Dietary patterns are associated with the risk of non-alcoholic fatty liver disease among Iranian population: A case-control study

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Abstract
Background Investigating effects of whole diets on non-alcoholic fatty liver disease can contribute to development of diet-based recommendations for prevention and treatment of this disease. The aim of the present study is the identification of major dietary patterns and their association with the risk of non-alcoholic fatty liver disease (NAFLD).

Methods A total of 244 individuals (122 NAFLD patients and 122 controls) participated in this case-control study. NAFLD patients were diagnosed by a gastroenterologist. Dietary intake data of participants were collected using a 147 item semi-quantitive food frequency questionnaire and major dietary patterns were identified by principal component analysis. The consumption of dietary patterns was divided into tertiles. The association of dietary patterns with the odds of NAFLD was investigated by multivariate logistic regression.

Results four major dietary patterns were recognized. The "ordinary pattern" adherence was positively associated with NAFLD risk. Although, results were statistically significant only for the third tertile versus the first tertile after adjusting for confounding factors (OR: 3.74, P-trend <0.001). Likewise, Adherence to the "traditional pattern" was associated with a higher risk for NAFLD. On the contrary, individuals in the third tertile of the "vegetable and dairy pattern" had a significantly decreased risk for NAFLD in comparison to the first tertile. Nevertheless, no significant association between "fast food type pattern" and the risk of NAFLD was found.

Conclusion there is a significant association between different dietary patterns and the risk of NAFLD. These results can potentially serve as a dietary strategy for the prevention of NAFLD in individuals who are at high risk for the progression of NAFLD.

Background
Non-alcoholic fatty liver disease (NAFLD) is identified by an excessive flux of free fatty acids (FFA) and triglycerides (TG) accumulation in the liver (1) and it is the most common cause of liver disease in the world (2). The prevalence of NAFLD is approximately 25% worldwide and 33.9% in the Iran population (3, 4). The consequence of NAFLD is increased inflammation and mitochondrial dysfunction in the liver that results 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 disease (7). The common causes of triglyceride accumulation in hepatocytes are insulin resistance, obesity and, dietary factors among individuals without excessive alcohol consumption, the use of steatogenic drugs or genetic diseases (8, 9). Indeed, no pharmacological therapy is confirmed for NAFLD yet and lifestyle modifications such as weight loss, dietary change, and increase in physical activity are the first-line treatment for patients with NAFLD (10, 11). Nutrition is a potential factor in the pathogenesis of NAFLD but also it plays an important role in its treatment (12). On the basis of previous studies, excessive energy intake or inappropriate diets, such as high carbohydrate or high-fat diet, have been associated with the onset and progression of this disease (13, 14). On the other hand, decrease energy intake, high protein, high monounsaturated and n-3 polyunsaturated fatty acids (PUFA) and antioxidant intake are thought to decrease hepatic steatosis (15–17).

Several epidemiological studies have investigated the relationship between single nutrients or foods and the risk of NAFLD, but studies that examine the role of the whole diet on the disease are scarce and the results of these studies are not similar (5). Some studies reported a negative association between diets full of plant foods, fish and less red meat and progression of the NAFLD. These food groups are rich in antioxidants vitamins and minerals, n-3 PUFA and dietary fibers while dietary patterns characterized by increased intake of red meat, fast food, sweets, refined grains, and soft drinks that rich in sugar and fat had a positive association with the risk of NAFLD (18–20). Considering the lack of available data about dietary patterns of NAFLD patients in Ahvaz city located in the south-west of Iran, this study is performed to identify the major dietary patterns that lead to NAFLD in the Ahvaz population.

Method
Study participants
This case-control designed study was conducted between November 2018 and May 2019 among patients who come to a gastroenterology outpatient clinic for a health check. 122 NAFLD patients and 122 non-NAFLD subjects aged 19–70 were recruited. Exclusion criteria included: physical or mental
disability, chronic disease such as diabetes mellitus and liver neoplasm, other liver disease like viral hepatitis and alcoholic fatty liver, immunodeficiency virus (HIV), hepatotoxic or contraceptive drugs use, alcohol consumption more than 20 gr per day for men and 10 gr per day for women and any type of malignancy (21). All study subjects were informed about the aim of this study and signed a consent form; the study protocol was confirmed by the ethics committee based on the ethical guidelines of the 1975 declaration of Helsinki at the Jundishapur University of Ahvaz.

A gastroenterologist diagnosed the patients with NAFLD and then referred them to the researchers. NAFLD was diagnosed by: 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).

Controls were age- (in the five-year categories), sex- (male/female), and BMI- (classified as Normal weight (BMI between 18 and 24.9 kg/m$^2$), overweight (BMI between 25 and 29.9) and obese (BMI above 30 kg/m2)) (23) matched with patients who had been performed an ultrasound examination and did not detect evidence of hepatic steatosis.

**Measurement of anthropometric and other variables**

The information regarding individual characteristics including age, sex, ethnicity, marital status, educational level, occupational status, and smoking were collected using a socio-demographic questionnaire. All anthropometric measurements were performed by the same interviewer. Body weight was measured with light clothes and without shoes by a digital scale and was recorded to the nearest 0.5 kg. Height was measured using the tape meter while a subject was standing in a normal position and don’t wearing shoes and was recorded to the nearest 0.1 cm (24). Body mass index, BMI, was computed as weight in kg divided by the square of height in meter. The waist circumference (WC) was measured nearest to 0.1 cm using a tape meter at the midpoint between the lowest rib and the iliac crest and the hip circumference was measured nearest to 0.1 cm by a tape meter at the greatest part of the buttock. the waist/height ratio (WHtR) and the waist/hip ratio (WHR) were also calculated (25, 26). Blood pressure was measured using a standardized sphygmomanometer. Hypertension was defined as systolic pressure > 140 mmHg and diastolic pressure > 90 mmHg or the use of
antihypertensive drugs. Physical activity was also assessed by using the metabolic equivalent task (MET) questionnaire (27).

**Dietary assessment**

Usual dietary intake of subjects was evaluated through a valid and reliable semi-quantitative food frequency questionnaire (FFQ), which consists of a list of 147 food items with standard serving size commonly consumed by Iranians. Participants were asked to report their frequency of consumption of an intended serving of each food item during the last year on a daily, weekly, monthly or annually basis. The selected frequency category for each food item converted into a daily intake. Household measures were used to converting the portion size of consumed foods to grams (28). Food items were classified into 19 food groups based on nutrient composition similarity and previous studies. The determination of major dietary patterns was undertaken by principal component analysis (PCA).

**Statistical analysis**

Data were analyzed using SPSS statistical software package (version 25; SPSS Inc., Chicago, IL, USA). Baseline characteristics between case and control subjects were compared using student's t-test (for normally distributed variables) and Mann Whitney test (for non-normally distributed variables) for continuous 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. the Kaiser-Meyer-Olkin (KMO) index and Bartlett’s sphericity test was used to check the sufficiency of the data. Sampling adequacy of components was approved by KMO values > 0.6 and P ≤0.05 for Bartlett’s test sphericity test. The number of factors (dietary patterns) was maintained respected to criteria of eigenvalue > 1.3 and analysis of scree plot. For the simplification of data interpretation, orthogonal rotation (varimax) was applied. Food groups with factor loading ≥ ±0.3 were included in the analysis (29). the name of patterns was chosen based on factor loadings that presented most highly to each pattern. Subsequently, dietary patterns divided into tertiles, where tertile 1 indicated low intake and tertile 3 indicated 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 illustrates the general characteristics of the participants. Dietary information of one of NAFLD patients was excluded because its energy intake was above 3 standard deviations of the mean log-transformed. A total of 243 subjects were included in the analysis. Patients have significantly higher waist circumference (p = 0.001), WHtR (p < 0.001), WHR (p < 0.001), and energy intake (p < 0.001). Moreover, patients were significantly less educated and smoke more than controls (p < 0.05).

Dietary information of participants was analyzed by principal component analysis and four dietary patterns were distinguished based on eigenvalue > 1.3 and analysis of scree plot. The first pattern was named "ordinary" pattern and 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" and identified by a high intake of sauces, pickles, fast foods, soft drinks, snacks, and biscuits. The third dietary pattern was labeled as the "traditional pattern" and characterized by a high amount 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" pattern and characterized by high amounts of vegetables, whole grains, legume and nuts, and dairy products. The food group list and the factor loadings of each food group for these dietary patterns are exhibited in Table 2. These dietary patterns explained 16.35%, 12.57%, 8.73% and 8.67% of the total variance, respectively.

Association between tertiles of dietary patterns and the risk of NAFLD shows in Table 3. 3 models of logistic regression were assessed. Model 1 is crude. Model 2 is adjusted for age, sex, energy intake and BMI, and Model 3 is further adjusted for smoking, educational status, and physical activity. After adjusting for confounding factors, individuals in the third tertile of "ordinary pattern" exhibited significantly elevated risk for NAFLD compared to the first tertile (OR: 3.74, CI: 1.23–11.42, P-trend < 0.001). Individuals in the second and third tertiles of the "traditional pattern" also were associated with the risk of NAFLD (OR: 2.37, CI: 1.02–5.27, and OR: 3.58, CI: 1.48–8.68, p-trend < 0.001, respectively). Individuals in the third tertile of "vegetable and dairy pattern" was inversely associated with NAFLD risk (OR: 0.23, CI: 0.09–0.58, P-trend = 0.02). No significant association between "fast food type pattern" and the risk of NAFLD was found.
Table 1. Characteristics of participants

1. P-value < 0.05 was considered significant.

2. P-value based on the Mann-Whitney test.

| Variables               | NAFLD (n = 121) | Control (n = 122) | P-value<sup>(1)</sup> |
|-------------------------|-----------------|-------------------|-----------------------|
| Age (year), Mean ± SD   | 42.95 ± 11.46   | 42.51 ± 11.52     | 0.71<sup>(2)</sup>    |
| Sex                     |                 |                   |                       |
| Male                    | 57 (47.1%)      | 58 (47.5%)        | 0.95<sup>(3)</sup>    |
| Female                  | 64 (52.9%)      | 64 (52.5%)        |                       |
| Weight, Kg              | 81.78 ± 13.12   | 80.76 ± 13.28     | 0.55<sup>(4)</sup>    |
| Height, cm              | 165.53 ± 10.16  | 165.97 ± 9.19     | 0.68<sup>(2)</sup>    |
| BMI, kg/m<sup>2</sup>   | 30.53 ± 5.04    | 29.32 ± 4.49      | 0.08<sup>(2)</sup>    |
| Waist circumference, cm | 102.86 ± 10.78  | 98.08 ± 10.55     | 0.001<sup>(4)</sup>  |
| Hip circumference, cm   | 105.91 ± 7.59   | 105.35 ± 7.41     | 0.58<sup>(4)</sup>    |
| WHtR                    | 0.62 ± 0.07     | 0.59 ± 0.07       | < 0.001<sup>(4)</sup>|
| WHR                     | 0.95 ± 0.07     | 0.92 ± 0.08       | 0.002<sup>(2)</sup>  |
| Systolic blood pressure, mmHg | 124.09 ± 12.29 | 121.02 ± 14.45   | 0.32<sup>(2)</sup>    |
| Diastolic blood pressure, mmHg | 81.35 ± 6.96   | 80.14 ± 6.44      | 0.28<sup>(2)</sup>    |
| Total energy intake, kcal | 4122.76±1624.85 | 3178.60±936.18   | < 0.001<sup>(4)</sup>|
| Met (Hour/day)          | 34.11 ± 5.87    | 35.94 ± 7.88      | 0.14<sup>(2)</sup>    |
| Marital status          |                 |                   | 0.72<sup>(3)</sup>    |
| Married                 | 105 (86.8%)     | 102 (83.6%)       |                       |
| Bachelor                | 16 (13.2%)      | 20 (16.4%)        |                       |
| Educational status      |                 |                   | 0.002<sup>(3)</sup>  |
| 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                   |                 |                   | 0.04<sup>(3)</sup>    |
| Yes                     | 12 (9.9%)       | 4 (3.3%)          |                       |
| No                      | 109 (90.1%)     | 118 (96.7%)       |                       |

<sup>(3)</sup> P-value based on the chi-squared test.

<sup>(4)</sup> 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.

| Food groups         | Ordinary patterns | Fast food type | Traditional       | Vegetables and 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          |                   |                |                   | 0.669                |
| Whole grains        |                   |                |                   | 0.603                |
| Legume and Nuts     |                   |                |                   | 0.576                |
| Dairy products      |                   |                | 0.340             | 0.474                |
| Total variance      | 16.35             | 12.57          | 8.73              | 8.67                 |
| explained           |                   |                |                   |                      |

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-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   |
| **Dairy and vegetable 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
This case-control study identified four major dietary patterns; "ordinary pattern", "fast food type pattern", "traditional pattern" and "vegetable and dairy pattern". We realized that "ordinary pattern" and "traditional pattern" were significantly increased the risk of NAFLD, while the "vegetable and dairy pattern" has an inverse association with NAFLD in the Ahvaz population. However, we don't find
any significant association between the “fast food type pattern” and the risk of NAFLD. Based on our search, this study is the first study investigated the association between dietary patterns and NAFLD in the Ahvaz population.

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

The "fast food type pattern" is characterized by the high consumption of "fast foods, pickles, sauces, soft drinks, snacks, and biscuits". Unlike most studies on this topic that reported a positive relationship between fast food patterns and risk of NAFLD, we don't identify any association between this dietary pattern and NAFLD.

The "traditional pattern" is characterized by high intakes of "condiments, red and organ meats, dairy products, salt, and tea and coffee". This pattern has also a direct association with NAFLD.

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

"ordinary pattern" adherence is 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- lead to a rapid increase in postprandial plasma glucose, insulin concentration, and diabetes (30). Such high glycemic index foods cause increase hepatic steatosis, especially in insulin-resistant subjects (31). Jia et al. also reported that a high carbohydrate/sugar pattern was associated with NAFLD in women (18). Moreover, our results are in line with the finding of another study in Japan that represented a high carbohydrate diet, especially sweets, resulting in a higher risk of NAFLD (32). However, Chung et al. did not find a relationship between the high carbohydrate diet and the risk of NAFLD (33). Our findings confirm the result 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. High intake
of fructose leads to de novo lipogenesis and lipid accumulation and steatosis in the liver. Moreover, chronic consumption of fructose enhances hepatic inflammation and oxidative stress which are responsible for the progression of the hepatic disease (36).

Some previous studies were suggested that a "fast food pattern" or a "western diet" is 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 has been prospectively associated with NAFLD risk in adolescence (19). Kalafati et al. reported similar results about fast food pattern and NAFLD risk with the previous study (5). However, we couldn’t find a significant association between the fast-food pattern and risk of NAFLD but the possible reason for this discrepancy could be due to the differences in dietary patterns between ethnicities, cultural groups, and gender. Also, dietary patterns may vary over time because of personal preferences and the availability of food (9).

Meats like red meat and visceral meat loaded relatively high in the "ordinary pattern" and "traditional pattern". studies that investigated the association between high protein and NAFLD are scarce. Zelber Sagi et al. illustrated that all types of meats were significantly associated with an increased risk for NAFLD (37). one explanation for this association could be that high protein intake is associated with insulin resistance and glucose intolerance and might even increase the incidence of type-2 diabetes (38, 39). Another possible explanation is a higher intake of iron and in particular, heme-iron that may play a role in the pathogenesis of NAFLD by increasing oxidative stress (40). the "traditional pattern" and "ordinary pattern" are high in salt. The findings of the studies about the role of sodium in NAFLD are controversial. A study of a Korean population reported that high salt dietary pattern was associated with an 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). More studies are required to clarify this association.

Yang et al. reported an inverse association between a "grain and vegetable pattern" and NAFLD and this association was independent of confounding factors like age, sex, BMI, physical activity (20). Another study in the Lebanese population also showed that a "traditional Lebanese" diet that consists of vegetables and legumes has a negative association with the risk of NAFLD (34). These results
confirmed our findings 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 possible strengths. This is the first study investigating the association between major dietary patterns and the risk of NAFLD in the Ahvaz population. Potential confounding factors were identified and controlled for in the analysis. Moreover, we used a semi-quantitative FFQ designed for the Iranian population, which result in a better representation of the dietary habits of the participants.

There are some limitations that should be considered. First, because of the case-control design of this study, it cannot confirm a causal relationship between dietary patterns and NAFLD. Second, the overestimation of energy intake because of using a FFQ for data collection is a great risk. Third, recall bias exists because of the self-reporting nature of the questionnaire.

Conclusion

In conclusion, these findings display that high adherence to the "ordinary" and "traditional" patterns increase the risk of NAFLD, while a "vegetable" pattern has a negative association with NAFLD in the Ahvaz population. The findings of this study could serve as a dietary strategy for the prevention and treatment of NAFLD. Nevertheless, more studies are required to confirm our results.

Declarations

**Ethics approval and consent to participate:** All study subjects were informed about the aim of this study and signed a consent form; the study protocol was confirmed by the ethics committee based on the ethical guidelines of the 1975 declaration of Helsinki at the Jundishapur University of Ahvaz (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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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.

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