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Long-term association of nut consumption and cardiometabolic risk factors

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Abstract *Background and aims:* Long-term associations between nut consumption and cardiometabolic risk factors are not well known. We investigated the relationship between nut consumption and cardiometabolic risk factors including dyslipidemia, hypertension, diabetes mellitus (DM), and obesity in a cohort of Iranian adults.
Methods and results: The study was conducted within the framework of the Isfahan Cohort Study on 1387 healthy participants. The participants were followed up for 12 years. A validated food frequency questionnaire was completed, and anthropometric measurements, blood pressure, and fasting serum lipids and blood sugar were evaluated in three phases. Mixed-effects binary logistic regression was applied to examine the associations between nut consumption and cardiometabolic risk factors. The participants were classified according to the tertiles of nut consumption as cut-points, and associations were evaluated between the thirds of nut intake.

Subjects in the last third were less likely to have hypercholesterolemia [OR (95% CI): 0.76 (0.60–0.97)], hypertriglyceridemia [OR (95% CI): 0.74 (0.58–0.93)], and obesity [OR (95% CI): 0.79 (0.50–0.98)] but more likely to have DM [OR (95% CI): 1.85 (1.27–2.68)] than those in the first third. However, after adjustment for various potential confounders, the associations remained significant only for obesity [OR (95% CI): 0.67 (0.48–0.94)] and DM [OR (95% CI): 2.23 (1.37–3.64)].
Conclusion: After adjustment for potential confounders, we observed an inverse association for nut consumption and obesity but positive association for DM and nut intake. On the basis of our findings, it is suggested that incorporation of nuts into people's usual diet may have beneficial effects for individuals with lower risk such as subjects without DM.

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Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide and accounted for 17 million deaths in 2015 [1]. Despite a 13% decline in the age-standardized rates of CVD deaths in low- and middle-income countries from 1990 to 2013, the number of deaths has increased by 66% (from 7.21 million in 1990 to 12 million in 2013) [1], and they impose a large economic burden on these countries [2]. The rapid increase in the prevalence of CVDs in low- and middle-income countries can be attributed to not only increased life expectancy but also changes in lifestyle-related risk factors. Some cardiometabolic risk factors such as obesity, dyslipidemia, hypertension, and diabetes mellitus (DM) can be controlled through diet and lifestyle modifications. Several lines of evidence suggest that diets high in unsaturated fatty acids [3], antioxidants [4], fiber [5], and plant sterol [6] can lower the CVD risk.

Nuts are one of the richest sources of unsaturated fatty acids, plant proteins, antioxidant vitamins (e.g., vitamin E), minerals (magnesium and potassium), and plant sterols, which all have cardioprotective effects. Findings from cross-sectional studies [7–10] and clinical trials [11–14] mostly confirm the favorable effects of nuts on cardiometabolic risk factors. Nevertheless, causal inference from cross-sectional studies requires to be considered. Moreover, findings from clinical trials may lead to less precise estimates owing to their often small sample size.

Data from prospective observational studies in this context are limited and provide inconsistent results. In two cohort studies on Iranian and Spanish individuals, greater nut consumption significantly reduced the risk of metabolic syndrome [15,16]. A meta-analysis on cohort studies indicated an inverse link between nut consumption and incident hypertension. However, no relationship was found between nut consumption and the incidence of DM [17]. Although the Nurses' Health Study (NHS) suggested favorable associations of frequent nut consumption with total cholesterol (TC) and low-density lipoprotein–cholesterol (LDL-C), it failed to find any relationships of nut consumption with high-density lipoprotein–cholesterol (HDL-C) and inflammatory biomarkers in women with DM [18]. In a Chinese cohort study, nut consumption was not associated with Framingham score, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum lipid profiles, and fasting blood glucose (FBG) [19]. In the SUN cohort project, nut intake was not related to the risk of hypertension and body weight changes [20,21].

To the best of our knowledge, available evidence in this context mainly came from Mediterranean and Western populations, and there is no prospective observational report from Middle-Eastern countries. Lifestyle, dietary patterns, amount of nuts consumed, and prevalence of various cardiometabolic risk factors in the Middle-Eastern population are different from those in Mediterranean and Western populations. Therefore, because of geographic variability in CVD risk factors, morbidity, and mortality, more prospective observational studies on nut consumption and cardiometabolic risk factors are needed in different geographical regions.

Hence, this study aimed to investigate the relationship between nut consumption and cardiometabolic risk factors such as dyslipidemia, hypertension, DM, and obesity in a cohort of healthy Iranian adults.

Methods

Design and subjects

This study derived data from Isfahan Cohort Study (ICS) [22]. The ICS was a population-based, prospective, observational study that recruited 6504 adults (3168 men and 3336 women) in 2001. The participants were aged ≥35 years and lived in three districts of central Iran, namely, Isfahan (n = 2153), Najaf-Abad (n = 1028), and Arak (n = 3323) [22]. To apply stratified cluster random sampling, we stratified the subjects by their living district and selected participants from chosen clusters in each district. At baseline (2001), data of lifestyle factors including dietary intake were collected through face-to-face interviews. To identify major cardiovascular events, participants were followed up biannually. When participants had no CVD events in annual evaluations, all variables were measured in the next six-year follow-up surveys (2007 and 2013). Finally, data of 1387 participants who had no CVD events, attended for repeated measurements in both 2007 and 2013, and had complete information of dietary intake, covariates, and outcome were included in the analysis. The study was approved by the Ethics Committee of the Research Council of Isfahan Cardiovascular Research Center, a World Health Organization collaborating center in Isfahan, Iran. Study design and details on subject recruitment and data collection methods have been described elsewhere [22].

Data collection

At baseline, trained health professionals conducted 30-min home interviews with eligible individuals to collect information of demographic and socioeconomic characteristics as well as behavioral features including dietary pattern, smoking, and physical activity [23,24]. Smoking status was categorized as current smoker, former smoker, and never smoker. A validated questionnaire was used to examine physical activity [25]. Trained physicians obtained past medical history, e.g., history of dyslipidemia, DM, and hypertension, as well as history of drug use.

Anthropometric measurements

Weight was measured on a scale to the nearest 0.5 kg, with minimal clothing. Height was measured to the nearest 0.5 cm using a nonelastic meter while the subjects were standing barefoot with shoulders in the normal state [21]. In the same standing position, waist circumference (WC) was also measured at a level midway between the lower

rib margin and the iliac crest, with the tape horizontally fixed around the body. Hip circumference was also measured at the point of maximum circumference over the buttocks using a nonelastic meter [26]. All measurements were performed in 2001 and repeated in 2007 and 2013. Obesity was defined as body mass index (BMI) $\geq$ 30 kg/m^2. According to Adult Treatment Panel III (ATP III), abdominal obesity was defined as WC $>$ 88 cm in women and WC $>$ 102 cm in men [27].

Blood pressure measurement

Trained nurses measured blood pressure using the standard protocol defined by the Joint National Committee (JNC) [28]. The subjects were asked to relax in the sitting position and a random-zero sphygmomanometer with an appropriate-sized cuff was used to perform the measurements twice with a 10-min rest period. The average of the two measures of the first and fifth Korotkoff phases was recorded as SBP and DBP, respectively. On the basis of the JNC criteria, hypertension was defined as SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg and/or current use of at least one type of antihypertensive medication [28].

Biochemical measurement

Blood samples were collected by trained nurses after 12–14 h of fasting. All blood samples were maintained at −20 °C and assayed within 72 h at the central laboratory of the Cardiovascular Research Institute (CRI). The laboratory met the criteria of the National Reference Laboratory (a WHO collaborating center). Serum TC and triglycerides (TG) were determined by the standard enzymatic method using special kits (Immunodiagnostic, Frankfurt, Germany) in a Hitachi autoanalyzer (Hamburg-Eppendorf, Germany). Enzymatic measurement of HDL-C was performed after precipitating other lipoproteins with dextran sulfate magnesium chloride [29]. LDL-C level was calculated using the Friedewald formula [30]. Direct measurement of LDL-C was performed with a turbidimetric method for those with TG $\geq$ 400 mg/dl [30]. Based on the National Cholesterol Education Panel ATP III (NCEP-ATP III), abnormal serum lipid profiles were defined as TC $\geq$ 240 mg/dl, TG $\geq$ 200 mg/dl, LDL-C $\geq$ 160 mg/dl, and HDL-C $<$ 40 mg/dl for men and $<$50 mg/dl for women [31]. FBG was measured using the enzymatic method. DM was defined as FBG $\geq$126 mg/dl or the use of insulin or oral hypoglycemic agents [31]. The coefficients of variation for inter-assay of TG, TC, LDL-C, HDL-C, and FBG were 3.6%, 3.2%, 3.5%, 3.5%, and 2.2%, respectively. The corresponding values for intra-assay of TG, TC, LDL-C, HDL-C, and FBG were 0.6%, 0.5%, 0.65%, 0.5%, and 0.8%, respectively.

Dietary assessment

Dietary intake data were collected at three phases using a validated 48-item food frequency questionnaire (FFQ) [32,33]. Trained health professionals conducted face-to-face interviews with the participants and completed the FFQs. The participants reported the frequency of consumption of each food item during the past year in an open-ended format (daily, weekly, or monthly). They were also asked to choose the “never/seldom” option if they never consumed a certain food item or consumed it less than once a month. This option was considered as “zero.” In each phase of the study, nut consumption was assessed using two separate questions: “How often do you eat almonds, pistachios, and hazelnuts?” and “How often do you eat walnuts?”. The consumption of all food items was determined from per month, per week, or per day values. We did not collect data of portion sizes of food items because the validation study of this FFQ concluded that for most food items, portion sizes vary less than frequencies of consumption [33]. The frequency of nut consumption obtained from our FFQ showed significant correlation with the mean intake of nuts obtained from a single 24-h recall and two food records (Spearman’s rank correlation coefficient = 0.468; $P < 0.001$).

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD), and qualitative variables were expressed as number (percent). Medians and interquartile ranges (IQRs) were calculated for data with a skewed distribution. The nonparametric test introduced by Cuzick (1985) [34] was performed for trend analysis between the thirds of nut intake in three phases.

To determine the associations of changes in nut consumption with cardiometabolic risk factors, mixed-effects logistic regression, using the logit link function, with time-varying covariates was applied. This model takes into account the normal random effects embedded within the linear predictor [35] to consider the repeated measurement of nut intake as the time-varying covariate and the repeated measurement of the outcome variable to include the change in nut intake during the long follow-up period (13 years). To predict the repeated measurements of the outcome variables, mixed-effects regression analysis was applied to construct models, where repeated measurements of the nut intake were inserted into the model. The models were adjusted for age, sex, education, place of residence, family history, smoking status, physical activity, dietary items, medications, and BMI. The confounders were repeated as time-varying covariates with three measurements.

To assess the statistical interactions between nut intake and age, sex, BMI, family history, smoking status, and physical activity, main-effect variables and their product terms were included in the mixed-effects logistic regression model. Stratified analyses were then performed on significant interaction items to evaluate their potential modifying effects on the status of metabolic risk factors. The adjusted models were also controlled for the same potential confounders (as mentioned above).

Energy intake adjustment is important in epidemiological studies of nutrition, as it controls the confounding effects of energy intake and body size. However, because of

the lack of data on energy intake in the current study, such adjustment was performed using BMI as a surrogate measure [36], and the residual method was applied to obtain energy-adjusted intake of nuts for each study year [37]. The participants were classified by the thirds of BMI-adjusted nut intake. To assess the overall trends of the odds ratios (ORs) between the thirds of nut consumption, nut intake was used as a continuous variable in the models.

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc.). All reported P-values were associated with two-tailed hypotheses with 95% confidence intervals (CIs).

Results

A total of 674 men (48.6%) and 713 women (51.4%) were included in this study. The median (IQR) of nut intake was 0.76 (0.57), 3.64 (1.33), and 2.21 (1.19) times/week in 2001, 2007, and 2013, respectively. The general characteristics of the participants between the thirds of nut consumption in the three years of data collection are shown in Table 1. In 2001, higher nut consumption was associated with younger age; higher physical activity levels; and lower BMI, WC, SBP, DBP, TG, TC, LDL-C, and FBG. Individuals in the highest third were more likely to be males, highly educated, and smokers but less likely to live in urban areas. Women in the highest third were less likely to be postmenopausal. In the years 2007 and 2013, higher nut consumption was associated with higher educational level and higher physical activity level. In 2007, individuals who consumed more nuts were more likely to have a family history of DM and CVD. In 2013, the participants who consumed more nuts were less likely to have a family history of DM, although they had higher FBG levels.

Table 2 summarizes the dietary intakes of the participants based on the tertiles of nut consumption and the year of data collection. In all the three years, individuals in the highest third of nut intake had higher intakes of legumes, fruits and vegetables, and fish. In 2001, fast food consumption was more frequent in participants in the highest third of nut consumption. In 2007 and 2013, the mean frequency of fast food consumption decreased and became similar between the thirds of nut consumption. Red meat, sweets, and beverages were consumed in greater amounts by the individuals in the highest third of nut consumption in 2001 and 2007 but not in 2013. Although dairy intake was similar between the thirds of nut consumption in 2001, its mean frequency intake was higher in the thirds of nut consumption in 2007 and 2013.

Table 3 provides the crude and multivariate-adjusted ORs for cardiometabolic risk factors between the thirds of nut consumption. In the crude model, the odds of hypercholesterolemia (OR = 0.76; 95% CI: 0.60–0.97; P = 0.025), hypertriglyceridemia (OR = 0.74; 95% CI: 0.58–0.93; P = 0.011), and obesity (OR = 0.70; 95% CI: 0.50–0.98; P = 0.033) were lower in the highest third of nut intake, while the odds of DM was higher (OR = 1.85). After adjustment for age and sex, this significance disappeared for hypercholesterolemia but not for other risk factors. Further control for lifestyle factors and dietary intakes slightly changed the associations but did not affect their significance. However, after additional adjustment for BMI, the associations remained significant only for DM (OR = 2.23; 95% CI: 1.37–3.64; P = 0.001). We also performed analysis where BMI was not used as a surrogate for energy. The results showed some differences, particularly in OR estimations (Supplementary Table 1). Therefore, because of the lack of data on energy intake in our study, we used BMI as surrogate measures as suggested by Jakes et al. [36].

Significant interactions were observed between nut intake and BMI (P = 0.025), sex (P < 0.001), physical activity (P = 0.017), and smoking status (P = 0.001), with dyslipidemia as the outcome. Significant interactions were also detected between nut intake and BMI, sex, family history of DM, and age, with DM as the outcome (P < 0.001 for all). Nut intake showed significant interactions with BMI, sex, family history of hypertension, and age, with hypertension as the outcome (P < 0.001 for all). Considering obesity as the outcome, nut intake showed significant interactions with sex, smoking status, and age (P < 0.001 for all). Finally, significant interactions existed between nut intake and sex, smoking status, and age, with abdominal obesity as the outcome (P < 0.05 for all).

Stratified analyses were conducted to examine the robustness of our findings when the participants were stratified by various confounders based on significant interactions (Table 4). The associations between nut consumption and dyslipidemia were similar in different subgroups of BMI, physical activity, and sex. The associations between nut consumption and hypertension were similar in different subgroups of age, BMI, sex, and family history of hypertension. While presence of dyslipidemia was less likely in the highest third of nut consumption in current smokers, no significant association was observed in nonsmokers. There was a direct association between nut consumption and DM in overweight individuals (OR = 2.06; 95% CI: 1.19–3.58; P trend = 0.010), women (OR = 2.79; 95% CI: 1.43–5.41; P trend = 0.002), and middle-aged participants (OR = 2.46; 95% CI: 1.40–4.32; P trend = 0.002). Individuals with a family history of DM were more likely to have DM in the highest third (OR = 1.89; 95% CI: 1.0–3.58; P trend = 0.052). In the highest third of nut consumption, the odds of obesity was 0.53 in women (95% CI: 0.34–0.83; P trend = 0.005), 0.67 in nonsmokers (95% CI: 0.47–0.97; P trend = 0.029), and 0.40 in older adults (95% CI: 0.17–0.93; P trend = 0.028).

Discussion

According to the findings of this prospective observational study on an Iranian adult population, there was an inverse association between nut consumption and obesity but a direct association between nut consumption and type 2 DM after controlling for potential confounders. In the stratified analysis, an inverse link was observed between nut consumption and obesity in women, physically

Table 1 General characteristics of the study population between the thirds of nut intake in each study year.

	2001				2007				2013			
	Nut intake thirds			P trend[a]	Nut intake thirds			P trend[a]	Nut intake thirds			P trend[a]
	Low (n = 463)	Medium (n = 462)	High (n = 462)		Low (n = 462)	Medium (n = 463)	High (n = 462)		Low (n = 462)	Medium (n = 463)	High (n = 462)	
Median of nut intake (IQR)	0.65 (0.005)	0.76 (0.12)	1.57 (1.27)	–	3.24 (0.18)	3.64 (0.27)	4.75 (0.46)	–	1.84 (0.08)	2.21 (0.33)	4.04 (1.06)	–
Age (years)	49.63 ± 9.83	47.45 ± 9.31	45.22 ± 7.81	<0.001	47.90 ± 9.48	47.29 ± 9.22	47.12 ± 8.87	0.283	47.25 ± 9.50	47.21 ± 9.04	47.85 ± 9.06	0.152
Male (%)	41.3	54.1	50.4	0.005	46.5	52.5	46.8	0.948	46.3	51.8	47.6	0.693
Education (%)				0.005				<0.001				<0.001
Illiterate and primary school	65.7	55.6	56.5		69.7	61.8	48.1		66.9	57.7	51.5	
Guidance and high school	28.5	34	35.7		23.6	29.6	39.2		28.8	30.7	33.3	
University	5.8	10.4	7.8		6.7	8.6	12.8		4.3	11.7	15.2	
Urbanization (%)	87.3	83.5	75.3	<0.001	79.7	85.1	81.4	0.493	81.8	83.6	80.7	0.668
Postmenopausal women (%)	42.1	34.4	26.6	<0.001	55.5	56.7	59.6	0.361	83.4	82.5	85.7	0.493
Smoker (%)	12.7	15.6	18.2	0.022	13.4	13.9	10.6	0.198	14.3	13.6	12.1	0.333
Physical activity (METS)	13.72 ± 8.56	15.63 ± 9.45	16.70 ± 10.07	<0.001	13.36 ± 8.07	14.57 ± 9.72	15.93 ± 9.83	<0.001	12.28 ± 10.97	13.09 ± 9.29	12.94 ± 9.13	0.003
Family history of diabetes (%)	24.8	24.2	24.9	0.968	23.3	30	30.9	0.011	69.3	60.9	60.8	0.008
Family history of hypertension (%)	29.5	29.3	28.2	0.672	37.7	42	40.1	0.449	51.3	47.9	45.7	0.087
Family history of CVD (%)	9.2	7.4	7.8	0.427	20.9	26.7	30.3	0.001	19.5	23.8	23.8	0.114
BMI (kg/m^2)	29.11 ± 3.89	26.77 ± 5.36	26.80 ± 4.46	<0.001	28.17 ± 4.54	27.42 ± 4.39	27.68 ± 4.27	0.192	28.13 ± 4.95	28.09 ± 4.58	27.96 ± 4.31	0.959
WC (cm)	101.94 ± 10.24	95.66 ± 11.95	96.04 ± 10.62	<0.001	94.64 ± 11.76	93.55 ± 11.03	94.01 ± 10.88	0.449	97.15 ± 11.23	97.81 ± 11.54	98.18 ± 11.12	0.120
SBP (mmHg)	122.16 ± 20.05	119.14 ± 18.30	117.13 ± 17.95	<0.001	125.01 ± 18.71	124.72 ± 18.95	123.55 ± 17.73	0.229	129.17 ± 18.50	128.10 ± 16.86	128.69 ± 17.63	0.950
DBP (mmHg)	78.20 ± 12.03	76.72 ± 12.19	75.50 ± 11.10	0.001	78.15 ± 10.35	78.72 ± 19.73	78.04 ± 10.10	0.697	83.60 ± 12.79	83.01 ± 11.86	82.00 ± 12.62	0.091
TG (mg/dL)[b]	221.33 ± 119.54	188.15 ± 103.28	194.59 ± 108.68	<0.001	174.70 ± 121.34	169.38 ± 113.34	172.24 ± 110.52	0.886	154.79 ± 92.81	156.50 ± 87.27	154.58 ± 73.84	0.393
TC (mg/dL)[b]	231.01 ± 54.60	214.32 ± 49.65	215.14 ± 49.44	<0.001	209.93 ± 42.44	208.74 ± 42.30	211.85 ± 42.89	0.610	201.20 ± 42.32	199.38 ± 38.42	199.20 ± 42.04	0.917
FPG (mg/dL)[b]	89.41 ± 30.82	84.81 ± 27.12	86.31 ± 30.52	0.002	99.24 ± 32.17	101.34 ± 39.08	104.73 ± 44.43	0.586	104.08 ± 35.83	107.37 ± 39.10	108.60 ± 39.12	0.005
HDL (mg/dL)[b]	47.76 ± 1085	46.75 ± 10.08	46.54 ± 10.17	0.133	46.72 ± 11.43	46.13 ± 11.18	47.12 ± 11.44	0.454	44.86 ± 23.15	45.05 ± 27.58	43.78 ± 10.54	0.958
LDL (mg/dL)[b]	138.98 ± 44.26	129.95 ± 42.25	129.69 ± 40.34	0.005	127.23 ± 30.35	125.54 ± 29.95	129.52 ± 30.09	0.204	111.64 ± 27.70	111.53 ± 27.97	111.59 ± 27.90	0.618

Quantitative variables were expressed as mean ± standard deviation, and qualitative variables were expressed as percent. CVD: Cardiovascular diseases; BMI: Body max index; WC; Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG; Triglyceride; TC: total cholesterol; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein−cholesterol; LDL-C: Low-density lipoprotein−cholesterol.

[a] P for trend between the thirds of nut in each study year.

[b] To convert TG from mg/dL to SI (in mmol/L), multiply by 0.01129; to convert TC, HDL, and LDL from mg/dL to SI (in mmol/L), multiply by 0.02586; and to convert FPG from mg/dL to SI (in mmol/L), multiply by 0.055.

Table 2 Dietary intakes of study population between the thirds of nuts intake in each study year.

	2001				2007				2013			
	Nut intake thirds			P trend[a]	Nut intake thirds			P trend[a]	Nut intake thirds			P trend[a]
	Low (n = 463)	Medium (n = 462)	High (n = 462)		Low (n = 462)	Medium (n = 463)	High (n = 462)		Low (n = 462)	Medium (n = 463)	High (n = 462)	
Fast food (time/wk)	−0.15 (0.32)	−0.15 (0.65)	0.17 (0.97)	<0.001	−0.10 (0.42)	−0.11 (0.43)	−0.12 (0.40)	0.372	−0.17 (0.44)	−0.17 (0.47)	−0.18 (0.46)	0.129
Legumes (time/wk)	2.28 (1.06)	2.28 (1.03)	2.74 (0.66)	<0.001	1.98 (0.72)	1.98 (0.71)	2 (1.33)	<0.001	1.20 (0.80)	1.94 (1.53)	1.94 (1.54)	<0.001
Fruit and vegetables (time/wk)	12.33 (0.95)	12.31 (1.24)	12.38 (0.95)	0.002	13.53 (1.24)	13.77 (0.99)	14.16 (0.97)	<0.001	11.85 (1.23)	12.10 (1.10)	12.64 (1.19)	<0.001
Grains (time/wk)	22.64 (1.63)	22.62 (1.56)	22.66 (1.13)	0.543	17.15 (1.38)	17.26 (1.47)	17.52 (1.51)	0.004	14.53 (1.56)	14.51 (1.65)	14.58 (1.74)	0.465
Red meat (time/wk)	3.31 (0.92)	3.38 (1.35)	3.39 (1.30)	<0.001	2.37 (0.49)	2.37 (0.50)	2.39 (0.49)	0.001	0.24 (0.07)	0.24 (0.05)	0.24 (0.04)	0.643
Dairy (time/wk)	0.20 (0.17)	0.19 (0.32)	0.20 (0.52)	0.833	16.75 (1.34)	16.94 (1.10)	17.06 (1.05)	<0.001	7.83 (1.21)	7.86 (1.10)	8 (1.67)	<0.001
Fish (time/wk)	0.14 (1.03)	0.18 (0.70)	0.21 (0.90)	<0.001	0.38 (0.30)	0.40 (0.57)	0.56 (0.57)	<0.001	0.72 (0.25)	0.78 (0.30)	0.81 (0.31)	<0.001
Sweet and beverage (time/wk)	1.72 (0.90)	1.73 (0.83)	2.06 (1.04)	<0.001	1.74 (0.63)	1.78 (0.72)	1.86 (0.88)	<0.001	2.17 (0.74)	2.21 (0.91)	2.27 (1.07)	0.054

Data are expressed as Median (IQR); all values are adjusted by BMI using residual model.
[a] P for trend between the thirds of nut in each study year.

inactive subjects, nonsmokers, and older adults. Furthermore, a direct association was found between nut consumption and DM in women, overweight individuals, physically inactive participants, nonsmokers, middle-aged subjects, and individuals with a family history of DM. Nut consumption had a significant inverse association with hypertriglyceridemia, but the association attenuated and became nonsignificant after adjusting for BMI. Hypertension, dyslipidemia, hypercholesterolemia, elevated LDL-C, and low HDL-C were not related to nut consumption.

The inverse link between nut consumption and obesity in this study was in agreement with the findings of earlier prospective observational studies [20,38–41]. Although NHS suggested no significant changes in body weight after a 16-year follow-up [40], a pooled analysis of the NHS, NHS II, and the Health Professionals Follow-up Study, as well as the results of SUN cohort project, revealed less weight gain in individuals who regularly consumed nuts [20,38,39,41]. The protective effect of nut consumption on obesity might be due to their high fiber and plant protein content that induce greater satiety [38,42]. Moreover, in addition to promoting fat oxidation [43], high levels of unsaturated fatty acids, together with high fiber and plant protein content, in nuts increase thermogenesis and resting energy expenditure and ultimately decrease body weight [16]. However, our stratified analysis indicated that the favorable effect of nut consumption on body weight was confined to the subgroups at higher risk of obesity, i.e., women, physically inactive individuals, nonsmokers, and older adults. We previously obtained similar results with regard to sex in an earlier cross-sectional analysis on the same population [10]. However, to the best of our knowledge, no other studies have examined this association in the mentioned subgroups.

Although we found no association between nut consumption and TC, LDL-C, and HDL-C, an inverse association, mediated through BMI, was observed in the case of TG. A meta-analysis on randomized controlled trials (RCTs) demonstrated favorable effects of nut consumption on TC, LDL-C, and TG [44]. However, the results of a recent Cochrane systematic review of long-term RCTs, which lasted for over three months, concluded that nut consumption had no beneficial effects on any serum lipids [45]. In our study, nut consumption showed an inverse association with TG by affecting BMI. This finding is highly valuable, as hypertriglyceridemia affects 40.6% of the Iranian population and is the second most prevalent type of dyslipidemia in the country [46]. In addition, the magnitude of this decrement was considerable, as participants in the highest third showed 23% lower odds for having hypertriglyceridemia even after adjustment for some relevant confounders. Although adjustment for BMI decreased this association because of a large beneficial association between BMI and nut, nut consumption for 2–3 times/week would be a helpful approach to reduce hypertriglyceridemia risk. Despite the high content of serum TC-lowering agents, e.g., phytosterols, L-arginine, and unsaturated fatty acids [47], nuts had no significant effects on serum TC and LDL-C. This finding remained

Table 3 ORs (95% CIs) for associations between the thirds of nut intake and dyslipidemia, diabetes, hypertension, overweight, and obesity.

	Nut intake thirds			P trend
	Low (n = 1387)[c]	Medium (n = 1388)[c]	High (n = 1386)[c]	
Dyslipidemia[a]				
Cases (%)[b]	1173 (84.6)	1144 (82.4)	1151 (83)	
Crude model	1	0.78 (0.60–1.01)	0.81 (0.62–1.05)	0.118
Model 1	1	0.75 (0.58–0.98)	0.80 (0.61–1.04)	0.109
Model 2	1	0.79 (0.60–1.03)	0.87 (0.66–1.15)	0.321
Model 3	1	0.86 (0.66–1.13)	0.96 (0.72–1.27)	0.768
Hypercholesterolemia				
Cases (%)[b]	477 (34.4)	423 (30.5)	423 (30.5)	
Crude	1	0.85 (0.68–1.07)	0.76 (0.60–0.97)	0.025
Model 1	1	0.91 (0.72–1.14)	0.82 (0.65–1.04)	0.103
Model 2	1	0.94 (0.74–1.18)	0.86 (0.67–1.10)	0.219
Model 3	1	0.98 (0.78–1.25)	0.91 (0.71–1.17)	0.463
Hypertriglyceridemia				
Cases (%)[b]	545 (39.3)	479 (34.5)	492 (35.5)	
Crude	1	0.74 (0.59–0.93)	0.74 (0.58–0.93)	0.011
Model 1	1	0.75 (0.60–0.94)	0.76 (0.60–0.96)	0.02
Model 2	1	0.76 (0.61–0.97)	0.77 (0.60–0.98)	0.034
Model 3	1	0.83 (0.65–1.04)	0.85 (0.67–1.08)	0.181
Elevated LDL-C				
Cases (%)[b]	367 (26.5)	326 (23.5)	334 (24.1)	
Crude	1	0.87 (0.69–1.10)	0.87 (0.68–1.10)	0.237
Model 1	1	0.93 (0.74–1.17)	0.93 (0.74–1.18)	0.551
Model 2	1	0.96 (0.76–1.21)	0.97 (0.76–1.24)	0.803
Model 3	1	0.99 (0.79–1.26)	1.02 (0.80–1.30)	0.893
Low HDL-C				
Cases (%)[b]	783 (56.5)	738 (53.2)	743 (53.6)	
Crude	1	0.88 (0.72–1.08)	0.89 (0.72–1.10)	0.276
Model 1	1	0.92 (0.75–1.12)	0.90 (0.73–1.10)	0.308
Model 2	1	0.95 (0.77–1.18)	0.96 (0.77–1.20)	0.749
Model 3	1	1 (0.81–1.24)	1.02 (0.82–1.28)	0.852
Diabetes				
Cases (%)[b]	162 (11.7)	185 (13.3)	202 (14.6)	
Crude	1	1.68 (1.17–2.42)	1.85 (1.27–2.68)	0.001
Model 1	1	1.76 (1.22–2.54)	1.96 (1.35–2.84)	<0.001
Model 2	1	1.56 (0.98–2.49)	2.06 (1.27–3.33)	0.003
Model 3	1	1.63 (1.02–2.62)	2.23 (1.37–3.64)	0.001
Hypertension				
Cases (%)[b]	494 (35.6)	465 (33.5)	441 (31.8)	
Crude	1	1.01 (0.81–1.26)	0.91 (0.72–1.14)	0.402
Model 1	1	1.06 (0.85–1.32)	0.98 (0.78–1.23)	0.854
Model 2	1	1.09 (0.85–1.40)	1.03 (0.79–1.34)	0.811
Model 3	1	1.16 (0.90–1.49)	1.11 (0.86–1.45)	0.404
Obesity (BMI ≥ 30 kg/m^2)				
Cases (%)[b]	466 (33.6)	368 (26.5)	370 (26.7)	
Crude	1	0.62 (0.45–0.87)	0.70 (0.50–0.98)	0.033
Model 1	1	0.66 (0.48–0.91)	0.70 (0.50–0.98)	0.034
Model 2	1	0.64 (0.46–0.89)	0.67 (0.48–0.94)	0.018
Central adiposity (women > 88 cm/men > 102 cm)				
Cases (%)[b]	1098 (79.2)	1006 (72.5)	1057 (76.3)	
Crude	1	0.70 (0.53–0.91)	0.88 (0.67–1.17)	0.402
Model 1	1	0.72 (0.55–0.94)	0.91 (0.68–1.20)	0.514
Model 2	1	0.70 (0.53–0.93)	0.89 (0.66–1.19)	0.426

Hypercholesterolemia: TC ≥ 240 mg/dl; hypertriglyceridemia: TGs ≥200 mg/dl; low HDL-C: HDL-C <40 mg/dl for males and <50 mg/dl for females; and high LDL-C: LDL-C ≥160 mg/dl.

Model 1: Adjusted for age (years) and sex (men/women). Model 2: Additionally, adjusted for education (illiterate and primary school/high school/university), residency (urban/rural), smoking status (never/past/current smoker), weekly physical activity (METs-h/wk), family history* (yes/no), postmenopause in women (yes/no), medications, fruits and vegetables, legumes, grains, red meat, fish, dairy, fast food, and sweet (g/d). Model 3: Additionally, adjusted for body mass index (kg/m^2).

[a] Having at least one of lipid profile disorders (hypercholesterolemia, hypertriglyceridemia, elevated LDL-c, or low HDL-c).

[b] Number of cases during 12-year follow-up.

[c] Number of individuals in each third of nut during 12-year follow-up.

Table 4 ORs (95% CIs) for associations between the thirds of nut intakes and dyslipidemia, diabetes, hypertension, overweight, and obesity stratified by major risk factors.

	Nut intake thirds			P trend
	Low (n = 1387)	Medium (n = 1388)	High (n = 1386)	
Dyslipidemia				
BMI (kg/m^2)[a]				
BMI < 25 (n = 890)	1	0.65 (0.40–1.06)	0.75 (0.45–1.24)	0.358
BMI ≥ 25 (n = 2578)		0.97 (0.69–1.37)	1.04 (0.73–1.48)	0.827
Sex[b]				
Male (n = 1767)	1	0.81 (0.53–1.24)	0.87 (0.55–1.37)	0.564
Female (n = 1701)	1	0.93 (0.65–1.33)	1.11 (0.76–1.61)	0.597
Physical activity[c]				
MET.h/wk < median (n = 1734)	1	0.76 (0.52–1.11)	1.23 (0.81–1.86)	0.415
MET.h/wk ≥ median (n = 1734)	1	0.94 (0.63–1.39)	0.83 (0.56–1.24)	0.360
Smoking[d]				
Nonsmokers (n = 2948)	1	0.86 (0.65–1.15)	1.10 (0.81–1.49)	0.537
Current smokers (n = 519)	1	0.77 (0.29–2.01)	0.38 (0.14–1.04)	0.048
Diabetes				
BMI (kg/m^2)[a]				
BMI < 25 (n = 91)	1	2.44 (0.62–9.53)	2.36 (0.59–9.50)	0.235
BMI ≥ 25 (n = 458)	1	1.49 (0.87–2.55)	2.06 (1.19–3.58)	0.01
Sex[b]				
Male (n = 230)	1	1.50 (0.73–3.07)	1.86 (0.87–3.97)	0.111
Female (n = 319)	1	1.75 (0.92–3.35)	2.79 (1.43–5.41)	0.002
Family history of diabetes[e]				
Yes (n = 322)	1	2.41 (0.96–6.05)	3.61 (1.41–9.22)	0.008
No (n = 222)	1	1.32 (0.71–2.44)	1.89 (1.0–3.58)	0.052
Age[f]				
Middle age (n = 395)	1	1.63 (0.94–2.83)	2.46 (1.40–4.32)	0.002
Old age (n = 154)	1	1.54 (0.58–4.12)	1.62 (0.57–4.62)	0.370
Hypertension				
BMI (kg/m^2)[a]				
BMI < 25 (n = 108)	1	0.55 (0.32–0.93)	0.58 (0.34–1)	0.056
BMI ≥ 25 (n = 475)	1	1.39 (1.04–1.85)	1.26 (0.93–1.70)	0.123
Sex[b]				
Male (n = 200)	1	1.13 (0.79–1.61)	1.07 (0.73–1.56)	0.719
Female (382)	1	1.22 (0.85–1.75)	1.21 (0.83–1.77)	0.303
Family history of hypertension[e]				
Yes (n = 375)	1	1.02 (0.68–1.53)	1.07 (0.70–1.63)	0.761
No (n = 208)	1	1.24 (0.89–1.72)	1.13 (0.80–1.60)	0.448
Age[f]				
Middle age (n = 370)	1	1.17 (0.88–1.57)	1.14 (0.84–1.55)	0.391
Old age (n = 213)	1	1.12 (0.67–1.86)	0.96 (0.55–1.69)	0.930
Obesity (BMI ≥ 30)				
Sex[b]				
Male (n = 335)	1	0.83 (0.49–1.41)	0.95 (0.55–1.66)	0.858
Female (n = 869)	1	0.55 (0.36–0.86)	0.53 (0.34–0.83)	0.005
Smoking[d]				
Nonsmokers (n = 1111)	1	0.61 (0.43–0.87)	0.67 (0.47–0.97)	0.029
Current smokers (n = 93)	1	0.70 (0.23–2.13)	0.56 (0.17–1.85)	0.337
Age[f]				
Middle age (n = 1031)	1	0.67 (0.46–0.98)	0.74 (0.50–1.08)	0.115
Old age (n = 173)	1	0.55 (0.26–1.14)	0.40 (0.17–0.93)	0.028
Central adiposity (women > 88 cm/men > 102 cm)				
Sex[b]				
Male (n = 1478)	1	0.76 (0.51–1.13)	0.92 (0.60–1.41)	0.732
Female (n = 1683)	1	0.70 (0.46–1.06)	0.91 (0.58–1.41)	0.634
Physical activity[c]				
MET.h/wk < median (n = 1615)	1	0.78 (0.53–1.15)	0.88 (0.58–1.34)	0.492
MET.h/wk ≥ median (n = 1546)	1	0.51 (0.32–0.80)	0.84 (0.53–1.35)	0.650
Smoking[d]				
Nonsmokers (n = 2765)	1	0.78 (0.57–1.06)	0.94 (0.67–1.31)	0.707
Current smokers (n = 396)	1	0.43 (0.21–0.89)	0.69 (0.32–1.48)	0.358
Age[f]				
Middle age (n = 2528)	1	0.70 (0.51–0.97)	1.01 (0.72–1.42)	0.923
Old age (n = 633)	1	0.72 (0.40–1.29)	0.58 (0.30–1.13)	0.103

*Note: For dyslipidemia, family history of lipid profiles was adjusted; for diabetes, family history of diabetes was adjusted; for hypertension, family history of hypertension was adjusted.

[a] Values were adjusted for age (years), sex (men/women), education (illiterate and primary school/high school/university), residency (urban/rural), smoking status (never/past/current smoker), weekly physical activity (METs-h/wk), family history* (yes/no), postmenopausal in women (yes/no), fruits and vegetables, grains, red meat, fish, dairy, fast food, and sweet (g/d).
[b] Values adjusted for age (years), education (illiterate and primary school/high school/university), residency (urban/rural), smoking status (never/past/current smoker), weekly physical activity (METs-h/wk), family history* (yes/no), postmenopausal in women (yes/no), medications, fruits and vegetables, grains, red meat, fish, dairy, fast food, sweet (g/d), and body mass index (kg/m^2).
[c] Values adjusted for age (years), sex (men/women), education (illiterate and primary school/high school/university), residency (urban/rural), smoking status (never/past/current smoker), family history* (yes/no), postmenopausal in women (yes/no), fruits and vegetables, legumes, grains, red meat, fish, dairy, fast food, sweet (g/d), and body mass index (kg/m^2).
[d] Values adjusted for age (years), sex (men/women), education (illiterate and primary school/high school/university), residency (urban/rural), weekly physical activity (METs-h/wk), family history* (yes/no), postmenopausal in women (yes/no), fruits and vegetables, grains, red meat, fish, dairy, fast food, sweet (g/d), and body mass index (kg/m^2).
[e] Values were adjusted for age (years), sex (men/women), education (illiterate and primary school/high school/university), residency (urban/rural), smoking status (never/past/current smoker), weekly physical activity (METs-h/wk), postmenopausal in women (yes/no), fruits and vegetables, grains, red meat, fish, dairy, fast food and sweet (g/d), and body mass index (kg/m^2).
[f] Values were adjusted for sex (men/women), education (illiterate and primary school/high school/university), residency (urban/rural), smoking status (never/past/current smoker), weekly physical activity (METs-h/wk), family history* (yes/no), postmenopausal in women (yes/no), fruits and vegetables, grains, red meat, fish, dairy, fast food and sweet (g/d), and body mass index (kg/m^2).

unchanged even after controlling for dairy products and meat as the main sources of saturated fatty acids.

Regarding hypertension, our findings were in accordance with those reported in a recent meta-analysis on 21 RCTs, which revealed that nut consumption did not decrease hypertension in the whole population. Furthermore, sensitivity analysis among subjects without diabetes indicated that nut intake had a beneficial effect on SBP [11]. As data about the forms of nuts consumed (salted or unsalted) were not collected in this study, we could not determine the effects of salt in our analysis.

Additionally, we found a direct association between nut consumption and DM. Studies in this context are limited and inconclusive. While two epidemiological studies [7,40] revealed an inverse link between DM and nut consumption, no significant association was found in the Physicians' Health Study [48]. In the Iowa Women's Health Study, after adjustment for various dietary and nondietary confounders, nut consumption more than once a month but less than four times a week reduced the risk of DM. However, nut consumption for more than five times a week was associated with an increased incidence of DM [49]. In a meta-analysis on four prospective cohort studies, the inverse link between nut consumption and DM was attenuated after adjustment for BMI [50]. Nevertheless, in the present study, the positive association remained significant even after controlling for BMI. Given the considerable association of DM following nut intake, lower consumption of nuts, particularly in subjects at risk for developing DM, is recommended. To the best of our knowledge, there is no known mechanism for this finding, and further investigations are needed to confirm our results.

Nuts have always been considered as the prominent constituent of Mediterranean diet. A recent prospective cohort study indicated that despite similar Mediterranean diet scores between individuals from high and low socioeconomic classes, adherence to Mediterranean diet was associated with lower cardiovascular risk in higher socioeconomic classes but not in lower classes [51]. The authors concluded that highly educated or high-income people were more likely to include a higher variety of vegetables in their diet; prefer whole-grain bread; and consume monounsaturated fatty acids, vitamin D, calcium, fiber, polyphenol, and antioxidants (beneficial cardiovascular effects are well established). In this Italian cohort study, food preparation methods were also different between high and low socioeconomic classes. Such a difference might have affected some bioactive contents of foods, such as antioxidants [51]. Although we controlled for the confounding effects of some nutrients, our study was conducted in a low-to-middle-income country. As previous studies were conducted in developed and high-income countries, socioeconomic disparities might have been responsible for the differences between our findings and those of earlier publications, particularly in case of TC and DM. This should be evaluated in future studies.

This study had some limitations. First, we could not examine the associations on the basis of the specific types of nuts because they were not separately asked in the FFQ used in this study. In addition, our FFQ just included the most common nuts used by Iranians, including pistachio, almonds, hazelnuts, and walnuts. Although not considering the intake of other nut types may cause a misclassification because of their low intake by Iranians [52], it would be unlikely that they can significantly affect health outcomes. Second, although our FFQ was a validated version, it had no data regarding portion sizes. Therefore, we could not measure total energy intake in this study. Using BMI as a surrogate for energy intake might not be clinically valid because some individuals including those engaged in manual work will have high energy intakes and low BMI. Hence, we further adjusted our model for physical activity during the statistical analysis [36]. Third, measurement errors and misclassification due to self-reported data are limitations inherent to all epidemiological studies. Fourth, the sample size of the current study was smaller than that of other prospective cohort studies examining nut consumption, and this may have affected the precision of estimates like the width of CI when compared with those studies where what counts as "wide" is often at least partially subjective. Moreover, because of the loss to follow-up and excluding those with a CVD event, our results may not be generalizable to other populations. However, a

comparison of nut intake between participants who were followed up and those who were lost to follow-up showed no significant difference (mean frequency intake (SD): 1.2 ± 2.2 vs. 1.1 ± 2.3, respectively; P = 0.1). Fifth, although controlling for mediators including BMI might lead to over-adjustment, we added them into the analysis after controlling for confounders. Therefore, the extent to which the associations between nut consumption and CVD risk are mediated by BMI would be calculable [53]. Our results showed a small proportion difference for CVD risks after adjustment for BMI. Sixth, despite adjustment for various known potential confounders, the effects of unknown and residual confounders could not be excluded. Finally, the observational cohort design of our study with repeated measurements implies that dietary measurements were conducted at the same time as the outcome measurements; thus, reverse causation bias may have occurred. RCTs are thus needed to identify causality.

The main strengths of this study included its prospective design, several measurements of dietary intake during the follow-up period, a reasonably long follow-up duration, a heterogeneous socioeconomic status population of Iranians, and multiple sensitivity analyses.

Conclusion

In conclusion, this prospective study of Iranian adults demonstrated that higher nut consumption showed inverse association with obesity but positive association with DM in overweight subjects, women, physically inactive individuals, nonsmokers, and middle-aged individuals. The inverse link between nut consumption and hypertriglyceridemia was dependent on BMI. Nut consumption had no significant associations with dyslipidemia and hypertension. On the basis of our findings, to improve public health, it is suggested that incorporation of nuts into people's usual diet may have beneficial effects for individuals with lower risk, for example, those without DM. However, well-designed controlled clinical trials and prospective cohorts are needed to confirm the findings observed in this study as well as to determine the associations of specific types of nuts with DM in this population.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.04.014.

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