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Consumption of energy-dense diets in relation to metabolic syndrome and inflammatory markers in Iranian female nurses

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Abstract

Objective: To examine the relationship between dietary energy density (DED) and risk of metabolic syndrome (MetS), its components and inflammatory markers.

Design: Cross-sectional study. Dietary intakes were assessed using a validated dish-based semi-quantitative FFQ. DED was calculated by dividing energy intake (kcal/d) by the total weight of foods only (g/d). MetS was defined based on the National Cholesterol Education Program Adult Treatment Panel III criteria. All associations were examined in the quartiles of DED, with higher quartiles indicating more energy-dense diets.

Setting: Isfahan, Iran.

Subjects: Female nurses (*n* 1036) aged >30 years.

Results: After controlling for potential confounders, individuals in the top quartile of DED had 78 % greater chance of MetS compared with those in the first (OR = 1·78; 95 % CI 1·36, 2·98; $P < 0·001$). Individuals in the highest quartile of DED were more likely to be abdominally obese (OR = 1·51; 95 % CI 1·00, 2·63) and have hypertriacylglycerolaemia (OR = 2·95; 95 % CI 1·58, 3·91) and low HDL cholesterol levels (OR = 1·36; 95 % CI 1·17, 2·54) compared with those in the lowest quartile. Mean concentration of plasma high-sensitivity C-reactive protein (hs-CRP) across increasing quartiles of DED was 1·7, 1·7, 2·0, 2·4 mg/l (*P* for trend = 0·04). Such increasing concentrations across increasing quartiles of DED were also seen for TNF-α (4·1, 4·5, 4·5, 4·8 ng/l; *P* for trend = 0·03) and IL-6 (1·6, 1·6, 1·5, 2·5 ng/l; *P* for trend <0·01).

Conclusions: Consumption of high-energy-dense foods was associated with increased chance of MetS, most of its features and inflammatory markers including hs-CRP, TNF-α and IL-6.

Keywords
Energy density
Inflammation
Metabolic syndrome
Lipids
Abdominal obesity

Metabolic syndrome (MetS), as a clustering of metabolic abnormalities, is a well-known risk factor for CVD, type 2 diabetes and early mortality. The growing trend in the prevalence of MetS is a global health problem in both developed and developing nations[1]. Several dietary and non-dietary factors have been involved in the pathogenesis of MetS. Among others, obesity, unhealthy food intake, lack of physical activity and smoking contribute extensively to these conditions[2]. Elevated concentrations of inflammatory biomarkers have also been suggested as a possible mediating mechanism through which dietary intakes and obesity might affect the risk of chronic disorders.

Dietary energy density (DED) is defined as the amount of energy per unit weight of food[3]. High-energy-dense diets are associated with higher energy intake and weight

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gain[4–9]. Excess body weight and fat mass are linked to greater inflammatory markers and chronic diseases. High-energy-dense diets are characterized mainly by low consumption of fresh fruits and vegetables but high consumption of fats and refined carbohydrates[10,11]. Although the association of dietary intakes with metabolic abnormalities has frequently been examined, data on the association of DED with chronic diseases are scarce. Examining the association of DED with chronic diseases could be more reliable than single dietary components, since it accounts for the enormous interactions between nutrients and foods.

Available evidence assessing the association between DED and risk of MetS is limited and inconsistent. While some epidemiological investigations indicated a positive link between DED and the odds of diabetes, insulin resistance, MetS and abdominal adiposity[10,12,13], others failed to find such significant relationships[4,14]. Besides cardiometabolic abnormalities, few studies have examined the association of DED with inflammation[4,7,15]. Despite a slight decrement in serum concentrations of C-reactive protein (CRP) following the consumption of a low-energy-dense diet in a short-term clinical trial[7], findings from a large population-based study and an 8-week clinical trial revealed no significant correlation between DED and serum high-sensitivity (hs)-CRP or other inflammatory adipokines[4,15].

It must be kept in mind that previous studies on diet–inflammation–CVD associations were mostly conducted in Western countries and limited data are available in this regard in the understudied region of the Middle East. Different dietary patterns and lifestyle in this part of the world might reveal different associations between energy density and these conditions. Due to low intakes of fruits and vegetables and high intake of refined grains, Middle Eastern populations consume more energy-dense diets than Europeans[10,11]. Therefore, assessing the association between DED and these cardiometabolic abnormalities is particularly relevant in these populations. We hypothesized that higher DED is associated with increased risk of MetS as well as higher levels of inflammatory biomarkers, and conducted the present study to identify the association of DED with inflammation and MetS in a large group of Iranian female nurses.

Materials and methods

Participants

The current cross-sectional study was conducted in a representative sample of Isfahani female nurses aged >30 years. To perform random sampling, we provided a list of all hospitals (both public and private) in different parts of Isfahan. Then, we randomly selected some hospitals considering the number of private and public hospitals in each area (*n* 12). Nurses in the selected hospitals were listed and then a random sample of nurses in each hospital was chosen based on the number of nurses working in that hospital. Totally, 1102 nurses of 1196 invited nurses agreed to participate in our study. We excluded individuals who had a prior history of CVD, diabetes, cancer and stroke (*n* 11), or infection (*n* 3). In addition, those who had left at least seventy items blank on the FFQ (*n* 12), those who reported a total daily energy intake outside the range of 3347–17 573 kJ (800–4200 kcal; *n* 29) and those who were taking medications that affect glucose homeostasis (*n* 11) were excluded. After these exclusions, the current analysis was done on 1036 nurses. All participants declared their willingness to participate in the current study by providing a written informed consent. The study was approved by the research council and ethics committee of the School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran.

Assessment of dietary intake

Dietary data were collected using a Willett-format[16], dish-based, 106-item semi-quantitative FFQ that was designed and validated specifically for Iranian adults. Detailed information about the design, the foods included[17] as well as the validity of this questionnaire to assess the association between food consumption and MetS[18] has been reported elsewhere. Briefly, the questionnaire contained five categories of foods and dishes: (i) mixed dishes (cooked or canned, twenty-nine items); (ii) starchy foods (different types of bread, cakes, biscuits and potato, ten items); (iii) dairy products (dairies, butter and cream, nine items); (iv) fruits and vegetables (twenty-two items); and (v) miscellaneous food items and beverages (including sweets, fast foods, nuts, desserts and beverages, thirty-six items). To develop the questionnaire, a comprehensive list of foods and dishes commonly consumed by Iranian adults was constructed. Then, we chose those foods that were nutrient-rich, consumed reasonably often or contributed to between-person variations. This process led to the remaining of the 106 food items in the questionnaire. The portion size for food items and mixed dishes was defined based on the most commonly consumed portion size for each item in the general population. To increase precision and accuracy of estimates, we attempted to give the portion size of foods and mixed dishes as a unit with the same perception for all people. Participants were asked to report their dietary intakes of foods and mixed dishes based on nine multiple-choice frequency response categories varying from 'never or less than once a month' to '12 or more times per day'. The number of frequency response categories was not constant for all foods. For foods consumed infrequently, we omitted the high frequency categories, while for common foods with a high consumption, the number of multiple-choice categories increased. The frequency response categories for the food list varied from six to nine choices. For instance, the frequency response for tuna consumption included six categories, as follows: never or less

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than once per month, 1–3 times/month, once per week, 2–4 times/week, 5–6 times/week, 1–2 times/d; and for tea consumption the frequency response included nine categories, as follows: never or less than 1 cup/month, 1–3 cups/month, 1–3 cups/week, 4–6 cups/week, 1 cup/d, 2–4 cups/d, 5–7 cups/d, 8–11 cups/d, ≥12 cups/d. Finally, we computed daily intakes of all food items and then converted to grams per day using household measures[19]. Daily intakes of nutrients for each participant were calculated using the US Department of Agriculture's national nutrient databank. Total energy intake was calculated by summing up energy intakes from all foods. Total weight of foods consumed by participants was calculated by summing up the weights of foods only. We did not consider weight of drinks consumed because findings from available publications supporting the effect of DED on body weight are based on changes in weight of food intake, not drinks[20]. In a systematic review Johnson *et al.* also concluded that focusing on weight of food consumed reduces the variability in the results and facilitates data interpretation[21]. To calculate DED, we divided each individual's reported daily energy intake (kcal/d) by the total weight of foods consumed (g/d).

Assessment of biochemical indicators

To quantify biomarkers of inflammation and metabolic profile, we collected blood samples after a 12 h overnight fast. Fasting plasma glucose was assessed on the day of blood sampling via an enzymatic colorimetric method. Serum TAG levels were measured using enzymatic colorimetric tests with glycerol phosphate. HDL cholesterol (HDL-C) concentrations were determined after precipitation of the apo B-containing lipoproteins with phosphotungstic acid. All measurements were done using commercially available enzymatic reagents (Pars Azmoon, Tehran, Iran), adopted to an auto-analyser system (Selectra E; Vitalab, Holliston, the Netherlands). Serum concentrations of IL-6, IL-2, TNF-α and amyloid A were determined with the use of ELISA by means of commercially available kits (Bender MedSystems and Biosource International, Vienna, Austria). hs-CRP was assayed by ultra-sensitive latex-enhanced immunoturbidimetric assay (Randox Laboratories, Crumlin, UK). Intra- and inter-assay CV for all biochemical measurements were less than 10 %.

Assessment of blood pressure and other variables

To evaluate blood pressure, we first asked participants to rest for 10 min. Blood pressure was then measured using a standard mercury sphygmomanometer, twice with a 5 min interval, while participants were sitting. The mean of the two measurements was considered as the participant's blood pressure. Physical activity was assessed by use of the short-form International Physical Activity Questionnaire and expressed as metabolic equivalent-hours/week (MET-h/week). Information about age, smoking habits, socio-economic status, medical history, menopause status and current use of medications was obtained using pre-tested questionnaires. Height, weight and waist circumference were measured based on standard protocols[22]. BMI was calculated as weight (in kilograms) divided by the square of height (in metres).

Definition of terms

Obesity was defined as BMI ≥30·0 kg/m^2. In the current study, MetS was defined as the presence of at least three components of the following abnormalities, according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III definition)[23]: (i) abdominal obesity (waist circumference > 88 cm); (ii) low HDL-C concentration (<50 mg/dl); (iii) high serum TAG (≥150 mg/dl); (iv) abnormal glucose homeostasis (fasting plasma glucose >100 mg/dl); and (v) elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg).

Statistical analysis

Participants were categorized based on quartile cut-off points of DED. Higher quartiles of DED indicate higher energy density than lower quartiles. General characteristics of study participants across quartiles of DED were examined using ANOVA for continuous variables or the χ^2 test for categorical variables. Age- and energy-adjusted intakes and food and nutrient consumption across quartiles of DED were calculated using ANCOVA. To determine the association between DED and MetS and its components, we used multivariable logistic regression analysis in different models. First, we controlled for the confounding effect of age. In the second model, we further adjusted for cigarette smoking (yes or no), physical activity (MET-h/week), socio-economic status (categorical), current oestrogen use (yes or no), menopausal status (yes or no) and family history of diabetes and stroke (yes or no). Further statistical control was performed for BMI (continuous) in the last model. The overall trend of odds ratios across quartiles of DED was calculated by considering the median of DED in each quartile as a continuous variable.

Due to the skewness in the distribution of inflammatory markers, all biomarkers of inflammation were first logarithmically transformed. Then, geometric means of inflammatory markers across quartiles of DED were estimated by ANCOVA in several models (covariates were same as above). All statistical analyses were performed by using the statistical software package PASW Statistics Version 18.0. $P < 0·05$ was considered significant.

Results

General characteristics of the study participants across quartiles of DED are shown in Table 1. Participants with higher DED were more likely to be older, obese and

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Table 1 General characteristics by quartile of dietary energy density among female nurses (*n* 1036) aged >30 years, Isfahan, Iran

	Quartile of dietary energy density								
	1 (lowest)		2		3		4 (highest)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P**
n	254		257		251		253		
Age (years)	34·9	6·5	36·8	7	37·8	7·2	38·7	7·2	<0·001
BMI (kg/m^2)	22·8	1·6	23·5	1·9	24·7	1·9	26·2	1·7	<0·001
WHR	0·79	0·01	0·83	0·01	0·89	0·01	0·93	0·01	<0·001
Fasting plasma glucose (mmol/l)	5·28	0·61	6·28	0·67	6·61	0·72	7·0	0·83	<0·001
TAG (mmol/l)	1·31	0·26	1·57	0·28	1·68	0·32	2·02	0·20	<0·001
Total cholesterol (mmol/l)	3·85	0·88	4·63	1·01	5·12	1·09	6·39	1·32	<0·001
LDL-C (mmol/l)	2·35	0·15	3·08	0·18	3·33	0·23	4·09	0·23	<0·001
HDL-C (mmol/l)	1·16	0·10	1·14	0·13	1·01	0·08	0·80	0·08	<0·001
Physical activity (MET-h/week)	13·2	2·8	14·5	2·9	11·2	2·5	15·3	2·4	<0·001
Family history of diabetes (%)	2		4		3		5		0·04
Family history of stroke (%)	1		1		2		1		0·69
Current daily smokers (%)	1		1		1		1		0·85
High socio-economic status†	27		33		42		31		0·03
Obese (%)‡	13		16		21		29		0·01
Current oestrogen use (%)	8		9		6		11		0·22
Postmenopausal (%)	3		3		4		6		0·37
Metabolic syndrome (%)§	8		12		18		27		<0·001
Features of metabolic syndrome§									
Abdominal adiposity (%)	16		25		35		57		<0·001
Elevated blood pressure (%)	8		17		21		39		<0·001
High serum TAG (%)	11		9		17		24		0·01
Low serum HDL-C (%)	31		35		41		56		<0·001
Abnormal glucose homeostasis (%)	3		5		7		9		0·11

WHR, waist-to-hip ratio; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; MET, metabolic equivalent of task.
Data are presented as means and standard deviations unless indicated otherwise.
*By using linear regression.
†High socio-economic status was defined based on educational level, income, family size, being owner of the house or renting the house, and house area.
‡Obesity: BMI ≥30·0 kg/m^2.
§Metabolic syndrome was defined as the presence of three or more of the following components: (i) abdominal adiposity (waist circumference >88 cm); (ii) low serum HDL-C (<50 mg/dl); (iii) high serum TAG (≥150 mg/dl); (iv) elevated blood pressure (≥130/85 mmHg); (v) abnormal glucose homeostasis (fasting plasma glucose ≥110 mg/dl).

physically active ($P<0·001$ for all). Prevalence of MetS and its components including central obesity, elevated blood pressure, hypertriacylglycerolaemia and low HDL-C were significantly higher in the top quartile of DED compared with the bottom quartile ($P<0·001$ for all except high serum TAG, where $P=0·01$). No other significant differences were seen in the general characteristics when comparing the quartiles of DED.

Age- and energy-adjusted dietary intakes of participants across quartiles of DED are presented in Table 2. As expected, individuals in the highest quartile of DED had significantly higher intakes of energy ($P=0·005$), fat ($P=0·001$), refined grains, and meat and fish ($P<0·001$). In contrast, they had lower intakes of carbohydrate ($P=0·01$), fibre, whole grains, fruits, vegetables, and nuts and legumes ($P<0·001$). Dietary intakes of other foods and nutrients were not significantly different across quartiles of DED.

Crude and multivariable-adjusted odds ratios for MetS across quartiles of DED are provided in Table 3. After accounting for potential confounders, we found that participants in the top quartile of DED had greater odds for MetS (OR = 1·78; 95 % CI 1·36, 2·98) compared with those in the bottom quartile. Further control for BMI attenuated this association slightly (OR = 1·59; 95 % CI 1·19, 2·81).

Multivariable-adjusted odds ratios for components of the MetS across quartiles of DED are indicated in Table 4. After adjustment for potential confounders, individuals in the highest quartile of DED were more likely to be abdominally obese (OR = 1·51; 95 % CI 1·00, 2·63), have hypertriacylglycerolaemia (OR = 2·95; 95 % CI 1·58, 3·91) and low HDL-C levels (OR = 1·36; 95 % CI 1·17, 2·54) compared with those in the lowest quartile. Consumption of energy-dense diets was not significantly associated with the odds of abnormal glucose homeostasis or elevated blood pressure either before or after controlling for confounding variables.

Geometric means of inflammatory markers across quartiles of DED are shown in Table 5. Compared with those in the lowest quartile of DED, participants in the highest quartile had greater concentrations of hs-CRP, TNF-α and IL-6, even after adjustment for potential confounders including BMI. Mean plasma hs-CRP concentrations across increasing quartiles of DED were 1·7, 1·7, 2·0, 2·4 mg/l (P for trend = 0·04). Such increasing concentrations across increasing quartiles of DED were also seen for TNF-α (4·1, 4·5, 4·5, 4·8 ng/l; P for trend = 0·03) and IL-6 (1·6, 1·6, 1·5, 2·5 ng/l; P for trend <0·01). We found no significant association between consumption of

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Table 2 Dietary intakes by quartile of dietary energy density among female nurses (*n* 1036) aged >30 years, Isfahan, Iran

	Quartile of dietary energy density								
	1 (lowest)		2		3		4 (highest)		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*
n	254		257		251		253		
Nutrients									
Total energy (kJ/d)	8293	1360	8414	1238	9560	1305	9707	1527	0·005
Total energy (kcal/d)	1982	325	2011	296	2285	312	2320	365	0·005
Carbohydrate (g/d)	235	76	226	94	222	56	212	49	0·01
Protein (g/d)	71	21	75	26	76	22	74	25	0·39
Fat (g/d)	82	38	85	35	97	40	113	36	0·001
Cholesterol (mg/d)	232	127	238	119	246	119	258	127	0·59
Dietary fibre (g/d)	19	9	18	8	13	6	8	6	<0·001
Food groups (g/d)									
Fruits	253	81	224	57	177	88	145	69	<0·001
Vegetables	238	86	279	74	225	189	174	89	<0·001
Meat and fish	136	90	131	90	135	87	157	90	<0·001
Whole grains	99	25	72	24	53	28	23	25	<0·001
Refined grains	323	149	375	150	393	159	431	156	<0·001
Dairy	252	42	257	50	265	58	284	85	0·35
Nuts and legumes	71	24	61	23	48	24	35	23	<0·001

Data are presented as means with their standard errors adjusted for age and energy intake. Data for energy intake have just been adjusted for age.

Table 3 Multivariable-adjusted odds ratios and 95 % confidence intervals for metabolic syndrome across quartile of dietary energy density among female nurses (*n* 1036) aged >30 years, Isfahan, Iran

	Quartile of dietary energy density							
		2		3		4 (highest)		
	1 (lowest)	OR	95 % CI	OR	95 % CI	OR	95 % CI	*P* for trend*
n	254	257		251		253		
Metabolic syndrome†								
Crude	1·00	1·25	0·75, 2·46	1·79	1·11, 3·25	1·96	1·52, 3·11	<0·001
Model I‡	1·00	1·21	0·76, 2·41	1·71	1·10, 3·21	1·90	1·48, 3·07	<0·001
Model II§	1·00	1·14	0·82, 2·28	1·65	1·07, 3·11	1·78	1·36, 2·98	<0·001
Model III‖	1·00	1·02	0·77, 2·01	1·54	1·01, 2·89	1·59	1·19, 2·81	<0·001

*By the use of Mantel–Haenszel extension χ^2 test.
†Metabolic syndrome was defined as the presence of three or more of the following components: (i) abdominal adiposity (waist circumference >88 cm); (ii) low serum HDL cholesterol (<50 mg/dl); (iii) high serum TAG (≥150 mg/dl); (iv) elevated blood pressure (≥130/85 mmHg); (v) abnormal glucose homeostasis (fasting plasma glucose ≥110 mg/dl).
‡Adjusted for age.
§Further adjusted for cigarette smoking, physical activity, socio-economic status, current oestrogen use, menopausal status and family history of diabetes and stroke.
‖Additionally adjusted for BMI.

energy-dense diets and serum concentrations of amyloid A and IL-2 either in crude or adjusted models.

Discussion

In the current cross-sectional study, DED was positively associated with MetS and features of MetS including abdominal adiposity, low HDL-C levels and hypertriacylglycerolaemia in Iranian female nurses. Additionally, individuals in the top quartile of DED had higher plasma concentrations of hs-CRP, TNF-α and IL-6. All associations were independent of BMI.

Despite a growing interest in evaluating health outcomes related to DED in nutritional epidemiology, there is still no standardized calculation method. The major controversy is related to including or excluding beverages in the calculations. The most common method in epidemiological studies is using foods only, excluding beverages, since it has been suggested this method could better demonstrate the meaning of DED[8,21,24]. Therefore, in the present study, we included only foods, not beverages, in DED calculation.

A growing body of evidence has demonstrated adverse effects of high-energy-dense diets on insulin resistance, metabolic profile and anthropometric measures. Therefore, as expected, high DED was associated with increased risk of MetS. This was in line with previous epidemiological studies[10,12,24]. This finding concurred with the results of a cross-sectional study among American adults, where Mendoza *et al.*[24] demonstrated that higher DED is

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Table 4 Multivariable-adjusted odds ratios and 95 % confidence intervals for components of the metabolic syndrome* across quartile of dietary energy density among female nurses (*n* 1036) aged >30 years, Isfahan, Iran

	Quartile of dietary energy density							
		2		3		4 (highest)		
	1 (lowest)	OR	95 % CI	OR	95 % CI	OR	95 % CI	*P* for trend†
n	254	257		251		253		
Abdominal adiposity								
Crude	1·00	1·17	0·75, 1·95	1·45	0·85, 1·92	1·76	1·02, 2·91	<0·001
Model I‡	1·00	1·14	0·71, 1·84	1·41	0·87, 1·90	1·69	1·05, 2·81	
Model II§	1·00	1·09	0·68, 1·89	1·35	0·82, 1·81	1·60	1·03, 2·74	
Model III‖	1·00	1·01	0·61, 1·80	1·28	0·77, 1·83	1·51	1·00, 2·63	
Elevated blood pressure								
Crude	1·00	1·06	0·69, 1·45	1·22	0·73, 1·85	1·42	0·91, 1·99	<0·001
Model I	1·00	1·03	0·61, 1·41	1·19	0·71, 1·80	1·37	0·89, 1·95	
Model II	1·00	0·98	0·62, 1·44	1·12	0·65, 1·81	1·34	0·86, 1·91	
Model III	1·00	0·94	0·58, 1·38	1·12	0·67, 1·75	1·20	0·80, 1·84	
High serum TAG								
Crude	1·00	1·45	0·97, 2·22	2·26	1·17, 2·97	3·25	1·67, 4·20	<0·001
Model I	1·00	1·40	0·92, 1·20	2·20	1·15, 2·94	3·19	1·68, 4·09	
Model II	1·00	1·37	0·94, 1·17	2·12	1·10, 2·90	3·08	1·64, 4·00	
Model III	1·00	1·24	0·88, 1·11	2·01	1·02, 2·81	2·95	1·58, 3·91	
Low serum HDL cholesterol								
Crude	1·00	1·29	1·02, 2·21	1·42	1·11, 2·31	1·56	1·25, 2·71	<0·001
Model I	1·00	1·21	0·99, 2·17	1·36	1·08, 2·27	1·50	1·21, 2·67	
Model II	1·00	1·13	0·94, 2·11	1·37	1·05, 2·18	1·42	1·19, 2·60	
Model III	1·00	1·07	0·91, 2·04	1·31	1·07, 2·15	1·36	1·17, 2·54	
Abnormal glucose homeostasis								
Crude	1·00	1·22	0·59, 3·19	1·21	0·59, 3·01	1·41	0·62, 2·96	0·55
Model I	1·00	1·20	0·57, 3·11	1·19	0·61, 2·96	1·38	0·60, 2·90	
Model II	1·00	1·14	0·58, 3·04	1·15	0·58, 2·91	1·35	0·61, 2·85	
Model III	1·00	1·07	0·53, 2·96	1·06	0·51, 2·84	1·28	0·65, 2·78	

*Components of the metabolic syndrome were defined as follows: abdominal adiposity (waist circumference >88 cm); low serum HDL cholesterol (<50 mg/dl); high serum TAG (≥150 mg/dl); elevated blood pressure (≥130/85 mmHg); abnormal glucose homeostasis (fasting plasma glucose ≥ 110 mg/dl).
†By the use of Mantel–Haenszel extension χ^2 test.
‡Adjusted for age.
§Further adjusted for cigarette smoking, physical activity, socio-economic status, current oestrogen use, menopausal status and family history of diabetes and stroke.
‖Additionally adjusted for BMI.

significantly associated with higher risk of MetS. In the current study, dietary data from a validated FFQ were used; however, the findings were similar to those of Mendoza *et al.*[24] in spite of the use of data from one-day 24 h dietary recall in their study. DED provides an overall picture of diet since it considers all foods together. Nevertheless, it has its own characteristics in each population and might lead to different and specific outcomes. For example, in the Mediterranean dietary pattern, despite the higher content of fat, an inverse correlation has been reported between olive oil consumption and DED. This might be attributed to consuming olive oil along with vegetables in salad. Further studies are required to clarify the associations between DED and metabolic abnormalities in different populations with different dietary patterns. Adverse effects of energy-dense diets on metabolic profile and inflammatory markers might be explained by their unhealthy components such as refined grains, *trans*- and saturated fatty acids, and processed and red meats. Furthermore, higher-energy-dense diets are associated with greater energy intake[8], but lower dietary diversity score, which leads to lower intakes of fruit, vegetables and whole grains[10,25]. Altogether, these dietary factors may lead to increased adiposity, particularly abdominal adiposity, and insulin resistance, as components of MetS[26–29]. On the other hand, regarding the poor diet quality of Iranians[30,31], lower-energy-dense diets may ameliorate metabolic abnormalities by improving diet quality.

The possible mechanisms underlying the association of DED and inflammation are not well understood. Earlier studies have indicated that consuming a more energy-dense diet is associated with weight gain[6,32] and greater adiposity tissue[33]. Adipose tissue is the main source of inflammatory biomarkers, and therefore this might be the link between DED and higher inflammatory biomarkers. However, even after adjustment for BMI, this association remained significant. It should be kept in mind that there is not a simple linear relationship between BMI and abdominal adiposity, as a component of MetS, and the main source of inflammatory biomarkers. It is possible that the saturated fat, cholesterol and refined carbohydrate contents of high-energy-dense diets, which are positively correlated with dietary inflammatory index[34], contribute to its relationship with chronic inflammation status.

The lack of association between DED and abnormal glucose homeostasis in the current study is in line with

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Table 5 Geometric means of inflammatory markers across quartile of dietary energy density among female nurses (*n* 1036) aged >30 years, Isfahan, Iran

	Quartile of dietary energy density								
	1 (lowest)		2		3		4 (highest)		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P**
hs-CRP (mg/l)									
Crude	1·9	1·8	2·1	1·8	2·6	1·9	3·2	2·0	<0·01
Model I†	1·8	1·7	2·0	1·7	2·6	1·8	3·1	1·9	<0·01
Model II‡	1·9	1·5	1·9	1·5	2·2	1·7	2·8	1·8	0·02
Model III§	1·7	1·6	1·7	1·6	2·0	1·6	2·4	1·7	0·04
TNF-α (ng/l)									
Crude	3·8	2·1	4·2	2·2	4·6	2·1	5·3	2·1	<0·01
Model I	3·9	2·0	4·1	2·1	4·4	2·0	5·4	2·0	<0·01
Model II	3·7	1·8	4·3	2·0	4·3	2·0	5·2	1·8	0·01
Model III	4·1	1·5	4·5	1·9	4·5	2·2	4·8	1·8	0·03
IL-6 (ng/l)									
Crude	1·3	1·0	1·7	1·5	2·1	1·9	2·9	2·1	<0·01
Model I	1·2	1·0	1·5	1·5	2·0	1·8	2·8	2·0	<0·01
Model II	1·4	1·1	1·4	1·6	1·8	1·8	2·8	1·8	<0·01
Model III	1·6	1·2	1·6	1·4	1·5	1·7	2·5	1·7	<0·01
SAA (mg/l)									
Crude	4·5	2·7	4·4	2·7	4·8	2·0	4·3	2·1	0·35
Model I	4·3	2·5	4·4	2·5	4·6	2·0	4·2	2·0	0·39
Model II	4·1	2·4	4·3	2·5	4·5	2·1	4·1	2·0	0·41
Model III	4·0	2·2	4·0	2·4	4·4	1·9	4·0	1·9	0·59
IL-2 (ng/l)									
Crude	1·5	2·1	1·6	2·1	1·4	1·8	1·6	1·5	0·47
Model I	1·4	2·0	1·5	2·1	1·4	1·7	1·6	1·4	0·42
Model II	1·3	2·0	1·4	1·9	1·6	1·6	1·5	1·4	0·57
Model III	1·3	1·8	1·6	1·8	1·5	1·6	1·4	1·3	0·63

hs-CRP, high-sensitivity C-reactive protein; SAA, serum amyloid A.
Data are presented as geometric means with their standard errors,
*By the use of ANOVA in crude models and ANCOVA in the adjusted models.
†Adjusted for age.
‡Further adjusted for cigarette smoking, physical activity, socio-economic status, current oestrogen use, menopausal status and family history of diabetes and stroke.
§Additionally adjusted for BMI.

earlier investigations[4,12,14]. The possible explanation for this finding might be the lower prevalence of abnormal glucose homeostasis in our study population. Another explanation might be the quality of fibre and fat, besides their quantity, which might differently affect glucose homeostasis[35–37]. Energy-dense diets contain greater amounts of *trans* and saturated fats[5]. Additionally, we have used only fasting plasma glucose to define abnormal glucose homeostasis, which might lead to the misclassification of study participants in terms of this condition. To further explore the relationship between DED and glycaemic control, one would need to consider fasting insulin levels as well.

Our study has several limitations that should be taken into account when interpreting our findings. The inherent limitation of its cross-sectional design does not allow us to draw conclusions on causality. Although having a metabolic disorder does not necessarily lead to unhealthy eating, longitudinal studies are required to investigate causal relationships. The study was conducted among female nurses, which may further limit the external validity of our findings. On the other hand, shift work and sleep deprivation in this population may affect their dietary intakes[38] as well as their metabolic profile and weight[39–41]. Using the US Department of Agriculture's food composition table to estimate nutrient and energy intakes in this population is another limitation of the present study, although efforts have been made to adapt this software for Iranians. Our observational study was conducted among free-living individuals, which could better reflect the real associations because of considering habitual dietary intakes rather than short-term intervention. Although we controlled for several potential confounders, unknown or unmeasured confounding variables like sleep deprivation cannot be excluded. Misclassification of participants due to using a self-administered, dish-based semi-quantitative FFQ is another limitation of our study, as with all other epidemiological studies. Substantially large sample size and considering the confounding effects of various variables are the strengths of the present study.

Conclusion

In summary, we found that consumption of high-energy-dense diets was associated with increased chance of MetS and most of its features in Iranian female nurses. Additionally, DED was positively associated with

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inflammatory markers including hs-CRP, TNF-α and IL-6 concentrations. Longitudinal studies are needed to explore the relationship of DED with MetS and inflammation.

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