

Dietary Fat Quality and Pre-diabetes: A Case-control Study

Abstract

Background: The relationship between dietary fat quality (DFQ) indices and pre-diabetes has not been well studied. This study aimed to determine the association of DFQ indices and fatty acid intake with pre-diabetes. **Methods:** This case-control study included 150 subjects with normal fasting blood glucose (FBG) and 147 pre-diabetic subjects. Dietary intake was assessed by a validated food-frequency questionnaire. DFQ indices including atherogenicity (AI) and thrombogenicity (TI), the ratios of hypo- and hypercholesterolemic (h:H), polyunsaturated:saturated (P:S) and *n-3:n-6* polyunsaturated fatty acids were calculated. FBG test and 2-hour oral glucose tolerance test (OGTT) were measured. **Results:** After adjustment for some confounding variables, a positive association was found between intake of total saturated fatty acids (SFA), myristic acid, palmitic acid, and pre-diabetes, and a negative association was observed among *n-3* polyunsaturated fatty acids, eicosapentaenoic, docosahexaenoic and arachidonic acids intake and pre-diabetes. AI was found to be positively associated with pre-diabetes (OR 6.68, 95% CI 2.57-17.34). An inverse relationship was observed between *n-3:n-6* (OR 0.37, 95% CI 0.14-0.93) and h:H (OR 0.20, 95% CI 0.07-0.52) ratios with pre-diabetes. **Conclusions:** Higher intake of dietary *n-3* fatty acids was adversely, whereas SFA intake was positively related to pre-diabetes morbidity. DFQ indices may be a useful measure to investigate fat intakes and blood glucose disturbances.

Keywords: Dietary fat quality, fatty acids, polyunsaturated fatty acids, pre-diabetes

Introduction

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), which often referred as “pre-diabetes”, are a pathological disturbance in insulin sensitivity and insulin secretion which causes the progress from a normal level of blood glucose to type 2 diabetes mellitus (T2DM).^[1] There has been a growing interest regarding the assessment of dietary fatty acids as the dietary adjustment for ameliorating insulin resistance.^[2] Different fatty acids exert various metabolic responses.^[3] In a cohort of 12 years follow-up, relatively high intake of MUFA (about 10%-15% of total energy intake) was associated with lower risk of IGF incidence, whereas higher *n-3* FA intake (more than 0.15% of total energy intake) was associated with higher risk of IGF incidence. Higher intake of *n-6* PUFA (4%-5% of total energy intake) was associated with a decreased risk of IFG and IGT incidence.^[4]

Previous studies demonstrated that to take into account the balance between

the beneficial and adverse effects of dietary fatty acids on the risk of diseases, investigation of dietary fat quality (DFQ) indices might be useful.^[5,6] To investigate the health outcomes that influenced by proportions of fatty acids in the diet, three indicators of fat quality including atherogenicity (AI), thrombogenicity (TI) and hypo- and hypercholesterolemic (h:H) fatty acids ratio indices were proposed.^[7,8] It was suggested that these indices may better reflect the atherogenic or thrombogenic potential of diet than simple assessment of total intake of SFA or P:S ratio.^[7] The positive association between gestational diabetes mellitus with TI and negative association with the h:H ratio was observed.^[9] This study aims to explore the association between dietary fatty acids intake and DFQ indices with pre-diabetes.

Materials and Methods

Study design

Participants were recruited from diabetes screening center in Shahreza, Iran in 2014. Written informed consent was obtained from all participants. The Ethics Committee of Tehran University of Medical

Maryam Abshirini,
Behzad Mahaki¹,
Fariba Bagheri,
Fereydoun Siassi,
Fariba Koohdani²,
Mostafa Qorbani^{3,4},
Parvaneh Yavari,
Gity Sotoudeh

Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, ¹Department of Epidemiology and Biostatistics, School of Public Health, Kermanshah University of Medical Sciences, Kermanshah, Iran, ²Department of Cellular, Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, ³Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran, ⁴Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence:

Dr. Gity Sotoudeh,
Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Hojatdost Street, Naderi Street, KeshavarzBlv., Tehran, Iran.
E-mail: gsotodeh@tums.ac.ir
Dr. Fereydoun Siassi,
Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Hojatdost Street, Naderi Street, KeshavarzBlv., Tehran, Iran.
E-mail: siassif@tums.ac.ir

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Sciences approved the protocol of the study. The method of this study is available in our previous article in detail^[10] and is described here in brief. Three hundred subjects, which were more than 30 years of age, were placed into two groups, 150 subjects with pre-diabetes (case) and 150 subjects in the control group. Three subjects in the case group reported energy intakes which were more than three standard deviations of the mean of energy. So they were excluded from the study [Appendices 1]. Using the frequency matching method, the two groups were matched by age and sex. The inclusion criteria for the pre-diabetic subjects were as follows: age range 35-65 years, fasting blood glucose (FBG) 100-125 mg/dl or 2-hour oral glucose tolerance test (OGTT) of 140-199 mg/dl diagnosed no longer than 3 months before the interview. The inclusion criteria for the control group were as follows: age range 35-65 years, FBG <100 mg/dl and 2-hour OGTT of <140 mg/dl during screening. Subjects with alcohol, drug, and any tobacco products usage, body mass index (BMI) ≥ 40 kg/m² or a special diet during the last year were not included in the study. In addition, pregnant or lactating women, subjects with heart disease, diabetes, hypertension, dyslipidemia, hepatic or renal impairment, and multiple sclerosis were excluded. The sample size was determined according to the previous study and using the sample size formula to estimate an odds ratio (OR). Types 1 (alpha) and 2 (beta) errors were considered as 0.05 and 0.2, respectively, and the estimated effect size (OR: 0.4) for diabetes in the highest polyunsaturated fatty acids consumer; thus, the calculated sample size was considered 150 subject in each group.^[9]

Measurement of anthropometry and physical activity

Height was measured using a standard medical grade scale. Weight was measured without shoes and in light clothes to the nearest 0.1 kg. Waist girths were measured nearest 0.5 cm at the midpoint between the lowest rib and the iliac crest. BMI was calculated as weight divided by height squared (kg/m²). Data on physical activity were collected using the short form of international physical activity questionnaire (IPAQ)^[11] which measures the physical activity based on the time spent on activities of daily living. Vigorous and moderate activities and walking for at least 10 min/day during the previous 7 days were asked. Then the duration and frequency of activity days were multiplied by the metabolic equivalent task (MET) value of the activity. The sum of the scores was calculated as the total physical activity per week.

Biochemical analysis

Following an 8-12-hour fast, blood samples were collected from each participant for assessing FBG. A 2-hour OGTT providing 75-g glucose was also performed. Plasma glucose was measured at 546 nm wavelength using the photometric method (glucose oxidase method).^[12]

Dietary assessment

Participants were interviewed to complete a valid semi-quantitative FFQ with 168 food items.^[13] All subjects reported their consumption frequency for each food items within last year on a daily, weekly or monthly basis. All food intakes were analyzed for macronutrient and energy intake using Nutritionist 4 software modified for Iranian foods.

Healthy eating index (HEI)^[14] score was calculated, which summarizes the consumption of 13 foods or nutrients (including consumption of total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, added sugars, and saturated fats). Each component was scored on a scale of 0-10. We excluded fatty acids and saturated fats when calculating the HEI score.

DFQ indices

The DFQ indices including AI, TI, and ratios of h:H, P:S and n-3:n-6 was investigated in this study. Equations (1) and (2) were used to assess the AI and TI. AI index takes into account the SFAs with the chain length of 12, 14 or 16 carbon atoms that are considered atherogenic due to their cholesterol-raising effect, whereas TI includes SFAs with chain length of 14, 16 or 18 carbon atoms that have the thrombogenic effect.^[7] Calculating the h:H ratio was performed using equation (3), considering the ratio between hypo- and hypercholesterolemic fatty acids (h:H) in diet.^[8]

$$AI = \frac{(12:0 + (4 \times 14:0) + 16:0)}{(\sum^{n-6} + \sum^{n-3} + \sum MUFA\ n-9)} \quad (1)$$

$$TI = \frac{(14:0 + 16:0 + 18:0)}{(0.5 \times MUFA)} + (0.5 \times \sum^{n-6}) + (3 \times \sum^{n-3}) + \left(\frac{\sum^{n-3}}{\sum^{n-6}}\right) \quad (2)$$

Where 12:0 = lauric acid, 14:0 = myristic acid, 16:0 = palmitic acid, \sum^{n-6} = sum of omega-6 polyunsaturated fatty acids, \sum^{n-3} = sum of omega-3 polyunsaturated fatty, $\sum MUFA\ n-9$ = sum of omega-9 monounsaturated fatty acids.

$$h:H = \frac{(18:1\ n-9 + 18:2\ n-6 + 20:4\ n-6 + 18:3\ n-3 + 20:5\ n-3 + 22:5\ n-3 + 22:6\ n-3)}{(14:0 + 16:0)} \quad (3)$$

Where 18:1 n-9 = oleic acid, 18:2 n-6 = linoleic acid, 20:4 n-6 = arachidonic acid, 18:3 n-3 = alpha-linolenic acid, 20:5 n-3 = eicosapentaenic acid, 22:5 n-3 = docosapentaenic acid, 22:6 n-3 = docosahexaenoic acid.

Statistical analysis

Data were analyzed using SPSS version 16 (SPSS Inc.). DFQ indices and fatty acid intakes were adjusted for energy intake as described by Willet.^[15] DFQ indices and fatty acid intake

were compared between the two groups using *t*-test and Mann-Whitney test for normal and non-normal distribution, respectively. For comparing quantitative and qualitative variables across the sex-specific and energy-adjusted quartiles of DFQ indices, ANOVA and Chi-square tests were performed, respectively. The relationship between fatty acid intakes and DFQ indices and the chance of pre-diabetes was analyzed by simple logistic regression.

Results

Table 1 shows DFQ indices and fatty acids intake in control and pre-diabetic subjects. Median of AI was higher in pre-diabetic subjects ($P < 0.001$). In addition, TI, h:H and P:S ratios had a lower median in this group ($P < 0.004$). However, no difference was found between the two groups with respect to *n*-3:*n*-6 ratio. Moreover, the median of SFAs was higher, but total PUFA, *n*-3, *n*-6 fatty acids and HEI were lower in the pre-diabetic subjects compared with the control group ($P < 0.02$).

Subject at higher quartiles of AI tend to have higher BMI (29.2 vs 27 kg/m²), WC (93.6 vs 88 cm), FBG (103.3 vs 88.2 mg/dl) and OGTT (137.8 vs 128 mg/dl) (p -trend < 0.002); whereas higher h:H ratio was related with lower BMI (26.5 vs 29.7 kg/m²), WC (87.3 vs 95.1 cm), FBG (88.4 vs 103.6 mg/dl) and OGTT (127.6 vs 139.5 mg/dl) (p -trend < 0.001). P:S ratio was associated with lower FBG (89.7 vs 103.3 mg/dl) and OGTT (126.5 vs 139.4 mg/dl) (p -trend < 0.001). TI also indicated a negative association with FBG (93.1 vs 100.3 mg/dl) and OGTT (129.6 vs 136.1 mg/dl) (p -trend < 0.01) (data not shown).

Table 1: Energy-adjusted DFQ indices and fatty acids intake* in control and pre-diabetic subjects

	Control (n=150)		Pre-diabetic (n=147)		P [†]
	Median	IQR	Median	IQR	
AI	0.6	0.28	0.9	0.45	<0.001**
TI	9.5	3.5	8.2	3.4	0.004**
h:H ratio	1.5	0.6	1.2	0.40	<0.001**
<i>n</i> -3: <i>n</i> -6 ratio	0.01	0.02	0.01	0.01	0.6
P:S ratio	0.70	0.44	0.45	0.36	<0.001**
SFA (g)	21.95	7.02	26.33	9.15	<0.001**
MUFA (g)	20.33	6.35	21.29	5.88	0.4
<i>n</i> -3 PUFA (g)	0.20	0.15	0.18	0.14	0.01**
<i>n</i> -6 PUFA (g)	13.9	7.7	11.01	7.78	0.003**
Total PUFA (g)	15.16	8.01	12	8.17	<0.001
HEI	55.05	9.94	47.20	8.50	<0.001**

AI=Atherogenicity index, TI=Thrombogenicity index, h:H=Hypocholesterolemic:hypercholesterolemic fatty acids, P:S=Polyunsaturated:saturated fatty acids, SFA=Saturated fatty acids, MUFA=Monounsaturated fatty acid. PUFA=Polyunsaturated fatty acid, HEI=Healthy eating index, IQR=Inter-quartile range, *Values are median±IQR. †*t*-test for normally distributed variables and Mann-Whitney test for non-normally distributed variables, **Significant at $P < 0.05$

After adjustment for confounding variables, a positive association between the highest intake of SFA, myristic, palmitic acid and pre-diabetes were found (p -trend < 0.04). An inverse association between intake of *n*-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid, arachidonic acid, and pre-diabetes were observed (p -trend < 0.05) [Table 2].

The OR of pre-diabetes across quartiles of DFQ indices is presented in the two different models in Table 3. After adjustment for confounders, subjects in the lowest AI had lower OR for pre-diabetes compared with those in the highest quartile (p -trend < 0.001). In addition, there was an inverse association between *n*-3:*n*-6 and h:H ratios with pre-diabetes (p -trend < 0.001). TI and P:S ratios showed a positive and negative association, respectively, in the unadjusted models. However, these results have not remained significant after adjustment.

Discussion

The result of the present study shows that AI was positively, whereas h:H and *n*-3: *n*-6 ratios were negatively associated with the chance of pre-diabetes. There was a significant positive relationship among SFA, myristic, palmitic acids and pre-diabetes. In addition, *n*-3 PUFA, EPA, DHA, ARA intake showed a negative association with pre-diabetes.

So far, the association between AI and h:H ratio with pre-diabetes have not been examined. The observed association between AI and h:H with pre-diabetes may be due to the effects of SFA such as myristic and palmitic acids which have been shown to induce insulin resistance in animals.^[16] Short-term consumption of SFAs enriched diet induced the whole body insulin resistance in both normal and impaired glucose tolerant subjects.^[17] Metabolic response to SFAs can be related to the induction of serine-phosphorylation through activating specific serine kinases which result to decrease in insulin-regulated glucose transporter-4 (GLUT-4) activity and consequently less glucose uptake.^[18] SFAs can also affect insulin sensitivity by altering the membrane lipid composition which leads to the disorientation of membrane glucose transporter molecules.^[19]

Inverse associations between *n*-3 PUFA, EPA, DHA, and *n*-3:*n*-6 ratio with pre-diabetes found in the present study is in line with an earlier study that found higher *n*-3 PUFA intake, particularly EPA and DHA from a marine source, may increase insulin sensitivity.^[20] Switching to diets with higher *n*-3:*n*-6 ratio such as the Mediterranean diet caused increased insulin sensitivity.^[21] High *n*-3:*n*-6 PUFA diets in rat exerted a positive effect on metabolic parameters including body and visceral fat weight, blood lipids, glucose tolerance, and insulin sensitivity as well as decreased expression of pro-inflammatory cytokines which all can decrease the risk of insulin resistance and metabolic disorders.^[22] A review study stated that lower *n*-3:*n*-6 ratio plays an important role in increasing the development of obesity which contributes

Table 2: OR and 95% CI for pre-diabetes across quartiles of sex specific and energy-adjusted dietary fat intake*

	Q1	Q2	Q3	Q4	P-trend
Total Fat					
Model 1	1 (REF)	0.79 (0.34-1.84)	0.60 (0.24-1.47)	1.75 (0.72-2.24)	0.3
Model 2		0.87 (0.30-2.0)	0.68 (0.27-1.70)	1.83 (0.75-4.47)	0.2
SFA					
Model 1	1.00	0.58 (0.24-1.36)	1.20 (0.52-2.80)	3.17 (1.28-7.85)	0.004**
Model 2, MUFA, PUFA, trans		0.70 (0.26-1.85)	1.49 (0.50-4.41)	3.84 (0.92-15.90)	0.03**
Lauric acid					
Model 1	1.00	1.04 (0.45-2.43)	1.51 (0.66-3.46)	3.31 (1.71-10.87)	0.001**
Model 2, MUFA, PUFA, trans		1.02 (0.39-2.65)	1.30 (0.46-3.66)	2.20 (0.50-9.59)	0.2
Myristic acid					
Model 1	1.00	1.06 (0.44-2.51)	2.25 (0.98-5.20)	9.11 (3.27-25.34)	<0.001**
Model 2, MUFA, PUFA, trans	1.00	1.40 (0.53-3.65)	3.13 (1.07-9.11)	11.39 (2.70-48.07)	0.001**
Palmitic acid					
Model 1	1.00	0.79 (0.33-1.90)	3.39 (1.42-8.12)	6.57 (2.51-17.15)	<0.001**
Model 2, MUFA, PUFA, trans		0.95 (0.37-2.47)	4.24 (1.58-11.36)	6.34 (1.96-20.52)	<0.001**
Stearic acid					
Model 1	1.00	0.62 (0.26-1.46)	2.13 (0.91-4.99)	1.33 (0.56-3.15)	0.1
Model 2, MUFA, PUFA, trans		0.61 (0.24-1.54)	1.80 (0.70-4.65)	0.78 (0.27-2.24)	0.8
MUFA					
Model 1	1.00	0.21 (0.008-6.07)	0.10 (0.006-1.97)	0.15 (0.009-2.60)	0.8
Model 2, SFA, PUFA, trans		0.24 (0.01 0-5.91)	0.08 (0.006-1.35)	0.07 (0.004-1.38)	0.2
Oleic acid					
Model 1	1.00	0.82 (0.35-1.93)	1.06 (0.47-2.39)	1.65 (0.70-3.89)	0.20
Model 2, SFA, PUFA, trans		0.89 (0.35-2.27)	1.07 (0.39-2.96)	2.20 (0.56-8.82)	0.28
PUFA					
Model 1	1.00	0.73 (0.30-1.74)	0.80 (0.34-1.92)	0.93 (0.38-2.27)	0.9
Model 2, SFA, MUFA, trans		0.88 (0.34-2.27)	1.15 (0.42-3.10)	1.10 (0.40-3.0)	0.7
Trans fatty acid					
Model 1	1.00	0.59 (0.25-1.39)	1.26 (0.55-2.90)	3.25 (1.25-8.42)	0.004**
Model 2, SFA, PUFA, trans		0.65 (0.26-1.61)	1.22 (0.48-3.10)	2.45 (0.79-7.59)	0.06
Dietary cholesterol					
Model 1	1.00	0.99 (0.42-2.31)	0.83 (0.36-1.95)	1.49 (0.64-3.43)	0.4
Model 2, SFA, MUFA, PUFA, trans		1.03 (0.40-2.61)	0.77 (0.29-2.05)	0.88 (0.31-2.48)	0.6
n-3 PUFA					
Model 1	1.00	0.80 (0.34-1.89)	0.69 (0.29-1.68)	0.21 (0.08-0.54)	0.001**
Model 2, SFA, MUFA, trans, n-6		0.90 (0.36-2.27)	0.52 (0.20-1.36)	0.12 (0.04-0.37)	<0.001**
α-Linolenic acid					
Model 1	1.00	0.86 (0.37-1.99)	0.79 (0.34-1.83)	1.90 (0.79-4.53)	0.1
Model 2, SFA, MUFA, trans, n-6		1.009 (0.41-2.47)	0.88 (0.35-2.22)	1.54 (0.56-4.21)	0.3
DHA					
Model 1	1.00	0.42 (0.16-1.07)	0.34 (0.14-0.84)	0.06 (0.02-1.76)	<0.001**
Model 2, SFA, MUFA, trans, n-6		0.45 (0.16-1.23)	0.39 (0.15-1.01)	0.06 (0.02-0.18)	<0.001**
EPA					
Model 1	1.00	0.34 (0.13-0.87)	0.31 (0.12-0.76)	0.05 (0.01-0.15)	<0.001**
Model 2, SFA, MUFA, trans, n-6		0.36 (0.13-0.98)	0.34 (0.13-0.88)	0.05 (0.01-0.16)	<0.001**

Contd...

Table 2: Contd...					
	Q1	Q2	Q3	Q4	P-trend
<i>n</i> -6 PUFA					
Model 1	1.00	0.76 (0.32-1.80)	0.76 (0.32-1.79)	0.94 (0.39-2.26)	0.9
Model 2, SFA, MUFA, trans, <i>n</i> -3		1.10 (0.40-3.01)	1.35 (0.46-3.90)	1.15 (0.40-3.27)	0.8
Linoleic acid					
Model 1	1.00	0.37 (0.15-0.89)	0.61 (0.25-1.46)	0.74 (0.30-1.82)	0.9
Model 2, SFA, MUFA, trans, <i>n</i> -3		0.50 (0.18-1.36)	1.10 (0.38-3.16)	0.86 (0.30-2.47)	0.9
Arachidonic acid					
Model 1	1.00	0.77 (0.30-1.92)	0.68 (0.30-1.54)	0.60 (0.25-1.43)	0.2
Model 2, SFA, MUFA, trans, <i>n</i> -3		0.67 (0.24-1.87)	0.58 (0.24-1.41)	0.34 (0.12-0.95)	0.04**

Model 1=Adjusted for waist circumference, physical activity, energy intake and HEI. Model 2=Adjusted for Model 1 and additional adjustment for fatty acids as indicated in the table. *Values are OR and 95% CI. **Significant at $P<0.05$

Table 3: OR and 95% CI for pre-diabetes across quartiles of sex specific and energy-adjusted dietary fat quality*						
Dietary fat quality indice	Odds ratio (95% CI)	Q1	Q2	Q3	Q4	P-trend
AI						
Model 1	OR (95% CI)	1.00	2.07 (1.01-4.25)	5 (2.45-10.20)	12.36 (5.70-26.80)	<0.001**
	<i>P</i>		0.04	<0.001	<0.001	
Model 2	OR (95% CI)	1.00	2.2 (0.91-5.50)	4 (1.64-9.82)	6.68 (2.57-17.34)	<0.001 **
	<i>P</i>		0.06	0.002	<0.001	
TI						
Model 1	OR (95% CI)	1.00	0.46 (0.25-0.96)	0.62 (0.20-0.75)	0.68 (0.21-0.80)	0.01**
	<i>P</i>		0.50	0.39	0.41	
Model 2	OR (95% CI)	1.00	0.71 (0.30-1.68)	0.96 (0.39-2.34)	0.82 (0.34-1.95)	0.8
	<i>P</i>		0.44	0.93	0.65	
h:H ratio						
Model 1	OR (95% CI)	1.00	0.31 (0.15-0.64)	0.14 (0.06-0.30)	0.08 (0.04-0.18)	<0.001 **
	<i>P</i>		0.002	<0.001	<0.001	
Model 2	OR (95% CI)	1.00	0.61 (0.24-1.55)	0.22 (0.08-0.55)	0.20 (0.07-0.52)	<0.001 **
	<i>P</i>		0.30	0.001	0.001	
P:S ratio						
Model 1	OR (95% CI)	1.00	0.36 (0.18-0.73)	0.20 (0.10-0.42)	0.13 (0.06-0.28)	<0.001 **
	<i>P</i>		0.005	<0.001	<0.001	
Model 2	OR (95% CI)	1.00	0.74 (0.30-1.81)	0.58 (0.23-1.43)	0.51 (0.19-1.32)	0.1
	<i>P</i>		0.52	0.24	0.16	
<i>n</i> -3: <i>n</i> -6 ratio						
Model 1	OR (95% CI)	1.00	1.20 (0.63-2.29)	1.37 (0.72-2.61)	1.17 (0.61-2.23)	0.7
	<i>P</i>		0.5	0.3	0.6	
Model 2	OR (95% CI)	1.00	0.60 (0.25-1.45)	0.67 (0.28-1.59)	0.37 (0.14-0.93)	<0.001**
	<i>P</i>		0.26	0.37	0.03	

Model 1=Crude, Model 2=Adjusted for waist circumference, physical activity, energy intake and healthy eating index, *Values are OR and 95% CI, **Significant at $P<0.05$

to the development of insulin resistance and T2DM.^[23] From a molecular perspective, omega-3 fatty acids pose the

protective effects against obesity by reducing fat deposition in adipose tissue, suppressing lipogenic enzymes and increasing

β -oxidation of fatty acids.^[24] Moreover, *n*-3 PUFA, especially EPA, exert anti-inflammatory properties. This effect seems to be reflected in protection against the development of insulin resistance and impaired glucose homeostasis.^[25]

In this study, we have controlled for important confounders that are known to affect insulin sensitivity and DFQ including WC, physical activity, energy intake, HEI, and dietary fatty acids. However, this case-control study has some limitations including the design of the study that impaired the ability to establish a causal relationship between dietary fatty acid intake, DFQ, and pre-diabetes. Moreover, the food frequency questionnaire is subject to some potential errors. Finally, these findings might not be generalizable to other populations, due to ethnic and cultural differences. However, we believe that our study brings new insights into the relationship between DFQ and chance of pre-diabetes. Our result suggests that overall DFQ may be important in pre-diabetes morbidity. Nevertheless, randomized controlled trials are required to adequately investigate the effect of DFQ on pre-diabetes prevention.

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Conflicts of interest

There are no conflicts of interest.

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Appendices I: STROBE Statement-Checklist of items that should be included in reports of case-control studies

	Item no	Recommendation	Reported on section
Title and abstract	1	(a) Indicate the study design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Title Title and abstract
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any pre-specified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (b) For matched studies, give matching criteria and the number of controls per case	Methods Methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement) Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Discussion
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how matching of cases and controls was addressed (e) Describe any sensitivity analyses	Methods - Methods Methods Methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study, for example, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Results Results -
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, and social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Results and tables Results
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Results and tables
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% CI). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results and tables - -