Equivalent (MET) hours per week. Data on physical activity status were obtained using the modified activity questionnaire (MAC). The MAQ determines the current (past year and past week) physical activity during occupation and leisure time. Total physical activities were explicit in hours of activity per week by adding leisure time physical activity to occupational activity.\textsuperscript{34} Other variables measured were as follows: weight (in kilograms: wearing minimum clothes, without shoes, using a seca weighing scale with an accuracy of 0.5 kg); height (without shoes, using a meter fixed on the wall with an accuracy of 1 cm); waist circumference (the circumference at the slimmest area between the lowest rib and the tip of the iliac crest); systolic and diastolic blood pressure (BP) (using a manual sphygmomanometer, the mean was considered as the person’s BP and reported in mm Hg); and finally, a family history of diabetes.

Moreover, the necessary data on age, gender, education (primary, intermediate, high school and high school graduate, academic education), narcotics use (never smoked, previous smoked, currently smoking), and drug or supplementary intake were collected using a general information questionnaire through an interview conducted by the nutritionist. A venous blood sample was taken after 10 h nocturnal fasting to measure serum HDL, glucose, triglycerides and cholesterol. Blood glucose was measured with glucose oxidase; serum triglycerides were measured with the Pars Azmoon Kit — with the AutoAnalyzer Selecta; and serum HDL was measured after precipitating \( \beta \) apolipoprotein with phosphotungstic acid solution.
Data analysis

We used bi-variable logistic regression to estimate the crude effect of each of the nutritional and non-nutritional variables on MetS. Then, we used multiple logistic regression to estimate the adjusted effect of variables. The backward-selection method was applied to choose the variables in this model. To remove the variables from the model, the P-value was set at 0.2. Seventy variables (three confounding variables of educational status, smoking history, and history of weight loss, in addition to 68 food items) were removed at this stage. In addition, six items were removed from the model because of their high correlation. These food items included the following: jam (and sugar); plum (and peach); lemon juice (and lemon); apple juice (and apple); orange juice (and orange); cooked vegetables (and cooked carrots). Between the two similar food items that were correlated one that was consumed more (specified in parentheses) was kept for the final analysis.

Moreover, 40 food items were removed as their consumption was very low in the individuals’ daily diets. These items were as follows: biscuits; crackers; mung beans; burgers; salami; sheep meat (such as, stomach, tongue, brain, head and feet); whipped cream; margarine; curd; pumpkin; zucchini; long green pepper; fig; green plum; grapefruit; strawberry; raisins; fresh mulberry; dried mulberry; dried plums; green olives; olive oil; animal fat; peanuts; cookies; pastry; gaz; sohaan; chocolates; crystallized sugar; halva shekari (a sweet breakfast food in Iran); homemade halva; cake; canned fruit; salt; and spices.

To be able to better interpret the effect of foodstuff on the incidence of MetS, valid references that had defined daily servings were used, and each food item’s parameter was transformed from ‘grams’ to specified servings.

Eventually, data analysis was done with STATA 11 (StataCorp, College Station, TX, USA), at a confidence interval of 95%.

To account for multiple testing, we used the Bonferroni correction and considered only those crude ORs for which P < 0.05/40 = 1.25 x 10–3 as significant. This correction is known to be a conservative one and thus we ‘over-corrected’ the raw P-values. To estimate the effect of the food items and other confounding variables on the incidence of MetS, we used multiple logistic regression and maximum likelihood estimation methods.

Results

Adults aged ≥20 years who had completed the FFQ were included in the study and followed for three years. Overall, among the 590 new cases of MetS (291 males and 299 females), with a median follow-up time of 24.6 months, an incidence rate of 821.62 cases per 10,000 person-years (95% CI: 757.93–890.67) was calculated. The incidence rate of MetS was 1255.88 (95% CI: 998.05–1119.56) and 652.60 (95% CI: 582.67–730.93) cases per 10,000 person-years among males and females respectively. Based on our findings, the incidence was statistically significant lower in females than in males (P < –0.001). In both genders, those affected with MetS were older, had higher systolic and diastolic BP, higher triglycerides, higher FBS, higher BMI and greater waist circumferences. Moreover, the consumption of antihypertensive, hypoglycemic, and lipid-lowering drugs was greater among them. The percentage of married individuals and those who had experienced a heart stroke were also higher. All the aforementioned differences were statistically significant (Table 1).

We estimated the adjusted and the crude odds ratio of food intakes and other covariates on MetS (Table 2). In the multiple logistic regression section, for every 5-year increase in age, the odds of acquiring the MetS decreased by 3%, though this association was not statistically significant (95% CI: 0.84–1.12). People with cancer had 5.21 times greater chance of having MetS than those who did not have cancer; this association was not statistically significant either (95% CI: 0.82–32.88). Hospitalization in the past three months increased the odds of MetS by 3.84 times, which was statistically significant (95% CI: 1.49–9.88). For every hour of job-related physical activity, the odds of MetS reduced by 31%. However, this association was not statistically significant (95% CI: 0.44–1.08). Compared to men, women were 68% less likely to acquire MetS, which was statistically significant (95% CI: 0.14–0.70; Table 2).

For every unit increase in BMI, the odds of being affected with MetS increased by 1.19 times, an association that was statistically significant (95% CI: 1.12–1.27). Married individuals were 4.38 times more likely to have MetS; this too was statistically significant (95% CI: 1.17–16.29).

For every 100 g consumption of pizza per day, the odds of MetS increased by 4.42 times, which was significant (95% CI: 1.01–19.54). And, for every 100 g consumption of chicken meat per day, the odds of acquiring MetS increased by 4.54 times, an association that was very significant (95% CI: 1.53–11.74).

For every tablespoon consumption of mayonnaise per day the chances of having MetS increased by 6.49 times, an association that was significant (95% CI: 1.18–35.52). For every tablespoon consumption of ketchup sauce per day the chances of having MetS increased by 5.06 times, an association that was significant (95% CI: 1.08–23.71).

For every 30 g consumption of grains per day the chances of having MetS increased by 7.28 times, an association that was significant too (95% CI: 1.43–36.94). Likewise, for every tablespoon consumption of honey per day the chances of having MetS increased by 2.82 times, an association that was significant (95% CI: 1.08–7.30).

The consumption of Sangak bread reduced the odds of MetS by 65%, which was statistically insignificant (95% CI: 0.11–1.56). The consumption of Lavash bread reduced the odds of MetS by 78%, which was statistically significant (95% CI: 0.04–0.99). The consumption of a peach a day reduced the incidence of MetS by 89%, which was statistically significant.

For everyone serving consumption of yoghurt a day (equivalent to 200 g), the incidence of MetS drops by 57%, a finding that was marginally significant (95% CI: 0.18–1.01). The odds of having MetS drops by 62% for every 50 g consumption of lettuce per day; this finding too was marginally significant (95% CI: 0.14–1.05). For every one-serving of lentils per day (equivalent to 50 g), the odds of MetS drops by 90%, which was very significant (95% CI: 0.02–0.34). Similarly, the odds is reduced by 74% for consuming a single cucumber a day (95%
CI: 0.06–1.11), an association that was marginally significant. The consumption of 20 g of mushroom per day reduces the odds of MetS by 72%, which was statistically significant (95% CI: 0.11–0.71).

Consuming one tablespoon of cooking oil reduced the incidence of MetS by 77%, a relationship that was statistically significant (95% CI: 0.11–0.51). For every 50 g of ice cream eaten per day, the odds of MetS reduced by 65%, which was marginally significant (95% CI: 0.12–1.06).

### Discussion

Five-hundred and ninety (590) new cases of metabolic syndrome were observed in three years of follow-up, with an incidence rate of 821.62 per 10,000 person-years. Moreover, based on our results, the percentage of hypoglycemic, lipid-lowering and antihypertensive drugs usage, married individuals and those afflicted with heart stroke were higher among the latter group. Results of the multiple logistic regression model showed that the following odds factors increased the likelihood of having MetS: history of hospitalization during the past 3 months; male gender; increased BMI; and being married; all of which were statistically significant too. The following significantly increased the odds of MetS too: pizza; mayonnaise; groats; corn; cooked carrots; peas; zucchini; chicken; eggs; ketchup; dates; honey; hazelnuts; and pomegranate. Other foodstuff raised the odds of MetS too, such as, Tafteh bread, pear, and tuna fish; however, they were marginally significant. On the other hand, foods such as Lavash bread, peach, lentils, cooked mushrooms, oil and potatoes significantly reduced the odds of MetS. Other foodstuff reduced the odds of MetS, but were marginally significant; lettuce, eggplant, yoghurt, cucumber, beef and ice cream. Some other whole grains like Sangak bread reduced the odds of MetS, although it was marginally significant.

The overall incidence of MetS showed a considerable rise in this study when compared to its counterpart conducted in similar settings (from 2001 to 2011) by Hadaegh et al. and has approximately doubled (821.62 vs 433.5 per 10,000 person-years). Moreover, we observed a significantly higher incidence of MetS among males than in females (1255.88 vs 652.60 per 10,000 person-years). Previously, studies in Iran showed the opposite, i.e. the prevalence of MetS was higher among women than in men. However, recent studies have
shown that males have MetS more than females. One reason behind this phenomenon may be the higher prevalence of the basic characteristics (MetS-related) in the males of our study, such as, mean age, waist circumference, FBS, triglycerides, higher systolic and diastolic BP, lower HDL, and BMI. Moreover, based on the census (2011) performed in Iran, women had an average 2.5 years greater life expectancy than men, which can explain the higher prevalence of MetS among men. Moreover, since waist circumference >90 cm in both genders was one of the quintuple criteria for MetS, thus, it is possible that fewer women were considered as new MetS cases. Consequently, a higher incidence rate was observed in men.

Similar to our study, Hadaegh et al. also observed a higher prevalence of the following variables in both genders afflicted with MetS; age, systolic and diastolic BP, triglycerides, FBS, BMI, and waist circumference. However, a history of diabetes was observed at a significantly higher rate among the afflicted than in the healthy group. Similar to our findings, no significant difference was observed in spite of the greater number of smokers among those with MetS.

The significant odds factors of MetS were, a history of hospitalization in the past three months, the male gender, increased BMI, and being married, all of which we observed too, and which had been previously discovered in studies like Hadaegh, Yang, and Sirdah. Although Sirdah had reported the role of younger age, history of cancer, and job-related physical activity too.

Esmailizadeh had exclusively investigated the role of whole grains in the prevalence of MetS and had observed that the consumption of whole grains was indirectly and that of refined grains was directly related to MetS. In this respect, only the effect of Sangak bread was in accordance with the
latter’s findings. However, Maras and Ruidavets have shown the protective effect of whole grains on the incidence of MetS.

Hashemi and Medjakovic demonstrated the protective effect of pomegranate in the incidence of MetS. Pomegranate contains soluble polyphenols like anthocyanins and tannins; it also has antioxidant and anti-atherosclerotic properties, causing BP to fall. We however, found a direct association between this fruit and the odds of MetS. Most probably, the results of this section have been exposed to the odds of information bias.

We detected a direct and significant association between mayonnaise and MetS. Although no study has investigated the effect of this food item in particular, but some studies have pointed towards the direct effects of fatty diets and particularly saturated fats in MetS, which support our findings.

Cohort studies conducted by Bahadoran and Devaraj had indicated the increased odds of pizza consumption and other fast foods on the incidence of MetS. We too found a strong positive and direct association between pizza consumption and the odds of MetS. Pizza contains harmful food combinations such as salt and saturated fats leading to an increased BP. Other substances such as sausages and salami contain preservatives and additives that cause the release of free radicals in the body, and prepare grounds for cancer.

Various studies have shown the protective effects of vegetables and fruits in acquiring MetS, even after controlling and adjusting the effects of other confounders. These substances exert their protective effects through beneficial combinations such as antioxidants, fibre, potassium and other herbal chemicals, and through reducing the concentration of CRP (C-reactive protein). We too observed the protective effects of some fruits and vegetables like peach, cooked mushrooms and potatoes, lettuce, eggplant and cucumber in the incidence of MetS.

Moreover, here we found an inverse relationship between dairy products (yoghurt and ice cream) and MetS, which was somewhat significant. Several studies have examined the protective effect of dairy products on MetS, wherein this effect has been preserved even after adjusting the effects of other factors. These studies have indicated the beneficial effects of consuming dairy products on weight control, glucose haemostasis, and BP (as components of MetS), and that the saturated fats present in dairy products such as pentadecanoic acid and heptadecanoic acid reduce oxidative inflammatory and stress indicators, and eventually reduce the odds of MetS and cardiovascular diseases.

### Limitations

An important limitation of this and in general traditional studies or so-called 'single-stage models' is the difficulty in estimating all the measured variables because of insufficient sample sizes. As a rule of thumb, there must be 10 cases of outcome in the data to estimate the required sample size for each parameter. In this study we had 147 food items and 15 other variables (individuals’ background variables and other confounding variables), i.e. a total 162 variables; hence requiring 1620 cases of outcome. However, we only had 590 new cases of MetS, so we could not estimate the effects of all the variables and in particular the effects of all the 147 food items.

Among the other limitations of traditional models is that usually the forward and backward techniques are applied to choose the variable in the final model. Since different variables are selected, different models and eventually, different interpretations result. By entering multiple variables into the usual models the power of the study decreases and leads to so-called high-dimensionality. Moreover, when a few variables remain in the final model they lead to bias. We too used the backward – selection technique to choose the variables of the final model, that led to the removal of a considerable number of variables, hence preventing the estimation of their effects. Furthermore, because of not taking into consideration the earlier distribution and its resultant uncertainty, traditional models result in estimates with overly narrow confidence intervals and underestimate variance. Subsequently, the major limitation of traditional models is the presumption that the effect of each independent variable is completely assessed; they do not allow the unmeasured effects of independent variables to enter the model.

On the other hand, the requirement for literacy in the study population, not providing meal pattern information, not being used over short time periods and relying on subject recall, may lead to measurement error (information bias). Some studies have shown these shortcomings to incline the results towards the null effect.

### Conclusion

After adjusting the effect of other variables, the male gender, being married and increased BMI were factors increasing the odds of MetS. Moreover, fast foods (like pizza) and other fatty foodstuffs (like mayonnaise) were odds factors for MetS. Several food items in the whole grains group (like Sangak bread), vegetables and fruits (like peach and mushroom), and dairy products (like yoghurt and ice cream) had protective effects on MetS.

### Recommendations

Traditional models and multiple variable logistic regression have certain limitations in simultaneously estimating many variables of high correlation. Therefore, we recommend the application of Bayesian models to reduce and remove the difficulties associated with traditional models and to raise the accuracy of predictions in nutritional studies.

### Author statements

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Ethical approval

This study obtained ethical approval from the Tehran University of Medical Sciences (TUMS)/Research Ethics Board.

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Competing interests

None declared.

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