Association between Major Dietary Patterns and Polycystic Ovary Syndrome: evidence from a case-control study

Farnaz Shahdadian [a], Reza Ghiasvand [b], Behnood Abbasi [c], Awat Feizi [d], Parvane Saneei[e], Zahra Shahshahan [f]

Corresponding Author: Reza Ghiasvand, Ph.D.
Department of Community Nutrition
School of Nutrition and Food Science
Isfahan University of Medical Sciences
PO Box 81745
Isfahan
Iran
Tel: +983137923153
Fax: +983136682509
Email: ghiasvand@hlth.mui.ac.ir

[a] MSc. Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran. fshahdadian@yahoo.com

[b] Ph.D. Associate Professor of Nutrition. Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran. ghiasvand@hlth.mui.ac.ir

[c] Ph.D. Assistant Professor of Nutrition. Department of nutrition, School of Medical Sciences, Islamic Azad University, Science and Research Branch, Tehran, Iran. abbasi.b@srbiau.ac.ir

[d] Ph.D. Associate Professor of Biostatistics, Department of Biostatistics and Epidemiology, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran. awat_feiz@hlth.mui.ac.ir

[e] Ph.D. Department of Community Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. saneei@nutr.mui.ac.ir

[f] Associate Professor of Gynecology, Department of Obstetrics and Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Shahshahan@med.mui.ac.ir

Running title: dietary patterns and polycystic ovary syndrome.

Abstract

Objective: Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder in women. Change in lifestyle, especially dietary pattern, might have a role in prevalence of PCOS. The limited number of studies has made it difficult to draw any conclusion about the dietary patterns with PCOS. This study aimed to investigate the association between dietary patterns with PCOS.

Methods: This case-control study was performed on 225 new diagnosed patients and 345 healthy women in Isfahan, Iran. The presence of PCOS was confirmed by the expert gynecologists based on Rotterdam criteria. Usual dietary intake was assessed by a 168-items food frequency questionnaire. Dietary patterns were identified by principal component analysis.

Results: Three major dietary patterns including western, plant-based, and mixed were identified that explained 53.93% of the variance of food intake. Top tertile of western dietary pattern significantly increased the odds of PCOS (OR, 2.03; 95%CI, 1.12-3.67), either before or after adjustments for covariates. After adjustments for potential confounders, the highest tertile of plant-based dietary pattern was related to higher odds of PCOS than the lowest one (OR, 2.32; 95%CI, 1.23-4.37). In addition, those in the second tertile of mixed dietary pattern were 66% less likely to have PCOS compared with the lowest one (OR, 0.34; 95%CI, 0.18-0.61).

Conclusions: We found that western and plant-based dietary patterns were associated with an increased risk of PCOS. Also, moderate adherence to the mixed dietary pattern was associated with reduced risk of PCOS. To confirm our findings more studies with longitudinal design are required.

Keywords: Dietary pattern; Polycystic ovary syndrome; Factor analysis

Abbreviations: PCOS, Polycystic ovary syndrome; FFQ, Food frequency questionnaire; PCA, Principal component analysis; BMI, Body mass index; IPAQ-SH, International physical activity questionnaire short form; MET, Metabolic equivalent; WC, Waist circumference; HC, Hip circumference; WHR, Waist to hip ratio; SES, Socioeconomic status; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; SAFA, Saturated fatty acids; MUFA, Monounsaturated fatty acids; PUFA, Polyunsaturated fatty acids; SHBG, Sex hormone-binding globulin; HPO axis, hypothalamic-pituitary-ovarian axis; LH, luteinizing hormone, FSH, Follicle stimulating hormone; OR, Odds ratio; CI, Confidence interval.

Introduction

Polycystic ovary syndrome (PCOS) is a complex heterogeneous and heritable endocrine disorder in women characterized by menstrual irregularities, hyperandrogenism, and ovaries with 12 or more follicles measuring 2–9 mm in diameter or ovarian volume more than 10 cm^3 (Stein and Leventhal 1935; Norman et al. 2007; Sirmans and Pate 2014). Globally, the prevalence of PCOS was estimated 15-20% (Sirmans and Pate 2014). According to Rotterdam criteria, it affects 17.8% and 19.5% of European and Iranian women, respectively (March et al. 2009; Jalilian et al. 2015). The main reproductive concern of PCOS is infertility (Hull 1987; Balen et al. 1995; Norman et al. 2007; Bhattacharya et al. 2009). In addition, 50-70% of women with PCOS suffer from insulin resistance that is associated with other adverse metabolic alteration, including obesity, cardiovascular diseases, and metabolic syndrome (Ovalle and Azziz 2002; Diamanti-Kandarakis 2006; Norman et al. 2007; Legro et al. 2013).

Although the cause of PCOS is still unclear, the genetic and environmental factors, as well as their interactions, may be implicated in etiology of this syndrome (Norman et al. 2007; Astrup et al. 2014). One of the most important causes of PCOS related to contribution of intrinsic and extrinsic insulin resistance in the pathophysiology of PCOS (Stepto et al. 2013). Unhealthy lifestyle, especially inappropriate diet, results in obesity and insulin resistance, and subsequently in uncontrolled production of androgens (hyperandrogenism) that is the leading feature of PCOS (Norman et al. 2002; Panagiotakos et al. 2004; Baillargeon and Nestler 2006; Norman et al. 2006; Norman et al. 2007; Huang et al. 2010; Fux et al. 2013). Some prior studies suggested that the risk of obesity especially central obesity as well as insulin resistance might possibly be decreased in healthy dietary pattern and might possibly be increased in western dietary pattern (Esmaillzadeh et al. 2007; Esmaillzadeh and Azadbakht 2008). Regarding the association of obesity and insulin resistance with PCOS, the major dietary patterns may play a significant role in prevalence and progression of PCOS.

Dietary pattern analysis provides a combined estimate of both the contribution of a number of factors and synergistic effect of the factors and depicts the broad aspects of diet. Assessment of dietary patterns is more informative than individual nutrients, foods, or food groups. In addition, unknown components of foods and the inherent interactions between nutrients and foods are considered in dietary pattern analysis. Thus, it can more effectively investigate the relationship between diet and diseases such as PCOS (Huijbregts et al. 1997; Hu 2002; McGuire 2016). Most of previous studies have evaluated the association between PCOS and individual nutrients, foods, food groups, or different types of diet. A systematic review in this regard reported no appreciable differences in the menstrual, reproductive or metabolic features with various dietary compositions in majority of included studies (Moran et al. 2013a). However, the other review suggested that high energy diet rich in saturated fatty acid and high glycemic index foods and inadequate fiber might have effects on metabolic outcomes in PCOS women (Lin and Lujan 2014). Stamets et al. demonstrated that adherence to two different energy-restricted diets (high protein and high carbohydrate) improved the reproductive function and there was no difference between these two diets (Stamets et al. 2004). In addition, another study investigated the influence of low carbohydrate diet or diet rich in monounsaturated fatty acids in comparison with the standard diet. This study showed that low carbohydrate diet increased insulin sensitivity, but had no effect on circulating reproductive hormones (Douglas et al. 2006a). Another population-based study demonstrated that intake of saturated fat was lower and low glycemic index diet as well as fiber were higher in PCOS women compared with non-PCOS females (Moran et al. 2013b). Although the results of one cohort study showed that the PCOS group tended to consume specific high glycemic index foods more than healthy women, the mean intakes of energy, micronutrients, and macronutrients were not significantly different in two groups (Douglas et al. 2006b). Ahmadi et al. assessed the dietary patterns in women with PCOS in a case-control study and reported that total energy and fat intake was higher in PCOS group with no difference in carbohydrate and protein intake (Ahmadi et al. 2013).

To the best of our knowledge, a few number of studies have evaluated major dietary patterns using factor analysis in women with PCOS (Moran et al. 2015) and majority of previous investigations have focused on assessment of food groups, total energy, and nutrients (Wright et al. 2004; Douglas et al. 2006b; Ahmadi et al. 2013). In addition, due to controversial results and lack of studies that have investigated major dietary patterns in Middle Eastern countries, especially in Iranian population, the current study was conducted in a case-control setting to evaluate the association of major dietary patterns with prevalence of PCOS in Iranian (Isfahanian) women.

Materials and methods

Study design and participants

A matched case-control study design was performed on a sample of women to determine the major dietary patterns in those with and without polycystic ovary syndrome. The study population involved women referring to "Isfahan Fertility and Infertility Center" and "Shahid Beheshti Hospital of Obstetrics and Gynecology" from October 2016 to May 2017. We also selected some cases from multiple clinics to obtain more generalizable results. The diagnosis of PCOS was performed by the expert gynecologists based on Standard Rotterdam Criteria (Fr and Tarlatzis 2004). Rotterdam criteria proposed that having two of the three following criteria are necessary for PCOS diagnosis: menstrual irregularities, clinical or biochemical hyperandrogenism, and ovaries with multiple cysts. The women, who were diagnosed as PCOS for the first time by the gynecologists, were considered as new cases in a consecutive manner. Control group was selected from the same center, hospital or clinics. Females with modified Ferriman-Gallwey (mF-G) score of <8 (Hatch et al. 1981) and regular menstruation were considered eligible to be included in the study as the control group (or healthy subjects). The frequency matching method was applied and two groups were matched using age and BMI. The inclusion criteria to be contributed in our study were females aged 18-45 with Iranian nationality. The subjects not included in our study were those with history of diseases such as hypothyroidism, Hyperprolactinemia, Cushing's syndrome, eating disorders, and congenital adrenal hyperplasia, drug use including hormonal drugs, contraceptive pills, and glucocorticoids, smoking, alcohol consumption, and use of special diet, taking multivitamins and minerals supplements. Females who were reporting their energy intake less than 800 Kcal or more than 4200 Kcal (Hu et al. 1999), and those who answered less than 35 food items of food frequency questionnaire (FFQ) were excluded from the study (n=14). The calculation of sample size was based on minimum sample size recommendation per each food item or food group in factor analyses (Mundfrom et al. 2005). In this study, we considered minimum 15 samples per each food groups. In addition, 10 % probability of sample loss was considered and finally, 225 newly diagnosed women with PCOS and 345 controls were recruited in our study. Demographic and anthropometric features, dietary intake, and physical activity were collected by separate valid questionnaires. All participants provided their signed written informed consent. The study protocol was approved by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.REC.1395, 3. 406).

Dietary intake assessment

Usual dietary intake during the last year was evaluated by a 168-items semi-quantitative food frequency questionnaire that validated in the Iranian population (Asghari et al. 2012). An expert dietitian fulfilled all questionnaires through face to face interview with participants. The portion sizes and frequency of consumption of each food and beverage items, on average, were inquired. The frequency was converted to daily intake and portion sizes were changed to gram, using household measurements. Finally, the actual food intake (g/day) was transferred to Nutritionist IV to compute the total energy and nutrients intake. Because of the large number of food items, 168 food items were categorized to 36 food groups for dietary pattern analysis (**Table 1**). Food items were included in the specific groups based on the similarity of their nutrients. Each food item included only in one group; since it had the unique content of nutrients.

Physical activity assessment

The International Physical Activity Questionnaire Short Form (IPAQ-SF) was used to collect physical activity data (Lee et al. 2011). Walking, moderate-intensity and vigorous-intensity activities are three types of activities that were evaluated in IPAQ-SF. In addition, for each type of activity, both the frequency (days per week) and duration (minutes per day) were gathered. The METs for Walking, moderate-intensity and vigorous-intensity activities are 3.3, 4.0, and 8.0, respectively. The Formula for computation of Met-minutes/week score of each type of activity was: MET of activity * minutes * days. To describe total score of activity, the score of each type of activity must be combined.

Anthropometric measurements

Anthropometric traits were measured in a fasting condition by using standardized protocols. Weight was measured by standard Seca digital scale to the nearest 0.1kg, while the participants were minimally clothed and not wearing shoes. Height was measured using tape measure in standing, normal breathing, and normal position of shoulders, with no shoes. Waist circumference (WC) was measured using non-elastic tape measure at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest (umbilical level) (WHO, 2008b). Hip circumference (HC) was measured around the widest portion of the buttocks. All measurements were recorded to the nearest 0.1 cm. BMI and WHR were calculated as weight (kg)/height (m^2) and WC (cm)/HC (cm), respectively.

Assessment of other variables

Socioeconomic status (SES) of the study participants was evaluated based on the following binary variables: education level of both subjects and the family head (academic/non-academic), job of both subjects and the family head (yes/no), family size (lower than 4/higher than 4), having a car (yes/no), home status (the owner/tenant), and having foreign travel (yes/no) by using self-reported questionnaire and then a total score was calculated. Demographic characteristics, menstrual duration, disease and drug history were assessed by general self-reported questionnaires.

Statistical analysis

To determine the major dietary patterns, factor analysis with principal components approach (PCA), as extraction method, was applied. Eigen values > 1 and the Scree plot determined that three major factors should be retained for final analysis. Varimax rotation (orthogonal) on extracted factors (dietary patterns) was conducted for interpretational purposes. The derived factors were named based on loaded factors of food groups in each dietary pattern (factor loading>0.2) and our interpretation from earlier studies. The factor scores for each pattern were computed by summing intake of food groups weighted by factor loading and each participant received a factor score for each identified pattern. In addition, KMO and Bartlett's Tests were applied to evaluate the adequacy of sample size and the ability to implement factor analysis method.

To compare quantitative variables between cases and controls, independent t-test was applied while for categorical variables chi-square was used. The Kolmogorov–Smirnov test was used to examine normality of quantitative variables. The continuous variables were presented as mean ± SD while qualitative variables as frequency (percentage). All participants were categorized according to the tertiles of dietary pattern scores. General characteristics of quantitative variables across tertiles of dietary patterns were evaluated by one-way analysis of variance and categorical ones using Chi-square test. The general linear model was performed to calculate energy-age adjusted means of dietary intake.

To identify the association between dietary patterns and PCOS, multivariable logistic regression was used. The odds ratio (OR) and 95% confidence interval for OR (95% CI) were calculated in crude and adjusted models. In model I, adjustments were made for age, marital status, BMI and physical activity. In model II, socioeconomic status was added to previous adjustments. In model III, energy intake and nutrients including fat, soluble fiber, vitamin E, vitamin C, zinc, calcium, and iron were added to previous adjustments. Since adjustment for weight, WC or WHR might increase the possibility of over-adjustment, we did not consider these variables in the analysis. To calculate the trend of OR across increasing tertiles of dietary patterns, we considered tertiles of each dietary pattern as an ordinal variable in the logistic regression model. The first tertile of each dietary pattern score was considered as the reference category. All analysis was performed using SPSS software version 16 (IBM, Chicago, IL) in which p-value < 0.05 (two-sided) was considered statistically significant.

Results

General characteristics, energy and macronutrients intake of cases and controls were illustrated in **Table 2**. No significant differences in age, BMI, hip circumference, and energy intake were observed between cases and controls. The means of weight, WC, and WHR in case group were significantly higher than control group ($p<0.05$). There was no significant association in drug use (including gastrointestinal and anti-allergic drugs) between cases and controls. In addition, mean value of physical activity was lower in cases compared to the controls ($p<0.001$) (**Table 2**). The mean values of nutrient intakes between cases and controls were demonstrated in **Table S 1**[1].

Using principal component analysis (PCA), three major dietary patterns were identified among participants. These dietary patterns labeled as western, plant-based, and mixed. Western dietary pattern was rich in processed and organs meats, high fat dairy, soft drinks, canned fruits, fast foods, mayonnaise, salty snacks, salt, sugar, sweets, and desserts. In plant-based dietary pattern, the intakes of legumes, yogurt drink, fruits, canned fruits, fruit juices, vegetables, nuts, olive, potato, garlic, and condiments were high. The consumption of grains, red meat, fish, poultry, eggs, fruits, vegetables, tomato sauce, mayonnaise, tea, vegetables oil, pickles, sugar, sweets and desserts were high in mixed dietary pattern. The factor loading matrix for the three major dietary patterns identified by PCA was shown in **Table 3**.

General characteristics, prevalence of PCOS, energy and nutrient intakes of the study participants across tertiles of three major dietary patterns were indicated in **Table S 2**[2] and **Table S 3**[3], respectively. Briefly, the mean age of participants in top tertile of western dietary pattern was higher than the lowest tertile, but in upper tertile of mixed dietary pattern was lower. There was no significant difference among age in tertiles of plant-based dietary pattern. Compared with the lowest tertiles of plant-based dietary pattern, subjects in the top tertile had more physical

[1] apnm-2018-0145.R2suppla.
[2] apnm-2018-0145.R2supplb.
[3] apnm-2018-0145.R2supplc.

activity. In addition, prevalence of PCOS in the highest tertile of western dietary pattern were more than the lowest one (46.8 vs. 33.3%, p=0.025). Prevalence of PCOS in the second tertile of plant-based and mixed dietary patterns was lower than the other tertiles (**Table S 2**). The total energy intakes in upper tertile of three dietary patterns were higher than lowest one (p<0.001). Intake of dietary fibers in the top tertile of western dietary pattern was lower than the bottom category. In contrast, those in the highest tertile of plant-based dietary pattern had more dietary fiber consumption than the lowest tertile. In the western dietary pattern, consumption of carbohydrate, protein and fat intake was significantly different among tertiles. The carbohydrate, protein and fat intakes were not varied among tertiles of plant-based dietary pattern, while carbohydrate and protein intakes were different among tertiles of mixed dietary pattern (**Table S 3**).

Multivariable adjusted odds ratio (95% Confidence Interval) for PCOS among tertiles of dietary patterns scores were shown in **Table 4**. In crude model, increased adherence to western dietary pattern elevated the odds of PCOS (OR, 1.76; 95% CI, 1.16-2.67). After adjusting for potential confounders, we observed that the highest tertile of western dietary pattern were associated with greater odds of having PCOS (OR, 2.03; 95% CI, 1.12-3.67). In addition, a significant linear association was observed between western dietary pattern and risk of PCOS in all models ($p_{trend}<0.05$). The subjects in the second tertile of plant-based and mixed dietary patterns had lowest odds for PCOS (OR, 0.42; 95% CI, 0.31-0.58 for plant-based dietary pattern; OR, 0.41; 95% CI, 0.30-0.57 for mixed dietary pattern). After adjustment for confounding variables, subjects in the highest tertile of plant-based dietary pattern had significantly more odds for having PCOS (OR, 2.32; 95% CI, 1.23-4.37).

Discussion

In the current case-control study, three major dietary patterns including western, plant-based, and mixed were identified among Iranian women. Analysis illustrated that an increase in adherence to western dietary pattern was associated with greater odds of PCOS. In the plant-based dietary pattern, the second tertile had a protective effect on PCOS; although this effect was attenuated after adjusting confounders and nutrients. In addition, the highest tertile of plant-based dietary pattern increased the odds of PCOS. To the best of our knowledge, this is the first study to examine the association between major dietary patterns with having PCOS in new diagnosed patients in a Middle Eastern country.

Studies that have investigated the relationship between major dietary patterns and PCOS are rare. One study assessed the dietary patterns in a large cohort of women and three major dietary patterns (including Mediterranean-style, Non-core foods, and Meats and take-away) were derived using factor analysis. The components of Mediterranean dietary pattern were similar to plant-based dietary pattern in the current study. In line with our study, the mentioned study showed that for one SD increase in the Mediterranean dietary pattern score, the chance of PCOS increased by 26%. Selection of subjects from a large cohort study might elevate the risk of bias. In other words, subjects might change their diet to healthier one, after awareness of their disorder (Moran et al. 2015).

Our findings showed that high adherence to western dietary pattern elevated the risk of having PCOS. The western dietary pattern is rich in simple sugar, trans and saturated fatty acids leading to an increase in obesity and insulin resistance (Esmaillzadeh et al. 2007; Esmaillzadeh and Azadbakht 2008). Elevated insulin levels resulted in reduced production of Sex hormone-binding globulin (SHBG) and hyperandrogenism. Hyperandrogenism disrupted the hypothalamic-pituitary-ovarian axis (HPO axis) function and subsequently resulted in disruption of ovulation which is involved in PCOS pathophysiology (Dunaif 1997; Norman et al. 2007; Astrup et al. 2014). Additionally, high intakes of saturated fatty acids and low intakes of fiber directly resulted in low concentration of SHBG and hyperandrogenism (Lima et al. 2013). Another possible mechanism that might involve in development of PCOS related to animal protein as a major component of western dietary pattern. Animal protein, in comparison to vegetable protein, increased serum concentration of insulin-like growth factor (IGF)-I which stimulate production of ovarian theca-interstitial cells that might lead to PCOS (Duleba et al. 1998; Thierry van Dessel et al. 1999; Chavarro et al. 2008) .The nitrite intake in western dietary pattern was also high due to the presence of processed meat. Nitrite could be converted to nitrous amine, destroyed the β cells and resulted in insulin resistance (Lijinsky 1999; Schulze et al. 2003)

Our study suggested that plant-based dietary pattern might have protective effects on PCOS. Although in crude model, second tertile of plant-based dietary pattern decreased the chance of PCOS by 58%, the highest tertile had no effect on PCOS. After adjustment for confounders, the protective effect in second tertile disappeared. In the highest tertile, after adjusting confounders, the associations became stronger and, compared with the lowest tertile, the chance of PCOS was higher. In other words, by adjusting physical activity, antioxidant vitamins and fiber intake, the protective effects of these factors were eliminated. This non-linear association might be related to chemical pesticides and heavy metals in fruits and vegetables. The chemical pesticides have several harmful effects on the health of body systems, especially reproductive and endocrine systems (WHO and UNEP 1990; Sanborn et al. 2007; Mnif et al. 2011; Nicolopoulou-Stamati et al. 2016). In line with our study, one study suggested that high consumption of fruits and vegetables with high concentration of pesticides might lead to reproductive abnormalities (Chiu et al. 2017). In addition, consistent with current study, earlier studies suggested that high intakes of fruits and vegetables might increase the risk of metabolic syndrome and subsequently PCOS due to high amount of carbohydrate in fruits as well as vegetables including glucose, sucrose and fructose. These studies have suggested that high fructose intake elevated the risk of obesity and insulin resistance which plays an important role in hyperandrogenism (Stanhope and Havel 2008; Stanhope and Havel 2009; Das 2015). Furthermore, Xia et al. reported that moderate consumption of fruits (99–162 gr/day) and vegetables (392–554 gr/day) have a protective effect on insulin resistance as the main cause of PCOS incidence (Xia et al. 2016).

Moderate adherence to mixed dietary pattern might have a protective effect on PCOS. However, high level of mixed dietary pattern scores compared with low level had no significant association with PCOS. It might be related to this point that in the second tertile, the consumption of healthy foods dominated to unhealthy ones and major proportion of scores was related to healthy foods compared to the highest tertile. Furthermore, the overlapping of healthy and unhealthy foods might play a role in reducing PCOS in second tertile. In addition, there were several unknown residual confounders that we could not measure them; these variables might affect the relationship between mixed dietary pattern and PCOS. Because of including both healthy and unhealthy foods in mixed dietary pattern, the evidence of significant association in the highest tertile was not clearly found.

We applied Rotterdam criteria to diagnose PCOS women in the present study. So, the controls may also have PCOS if they have biochemical hyperandrogenism and polycystic ovaries on ultrasound. However, based on a previous study that assessed the prevalence of PCOS in Iran, the women with modified Ferriman-Gallwey (mF-G) score of <8 and regular menstruation were deemed not to have PCOS and should be considered as healthy women (Mehrabian et al. 2011). In addition, As the use of multivitamins might neutralize the effect of unhealthy diet and change the status of the disorder, those women who used multivitamins and minerals supplements were not included in the study to avoid bias. Individuals who using multivitamins might actually have a healthier diet due to being more health-conscious; therefore, this exclusion might increase the risk of bias. These points should be considered in the interpretation of our findings.

This is the first study in a Middle Eastern country that evaluated the association between major dietary patterns and new diagnosed patients with a large sample size. In addition, we selected new diagnosed patients that reduced the possibility of changing diet. However, several limitations should be taken into account in this study. First, using the semi-quantitative FFQ to assess the usual dietary intake increases the possibility of under-over report of either energy intake or special food groups and the risk of recall bias due to the assessment of dietary intakes during the last year. Second, although we adjusted the effects of several potential confounders the analysis, the effect of unknown or residual confounders might not be excluded in the analysis. Third, we applied factor analysis to identify major dietary patterns and we encountered problems such as including food items into food groups, determining the number of factors, and labeling the dietary pattern. In addition, in factor analysis some food groups might not be placed in any of dietary patterns. Fourth, the amount of heavy metals and pesticides was not measured directly in this study and we had to explain our results based on the previous studies. So, the association between pesticides and PCOS that can confound the link between plant-based dietary pattern and PCOS should be interpreted with caution. Fifth, we included women who were referring to an infertility center, a hospital and some clinics. Healthy individuals who attended in these centers along with patients were considered as controls; so, generalization of the findings to other populations should be cautiously done. Finally, different phenotypes of PCOS were not considered in this study.

In conclusion, our study suggested that western and plant-based dietary patterns were associated with an increased risk and moderate adherence to mixed dietary pattern was associated with reduced risk of PCOS among Iranian women. To confirm our findings, more studies with longitudinal design are required.

Acknowledgment

This study was extracted from MSc dissertation which was approved by School of Nutrition & Food Science, Isfahan University of Medical Sciences (code: IR.MUI.REC.1395, 3. 406).

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest The authors declare no conflict of interest.

Author's contributions Study concept and design: FS and RG; Statistical analysis: AF; Data analysis and interpretation: FS, RG, AF, BA, PS; Manuscript drafting: FS; Revision of manuscript: RG, PS, AF, ZS.

References

Ahmadi, A., Akbarzadeh, M., Mohammadi, F., Akbari, M., Jafari, B., and Tolide-Ie, H.R. (2013). Anthropometric characteristics and dietary pattern of women with polycystic ovary syndrome. **Indian. J. Endocrinol. Metab.** 17: 672. doi: 10.4103/2230-8210.113759. PMID: 23961484.

Asghari, G., Rezazadeh, A., Hosseini-Esfahani, F., Mehrabi, Y., Mirmiran, P., and Azizi, F. (2012). Reliability, comparative validity and stability of dietary patterns derived from an FFQ in the Tehran Lipid and Glucose Study. **Br. J. Nutr.** 108: 1109-1117. doi: 10.1017/S0007114511006313.

Astrup, A., Larsen, M.L., Stender, S., and Dyerberg, J. (2014). Effect of fats on cardiovascular disease prevention in Denmark. **Ugeskr Laeger,** 176. PMID:25351669.

Baillargeon, J.-P. and Nestler, J.E. (2006). Polycystic Ovary Syndrome: A Syndrome of Ovarian Hypersensitivity to Insulin? **J. Clin. Endocrinol. Metab.** 91: 22-24. doi: 10.1210/jc.2005-1804. PMID:16263814.

Balen, A.H., Conway, G.S., Kaltsas, G., Techatraisak, K., Manning, P.J., West, C., et al. (1995). Andrology: Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. **Hum. Reprod.** 10: 2107-2111. doi: 10.1093/oxfordjournals.humrep.a136243.

Bhattacharya, S., Porter, M., Amalraj, E., Templeton, A., Hamilton, M., Lee, A., et al.. (2009). The epidemiology of infertility in the North East of Scotland. **Hum. Reprod.** 24: 3096-3107. doi: 10.1093/humrep/dep287.

Chavarro, J.E., Rich-Edwards, J.W., Rosner, B.A., and Willett, W.C. (2008). Protein intake and ovulatory infertility. **Am. J. Obstet. Gynecol.** 198: 210.e1-210.e7.doi: 10.1016/j.ajog.2007.06.057.

Chiu, Y.-H., Williams, P.L., Gillman, M.W., Gaskins, A.J., Mínguez-Alarcón, L., Souter, I., et al. (2017). Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology. **JAMA Intern. Med.** doi:10.1001/jamainternmed.2017.5038.

Das, U.N. (2015). Sucrose, fructose, glucose, and their link to metabolic syndrome and cancer. **Nutrition,** 31: 249-257. doi: 10.1016/j.nut.2014.05.015.

Diamanti-Kandarakis, E. (2006). Insulin resistance in PCOS. **Endocrine,** 30: 13-17. doi: 10.1385/ENDO:30:1:13.

Douglas, C.C., Gower, B.A., Darnell, B.E., Ovalle, F., Oster, R.A., and Azziz, R. (2006a). Role of diet in the treatment of polycystic ovary syndrome. **Fertil. Steril.** 85: 679-88. doi:10.1016/j.fertnstert.2005.08.045.

Douglas, C.C., Norris, L.E., Oster, R.A., Darnell, B.E., Azziz, R., and Gower, B.A. (2006b). Difference in dietary intake between women with polycystic ovary syndrome and healthy controls. **Fertil. Steril.** 86: 411-7. doi: 10.1016/j.fertnstert.2005.12.054.

Duleba, A.J., Spaczynski, R.Z., and Olive, D.L. (1998). Insulin and insulin-like growth factor I stimulate the proliferation of human ovarian theca-interstitial cells. **Fertil. Steril.** 69: 335-340. doi: 10.1016/S0015-0282(97)00473-1.

Dunaif, A. (1997). Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. **Endocr. Rev.** 18: 774-800. doi: 10.1210/edrv.18.6.0318. PMID: 9408743.

Esmaillzadeh, A. and Azadbakht, L. (2008). Major dietary patterns in relation to general obesity and central adiposity among Iranian women. **J. Nutr.** 138: 358-363. doi:10.1093/jn/138.2.358.

Esmaillzadeh, A., Kimiagar, M., Mehrabi, Y., Azadbakht, L., Hu, F.B., and Willett, W.C. (2007). Dietary patterns, insulin resistance, and prevalence of the metabolic syndrome in women. **Am. J. Clin. Nutr.** 85: 910-918. doi:10.1093/ajcn/85.3.910.

Fr, D.D. and Tarlatzis, R. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. **Fertil. Steril.** 81. doi: 10.1016/j.fertnstert.2003.10.004.

Fux, O.C., Fiol, d.C.M., and Szafryk, d.M.P. (2013). Polycystic ovary syndrome: physiopathology review. **Rev. Fac. Cien. Med. Univ. Nac. Cordoba,** 70: 27-30. PMID:23920100.

Hatch, R., Rosenfield, R.L., Kim, M.H., and Tredway, D. (1981). Hirsutism: implications, etiology, and management. **Am. J. Obstet. Gynecol.** 140: 815-830. PMID:7258262.

Hu, F.B. (2002). Dietary pattern analysis: a new direction in nutritional epidemiology. **Curr. Opin. Lipidol.** 13: 3-9.

Hu, F.B., Rimm, E., Smith-Warner, S.A., Feskanich, D., Stampfer, M.J., Ascherio, A., et al. (1999). Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. **Am. J. Clin. Nutr.** 69: 243-249. doi: 10.1093/ajcn/69.2.243.

Huang, J., Ni, R., Chen, X., Huang, L., Mo, Y., and Yang, D. (2010). Metabolic abnormalities in adolescents with polycystic ovary syndrome in south china. **Reprod. Biol. Endocrin.** 8: 142. doi: 10.1186/1477-7827-8-142.

Huijbregts, P., Feskens, E., Räsänen, L., Fidanza, F., Nissinen, A., Menotti, A., et al. (1997). Dietary pattern and 20 year mortality in elderly men in Finland, Italy, and The Netherlands: longitudinal cohort study. **Bmj,** 315: 13-17. doi:10.1136/bmj.315.7099.13.

Hull, M. (1987). Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. **Gynecol. Endocrinol.** 1: 235-245. doi: 10.3109/09513598709023610.

Jalilian, A., Kiani, F., Sayehmiri, F., Sayehmiri, K., Khodaee, Z., and Akbari, M. (2015). Prevalence of polycystic ovary syndrome and its associated complications in Iranian women: A meta-analysis. **Iran. J. Reprod. Med.** 13: 591. PMID: 26644787.

Lee, P.H., Macfarlane, D.J., Lam, T., andStewart, S.M. (2011). Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. **Int. J. Behav. Nutr. Phys. Act.** 8: 115. doi: 10.1186/1479-5868-8-115.

Legro, R.S., Arslanian, S.A., Ehrmann, D.A., Hoeger, K.M., Murad, M.H., Pasquali, R., et al. (2013). Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. **J. Clin. Endocrinol. Metab.** 98: 4565-4592. doi: 10.1210/jc.2013-2350.

Lijinsky, W. (1999). N-Nitroso compounds in the diet. **Mutat. Res. Genet. Toxicol. Environ. Mutagen.** 443: 129-138. doi: 10.1016/S1383-5742(99)00015-0.

Lima, S.T., da Silva Nalin de Souza, B., Franca, A.K., Salgado Filho, N., and Sichieri, R. (2013). Dietary approach to hypertension based on low glycaemic index and principles of DASH (Dietary Approaches to Stop Hypertension): a randomised trial in a primary care service. **Br. J. Nutr.** 110: 1472-9. doi: 10.1017/S0007114513000718.

Lin, A.W. and Lujan, M.E. (2014). Comparison of dietary intake and physical activity between women with and without polycystic ovary syndrome: a review. **Adv. Nutr.** 5: 486-496. doi:10.3945/an.113.005561.

March, W.A., Moore, V.M., Willson, K.J., Phillips, D.I., Norman, R.J., and Davies, M.J. (2009). The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. **Hum. Reprod.** 25: 544-551. doi:10.1093/humrep/dep399.

McGuire, S. (2016). Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Washington, DC: US Departments of Agriculture and Health and Human Services, 2015. **Adv. Nutr.** 7: 202-204. doi: 10.3945/an.115.011684.

Mehrabian, F., Khani, B., Kelishadi, R., and Ghanbari, E. (2011). The prevalence of polycystic ovary syndrome in Iranian women based on different diagnostic criteria. **Endokrynol. Pol.** 62: 238-242. PMID: 21717406.

Mnif, W., Hassine, A.I.H., Bouaziz, A., Bartegi, A., Thomas, O., and Roig, B. (2011). Effect of endocrine disruptor pesticides: a review. **Int. J. Environ. Res. Public. Health.** 8: 2265-2303. doi:10.3390/ijerph8062265. PMID:21776230.

Moran, L.J., Grieger, J.A., Mishra, G.D., and Teede, H.J. (2015). The association of a mediterranean-style diet pattern with polycystic ovary syndrome status in a community cohort study. **Nutrients,** 7: 8553-8564. doi:10.3390/nu7105419.

Moran, L.J., Ko, H., Misso, M., Marsh, K., Noakes, M., Talbot, M., et al. (2013a). Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. **J. Acad. Nutr. Diet,** 113: 520-545. doi:10.1016/j.jand.2012.11.018.

Moran, L.J., Ranasinha, S., Zoungas, S., McNaughton, S.A., Brown, W.J., and Teede, H.J. (2013b). The contribution of diet, physical activity and sedentary behaviour to body mass index in women with and without polycystic ovary syndrome. . **Hum. Reprod.** 28: 2276-2283. doi: 10.1093/humrep/det256.

Mundfrom, D.J., Shaw, D.G., and Ke, T.L. (2005). Minimum Sample Size Recommendations for Conducting Factor Analyses. **International Journal of Testing.** 5: 159-168. doi: 10.1207/s15327574ijt0502_4.

Nicolopoulou-Stamati, P., Maipas, S., Kotampasi, C., Stamatis, P., and Hens, L. (2016). Chemical pesticides and human health: the urgent need for a new concept in Agriculture. **Front. Public. Health,** 4. doi:10.3389/fpubh.2016.00148. PMID:27486573.

Norman, R., Homan, G., Moran, L., and Noakes, M. (2006). Lifestyle choices, diet, and insulin sensitizers in polycystic ovary syndrome. **Endocrine,** 30: 35-43. doi: 10.1385/ENDO:30:1:35.

Norman, R.J., Davies, M.J., Lord, J., and Moran, L.J. (2002). The role of lifestyle modification in polycystic ovary syndrome. **TEM,** 13: 251-257.doi:10.1016/S1043-2760(02)00612-4.

Norman, R.J., Dewailly, D., Legro, R.S., and Hickey, T.E. (2007). Polycystic ovary syndrome. **Lancet,** 370: 685-697.

Ovalle, F. and Azziz, R. (2002). Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. **Fertil. Steril.** 77: 1095-1105. PMID: 12057712.

Panagiotakos, D.B., Pitsavos, C., Chrysohoou, C., Skoumas, J., Tousoulis, D., Toutouza, M., et al. (2004). Impact of lifestyle habits on the prevalence of the metabolic syndrome among Greek adults from the ATTICA study. **Am. Heart J.** 147: 106-112. doi: 10.1016/S0002-8703(03)00442-3.

Sanborn, M., Kerr, K., Sanin, L., Cole, D., Bassil, K., and Vakil, C. (2007). Non-cancer health effects of pesticides. **Can. Fam. Physician.** 53: 1712-1720. PMID:17934035.

Schulze, M.B., Manson, J.E., Willett, W.C., and Hu, F.B. (2003). Processed meat intake and incidence of Type 2 diabetes in younger and middle-aged women. **Diabetologia,** 46: 1465-1473. doi:10.1007/s00125-003-1220-7.PMID:14576980.

Sirmans, S.M. and Pate, K.A. (2014). Epidemiology, diagnosis, and management of polycystic ovary syndrome. **Clin. Epidemiol.** 6: 1. doi: 10.2147/CLEP.S37559. PMID: 24379699.

Stamets, K., Taylor, D.S., Kunselman, A., Demers, L.M., Pelkman, C.L., and Legro, R.S. (2004). A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. **Fertil. Steril.** 81: 630-637. doi:10.1016/j.fertnstert.2003.08.023.

Stanhope, K.L. and Havel, P.J. (2008). Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance. **Curr. Opin. Lipidol.** 19: 16. doi: 10.1097/MOL.0b013e3282f2b24a. PMID: 18196982.

Stanhope, K.L. and Havel, P.J. (2009). Fructose consumption: considerations for future research on its effects on adipose distribution, lipid metabolism, and insulin sensitivity in humans. **J. Nutr.** 139: 1236S-1241S. doi:10.3945/jn.109.106641. PMID: 19403712.

Stein, I.F. and Leventhal, M.L. (1935). Amenorrhea associated with bilateral polycystic ovaries. **Am. J. Obstet. Gynecol.** 29: 181-191. doi:1016/S0002-9378(15)30642-6.

Stepto, N.K., Cassar, S., Joham, A.E., Hutchison, S.K., Harrison, C.L., Goldstein, R.F., et al. (2013). Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic–hyperinsulaemic clamp. **Fertil. Steril.** 28: 777-784. doi:10.1093/humrep/des463.PMID: 23315061.

Thierry van Dessel, H.J., Lee, P.D., Faessen, G., Fauser, B.C., and Giudice, L.C. (1999). Elevated serum levels of free insulin-like growth factor I in polycystic ovary syndrome. **J. Clin. Endocrinol. Metab.** 84: 3030-5. doi: 10.1210/jcem.84.9.5941. PMID: 10487660.

World Health Organization & United Nations Environment Programme. (1990). Public health impact of pesticides used in agriculture. Geneva : World Health Organization. http://www.who.int/iris/handle/10665/39772.

Wright, C., Zborowski, J., Talbott, E., McHugh-Pemu, K., and Youk, A. (2004). Dietary intake, physical activity, and obesity in women with polycystic ovary syndrome. **INT. J. OBESITY,** 28: 1026. doi: 10.1038/sj.ijo.0802661.PMID: 15159768.

Xia, Y., Gu, Y., Yu, F., Zhang, Q., Liu, L., Meng, G., et al. (2016). Association between dietary patterns and metabolic syndrome in Chinese adults: a propensity score-matched case-control study. **SCI. REP-UK,** 6. doi: 10.1038/srep34748.

Table 1

Food grouping applied in dietary pattern analysis.

Food groups	Food items
Refined grains	White breads, French bread, white rice, spaghetti, vermicelli, noodles, wheat flour, biscuits
Whole grains	Iranian dark breads, barely
Legumes	Lentils, kidney beans, chickpeas, broad beans, soy beans, mung beans, split peas
Processed meats	Beef sausages
Red meats	Lamb, veal, ground lamb
Organ meats	Lamb liver, lamb kidneys, lamb heart, lamb tongue, lamb brain
Fish	Other fish, fish tuna canned
Skinless poultry	Poultry without skin
Poultry with skin	Poultry with skin
Eggs	eggs
Low fat dairy	Skim milk, low fat milk, low fat yogurt, kashk
High fat dairy	High fat milk, whole chocolate and cocoa milk, high fat yogurt, creamy yogurt, cream cheese, other cheese, cream, chocolate ice cream, vanilla ice cream
Yogurt drink	Dough
Soft drinks	Soft drinks
Fruits	Melon, honeydew melon, watermelon, pear, apricot, cherries, apple, peach, nectarine, Japanese plums, fig, grape, kiwifruit, grapefruit, orange, persimmon, tangerine, pomegranate, date, plums, sour cherries, strawberry, banana, lime, sweet lemon, pineapple, cranberry, mulberries
Fruit juices	Grapefruit juice, orange juice, apple juice, melon juice
Canned fruits	Canned pineapple, canned mixed fruit
Dried fruits	Dried fig, raisin, dried mulberry, dehydrated peach, dehydrated apricot
Vegetables	Lettuce, tomato, cucumber, fresh basil, mixed vegetables, squash, eggplant, celery, green peas, green beans, carrot, onion, cabbage, spinach, bell pepper, mushroom, turnip
Nuts	Peanuts, almonds, walnuts, pistachios, hazelnuts, sunflower seeds
Fast foods	Hamburger, pizza, French fries
Mayonnaise	Mayonnaise
Tomato sauce	Tomato sauce
Salty snacks	Cracker, potato chips, salty snacks
Olive	Green olives, olive oil
Tea	Tea
Coffee	coffee
Sugar, sweets, and desserts	Muffins, other cakes, sugar, white granulated sugar, honey, jam, gaz (Iranian sweet), hard candy, chocolates, caramel flan, donuts
Solid fats	Butter, margarine, Hydrogenated fats, animal fats
Vegetable oils	Vegetable oils
Potato	Boiled potato
Garlic	Garlic
Condiments	Pepper, lime juice
Salt	Salt
Pickles	Cucumber pickles, mixed vegetables pickles
Broth	broth

Table 2
General characteristics, energy and macronutrients intake of women with and without PCOS

Variables	Cases	Controls	P-value [a]
Age (year)	29.51±6.52	28.56±6.43	0.088
Weight (kg)	65.45±10.00	63.77±9.36	0.043
BMI (kg/m2)	24.87±3.84	24.35±3.38	0.088
Waist circumference (cm)	85.49±9.66	83.39±9.20	0.009
Hip circumference (cm)	103.12±9.36	102.35±8.82	0.325
WHR	0.82±0.06	0.81±0.06	0.011
Socioeconomic status (SES) [c]	11.84±1.78	12.59±1.86	<0.001
Marital status			< 0.001
single	49 (21.8%)	154 (44.6%)	
married	172 (76.4%)	183 (53.3%)	
separated	4 (1.8%)	8 (2.3%)	
Disease history			< 0.001
No	200 (88.9%)	334 (96.8%)	
yes	25 (11.1%)	11 (3.2%)	
Drug use [d]			0.552
No	224 (99.6%)	342 (99.1%)	
Yes	1 (0.4%)	3 (0.7%)	
Education			0.001
lower than diploma	27 (12.0%)	42 (12.2%)	
diploma	108 (48.0%)	116 (33.6%)	
bachelor	74 (32.9%)	134 (38.8%0	
higher than bachelor	16 (7.1%)	53 (15.4%)	
Energy intake (Kcal)	2501.63±902.83	2375.28±719.48	0.078
Carbohydrate (gr)	353.18±55.8	339.77±55.89	0..005[b]
Protein (gr)	89.36±20.4	82.04±20.24	<0.001[b]
Fat (gr)	85.17±22.65	79.28±22.65	0.003[b]
Physical activity (MET-min/week)	787.07±797.37	1829.36±1870.12	<0.001

[a] Resulted from independent t-test for quantitative variables and chi-square for test for categorical variables
[b] Obtained from the general linear model and adjusted for energy intake and age
[c] Socioeconomic status (SES) score was evaluated based on education level of both subjects and the family head (academic/non-academic), job of both subjects and the family head (yes/no), family size (lower than 4/higher than 4), having a car (yes/no), home status (the owner/tenant), and foreign travel (yes/no) by using self-reported questionnaire
[d] gastrointestinal and anti-allergic drugs
Quantitative variables: mean ± SD
Qualitative variables: frequency (percentage)

Table 3

Factor loading matrix for the three major dietary patterns identified by PCA

	Dietary patterns		
Food groups	Western	Plant-based	Mixed
Refined grains	-	-	0.575
Whole grains	-	-	0.254
Legumes	-	0.364	-
Processed meats	0.591	-	-
Red meats	-	-	0.572
Organ meats	0.257	-	-
Fish	-	-	0.369
Skinless poultry	-	-	0.446
Poultry with skin	-	-	0.377
Eggs	-	-	0.444
Low fat dairy	-	-	-
High fat dairy	0.328	-	-
Yogurt drink	-	0.41	-
Soft drinks	0.647	-	-
Fruits	-	0.475	0.433
Fruit juices	-	0.307	-
Canned fruits	0.213	0.378	-
Dried fruits	-	0.427	-
Vegetables	-	0.675	0.269
Nuts	-	0.513	-
Fast foods	0.656	-	-
Mayonnaise	0.304	-	0.216
Tomato sauce	-	-	0.37
Salty snacks	0.64	-	-
Olive	-	0.306	-
Tea	-	-	0.436
Coffee	-	-	-
Sugar, sweets, and desserts	0.573	-	0.303
Hydrogenated fats	0.38	-	-
Vegetable oils	-	-	0.442
Potato	-	0.248	-
Garlic	-	0.411	-
Condiments	-	0.356	-
Salt	0.348	-	-
Pickles	-	0.287	0.303
Broth	-	0.329	-
Percentage of variance explained	18.37	17.90	17.64

Cumulative percentage of variance explained by three dietary patterns was 53.93%

factor loadings <0.20 were excluded

Table 4
Multivariate adjusted odds ratio (OR) and 95% confidence interval (CI) for PCOS among tertiles of dietary patterns scores

	Western pattern			Plant-based pattern			Mixed pattern		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
Crude model	1	1.24 (0.81-1.90)	1.76 (1.16-2.67)	1	0.42 (0.31-0.58)	0.91 (0.69-1.22)	1	0.41 (0.30-0.57)	1.13 (0.85-1.50)
Model I [1]	1	1.60 (0.99-2.57)	1.94 (1.21-3.11)	1	0.64 (0.40-1.02)	2.16 (1.33-3.49)	1	0.41 (0.24-0.70)	1.22 (0.73-2.04)
Model II [2]	1	1.61 (1.01-2.57)	2.02 (1.28-3.20)	1	0.66 (0.41-1.07)	2.15 (1.33-3.48)	1	0.45 (0.26-0.76)	1.28 (0.76-2.13)
Model III [3]	1	1.72 (1.04-2.85)	2.03 (1.12-3.67)	1	0.72 (0.43-1.19)	2.32 (1.23-4.37)	1	0.34 (0.18-0.61)	0.96 (0.48-1.90)

[1] Adjusted for age, marital status, BMI, and physical activity
[2] Adjusted for age, marital status, BMI, physical activity, and socioeconomic status
[3] Adjusted for age, marital status, BMI, physical activity, socioeconomic status, energy intake, fat, soluble fiber, vitamin E, vitamin C, zinc, calcium, and iron