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The Association between Nuts Intake and Non-Alcoholic Fatty Liver Disease (NAFLD) Risk: a Case-Control Study

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Conflict of Interest
The authors declare that they have no competing interests.

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. Nuts are nutrient- and calorie-dense foods with several health-promoting compounds. In this case-control study, we investigated the association between nut intake and NAFLD risk. Hundred ninety-six subjects with NAFLD and eight hundred three controls were recruited. The participants' dietary intakes were assessed by a valid and reliable semi-quantitative food frequency questionnaire (FFQ). Participants were categorized according to deciles of daily nuts intake. Multivariable logistic regression models were used with NAFLD as the dependent and deciles of daily nuts intake as an independent variables. Range of age was 18 to 75 years. Forty three percent of participants were male. Range of nuts intake was between 0 to 90.90 g/day. In model 3, after adjusting for potential confounding variables including, age, sex, BMI, alcohol consumption, smoking, diabetes and physical activity, the relation between daily nuts intake and risk of NAFLD was positive and significant in the deciles 9 and 10 compared to the lowest decile (odds ratio [OR], 3.22; 95% confidence interval [CI], 1.04–7.49; p = 0.039 and OR, 3.03; 95% CI, 1.03–8.90; p = 0.046, respectively). However, in the final model after additional adjusting for energy intake, no significant association was found. According to the findings, there is not any significant relationship between nuts intake and NAFLD risk; while higher intake of nuts is related to the higher risk of NAFLD mediated by energy intake.

Keywords: Non-alcoholic fatty liver disease; NAFLD; Nuts; Energy intake; Diet

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease [1,2]. NAFLD is described by excessive fat accumulation in the liver or presence of ≥ 5% of hepatic steatosis in the absence of factors for secondary liver fat deposition,such as alcohol abuse, taking drugs or parenteral nutrition [3]. NAFLD is associated with metabolic diseases such as obesity, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidaemia [4]. The global prevalence of NAFLD is estimated to be about 25% [5]. Its prevalence in the United States, Europe, and Asia is similarly reported to be between 10%

and 30% [6,7], and it is more common in men than women [8]. NAFLD is now recognized as a global health challenge. In recent years, with the increasing changes in lifestyle such as poor eating habits and sedentary lifestyle, the prevalence of NAFLD is increasing worldwide, especially in Asia [9,10]. To date, there is no confirmed medication for NAFLD, and the most important recommendations are lifestyle changes including adherence to a low calorie, healthy diet [11-14].

Nuts are nutrient-dense foods with several health-promoting compounds such as macronutrients (especially unsaturated fatty acids and high-quality protein), micronutrients (minerals, water-soluble vitamins such as folate, and fat-soluble bioactives), and fiber and on the other hand, it is also considered a calorie-dense food item [15,16]. It seems some of the beneficial effects of nut consumption on the health is due to the fat-soluble bioactive compounds (tocopherols, tocotrienols, phytosterols, sphingolipids, carotenoids and chlorophylls) and essential fatty acids such as monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) [17,18].

Some epidemiological studies have shown a direct link between continuous consumption of nuts and reduced levels of inflammation, insulin resistance, oxidative stress and metabolic syndrome, which all of the above are involved in the NAFLD pathogenesis [19-24]. In this regard, some other studies have reported that the consumption of nuts relates inversely to the incidence of cardiovascular disease (CVD) and coronary heart disease (CHD), total cancer, and all-cause mortality [25,26]. In addition, nuts have antioxidant properties,thus reducing lipid peroxidation and protecting against oxidative DNA damage [27]. According to our literature review, only 2 studies have been conducted regarding to the association between nuts intake and NAFLD risk in China. Zhang et al. [28] have shown an inverse association between them and Chen et al. [29] concluded that nut consumption was not associated with NAFLD risk in the overall sample.

Considering the results of previous studies and reports on the beneficial impacts of nuts on improving insulin resistance, glycemic control, lipid profile levels and reducing the level of inflammation, it seems that consuming nuts might be effective in reducing the incidence of NAFLD [27,30,31]. Therefore, due to the rare and inconsistent evidence in this regard, we decided to investigate the association of nuts consumption with the incidence of NAFLD using a case-control study.

MATERIALS AND METHODS

The details of procedure described in our previous studies [32,33]. Hundred ninety-six subjects diagnosed with NAFLD and 803 controls were registered from a gastrointestinal therapy clinic. Participants were obtained through convenience sampling. For cases, the inclusion criteria were NAFLD diagnosis by a relevant specialist, according to the controlled attenuated parameter (CAP) score of more than 263 in Fibroscan examination, age > 18 year-old, and alcohol use < 20 g/day in women, and < 30 g/day in men. Controls were age and sex-matched from that clinic among subjects with pancreatobiliary disorders who had been undertaken an ultrasound (US) with no evidence of NAFLD. The inclusion criteria for controls included age more than 18 years, and failure to detection of steatosis in hepatic US. The subjects on a particular diet or those who did not completed more than 10% of food frequency questionnaire (FFQ), or their calculated energy intakes were < 500 or > 4,500 kcal/day were excluded. The participation rate for cases

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and controls was 98% and 94%, respectively. The study protocol was approved by the ethics committee of Tehran University of Medical Sciences. Written informed consent was obtained from all included subjects. The authors adhered to STROBE guidelines. All experiments were performed in accordance with relevant guidelines and regulations.

Dietary intake assessment

The participants' dietary intake was assessed by a valid and reliable semi-quantitative FFQ [34], which included 168 food items with standard serving sizes, as commonly used by Iranians. Frequency of each food item was asked on daily, weekly, or monthly basis consumptions and calculated as daily intakes. The collected data were analyzed by Nutritionist IV software.

The amount of daily nuts intake was calculated using the sum of main consumed nuts including almonds, peanuts, walnuts, hazelnuts, and pistachios for each participant. Then, we categorized all participants according to the deciles of nuts intake cutoff points.

Biochemical assessments

Venous blood sample after 10–12 h fasting state was taken and centrifuged for plasma separation. Fasting plasma glucose (FPG) assessed by an enzymatic method (Inter- and intra-assay coefficient variations (CV): 2.2%, Pars Azmoon, Tehran, Iran). Plasma triglyceride (TG) measured by an enzymatic calorimetric method (Inter- and intra-assay CV: 0.6% and 1.6%, respectively). Total cholesterol (TC) measured by enzymatic method. High-density lipoprotein cholesterol (HDL-C) was measured using precipitation method (Inter- and intra-assay CV for both TC and HDL-C were 0.5% and 2%, respectively). Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula.

Assessment of other variables

Demographic data of participants were obtained using standard questionnaires. Physical activity was assessed by the metabolic equivalent task (MET) questionnaire [35,36]. Anthropometric assessments were done by the expert dietitians according to the standard methods. Body mass index (BMI) was calculated as weight in kilograms divided by height square in meters. Diabetes Diagnosis was based on the participants' recent medical records and examinations.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) (version 20.0; SPSS, Chicago, IL, USA). The normality of the variables was evaluated using histogram charts and a Kolmogorov-Smirnov analysis, which indicated that all of the variables had normal distribution. Chi-square test and independent t-test were used to check differences in the distribution of categorical variables and continuous variables, respectively. Participants were categorized according to deciles of daily nuts intake cutoff points (D1: 0 to 0.99, D2: 1 to 2.09, D3: 2.09 to 3.17, D4: 3.17 to 4.39, D5: 4.41 to 5.77, D6: 5.82 to 8.06, D7: 8.08 to 10.37, D8: 10.40 to 14.15, D9: 14.15 to 21.84 and D10: 21.89 to 90.90). First decile was considered as the reference category for all logistic regression analyses. To estimate the risk of NAFLD across deciles of daily nuts intake, multivariable logistic regression models were used with NAFLD as the dependent variable and deciles of daily nuts intake as an independent variable; the odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Logistic regression models were adjusted for age, sex, and BMI in model 1. Additionally, adjustments for alcohol consumption, smoking, diabetes and physical activity were done in model 2. In final model we adjusted energy intake. The p values < 0.05 were considered as statistically significant.

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RESULTS

Baseline subject's characteristics according to deciles of daily nuts intake are shown in **Table 1**. The range of age in this study population was 18 to 75 years. The mean ± standard deviation (SD) of BMI was 29.31 ± 6.99 kg/m^2, and 43% of participants were male. Range of nuts intake was between 0 to 90.90 g/day. Also, the mean ± SD of daily energy intake was 2,795 ± 865 kcal for all subjects.

The association between daily nuts intake and risk of NAFLD is given in **Table 2**. A positive association was seen between daily nuts intake and risk of NAFLD in the deciles 9 and 10 compared to the lowest decile, in crude model (OR, 2.54; 95% CI, 1.27–5.09; p = 0.008 and OR, 2.41; 95% CI, 1.15–4.30; p = 0.036, respectively). In model 3 after adjusting for potential confounding variables including age, sex, BMI, alcohol consumption, smoking, diabetes and physical activity, the association between daily nuts intake and NAFLD risk in the deciles 9 and 10 compared to the lowest decile remained positive and significant (OR, 3.22; 95% CI, 1.04–7.49; p = 0.039 and OR, 3.03; 95% CI, 1.03–8.90; p = 0.046, respectively). In final model, after additional adjusting for energy intake, no significant relationship was found between deciles of daily nuts intake and NAFLD risk in participants.

To explore the relationship between the amount of nuts and energy intake, Pearson correlation was applied. Daily nuts intake was positively correlated with energy intake (r = 0.55; p < 0.001).

Table 1. Baseline characteristics of subjects across deciles of daily nuts intake

Characteristics	Deciles of daily nuts intake									
	D1 (n = 100)	D2 (n = 100)	D3 (n = 100)	D4 (n = 100)	D5 (n = 99)	D6 (n = 101)	D7 (n = 100)	D8 (n = 100)	D9 (n = 100)	D10 (n = 99)
Age (yr)	46.90 ± 14.24	45.36 ± 13.94	42.96 ± 12.86	43.83 ± 15.34	43.32 ± 14.12	40.36 ± 13.57	43.23 ± 12.88	42.79 ± 14.93	42.71 ± 14.51	41.07 ± 12.73
Male (%)	34	32	41	50	46.5	45.5	45	45	48	34.4
BMI (kg/m^2)	31.15 ± 8.12	29.01 ± 5.66	29.05 ± 6.40	29.89 ± 8.46	27.95 ± 6.60	29.00 ± 6.44	29.60 ± 6.25	28.74 ± 7.13	29.91 ± 7.73	29.04 ± 6.75
PA (MET)	35.09 ± 4.44	34.11 ± 5.33	34.06 ± 6.76	33.26 ± 4.90	33.11 ± 5.57	34.12 ± 4.71	33.22 ± 4.89	32.78 ± 6.44	33.05 ± 4.34	31.87 ± 5.27
Alcohol (%)	6	5	9	5	8.1	11.9	10.1	15	17	11.1
Smoking (%)	25	32	25	35	25.3	37.6	32.3	33	42	39.4
Diabetes (%)	9	11.1	8	7	4.1	6.9	8.1	14	8	11.1
FPG (mg/dL)	96.18 ± 34.93	90.32 ± 28.15	95.05 ± 40.81	89.86 ± 20.32	88.76 ± 17.74	90.48 ± 27.30	90.67 ± 29.71	94.66 ± 39.87	91.02 ± 25.11	96.31 ± 40.70
TG (mg/dL)	135.18 ± 62.42	132.39 ± 72.50	130.02 ± 64.18	144.61 ± 46.99	135.73 ± 88.70	131.92 ± 67.92	137.89 ± 84.26	136.04 ± 66.46	147.90 ± 120.53	134.71 ± 69.27
TC (mg/dL)	189.43 ± 36.13	179.51 ± 38.42	173.34 ± 37.50	179.12 ± 43.95	180.13 ± 41.49	181.35 ± 34.60	178.12 ± 40.47	173.07 ± 36.90	183.06 ± 39.39	176.29 ± 36.15
LDL-C (mg/dL)	113.78 ± 29.06	105.10 ± 33.24	100.98 ± 30.53	103.26 ± 33.99	104.90 ± 33.19	108.51 ± 27.87	102.61 ± 31.68	97.96 ± 33.27	107.35 ± 33.22	102.41 ± 31.90
HDL-C (mg/dL)	48.61 ± 11.23	47.93 ± 10.13	46.35 ± 8.98	46.94 ± 10.34	48.09 ± 11.44	46.46 ± 12.89	47.93 ± 10.02	47.90 ± 11.10	46.13 ± 11.49	46.94 ± 10.75
Energy intake (kcal)	2,387.04 ± 929.36	2,385.60 ± 627.63	2,487.51 ± 672.80	2,651.73 ± 756.28	2,860.97 ± 904.21	2,842.84 ± 697.54	2,790.88 ± 849.87	2,886.84 ± 788.52	3,119.31 ± 885.02	3,448.49 ± 903.36
Nuts intake (g)	0.55 ± 0.28	1.49 ± 0.32	2.62 ± 0.31	3.80 ± 0.36	5.09 ± 0.39	6.96 ± 0.69	9.05 ± 0.63	12.03 ± 1.15	17.75 ± 2.12	38.09 ± 7.08

Quantitative data are presented as mean ± standard deviation and qualitative dada showed as percent.
BMI, body mass index; PA, physical activity; MET, metabolic equivalent task; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 2. The odds ratio (95% confidence interval) of non-alcoholic fatty liver risk in subjects across deciles of daily nuts intake

Characteristics	Deciles of daily nuts intake									
	D1 (n = 100)	D2 (n = 100)	D3 (n = 100)	D4 (n = 100)	D5 (n = 99)	D6 (n = 101)	D7 (n = 100)	D8 (n = 100)	D9 (n = 100)	D10 (n = 99)
Cases/control	15/85	16/84	16/84	20/80	17/82	18/83	17/83	17/83	31/69	29/70
Model 1*	1.00 (Ref)	1.07 (0.50–2.32)	1.07 (0.50–2.32)	1.69 (0.82–3.47)	1.09 (0.50–2.35)	1.22 (0.58–2.59)	1.16 (0.54–2.47)	1.16 (0.54–2.47)	**2.54 (1.27–5.09)**	**2.41 (1.15–4.30)**
Model 2†	1.00 (Ref)	1.73 (0.72–4.16)	1.66 (0.68–4.04)	2.38 (0.91–4.63)	1.97 (0.81–4.77)	1.80 (0.75–4.33)	1.55 (0.65–3.73)	1.79 (0.74–4.35)	**3.72 (1.81–6.38)**	**3.52 (1.52–6.11)**
Model 3‡	1.00 (Ref)	1.67 (0.54–5.13)	2.41 (0.71–8.07)	2.53 (0.83–7.72)	2.85 (0.91–7.68)	1.22 (0.40–3.73)	1.28 (0.41–3.91)	1.60 (0.52–4.94)	**3.22 (1.04–7.49)**	**3.03 (1.03–8.90)**
Model 4$^{\delta}$	1.00 (Ref)	1.58 (0.51–4.94)	2.28 (0.66–7.78)	2.78 (0.89–8.69)	2.95 (0.92–8.10)	1.31 (0.42–4.13)	1.49 (0.47–4.69)	1.75 (0.55–5.54)	2.91 (0.98–6.83)	2.52 (0.94–6.03)

Bold-faced values presented as significant association.
*Crude model; †Adjusted for age, sex, and BMI; ‡Additionally adjusted for alcohol consumption, smoking, diabetes and physical activity; $^{\delta}$Additionally adjusted for energy intake.

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DISCUSSION

The present study investigated the association of daily nuts intake with NAFLD risk in adult population. According to the findings, there is not any significant relationship between nuts consumption and NAFLD risk; while higher intake of nuts is related to the higher risk of NAFLD mediated by calorie intake. In addition, this association seemed to be independent of other predictors including age, sex, BMI, alcohol consumption, smoking, diabetes and physical activity. The association of nuts intake with NAFLD risk was disappeared after controlling for daily energy intake.

Some previous epidemiological and interventional studies showed that diets high in nuts are associated with a lower risk of developing NAFLD [28,37]. For example, Katsagoni et al. showed that consumption of nuts are associated with a lower NAFLD likelihood. The association disappeared after adjusting for age, sex, waist circumference, homeostatic model assessment for insulin resistance, adiponectin, and tumor necrosis factor-α [38]. However, our findings are consistent with the results of a study by Chen et al. [29], which failed to find a significant inverse relationship between high nut consumption and NAFLD risk among the overall samples. Interestingly, the current study indicated that compared to the first decile, higher consumption of nuts (in the deciles 9 and 10) was significantly associated with a higher risk of NAFLD. The mean ± SD values of nuts consumed in the ninth and tenth deciles in this study were 17.75 ± 2.12 g/day and 38.09 ± 7.08 g/day, respectively. However, nuts consumption levels appeared to be lower in the other two previous studies. The median intake of the highest frequency of nut consumption class in the Zhang et al. study was 21.88 g/day [28]. Also, in Chen et al.' study [29] the median of nut intake was 3.15 g/day in cases and 2.86 g/day in control group. Though most case-control studies showed protective effects on nut consumption on risk of NAFLD, high intake of nuts should be able to increase the prevalence of NFLD in other ways.

We assume several reasons for the null relation between high nut consumption and the prevalence of NAFLD in our study. Firstly, most of previous studies did not consider manufacturing methods (e.g., raw, roasted or boiled) or extra ingredients (e.g., raw or salted). It has been mentioned that preparation methods can affect the nutrient composition and ingredients in the nuts [39,40]. The common types of nuts, typically consumed in Iran, are salted and roasted [41]. In Iran, nuts are usually consumed as salted products, except for walnuts. Low moisture content of salted and roasted pistachio which is in the range of single layer water prevents mold and pest growth [42]. A study by Kouchakzadeh and Tavakoli [43] reported that more than 90% of the pistachios sold in Iran are roasted and salted. High intake of salted nuts contain significant amounts of sodium. Large-scale evidence from epidemiological studies showed that high sodium intake has an adverse effect on pathogenesis of chronic metabolic disorders such as NAFLD [44-47]. However, the higher prevalence of NAFLD associated with a greater sodium intake is not completely understood [47]. Further studies are needed to reveal the potential association of salted vs. raw nuts on NAFLD and their possible mechanisms.

Secondly, some studies reported the possibility of contamination of nut products by a form of mycotoxins, called aflatoxin [48]. According to the Food and Agriculture Organization, globally, up to 25% of the foodstuffs are contaminated with mycotoxins [49]. It is estimated that four billion people are at the risk of exposure to aflatoxins globally [50]. The main source of risk of aflatoxins for human and also animals is due to chronic dietary exposure [51]. In

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Iran, among the nut products, pistachios are extremely contaminated with aflatoxins [52]. There are some evidences that chronic aflatoxin intoxication induces hepatic injury [53]. Animal and human studies showed that acute liver damage due to aflatoxin causes a rise in circulating level of enzymes including aspartate aminotransferase, lactate dehydrogenase, glutamate dehydrogenase, gamma-glutamyltransferase and alkaline phosphatase and bilirubin that reflect liver damage [54,55]. Therefore, the increased risk of NAFLD may be due to aflatoxin contamination of consumed nuts. Further studies are needed to draw deep conclusions from the association of aflatoxin contaminated nuts and NAFLD. Moreover, our results showed that the amount of nuts consumption and subsequent received energy intake are the most important factors in relation to the consumption of nuts and the incidence of NAFLD so that adjusting for energy intake in the 4th model, diminished the significant associations. This might be explained by the high-density energy content of nuts. In line with our study, Wehmeyer et al. [56] indicated that NAFLD risk is relation to the excessive energy intake rather than a specific dietary pattern and concluded that NAFLD patients have a significantly higher daily average energy intake while the general dietary components lead to only moderate effects. Energy intake has been known as a key regulator of liver steatosis through changes in body weight and/or substrate availability [57]. Generally, hypercaloric diets, especially rich in trans/saturated fat and cholesterol, high intake of red and processed meat, and fructose-sweetened beverages seem to raise NAFLD risk, whereas decrease in energy intake, eating low glycemic index foods, high intake of monounsaturated fatty acids, omega-3 fatty acids, fibers, and fish and poultry have protective effects [58].

The strengths of our study include relatively large sample size, sampling of cases and controls from the same clinics, which matches the socio-economic status of them, and Fibroscan examination for NAFLD patients detection that is the best clinical tool after liver biopsy (the gold standard in diagnosing NAFLD) [59]. However, there are some limitations in this study that could be addressed in future researches. First, we did not consider any subgroup for manufacturing processing nuts (e.g., raw, salted or roasted). Second, although FFQ is widely used in the nutrition/dietetics field as a valid and reliable method [60], it has some limitations. Because of a difficult cognitive task for the respondents, it does not quantify foods very precisely, and aggregate foods in groups and closed lists limiting the usual diversity of dietary intakes. Moreover, FFQ does not provide the full picture of dietary intake, and recall bias, and measurement error are inevitable errors [61].

CONCLUSION

In conclusion, our findings suggested that nuts intake was not relation to the risk of NAFLD. However, nut consumption in the higher deciles (i.e., decile 9 and 10) was related to a higher NAFLD likelihood. The association was independent of lifestyle and dietary factors including, age, sex, BMI, alcohol consumption, smoking, diabetes and physical activity. Further studies are warranted for confirmation of our results.

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