



## The Association of Dietary Inflammatory Index with the Risk of Type 2 Diabetes: A Case-Control Study

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### ABSTRACT

**Background:** The prevalence rate of type 2 diabetes (T2DM) is increasing worldwide, and the role of diet in its etiology has been established. The Dietary inflammatory index (DII) has attracted significant attention in evaluating associations between diet and diseases due to the role of chronic inflammation as an underlying cause of numerous disease processes. Therefore, the relationship between DII score and the risk of T2DM is evaluated in the Iranian population for the first time. **Methods:** 113 newly diagnosed T2DM patients and 226 apparently disease-free control cases aged 23-59 participated in this case-control study. A valid semi-quantitative food frequency questionnaire was used to assess dietary intake. Then, energy-adjusted DII (E-DII) scores were computed and categorized into quartiles based on values in the population study. A logistic regression model was used to estimate the association between DII and the risk of T2DM after controlling for important potential confounders and effect modifiers. **Results:** A significant association was observed between E-DII score and T2DM in the crude model ( $P_{\text{trend}} < 0.001$ ), model I (adjusted for physical activity, gender, education level, and family history of T2DM,  $P_{\text{trend}} < 0.001$ ), model II (adjusted for model I + body mass index,  $P_{\text{trend}} = 0.005$ ) ( $OR_{\text{quartile4vs1}} = 2.98$  (95% CI: 1.18, 9.12;  $P = 0.005$ )). **Conclusions:** A direct association was observed between DII score and the risk of T2D, implying that consuming a more anti-inflammatory diet would help to prevent T2DM. Future longitudinal studies should be conducted to further explore this association.

**Keywords:** Dietary inflammatory index; Diabetes mellitus; Case-control studies.

### Introduction

According to the International Diabetes Federation (IDF), about 425 million adults aged 20–79 had type 2 diabetes mellitus (T2DM) in 2015, while almost half of them were unaware

of their disease. It is estimated that the number of people with T2DM will increase to about 629 million by 2045 (Cho *et al.*, 2018). Approximately, 4.5 million Iranians were diagnosed with diabetes

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in 2011, which is estimated to increase to 9.2 million in 2030 (Esteghamati *et al.*, 2017). Chronic systemic inflammation plays an essential role in pathogenesis of T2DM. This condition is characterized by continued presence of high circulating levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), c-reactive protein (CRP), and infiltration of macrophages into insulin-dependent tissues, which may lead to insulin resistance (IR) and, subsequently, to T2DM (Kim *et al.*, 2006). Several factors can be involved in inflammation, including obesity, inactivity, diet, and psychological stress (Calder *et al.*, 2011, Saboori *et al.*, 2019a). Diet, prominent among modifiable risk factors, is one of the most important modulators of inflammation (Smidowicz and Regula, 2015). Accordingly, several studies indicated that unhealthy diets, for example Western dietary patterns, are characterized by high consumption of red meat, ultra-processed foods, and refined grains, which may impact the pathogenesis of chronic diseases through their unique effects on increasing inflammation (Ruiz-Canela *et al.*, 2015, Saboori *et al.*, 2016, Shivappa *et al.*, 2014). Conversely, some nutrients and healthy diets such as the Mediterranean diet, which is rich in vegetables, fruits, olive oil, and fish, are associated with lower levels of inflammation and protect individuals against T2DM and metabolic abnormalities (Grosso *et al.*, 2017, Montonen *et al.*, 2013, Rad *et al.*, 2019, Ruiz-Canela *et al.*, 2015). Dietary components can exert anti-inflammatory or pro-inflammatory effects, influencing the risk of inflammatory diseases (Montonen *et al.*, 2013, Ruiz-Canela *et al.*, 2015). Dietary inflammatory index (DII) is an important tool in assessing diet quality with specific focus on the inflammatory potential of diet based on intake of macronutrients, micronutrients, and some other dietary constituents (Shivappa *et al.*, 2014). However, the results of previous studies regarding the association between DII and the risk of T2DM showed inconclusive results. While some studies revealed an association between pro-inflammatory diet and the risk of T2DM and between DII and Homeostatic Model

Assessment for Insulin Resistance (HOMA-IR) (Denova-Gutiérrez *et al.*, 2018, van Woudenberg *et al.*, 2013), other studies failed to report this association (Moslehi *et al.*, 2016). Because of these discrepancies between the findings, more studies are needed to investigate this association. To the authors' knowledge, no study has so far explored the association between DII and T2DM among Iranians. Therefore, this study aims to examine the association between DII and the risk of developing T2DM in Iranian population.

## Materials and Methods

### Study design

This case-control study enrolled patients who were newly diagnosed (<6 months) with T2DM and aged between 23 and 59. Participants were selected from those referred to Lorestan University of Medical Sciences clinic between January 2020 and April 2020. Ineligibility criteria included the following: pregnant or lactating women, people with any established chronic disease (cardiovascular diseases, liver failure, kidney failure, thyroid disorders, cancer, and other chronic disorders except diabetes). The clinical diagnosis of T2DM in the case group was made by a physician and documented by an oral glucose tolerance test (OGTT). According to the World Health Organization's (WHO), people with fasting blood sugar (FBS) of  $\geq 126$  mg/dl and 2-h postprandial (2h-PG)  $\geq 200$  mg/dl were included in the case group (World Health Organization, 2006). Controls were randomly selected from general population, all of whom had normal blood glucose levels (FBS <100 mg/dl). A total of 113 cases and 226 healthy individuals were enrolled.

### Dietary assessment

Diet was assessed by trained dietitians using a valid and reliable 168-item FFQ with standard size servings commonly consumed by Iranians (Mirmiran *et al.*, 2010). Individuals were asked about the frequency of their food consumption on a daily, weekly, or monthly basis one year before the interview. Amounts reported for each type of food were converted to grams per day. After that, daily energy and nutrient consumption were determined

via multiplying the daily frequency of intake by the nutrient content of the specified portion size, and using food composition tables provided by N4 software (provided by N-squared Computing Nutritionist IV). Nutrient values were based on nutrient composition of the Iranian foods (Azar and Sarkisian, 1980). The United States Department of Agriculture (USDA) food composition data were used for foods or food ingredients that were not included in the nutrient composition of Iranian foods (Merchant and Dehghan, 2006).

#### **Other variables**

The interviewer asked the participants general information, including age, education, occupation, place of residence, monthly income, marital status, smoking habits, and medical history. The participants' weight was measured without shoes and with light clothing and a digital scale (accuracy of 100 grams), and height was measured without shoes and in a static position using a measuring tape installed on the wall (accuracy of 0.1 cm). Body mass index (BMI) was calculated through dividing weight (kg) by the square of height (m). Waist circumference (WC) was also measured with a plastic measuring tape at the midpoint between the lowest rib cage and above the top of the iliac crest to the nearest 0.1 cm. Next, physical activity was evaluated through a valid and reliable questionnaire (Kriska *et al.*, 1990, Mirshekarlou *et al.*, 2015). Physical activity was calculated to produce Metabolic Equivalent (MET) which was reported as MET h/weeks (Ainsworth *et al.*, 2000).

#### **Calculation of DII scores**

To calculate DII score in each group, FFQ-derived dietary data were used. A comprehensive explanation of DII was conducted, which was based on the review of publications between 1950 and 2010 that reported one or more relations between any dietary component (the list included about 200 individual foods, nutrients and other constituents) and these inflammatory markers: IL-1 $\beta$ , IL-4, IL-6, IL-10, TNF- $\alpha$ , and CRP (Shivappa *et al.*, 2014).

In creating DII, a careful search of nearly 2000 articles in the National Library of medicine identified 45 food parameters related to the 6 inflammatory biomarkers. Each food parameter was allocated a “food parameter-specific inflammatory effect score”. To compute DII scores for the participants, first, dietary data were linked to the world database (based on 11 diverse populations around the world), which provided estimates of the mean intake and standard deviation for each food parameter (Shivappa *et al.*, 2014). A person's diet was then linked to the world food database by creating a z-score, calculated by subtracting the “standard global mean” and dividing this value by standard deviation. To minimize the risk of “right skewing”, this z-score was converted to a proportion and was centered on zero by multiplying each proportion by 2 and subtracting 1. These food parameter-specific inflammatory effect scores were then summed to create the overall DII score (Shivappa *et al.*, 2014). The overall DII score can take on values from about -9 to +8. Higher, i.e., more positive DII scores indicate more pro-inflammatory diets, and more negative scores denote more anti-inflammatory diets. In this study, 36 of the 45 possible dietary components were available from the food frequency questionnaire and were used for DII calculation. These parameters included total calories, carbohydrate, fat, protein, cholesterol, saturated fatty acids, vitamin B12, iron, mono-unsaturated fatty acids, polyunsaturated fatty acids, fiber, vitamin B6, folic acid, niacin, riboflavin, thiamin, vitamin A, vitamin C, vitamin D, vitamin E, beta carotene, caffeine, garlic, onion, tea, zinc, selenium, magnesium, omega 3 and omega 6 fatty acid, saffron, turmeric, pepper, rosemary, ginger, and thyme. In this study, the authors calculated the DII score per 1000 calories using the energy-standardized version of the world database to control the influence of total energy intake. E-DII score was calculated in a manner analogous to DII score (Hébert *et al.*, 2019).

#### **Ethical considerations**

This study was supported by the School of

Nutritional Health in Lorestan University of Medical Sciences (ID: IR.LUMS.REC.1398.076). All the participants gave written informed consent before beginning the study.

**Data analyses**

All the analyses in this study were conducted using SPSS software version 16. The Kolmogorov–Smirnov test was applied to examine the distribution of the data related to normality. E-DII score was analyzed as a continuous variable and as a categorical variable with cut-points derived from controls. One-way analysis of variance (ANOVA) was used for testing variances for general characteristics across quartiles of DII. Furthermore, chi-square test was used to compare categorical variables. To assess the strength of the

association between E-DII score and T2DM, the authors estimated multivariable-adjusted odds ratios (OR) and 95% CI using logistic regression models, and the results were reported at the significance level of 0.05.

**Results**

**Table 1** shows the characteristics of 113 cases of T2DM and 226 healthy controls (i.e., without T2DM), according to the selected variables. Cases had significantly higher E-DII scores, weight, BMI, and total energy intake and were more likely to have a positive family history of T2DM than controls ( $P \leq 0.001$ ). Significant differences were observed in physical activity during leisure time, and controls reported being more physically active.

**Table 1.** Characteristics of T2DM cases and controls according to the selected variables.

Variables	Case (n=113)	Control (n=226)	P-value <sup>b</sup>
<b>Continuous variables</b>			
Age (years)	45.66 ± 7.04 <sup>a</sup>	33.57 ± 5.52	<0.001
Weight (kg)	79.30 ± 9.08	70.25 ± 8.94	<0.001
Body mass index (kg/m <sup>2</sup> )	28.82 ± 2.22	23.80 ± 2.64	<0.001
Physical activity (Mets/day)	481.5 ± 192.0	934.4 ± 463.1	<0.001
Total energy (kcal/day)	2157.0 ± 331.2	1992.7 ± 332.9	<0.001
Dietary inflammatory index (DII)	0.75 ± 1.53	-0.41 ± 1.85	<0.001
<b>Categorical variables</b>			
Sex			
Male	41 (36.3) <sup>c</sup>	101 (44.7)	0.14
Female	72 (63.7)	125 (55.3)	
Marital status			
Married	18 (15.9)	102 (45.1)	<0.001
Single	95 (84.1)	124 (54.9)	
Education			
Illiterate	15 (13.3)	11 (4.9)	<0.001
Below high school diploma	31 (27.4)	40 (17.7)	
High school diploma	35 (31.0)	122 (54.0)	
Above high school diploma	32 (28.3)	53 (23.5)	
Job status			
Permanent employment	38 (33.63)	72 (31.86)	0.92
Freelance	29 (25.66)	57 (25.22)	
Unemployed	46 (40.71)	97 (42.49)	
Smoking status			
Nonsmoker	31 (27.4)	74 (32.7)	0.32
Smoker	82 (72.6)	152 (67.3)	
Family history of diabetes mellitus			
Yes	47 (41.6)	60 (26.5)	0.005
No	66 (58.4)	166 (73.5)	

<sup>a</sup>: Mean ± SD; <sup>b</sup>: Two-sample t-test for continuous and chi-squared test or Fisher’s exact test for categorical variables; <sup>c</sup>: n(%).

E-DII score range was divided into quartiles. The upper bound of the lowest E-DII quartile was  $\leq -1.33$ , and the lower bound of the upper E-DII quartiles was  $\geq 1.12$ . **Table 2** shows the characteristics of the study population among the quartiles of the E-DII score. The results showed that mean age, BMI, and physical activity were significantly different between the quartiles of the

E-DII score. Subjects in the most pro-inflammatory E-DII quartile had a higher intake of unsaturated fatty acids, omega 6 fatty acids, and ginger and a lower intake of cholesterol, fiber, vitamin B6, B2, A, C, D, Folic acid, beta carotene, garlic, onion, omega 3 fatty acids, saffron, turmeric, black pepper, rosemary, and thyme (**Table 3**).

**Table 2.** Characteristics of the T2DM case and control groups according to quartiles of the dietary inflammatory index..

Variables	Quartiles of the dietary inflammatory index				P-value <sup>b</sup>
	Q1 (DII $\leq$ -1.33)	Q2 (-1.33<DII<0.02)	Q3 (0.02 $\leq$ DII<1.12)	Q4 (DII $\geq$ 1.12)	
Age (years)	36.00 $\pm$ 7.37 <sup>a</sup>	36.66 $\pm$ 7.39	39.39 $\pm$ 8.27	38.35 $\pm$ 9.32	0.03
Body mass index (kg/m <sup>2</sup> )	24.37 $\pm$ 2.86	25.05 $\pm$ 3.53	26.01 $\pm$ 3.60	26.47 $\pm$ 3.41	<0.001
Physical activity (mets/day)	908.89 $\pm$ 500.55	790.34 $\pm$ 420.00	718.87 $\pm$ 421.71	724.23 $\pm$ 429.78	0.02
<b>Sex</b>					
Male	165 (48.8) <sup>c</sup>	122 (36)	127 (37.6)	153 (45.2)	0.28
Female	173 (51.2)	217 (64)	212 (62.4)	186 (54.8)	
<b>Marital status</b>					
Married	206 (60.7)	213 (62.8)	239 (70.6)	218 (64.3)	0.57
Single	123 (39.3)	126 (37.2)	100 (29.4)	121 (35.7)	
<b>Education level</b>					
Illiterate	36 (10.7)	20 (5.8)	28 (8.2)	20 (6.0)	0.41
Below high school Diploma	77 (22.6)	76 (22.4)	92 (27.1)	40 (11.9)	
High school diploma	145 (42.9)	151 (47.7)	147 (43.5)	173 (51.1)	
Above high school diploma	81 (23.8)	92 (24.4)	72 (21.2)	106 (31.0)	
<b>Job status</b>					
Permanent employment	77 (22.6)	87 (25.6)	92 (27.1)	89 (26.2)	0.58
Freelance	141 (41.7)	106 (31.4)	100 (29.4)	93 (27.4)	
Unemployed	121 (35.7)	146 (43.0)	147 (43.5)	157 (46.4)	
<b>Smoking status</b>					
Non-smoker	226 (66.7)	237 (69.8)	219 (64.7)	254 (75.0)	0.50
Smoker	113 (33.3)	102 (30.2)	120 (35.3)	85 (25.0)	
<b>Family history of type 2 diabetes mellitus</b>					
Yes	294 (86.9%)	248 (73.3)	191 (56.5)	170 (50.1)	<0.001
No	45 (13.1%)	91 (26.7)	148 (43.5)	169 (49.9)	

<sup>a</sup>: Mean  $\pm$  SD; <sup>b</sup>: ANOVA was used for continuous variables and Chi-square was used for categorical variables; <sup>c</sup>: n(%).

**Table 4** demonstrates odds ratio (OR) and 95% confidence intervals (CI) for the association between DII and T2DM. In the crude model, people in the fourth quartile of DII had an OR of 2.83 (95% CI: 1.28, 5.15) in comparison to people in the first quartile. In the first model, after adjusting based on the level of activity, education, gender, and family history of T2DM, the results revealed that people in the fourth quartile of DII had an OR of 4.06 (95%

CI: 2.45, 8.72) versus the first quartile. Additional adjustment for BMI in the second model showed that individuals with the most pro-inflammatory diet had approximately three times greater odds of T2DM (OR: 2.98, 95% CI: 1.18, 9.12) compared with the individuals in the lowest DII quartile. Because of collinearity between age and BMI, this model was conducted without adjusting for age variable (data are not shown).

**Table 3.** Food and nutrient consumption regarding T2DM cases and controls according to quartiles of dietary inflammatory index.

Variables	Quartiles of the dietary inflammatory index				P-value <sup>b</sup>
	Q1 (DII≤-1.33)	Q2 (-1.33<DII<0.02)	Q3 (0.02≤DII<1.12)	Q4 (DII≥1.12)	
Energy (kcal/d)	2030.78±378.78 <sup>a</sup>	1998.72±329.65	2055.71±347.27	2107.08±300.05	0.21
Carbohydrate intake(g/d)	296.42±67.36	293.85±57.16	305.71±60.19	313.90±51.22	0.13
Protein intake(g/d)	79.79±14.89	77.03±12.41	78.21±14.10	75.40±11.76	0.18
Total fat intake(g/d)	66.91±8.06	64.91±9.57	65.76±10.45	68.02±11.28	0.13
Cholesterol(mg/d)	273.77±59.05	250.50±70.89	259.83±79.59	242.56±83.95	0.04
Saturated fats(g/d)	18.81±3.80	18.71±3.72	19.34±4.29	20.05±4.42	0.13
Monounsaturated fats(g/d)	19.39±2.75	18.91±3.34	18.83±3.47	20.59±4.00	0.003
Polyunsaturated fats(g/d)	11.34±1.33	11.58±2.54	11.41±2.57	13.02±3.72	<0.001
Fiber (g/day)	18.49±2.89	17.70±3.10	17.35±3.05	16.78±2.46	0.002
Vitamin B1(mg/d)	1.91±0.42	1.86±0.34	1.91±0.34	1.95±0.27	0.37
Vitamin B2(mg/d)	1.78±0.42	1.68±0.31	1.71±0.37	1.62±0.31	0.04
Vitamin B3(mg/d)	21.10±3.63	20.85±3.52	21.42±3.55	21.71±3.33	0.41
Vitamin B6(μg/d)	1.76±0.34	1.61±0.30	1.61±0.29	1.54±0.24	<0.001
Vitamin B9(μg/d)	284.53±47.31	265.16±45.94	265.04±49.77	268.31±48.70	0.004
Vitamin A(RE)	1359.70±210.07	1244.89±248.88	1142.18±245.51	1004.68±218.27	<0.001
Vitamin D(μg/d)	1.02±0.92	0.76±0.66	0.62±0.66	0.51±0.57	<0.001
Vitamin E(mg/d)	3.90±0.84	3.68±0.88	3.56±0.77	3.53±0.92	0.24
Vitamin C(mg/d)	93.00±11.91	87.74±14.17	83.16±14.37	75.28±13.98	<0.001
Beta-carotene(μg/d)	629.88±163.13	561.81±167.40	461.16±164.86	361.13±125.29	<0.001
Caffeine(g/d)	0.21±0.10	0.19±0.09	0.20±0.09	0.21±0.10	0.27
Garlic(g/d)	0.26±0.13	0.18±0.11	0.17±0.11	0.10±0.07	<0.001
Onion(g/d)	17.44±4.44	16.33±6.51	13.20±6.42	8.81±6.60	<0.001
Tea(g/d)	900±563.62	747.90±470.61	869.64±64	905.71±905.71	0.15
Zinc(mg/d)	9.59±1.86	9.19±1.65	9.26±1.95	8.94±1.71	0.14
Selenium(μg/d)	0.12±0.03	0.11±0.03	0.11±0.02	0.11±0.02	0.30
Magnesium(mg/d)	284.96±58.60	270.11±54.65	267.24±58.71	236.25±44.91	0.057
Omega 3(g/d)	0.22±0.05	0.19±0.05	0.18±0.06	0.17±0.05	<0.001
Omega 6(g/d)	10.07±1.28	10.39±2.48	10.25±2.59	11.89±3.72	<0.001
Saffron(g/d)	0.13±0.03	0.11±0.04	0.10±0.05	0.06±0.05	<0.001
Turmeric(g/d)	2.28±0.39	2.03±0.61	1.90±0.63	1.33±0.74	<0.001
Black pepper(g/d)	3.77±1.28	3.32±1.28	3.39±1.29	2.59±1.81	0.003
Rosemary(g/d)	0.04±0.08	0.01±0.06	0.004±0.02	0.002±0.003	<0.001
Ginger(g/d)	0.57±0.37	0.58±0.33	0.63±0.30	0.74±0.27	0.002
Thyme(g/d)	0.43±0.34	0.33±0.28	0.28±0.27	0.16±0.14	<0.001

<sup>a</sup>: Mean ± SD; <sup>b</sup>: ANOVA test.

**Table 4.** Odds ratio and 95% CI for cases and controls regarding the relation between dietary inflammatory index and T2DM,

	Q1 (DII≤-1.33)	Q2 (-1.33<DII<0.02)	Q3 (0.02≤DII<1.12)	Q4 (DII≥1.12)	P <sub>trend</sub>
Crude model	1.0	1.38(0.92,1.85) <sup>a</sup>	2.11(1.28,4.39)	2.83(1.28,5.15)	<0.001
Model I	1.0	1.35(0.90,2.05)	2.08(1.30,4.01)	4.06(2.45,8.72)	<0.001
Model II	1.0	1.61(1.06, 2.43)	1.86(1.09, 3.32)	2.98(1.18,9.12)	0.005

<sup>a</sup>: Odds (95% CI); Model I: Adjusted for physical activity, gender, education level, and family history of T2DM. Model II: Model I plus BMI.

## Discussion

In the present study, a significant association was found between an increase in E-DII score and the risk of T2DM. E-DII score in the second, third, and fourth quartiles increased the risk of T2DM by 1.38, 2.11, and 2.83-folds compared to the lowest quartile. Adjusting for variables of the level of physical activity, education, gender, and family history of T2DM, a significant correlation was observed except in the second quarter. Finally, after additional adjustment for BMI, the most pro-inflammatory diet had approximately 2.98-folds, which increased the odds of T2DM compared with the lowest E-DII quartile.

Studies on the role of inflammation in health and disease have increased exponentially over the last decades. DII, as a relatively new tool to quantify the inflammatory potential of diet, was calculated via inflammatory scores of each food parameter and their standardized consumptions relative to the global values. Previous studies revealed that DII/E-DII was associated with increased inflammatory biomarkers and incidence of chronic diseases such as cancer, cardiovascular disease, obesity, respiratory diseases, and T2DM (Ruiz-Canela *et al.*, 2015, Shivappa *et al.*, 2015, Shivappa *et al.*, 2014, Wood *et al.*, 2015). However, the reported results on this association were inconclusive (Denova-Gutiérrez *et al.*, 2018, Moslehi *et al.*, 2016, Vahid *et al.*, 2017).

Inflammation is a biological response to danger which is mediated via cytokine and chemokine production (James R and Lorne J, 2022). In addition to total energy intake, specific dietary components also can affect metabolic and endocrine functions (Mousavi *et al.*, 2020, Rezagholizadeh *et al.*, 2019, Saboori *et al.*, 2019b). This motivated the creation of the first version of DII, linking any aspect of diet to  $\geq 1$  of 6 inflammatory biomarkers: IL-1 $\beta$ , IL-4, IL-6, IL-10, TNF- $\alpha$ , and CRP (Shivappa *et al.*, 2014). Nutrients such as complex carbohydrates, fiber, omega -3 fatty acids, vitamin E and C, and beta-carotene and magnesium decreased inflammation in body (Shivappa *et al.*, 2017). One study reported anti-inflammatory effects on dietary bioactive

compounds, including polyphenols, unsaturated fatty acids, and conjugated linoleic acid (Siriwardhana *et al.*, 2013). The potential underlying mechanisms were an increase in mitogen-activated protein kinases (MAPK) and a decrease in 5' adenosine monophosphate-activated protein kinase (AMPK) activation, which led to more inflammation (Gauthier *et al.*, 2011). Catechins, quercetin, and isoflavones suppressed nuclear factor- $\kappa$ B (NF- $\kappa$ B) and MAPK while activating AMPK pathways. Dietary saturated fatty acids were active toll-like receptors (TLRs) that induced NF- $\kappa$ B pathway, resulting in overexpression of IL-6 and TNF- $\alpha$  genes (Vitseva *et al.*, 2008). As an anti-inflammatory cytokine associated with insulin sensitivity, adiponectin was lower in patients with T2D but increased with grape polyphenol consumption (Décordé *et al.*, 2009). Grape polyphenols suppressed NF- $\kappa$ B and extracellular signal-regulated kinase (ERK) activation and activated sirtuin-1 (silent mating type information regulator 2 homolog 1 pathway) (Ølholm *et al.*, 2010). These pathways, plus resistin and retinol-binding protein-4 (RBP-4) downregulate pro-inflammatory responses, leading to more insulin sensitivity, thus preventing T2DM occurrence and progression (Mercader *et al.*, 2011). Serum levels of FBS were changed significantly across DII quartiles in a study by Wirth *et al.* (Wirth *et al.*, 2014). The results of their study was in line with the results of the current study. One cross-sectional study in Mexico City reported that the odds of T2D increased in subjects in the highest DII quintile (OR = 3.02; 95% CI: 1.39, 6.58;  $P=0.005$ ) compared to the lowest one. An association with T2DM was observed when comparing DII quintile 5 to 1 in the people  $\geq 55$  (Alberti and Zimmet). In a recent systematic review, a higher DII score increased the risk of T2DM (pooled OR 1.32, 95% CI 1.01–1.72, I<sup>2</sup> 58.6%,  $P<0.05$ ) (Tan *et al.*, 2021). However, studies were performed in various countries with small numbers and heterogenic populations and produced different results. In some studies, there was a close association between DII scores and consuming pro-inflammatory diet and between DII

and HOMA-IR (Denova-Gutiérrez *et al.*, 2018, van Woudenberg *et al.*, 2013). Of the two studies in Iran, one studied the possible relationship between DII and the risk of gestational diabetes mellitus (GDM). Subjects with higher DII scores showed increased odds of GDM with DII being used as both continuous (OR=1.20; 95% CI=0.94–1.54) and categorical (OR<sub>tertile3vs1</sub>=2.10; 95% CI=1.02–4.34, P<sub>trend</sub>=0.03) (Shivappa *et al.*, 2019). The other one investigated the association between DII and glucose-insulin and homeostasis markers, including FBS, 2h-PG, fasting serum insulin, homeostatic model assessment of insulin resistance index,  $\beta$ -cell function, quantitative insulin sensitivity check index, and the risk of glucose intolerance in a cross-sectional study. Among all the parameters, DII showed a weak positive association only with 2h-PG (Moslehi *et al.*, 2016). It should be mentioned that this study was different in terms of the type of patients and design.

Iranians have a special dietary pattern, and dietary carbohydrates are major macro-nutrient which can provide a significant part of the energy required for this country. The intake of carbohydrates may have a crucial role in health outcomes (Majdi *et al.*, 2022). This study had some limitations. The most important one was the possibility of recall bias due to FFQ assessment tool, and over or under-reporting may distort the results. The number of participants was another limitation of this study which was not large enough for these type of studies. Another limitation was associated with assessing specific cultural food items. Moreover, the authors did not measure the serum levels of inflammatory markers including CRP and Interleukins to assess the association between DII scores and these inflammatory markers which was another important limitation of this study.

### Conclusion

In conclusion, diets resulting in high DII scores are associated with an increased risk of T2DM in the Iranian population. However, the results of the current study results are based on a case-control design and further high-quality research with larger

studies of prospective design are needed to explore this association.

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### Authors' contributions

Yousefi Rad E, Hebert J and Choobkar S designed the study. Asbaghi O, Choobkar S, BahramFard T and Saboori S performed field works under the supervision of Yousefi Rad E. Vahid F, Birjandi M, Mousavi N and Asbaghi O performed nutritional analysis of the FFQs and data analysis and interpretation under the supervision of Yousefi Rad E. All the authors contributed to drafting the manuscript. Finally, Yousefi Rad E, Vahid F, and Hebert J revised the article for important intellectual content.

### Conflict of interest

There is any conflict of interest

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