Association of the Dietary Patterns with the Risk of Non-alcoholic Fatty Liver Disease among Iranian Population: A case-control study

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Abstract
Background: Diet-based recommendations can be developed for preventing and treating non-alcoholic fatty liver disease (NAFLD) after investigating the effects of whole diets on NAFLD. The aim of this study was to identify major dietary patterns and their association with the risk of NAFLD.

Methods: A total of 244 individuals (122 NAFLD patients and 122 controls) participated in this case-control study. The NAFLD patients were diagnosed by a gastroenterologist. The participants' dietary intake data were collected using a 147-item semi-quantitative food frequency questionnaire and major dietary patterns were identified by principal component analysis. Adherence to dietary patterns was divided into tertiles and its association with odds of NAFLD was investigated by multivariate logistic regression. Results: The results showed four major dietary patterns, among which adherence to the "ordinary pattern" was positively associated with NAFLD risk. After adjusting for all confounding factors, individuals in the medium and highest tertiles of "ordinary pattern" exhibited a significantly elevated risk of NAFLD compared to the lowest tertile (medium vs. lowest tertile: OR= 1.71, 95%CI= 0.71-4.11; highest vs. lowest tertile: OR= 3.74, 95%CI= 1.23-11.42, P trend <0.001). As well as, individuals in the second and third tertiles of the "traditional pattern" were associated with the risk of NAFLD compared to the lowest tertile (medium vs. lowest tertile OR= 2.37, 95%CI= 1.02-5.27; highest vs. lowest tertile OR=3.58, 95% CI= 1.48-8.68, P trend <0.001). The highest tertile of "vegetable and dairy pattern" compared to the lowest tertile was inversely associated with NAFLD risk (OR= 0.23, 95%CI= 0.09-0.58, P trend =0.02). No significant association was found between "fast food type pattern" and the risk of NAFLD. Conclusion: A significant association was observed between different dietary patterns and the risk of NAFLD. These results can potentially serve as a dietary strategy for preventing NAFLD in individuals who are at a high risk for progression of NAFLD.

Background
Non-alcoholic fatty liver disease (NAFLD), the most common worldwide cause of liver disease (2), is identified by an excessive flux of free fatty acids (FFA) and accumulation of triglycerides (TG) in the liver (1). The prevalence of NAFLD is approximately 25% and 33.9% in the world and Iran, respectively (3, 4). The NAFLD increases inflammation and mitochondrial dysfunction in the liver that
result in hepatic steatosis (5). It may develop into steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma in some individuals (6). Moreover, NAFLD patients have an increased risk of cardiovascular diseases (7). The common causes of triglyceride accumulation in hepatocytes are insulin resistance, obesity, and, dietary factors among individuals without excessive alcohol consumption, use of steatogenic drugs, or genetic diseases (8, 9). Indeed, no pharmacological therapy has been confirmed for NAFLD, but lifestyle modifications such as weight loss, dietary change, and increased physical activity are among the first-line treatment for patients with NAFLD (10, 11). Nutrition not only is a potential factor in pathogenesis of NAFLD, but also plays an important role in its treatment (12). According to the literature, excessive energy intake or inappropriate diets, such as high carbohydrate or high-fat diet, were associated with the onset and progression of this disease (13, 14). However, decreased energy intake or adherence to high protein, high monounsaturated, and n-3 polyunsaturated fatty acids (PUFA), and antioxidant intake were reported to decrease the hepatic steatosis (15-17).

Several epidemiological studies investigated the relationship of single nutrients or foods with the risk of NAFLD, but few studies examined the effect of a whole diet on the disease and the results are controversial (5). Some studies reported a negative association between NAFLD development and diets full of plant foods and fish with less red meat. These food groups are rich in antioxidants, vitamins, minerals, n-3 PUFA, and dietary fibers. However, dietary patterns rich in sugar and fat such as red meat, fast food, sweets, refined grains, and soft drinks had a positive association with the risk of NAFLD (18-20).

Considering lack of the related information in Iran, NAFLD patients' dietary patterns were investigated in Ahvaz City, located in the south-west of Iran to identify the major dietary patterns leading to NAFLD.

Method

Study participants

This case-control study was conducted from November 2018 to May 2019 among patients who referred to a gastroenterology outpatient clinic for health check. As a result, 122 NAFLD patients and
122 non-NAFLD participants aged 19-70 years were recruited. Exclusion criteria were physical or mental disability, chronic diseases such as diabetes mellitus and liver neoplasm, other liver diseases like viral hepatitis and alcoholic fatty liver, immunodeficiency virus, hepatotoxic or contraceptive drugs use, alcohol consumption of more than 20 gr for men and 10 gr for women per day, and any type of malignancy (21). All participants were informed about the study goals and were asked to sign a consent form to enter the study. Furthermore, the study protocol was confirmed by the Ethics Committee in Jundishapur University of Ahvaz based on the ethical guidelines of the 1975 declaration of Helsinki.

The NAFLD was diagnosed by a gastroenterologist considering the elevated alanine aminotransferase (normal range: 29 to 33 IU/l for males and 19 to 25 IU/l for females), elevated aspartate aminotransferase (normal range: 10-40 IU/l for males and 9-32 IU/l for females), and confirmed liver steatosis in the ultrasound examination (22). The control group members were matched with the patients in terms of their age (in five-year categories), gender (male/female), and body mass index (BMI). The participants were classified as normal-weight, over-weight, and obese according to their BMI of 18 - 24.9, 25 - 29.9, and above 30 kg/m², respectively (23). In addition, all patients underwent an ultrasound examination and no evidence of hepatic steatosis was observed among the control group.

**Measurement of anthropometrics and other variables**

The participants' demographic information including age, gender, ethnicity, marital status, educational level, occupational status, and smoking was collected using a socio-demographic questionnaire. All anthropometric measurements were performed by the same interviewer. The participants' body weight was measured and recorded to the nearest 0.5 kg in light clothes and without shoes by a digital scale. Height was also measured to the nearest 0.1 cm using a tape meter while the participant was standing in a straight position leaning against the wall with no shoes (24). The participants' BMI was also computed by dividing weight in kg by the square of height in meter. The waist circumference (WC) was measured to the nearest 0.1 cm using a tape meter at the midpoint between the lowest rib and the iliac crest. In addition, the hip circumference was measured
to the nearest 0.1 cm by a tape meter at the largest circumference of the buttocks. The waist/height ratio (WHtR) and the waist/hip ratio (WHR) were also calculated (25, 26). Later, blood pressure was measured using a standardized sphygmomanometer. Hypertension was defined as systolic pressure > 140 mmHg and diastolic pressure > 90mmHg or intake of antihypertensive drugs. Finally, the participants' physical activity was assessed using the metabolic equivalent task (MET) questionnaire (27).

**Dietary assessment**

A valid and reliable semi-quantitative 147-item food frequency questionnaire (FFQ) was administered to evaluate the individuals' usual dietary intake using the standard serving size commonly consumed by Iranians. Participants were required to report their consumption frequency of an intended serving of each food item during the last year on a daily, weekly, monthly, or annually basis. Later, the selected frequency category for each food item was converted into a daily intake. Household measures were applied to convert portion size of the consumed foods to grams (28). Food items were classified into 19 food groups based on their similarity in nutritional composition and previous studies. The major dietary patterns were determined by principal component analysis.

**Statistical analysis**

Data were analyzed using SPSS (version 25; SPSS Inc., Chicago, IL, USA) by running the student's t-test for normally distributed variables, Mann Whitney test for non-normally distributed variables, and chi-score tests for categorical variables. Quantitative and qualitative variables were expressed as mean ± SD and percentage, respectively. The dietary patterns were identified by principal component analysis. Sufficiency of the sampling and data was approved by Kaiser-Meyer-Olkin values > 0.6 and P £0.05 for Bartlett's test sphericity test. The number of factors (dietary patterns was determined considering the criteria of eigenvalue> 1.3 and analysis of the scree plot. For simplification of the data interpretation, orthogonal rotation (varimax) was applied. Food groups with factor loading of ±0.3 were included in the analysis (29). The patterns were named based on the highest factor loadings on each pattern. Subsequently, dietary patterns were divided into tertiles; where, the first tertile indicated low intake and the third one showed high adherence to the dietary pattern. The
association between tertiles of 4 dietary patterns and risk of NAFLD was calculated by odds ratio (OR) and the 95% confidence intervals (CIs) using multivariable logistic regression.

**Result**

Table 1 shows the participants' demographic characteristics. Dietary information of one of the NAFLD group members was excluded because this patient's energy intake was more than 3 standard deviations of the mean log-transformed. Finally, a total of 243 participants were included in the analysis. Patients have significantly higher WC (p=0.001), WHtR (p<0.001), WHR (p<0.001), and energy intake (p<0.001). Moreover, patients were significantly less educated and smoked more frequently than the controls (p<0.05).

Dietary information of participants was analyzed by principal component analysis and four dietary patterns were distinguished based on the eigenvalue >1.3 and scree plot analysis. The first pattern was named "ordinary" pattern, identified by high intakes of sweets, oils, fruits, white meats, refined grains, tea and coffee, salt, biscuits, snacks, red, and organ meats. The second pattern was named the "fast-food type" identified by a high intake of sauces, pickles, fast foods, soft drinks, snacks, and biscuits. The third dietary pattern was labeled as "traditional pattern" characterized by high amounts of red and organ meats, dairy products, condiments, salt, tea and coffee, and low intake of fruits. The fourth pattern was named "vegetable and dairy" characterized by high amounts of vegetables, whole grains, legume and nuts, and dairy products. The list of food groups and their factor loadings are included in Table 2. These dietary patterns explained 16.35%, 12.57%, 8.73%, and 8.67% of the total variance, respectively.

Table 3 indicates the association between tertiles of dietary patterns and the risk of NAFLD. In this regard, three models of logistic regression were assessed; model 1 was crude, model 2 was adjusted for age, gender, energy intake, and BMI, and model 3 was further adjusted for smoking, educational status, and physical activity. After adjusting for all confounding factors (model 3), individuals in the medium and highest tertiles of "ordinary pattern" exhibited a significantly elevated risk of NAFLD compared to the lowest tertile (medium vs. lowest tertile: OR= 1.71, 95%CI= 0.71-4.11; highest vs. lowest tertile: OR= 3.74, 95%CI= 1.23-11.42), and there was a significant dose-response relationship...
(P\text{\textsubscript{trend}}<0.001). As well as, Individuals in the second and third tertiles of the "traditional pattern" were associated with the risk of NAFLD compared to the lowest tertile (medium vs. lowest tertile OR= 2.37, 95\%CI= 1.02-5.27; highest vs. lowest tertile OR=3.58, 95\% CI= 1.48-8.68), and there was a significant dose-response relationship (P\text{\textsubscript{trend}}<0.001). The highest tertile of "vegetable and dairy pattern" compared to the lowest tertile was inversely associated with NAFLD risk (OR= 0.23, 95\%CI= 0.09-0.58), and the test for trend was significant (P\text{\textsubscript{trend}}=0.02). No significant association was found between "fast food type pattern" and the risk of NAFLD.

Table 1. Characteristics of participants

(1) P-value <0.05 was considered significant.
(2) P-value based on the Mann-Whitney test.
(3) P-value based on the chi-squared test.
(4) P-value based on the t-test.
NAFLD: nonalcoholic fatty liver disease; BMI: body mass index; WHtR: waist to height ratio; WHR: waist to hip ratio; MET: the metabolic equivalent of tasks.

Table 2. Rotated factor loading matrix for the four dietary patterns.
| Variables                        | NAFLD (n=121)     | Control (n=122)  |
|---------------------------------|-------------------|------------------|
| Age (year), Mean ± SD           | 42.95 ± 11.46     | 42.51 ± 11.52    |
| Sex                             |                   |                  |
| Male                            | 57 (47.1%)        | 58 (47.5%)       |
| Female                          | 64 (52.9%)        | 64 (52.5%)       |
| Weight, Kg                      | 81.78 ± 13.12     | 80.76 ± 13.28    |
| Height, cm                      | 165.53 ± 10.16    | 165.97 ± 9.19    |
| BMI, kg/m²                      | 30.53 ± 5.04      | 29.32 ± 4.49     |
| Waist circumference, cm         | 102.86 ± 10.78    | 98.08 ± 10.55    |
| Hip circumference, cm           | 105.91 ± 7.59     | 105.35 ± 7.41    |
| WHtR                            | 0.62 ± 0.07       | 0.59 ± 0.07      |
| WHR                             | 0.95 ± 0.07       | 0.92 ± 0.08      |
| Systolic blood pressure, mmHg   | 124.09 ± 12.29    | 121.02 ± 14.45   |
| Diastolic blood pressure, mmHg  | 81.35 ± 6.96      | 80.14 ± 6.44     |
| Total energy intake, kcal       | 4122.76±1624.85   | 3178.60±936.18   |
| Met (Hour/day)                  | 34.11 ± 5.87      | 35.94 ± 7.88     |
| Marital status                  |                   |                  |
| Married                         | 105 (86.8%)       | 102 (83.6%)      |
| Bachelor                        | 16 (13.2%)        | 20 (16.4%)       |
| Educational status              |                   |                  |
| Illiterate                      | 14 (11.6%)        | 2 (1.6%)         |
| Elementary                      | 36 (29.8%)        | 30 (24.6%)       |
| Diploma                         | 34 (28.1%)        | 31 (25.4%)       |
| College                         | 37 (30.6%)        | 59 (48.4%)       |
| Smoke                           |                   |                  |
| Yes                             | 12 (9.9%)         | 4 (3.3%)         |
| No                              | 109 (90.1%)       | 118 (96.7%)      |
| Food groups         | Ordinary | Fast food type | Traditional | Vegetable Dairy |
|--------------------|----------|----------------|-------------|-----------------|
| Sweets             | 0.721    | -              | -           | -               |
| Oils               | 0.654    | -              | -           | -               |
| Fruits             | 0.631    | -              | -0.330      | -               |
| White meats        | 0.592    | -              | -           | -               |
| Refined Grains     | 0.573    | -              | -           | -               |
| Tea and Coffee     | 0.477    | -              | 0.329       | -               |
| salt               | 0.466    | -              | 0.316       | -               |
| Biscuits           | 0.398    | 0.371          | -           | -               |
| Sauces             | -        | 0.764          | -           | -               |
| Pickles            | -        | 0.618          | -           | -               |
| Fast foods         | -        | 0.603          | -           | -               |
| Soft drinks        | -        | 0.571          | -           | -               |
| Snacks             | 0.390    | 0.556          | -           | -               |
| Condiments         | -        | -              | 0.797       | -               |
| Red & organ Meats  | 0.365    | -              | 0.490       | -               |
| Vegetables         | -        | -              | -           | 0.66€           |
| Whole grains       | -        | -              | -           | 0.60€           |
| Legume and Nuts    | -        | -              | -           | 0.57€           |
| Dairy products     | -        | -              | 0.340       | 0.47€           |
| Total variance explained | 16.35     | 12.57          | 8.73        | 8.67            |

Values less than |0.3| were excluded. Bartlett’s test of sphericity: 964.12, significance <0.0001; Kaiser–Meyer–Olkin test = 0.74.

Table 3. Odds ratio and 95% confidence intervals for the association between dietary patterns and NAFLD.
|                  | Q1     | Q2     | Q3     | P\(_{\text{trend}}\) |
|------------------|--------|--------|--------|-----------------------|
| **Ordinary pattern** |        |        |        |                       |
| Model 1          | 1      | 2.95 (1.45-6.03) | 11.86 (5.36-26.21) | <0.001                |
| Model 2          | 1      | 2.14 (0.97-4.75) | 4.55 (1.66-12.46)  | <0.001                |
| Model 3          | 1      | 1.71 (0.71-4.11) | 3.74 (1.23-11.42)  | <0.001                |
| **Fast food type pattern** |        |        |        |                       |
| Model 1          | 1      | 0.80 (0.39-1.62) | 1.01 (0.50-2.05)   | 0.19                  |
| Model 2          | 1      | 0.82 (0.38-1.81) | 0.76 (0.30-1.93)   | 0.24                  |
| Model 3          | 1      | 0.91 (0.39-2.14) | 0.72 (0.26-1.96)   | 0.19                  |
| **Traditional pattern** |        |        |        |                       |
| Model 1          | 1      | 2.12 (1.04-4.33) | 3.03 (1.41-6.53)   | <0.001                |
| Model 2          | 1      | 2.57 (1.19-5.54) | 3.78 (1.66-8.65)   | <0.001                |
| Model 3          | 1      | 2.37 (1.02-5.53) | 3.58 (1.48-8.68)   | <0.001                |
| **Vegetable and Dairy pattern** |        |        |        |                       |
| Model 1          | 1      | 0.79 (0.39-1.59) | 0.41 (0.20-0.86)   | 0.02                  |
| Model 2          | 1      | 0.59 (0.28-1.25) | 0.21 (0.09-0.49)   | 0.005                 |
| Model 3          | 1      | 0.60 (0.26-1.37) | 0.23 (0.09-0.58)   | 0.02                  |

Model 1: crude  
Model 2: adjusted for age, sex, BMI and energy intake  
Model 3: further adjusted for smoking, educational status, and physical activity.  

**Discussion**

In this case-control study, four major dietary patterns were identified: "ordinary pattern", "fast food type pattern", "traditional pattern", and "vegetable and dairy pattern". The findings showed that "ordinary" and "traditional" patterns increased the risk of NAFLD significantly, while the "vegetable
and dairy pattern" had an inverse association with NAFLD in our study population. However, no significant association was observed between the "fast food type pattern" and the risk of NAFLD. To the best of our knowledge, this is the first study on the association between dietary patterns and NAFLD in Ahvaz City.

The "ordinary pattern" was characterized by high intakes of "sweets, oils, fruits, white meats, refined grains, tea and coffee, salt, Biscuits, snacks, as well as red and organ meats". Most food groups in this dietary pattern contain high amounts of carbohydrates especially refined sugars, which enhance de novo fatty-acid synthesis in the liver.

The "fast food type pattern" was characterized by high consumption of "fast foods, pickles, sauces, soft drinks, snacks, and biscuits". Although most related studies reported a positive relationship between fast food patterns and risk of NAFLD, we found no association between this dietary pattern and NAFLD.

The "traditional pattern", characterized by high intake of condiments, red and organ meats, dairy products, salt, as well as tea and coffee, had a direct association with NAFLD.

The "vegetable and dairy pattern" was characterized by high intakes of "vegetables, whole grains, legume and nuts, and dairy products. We found that high adherence to this pattern reduced the risk of NAFLD, which is probably due to the high amounts of vitamins, minerals, and fiber.

The "ordinary pattern" adherence was associated with high intakes of energy-dense foods with relatively high amounts of fat, animal protein, and refined sugars. Some foods in this dietary pattern, including refined grains, white bread, biscuits, and sweets, led to a rapid increase in postprandial plasma glucose, insulin concentration, and diabetes (30). Such high glycemic index foods increase hepatic steatosis, especially in insulin-resistant participants (31). Jia et al. also reported that a high carbohydrate/sugar pattern was associated with NAFLD in women (18). Our results are in line with the finding of another study in Japan over a population with high intake of carbohydrate, especially sweets. Their results showed a higher risk of NAFLD (32). However, Chung et al. did not find any relationship between high adherence to the carbohydrate diet and the risk of NAFLD (33). Our findings confirm results of the studies suggesting that a high fruit diet is associated with NAFLD (34,
35). Fruits are rich in simple carbohydrates particularly fructose. Fructose has a role in the pathophysiology of NAFLD and high intake of fructose leads to de novo lipogenesis, lipid accumulation, and steatosis in the liver. Moreover, chronic consumption of fructose enhances the hepatic inflammation and oxidative stress, which are responsible for progression of the hepatic disease (36).

Some previous studies suggested that a "fast food pattern" or a "western diet" was associated with NAFLD (5, 19). A western diet, characterized by high intakes of fried foods, red and processed meat, refined grains, snacks, sauces, and soft drinks was prospectively associated with NAFLD risk in adolescents (19). Kalafati et al. also reported similar results about fast food dietary pattern and NAFLD risk (5). However, we found no significant association between the fast-food pattern and risk of NAFLD. This finding can be due to the differences in dietary patterns ethnicities, cultural groups, and gender. Moreover, dietary patterns may vary over time because of personal preferences and availability of foods (9).

Although meats, such as red meat and visceral meat, are highly loaded with "ordinary pattern" and "traditional pattern", very few studies have investigated the association between high protein dietary patterns and NAFLD. According to Zelber Sagi et al., all types of meats were significantly associated with an increased risk of NAFLD (37). This association can be justified by mentioning that high protein intake is associated with insulin resistance and glucose intolerance, which might even increase the incidence of type-2 diabetes (38, 39). Another possible explanation is that a higher intake of iron and in particular, heme-iron may play a role in the pathogenesis of NAFLD by increasing oxidative stress (40). The "traditional " and "ordinary" patterns were high in salt, but findings of the studies are controversial about the role of sodium in NAFLD. A study among a Korean population reported that high salt dietary pattern was associated with increased risk of NAFLD, while another study in the Chinese population detected no significant association between a high salt dietary pattern and NAFLD (20, 41). Consequently, more studies are required to clarify this association.

Yang et al. reported an inverse association between a "grain and vegetable pattern" and NAFLD and mentioned that this association was independent from the confounding factors such as age, gender,
BMI, and physical activity (20). Another study in a Lebanese population also showed that a "traditional Lebanese" diet consisting of vegetables and legumes had a negative association with the odds of NAFLD (34). These results confirmed our findings by maintaining that a dietary pattern rich in vegetables, legume, and nuts could reduce the risk of NAFLD. This protective effect against NAFLD might be because of the high fiber content in this pattern.

This study has some strengths. This is the first study over the association between major dietary patterns and the risk of NAFLD in Ahvaz City, Iran. Potential confounding factors were identified and controlled in the analysis. Moreover, we used a semi-quantitative FFQ designed for the Iranian population, which resulted in better representation of the participants' dietary habits.

Some limitations also exist that should be considered. First, regarding the case-control design of this study, it could not confirm a causal relationship between dietary patterns and NAFLD. Second, application of a FFQ for data collection may overestimate the participants' energy intake, which is a great risk. Third, recall bias exists because of the self-reporting nature of the questionnaire.

Conclusion
The results display that high adherence to the "ordinary" and "traditional" dietary patterns increases the risk of NAFLD, while adherence to a "vegetable" pattern has a negative association with NAFLD in Ahvaz population. The findings can be served as a dietary strategy for preventing and treating NAFLD. Nevertheless, more studies are required to confirm our results.

List Of Abbreviations
NAFLD: nonalcoholic fatty liver disease; FFA: free fatty acid; TG: triglyceride; PUFA: polyunsaturated fatty acid; BMI: body mass index; WC: waist circumference WHtR: waist to height ratio; WHR: waist to hip ratio; MET: the metabolic equivalent of tasks; FFQ: food frequency questionnaire; OR: Odds ratio; CI: confidence interval.

Declarations
**Ethics approval and consent to participate:** All study participants were informed about the study goals and procedure. They were also required to sign informed consent forms to enter the study. The study protocol was confirmed by the Ethics Committee of Jundishapur University of Ahvaz based on the ethical guidelines of 1975 declaration of Helsinki (IR.AJUMS.REC.1397.939).
Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors’ contributions: AM designed the original intervention. ND collected the data. All authors contributed in the analyses design. AM and ND analyzed and interpreted the data and were the major contributors in writing the manuscript. All authors reviewed and confirmed the final manuscript.

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