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Association between dietary insulin index and load and psychological disorders

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Abstract

The present study was carried out to determine whether the dietary insulin index (DII) and dietary insulin load (DIL) are related to psychological disorders in a cross-sectional study among adults. A total of 3172 Iranian adults (age range of 18–55 years) were included. Data on dietary intakes were collected using a validated dish-based 106-item semi-quantitative FFQ. DII and DIL were calculated using food insulin index values published earlier. To assess depression and anxiety, an Iranian validated version of the Hospital Anxiety and Depression Scale was used. Furthermore, psychological distress was examined using the General Health Questionnaire. Among women, a significant positive association was seen; such that women in the highest quartile of DIL had higher odds of depression than those in the lowest quartile (OR 1·84; 95 % CI 1·14, 2·96). In terms of DII, in the fully adjusted model, women in the top quartile of DII were more likely to be depressed compared with those in the bottom quartile (OR 1·65; 95 % CI 1·05, 2·58). In conclusion, we found a significant positive association between DIL and DII and odds of depression among women, but not in men. However, such findings were not seen for anxiety and psychological distress.

Key words: **Anxiety: Depression: Dietary insulin index: Dietary insulin load: Psychological distress**

Hyperinsulinaemia is linked to the development of various chronic diseases including obesity, diabetes, CVD and some cancers[1–3]. It has been reported that hyperinsulinaemia is also involved in the pathophysiology of psychological disorders[4–6]. Coexistence of psychological disorders and diabetes might further highlight the role of hyperinsulinaemia in these conditions[7]. However, the underlying mechanistic link between depressive symptoms and insulin resistance remains unknown.

Given the role of lifestyle-related factors, including diet, in both psychological disorders and diabetes, finding a common dietary factor that might contribute to both conditions is of high interest. Great attention has been given to carbohydrate consumption in this regard. Consumption of a high-glycaemic index (GI) and high-glycaemic load (GL) diet has been associated with increased risk of psychological disorders[8]. This direct association might be explained by the post-ingestive tendency to hypoglycaemia following such a diet, eliciting central dysfunction and depression[7]. Some studies have also attributed such an association to hyperinsulinaemia, which has been independently related to psychological disorders[9,10]. The link between hyperinsulinaemia and psychological disorders might be explained by facilitating the transport of tryptophan, a precursor of serotonin, into the brain[11]. Indeed, the synthesis of serotonin is a function of the tryptophan level in the brain, which, in turn,

Abbreviations: DII, dietary insulin index; DIL, dietary insulin load; DS-FFQ, dish-based 106-item semi-quantitative FFQ; FII, food insulin index; GHQ, General Health Questionnaire; GI, glycaemic index; GL, glycaemic load; SEPAHAN, Study on the Epidemiology of Psychological, Alimentary Health and Nutrition.

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depends upon the uptake of this amino acid from circulating blood. Due to the competition between tryptophan and other large neutral amino acids, it has been suggested that the rate of serotonin synthesis in human brain would also be dependent to the alterations in plasma amino acid ratios, which in turn can be influenced by changes in insulin concentrations[11]. Thus, it is evident that hyperinsulinaemia may contribute to the development of serious mental disorders including depression. It must be kept in mind that dietary GI or GL does not consider the role of other insulinotropic factors including certain amino acids and fatty acids[12,13]. Therefore, a dietary insulin index (DII), which systematically quantifies postprandial insulin responses to all dietary factors, has been suggested[14]. Dietary insulin load (DIL), which is calculated by summing up the product of food insulin index (FII), energy content and consumption frequency of food items, has been indicated to provide a more accurate prediction of insulin demand than carbohydrate content or glycaemic load[15]. These indices have been linked with several chronic conditions in earlier studies; however, we are aware of no earlier study linking DII and DIL with the risk of psychological disorders. Given the lack of evidence of the association between DII and DIL and psychological disorders along with the high consumption of carbohydrates, in particular refined carbohydrates in the Middle-East, we thought that examining the association between DII and DIL and psychological disorders in this part of the world might provide additional information for nutritionists. We hypothesised that a high DII might be associated with a greater risk of psychological disorders. Therefore, the purpose of the present study was to investigate the association between DII and DIL and psychological disorders among Iranian adults.

Study population and methods

Participants

The present cross-sectional study was conducted within the framework of the Study on the Epidemiology of Psychological, Alimentary Health and Nutrition (SEPAHAN) project, which was performed on a large population of Iranian adults working in fifty different health centres in Isfahan, Iran. Detailed information about SEPAHAN project has been described elsewhere[16]. Briefly, data collection was done in two separate main phases to achieve greater high accuracy of collected data. At the first phase, data on demographic variables along with dietary intakes were collected for 8691 people. At the second phase, data regarding psychological health were collected. By merging data from both phases, we had complete information for 4763 people[16]. In the present analysis, we excluded participants who did not have total energetic intakes at the range of 3347–17 573 kJ/d as under-reporters and over-reporters of energy intake (n 1271). Furthermore, women with pregnancy and lactation (n 190) and also participants with missing data on anthropometric information as well as dietary intakes were excluded (n 130). After these exclusions, a dataset of 3172 participants including 1398 men and 1774 women was available for the present analysis. Comparing individuals participated at first and those remained for final analysis, no significant difference was found between the general characteristics[17]. All participants provided signed informed written consent forms. The whole project of SEPAHAN was ethically approved by the Bioethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran[16].

Dietary intake assessment

The usual dietary intakes of participants were assessed via a validated Willett-format[18] dish-based 106-item semi-quantitative FFQ (DS-FFQ) which was designed particularly for Iranian adults[19]. Details on design, food items and validity of this FFQ have been reported previously[19]. In brief, first, we prepared a comprehensive list of foods and dishes commonly consumed by Iranian adults. Then, we chose those foods which were nutrient-rich, consumed reasonably often or contributed to between-person variations from this list. Selecting a food as a usual food item was done according to dietary records and recalls that had been collected in our prior investigations. Finally, 106 food items in five different categories were included in this questionnaire: (1) mixed dishes (cooked or canned, twenty-nine items); (2) carbohydrate-based foods (different types of bread, cakes, biscuits and potatoes, ten items); (3) dairy products (dairies, butter and cream, nine items); (4) fruits and vegetables (twenty-two items) and (5) miscellaneous food items and beverages (including sweets, fast foods, nuts, desserts and beverages, thirty-six items).

We asked individuals to report their dietary intakes of foods and mixed dishes based on nine multiple-choice frequency response categories varying from 'never or less than once a month' to 'twelve or more times per day.' The frequency response categories for all food items were not constant and varied from six to nine choices. We omitted the high-frequency categories for foods consumed infrequently and increased the number of multiple-choice categories for common foods with a high frequency. Furthermore, in order to increase the accuracy of responses, we used the most popular serving sizes familiar to Iranian adults. Finally, we calculated daily intakes of all foods and dishes and converted to g/d using household measures[20]. Then, in order to compute the daily energy and nutrient intakes of each participant, we summed up the energy and nutrient contents of all foods and dishes. Energy and nutrient contents of each food were obtained using the US Department of Agriculture's national nutrient databank[21].

The validity of the DS-FFQ was evaluated in a subgroup of 200 randomly selected participants of SEPAHAN project[19,22]. All participants in the validation study completed the DS-FFQ at study baseline and 6 months later. During this validation study, 3-d detailed dietary records, which were used as a 'gold standard', were provided by individuals. According to findings from the present study, the DS-FFQ could provide reasonably valid and reliable measures of long-term dietary intakes in Iranian population; for instance, dietary carbohydrate intake estimated from the DS-FFQ was significantly correlated with the values obtained from the average of 3-d dietary records (r 0·81). Such correlation coefficients were also seen for other food groups and nutrients including Mg (r 0·61), proteins (r 0·72) and legumes and nuts consumption (r 0·69).

Calculation of dietary insulin index and load

After considering the components of mixed dishes, we converted all items in the DS-FFQ into a separate food item. FII refers to the incremental insulin AUC over 2 h in response to the consumption of a 1000-kJ portion of the test food divided by the AUC after ingestion of a 1000-kJ portion of the reference food. FII for each food item was obtained from previous studies published by Brand-Miller *et al.*[14]. For food items in the present study that was not available in the food list published by Brand-Miller *et al.*, we used the FII for similar food items. To determine DIL, we first calculated the insulin load of each food using the following formula:

$$\text{Insulin load of a given food} = \text{insulin index of that food} \times \text{energy content of that food (kJ/d)}$$

By summing up the insulin load of each food, DIL was obtained for each person. Then, we calculated the DII for each participant by dividing DIL by total energy intake.

Psychological profile assessment

Anxiety and depression were assessed by the Iranian validated version of Hospital Anxiety and Depression Scale which provided valid measures of mental health on the basis of the previous study[23]. This scale is a brief and useful questionnaire to examine psychological disorders in addition to symptom and severity of anxiety disorders and depression[23]. It contains fourteen items with a four-point scale for each item and consists of two subscales: anxiety and depression; higher scores indicate the greater degree of anxiety and depression. The possible score range is from 0 to 21 for each subscale. Scores of 8 or more on either subscale were considered to indicate the presence of psychological disorders, and scores of 0–7 were defined as 'normal' in the present study[23]. Overall, our previous investigations revealed that the questionnaire provides relatively valid measures of mental health[23].

To assess psychological distress, we used the Iranian validated version of the General Health Questionnaire (GHQ) which contained twelve items[24]. Each item constitutes a four-point rating scale (less than usual, no more than usual, rather more than usual or much more than usual). We used the bimodal scoring method (0-0-1-1) in order to calculate the total score of psychological distress for each participant. The scores obtained by this method ranges from 0 to 12; higher scores indicate a greater degree of psychological distress. In our study, we considered the score of 4 or more as having psychological distress[25]. The validity of these scores to identify patients with psychological distress was examined in earlier studies[26]. Based on comparison with clinical cases, the investigators reported that the cutoff score of 4 or more was more accurate to effectively identify persons with mental illness[27]. Therefore, in order to determine the thresholds linked with optimum sensitivity and specificity of the GHQ-12, we considered this cutoff score as well.

The convergent validity of GHQ-12 was examined in 748 Iranian young people. A significant inverse correlation was observed between the GHQ-12 and global quality of life scores (r −0·56, $P < 0·0001$)[24].

Assessment of covariates

We used a self-administered questionnaire in order to obtain data on age, sex, marital status (single/married), education (high school diploma or below/above high school diploma), smoking status (non-smoker/former smoker/current smoker), family size (≤4/>4 members), homeownership (owner/non-owner), disease history (diabetes, asthma, colitis, stroke, myocardial infarction, heart failure and cancers), current use of antipsychotic medications (including nortriptyline, amitriptyline or imipramine, fluoxetine, citalopram, fluvoxamine and sertraline) and dietary supplements (including intake of Fe, Ca, vitamins and other dietary supplements). Assessing physical activity of study participants was carried out via a General Practice Physical Activity Questionnaire which is a simple validated screening tool for grading adult people's physical activity by focusing on current general activities. In the present analysis, participants were classified into two categories: physically active (≥1 h/week) and physically inactive (<1 h/week). The validity of the General Practice Physical Activity Questionnaire for assessment of habitual physical activity levels has been examined elsewhere[16]. To gather information on anthropometric measures including weight and height, we used a self-reported questionnaire. BMI was calculated as weight in kg divided by the height in m^2. The validity of self-reported weight and height was examined in a pilot study on 200 participants from the same population. This validation study revealed that correlation coefficients for self-reported weight and height *v.* technician-measured values were 0·95 ($P < 0·001$) and 0·83 ($P < 0·001$), respectively. Also, the correlation coefficient for computed BMI from self-reported values and the one from measured values was 0·70 ($P < 0·001$). Therefore, self-reported values of anthropometric indices provide reasonably valid measures in the present study[28].

Statistical analysis

In the present study, we first obtained energy-adjusted DIL and DII by the use of the residual method[29]. In this method, a linear regression model was constructed, in which total energy intake was considered as an independent variable and DII and DIL as a dependent variable. Then, the mean DII and DIL in the whole study population plus residuals from this regression model were considered as energy-adjusted DII and DIL. The bivariate Pearson correlation revealed that these values were no longer correlated with total energy intake. Then, we categorised men and women by quartiles of energy-adjusted DIL and DII, and all statistical analyses were separately done for both sex. We applied the one-way ANOVA to examine significant differences in continuous variables including age, BMI and the prevalence of psychological disorders across quartiles of DIL and DII. The χ^2 test was used to assess the distribution of men and women in terms of categorical variables across quartiles of DIL and DII. To compare dietary intakes of food groups and nutrients across quartiles of DIL and DII, ANCOVA was applied. To determine the association of DIL and DII with psychological disorders, binary logistic regression was used in different models. In the first model, we adjusted for age (continuous) and energy intake. Further adjustment was done for marital status (single/married),

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education (under university/university graduated), smoking status (non-smoker/former smoker/current smoker), family size (≤4/>4 members), homeownership (owner/non-owner), diabetes mellitus (yes/no), dietary supplement use (yes/no) and antipsychotic medications (yes/no) in the second model. In the final model, BMI (continuous) was additionally controlled to see if the associations are independent of obesity. All confounding variables were established risk factors for psychological disorders based on literature. The first quartile of DIL and DII was considered as the reference category in all analyses. To find the overall trend of OR across increasing quartiles of DIL and DII, we considered these quartiles as an ordinal variable in the logistic regression models. Education-stratified analysis (under university/university graduated) was also done. Moreover, in additional analysis, DII and DIL, as well as scores of psychological disorders, were considered as continuous variables and the associations were examined through linear regression analysis. All statistical analyses were conducted using SPSS software (version 19.0; SPSS Inc.). *P* values were considered significant at <0·05.

Results

The mean age of men and women was 38·4 (SD 8·2) and 35·1 (SD 7·4) years, respectively. Prevalence of depression, anxiety and psychological distress was 6·5, 3·7 and 16·6 % among men and 12·9, 6·8 and 27·1 % among women, respectively.

General characteristics of men and women across quartiles of DIL and DII are provided in Table 1. Compared with women in the bottom quartile, those in the top quartile of DIL were less likely to be a current smoker. However, men in the highest quartile of DIL were more likely to be university graduated compared with those in the lowest quartile. In terms of DII, women in the fourth quartile of DII were less likely to be a current smoker than those in the first quartile. In addition, men in the highest quartile of DII were more likely to be university graduate than those in the lowest quartile.

Selected food and nutrient intakes of men and women across quartiles of DIL and DII are shown in Table 2. Men and women in the top quartile of DIL had greater intakes of whole grains, refined grains, dairy products and carbohydrate and had lower intakes of fruits, red meat, fish, legume and nuts, energy, protein and fat compared with those in the bottom quartile. Within DII, men and women in the top quartile had greater intakes of whole grains, refined grains, dairy products, carbohydrate and fibre and had lower intakes of fruits, vegetables, red meat, fish, legume and nuts, protein and fat than those in the bottom quartile.

Multivariable-adjusted OR for depression, anxiety and psychological distress across quartiles of DIL and DII in men and women are indicated in Table 3. After controlling for confounders, women in the top quartile of DIL had higher odds of depression compared with those in the first quartile (OR 1·84; 95 % CI 1·14, 2·96). No other significant association was found between DIL and psychological disorders either in men or in women. In terms of DII, in the fully adjusted model, women in the top quartile of DII were more likely to be depressed compared with those in the bottom quartile (OR 1·65; 95 % CI 1·05, 2·58). Neither in crude nor in adjusted models, we observed other significant relationships between DII and psychological disorders among men and women.

Education-stratified multivariable-adjusted OR for depression, anxiety and psychological distress across quartiles of DIL and DII are shown in Table 4. Neither in crude nor in adjusted models, we observed a significant relationship between DII and DIL and psychological disorders among men and women based on their educational levels.

Regression coefficients for the relationship between DIL and DII and psychological disorders, when all were considered as continuous variables, are indicated in Table 5. Although no significant linear association was seen between DIL and DII and depression as well as anxiety scores, we found that DIL and DII were significantly associated with scores of psychological distress.

Discussion

In this cross-sectional study, we found that greater DIL, as well as DII, was linked significantly with higher odds of depression among women, even after adjustment for potential confounders. However, no significant association was seen among men. To our knowledge, the present study is the first to examine the relationship between DIL and DII and depressive symptoms worldwide.

It has long been recognised that major depressive disorders are more prevalent among low socio-economic groups[30]. However, the apparently adverse associations of DIL and DII with psychological disorders persisted in multivariate models accounting for known risk factors. For instance, we controlled the analyses for several variables of economic situation such as family size and homeownership. In addition, most dietary supplements contain several forms of B vitamins and *n*-3 fats, which play a neuroprotective role[31]; therefore, we have taken supplement use into account as a confounder to reach an independent association between DII and DIL and psychological disorders. Some intermediary events, including dyslipidaemia or hypertension, might have led to changes in diet and may, therefore, confound the association between DIL and DII and depression. However, in the present study, we excluded all participants with self-reported chronic conditions.

Depression, a common mental illness, is a globally increasing condition associated with poor quality of life and social outcomes[32,33]. Psychological disorders could be prevented through several strategies emphasising on environmental factors including dietary intakes[34]. Although the link between dietary GI and GL and mental health status has been evaluated in several studies[35], there is no study examining DIL and DII in relation to these disorders.

In the present study, we found a significant positive association between DIL, DII and depression among women, but not in men. Similar to our observations, a cross-sectional study carried out on 976 homebound elderly US subjects, demonstrated that higher GL and GI were associated with a higher risk of depression[8]. Such a positive relationship between dietary GI and depression was also seen in other publications[36]. Dietary GL (but not GI) was inversely linked with depression in 140 elderly Spanish people aged 65–90 years[37]. Others reported

Table 1. General characteristics of men and women across quartiles (Q) of dietary insulin load (DIL) and dietary insulin index (DII) (Mean values and standard deviations; percentages)

	Quartiles of DIL					Quartiles of DII				
	Q1	Q2	Q3	Q4	*P**	Q1	Q2	Q3	Q4	*P**
Men										
n	349	350	350	349	–	349	350	350	349	–
Q ranges	<80 653	80 653 to <94 875	94 875 to <103 945	≥103 945	–	<34	34 to <38	38 to <43	≥43	–
Age (years)					0·91					0·40
Mean	38·2	38·4	38·7	38·3		37·9	38·6	39	38·1	
SD	8·3	8·6	7·9	8·0		8·2	8·9	7·5	8·1	
BMI (kg/m^2)					0·63					0·56
Mean	25·5	25·3	25·3	25·1		25·5	25·4	25·2	25·2	
SD	3·5	3·4	3·5	3·2		3·5	3·5	3·4	3·2	
Marital status (married) (%)	86·8	91·3	90·9	90·7	0·36	86·5	90·7	92·7	89·8	0·12
Education (university graduated) (%)	50·4	45·1	50·6	57·0	0·01	50·7	46·0	49·7	56·7	0·04
Physically active (≥1 h/week) (%)	23·5	22·9	22·3	20·1	0·71	22·9	22·0	24·3	19·5	0·47
Family size (>4 people) (%)	14·0	12·9	12·3	16·9	0·29	13·8	14·0	10·9	17·5	0·09
Smoking status (current smoker) (%)	16·0	15·7	12·9	13·5	0·87	16·6	14·9	12·3	14·3	0·64
Diabetes (%)	4·0	3·7	2·3	1·4	0·13	4·3	3·1	2·3	1·7	0·19
Home ownership (owner) (%)	59·6	58·0	57·4	57·3	0·88	57·6	57·4	59·7	57·6	0·90
Dietary supplement use (%)	12·9	12·6	12·0	9·7	0·56	13·8	12·0	11·7	9·7	0·43
Anti-psychotic medications (%)	3·2	3·7	5·1	2·6	0·30	3·2	4·3	4·6	2·6	0·45
Depression	7·6	5·2	7·7	5·3	0·35	7·4	6·1	6·5	5·9	0·86
Anxiety	4·7	2·9	3·8	3·5	0·66	4·4	3·5	3·9	3·2	0·86
Psychological distress	18·6	14·6	17·1	16·0	0·52	18·6	15·4	16·9	15·5	0·63
Women										
n	443	444	444	443	–	443	444	444	443	–
Q ranges	<80 485	80 485 to <94 957	94 957 to <103 233	≥103 233	–	<34	34 to <38	38 to <42	≥42	–
Age (years)					0·14					0·43
Mean	34·4	35·5	35·5	35·2		34·6	35·3	35·4	35·2	
SD	7·2	7·5	7·6	7·4		7·3	7·3	7·7	7·4	
BMI (kg/m^2)					0·57					0·25
Mean	24·2	24·5	24·6	24·5		24·4	24·6	24·2	24·7	
SD	3·8	4·2	4·0	4·0		4·0	4·0	3·8	4·1	
Marital status (married) (%)	70·1	76·2	75·7	71·4	0·26	70·3	76·7	73·8	72·5	0·48
Education (university graduated) (%)	73·8	69·1	66·0	71·3	0·07	71·3	70·5	68·2	70·2	0·78
Physically active (≥1 h/week) (%)	8·1	8·3	6·5	4·7	0·12	8·8	7·4	6·5	5·0	0·14
Family size (>4 people) (%)	13·3	11·7	12·6	11·3	0·79	13·8	11·0	13·5	10·6	0·34
Smoking status (current smoker) (%)	17·6	14·0	10·6	12·0	0·03	18·7	13·1	9·2	13·1	0·002
Diabetes (%)	1·4	1·1	0·9	0·9	0·89	1·4	1·6	0·5	0·9	0·37
Home ownership (owner) (%)	61·9	59·0	57·4	61·4	0·42	61·2	57·7	59·9	60·9	0·85
Dietary supplement use (%)	44·9	41·7	44·8	38·8	0·20	43·3	43·2	43·0	40·6	0·82
Anti-psychotic medications (%)	7·2	8·8	8·8	5·0	0·09	7·9	8·8	7·4	5·6	0·33
Depression	9·8	13·8	14·0	14·1	0·17	11·4	11·9	13·9	14·6	0·40
Anxiety	6·4	6·7	7·4	6·6	0·94	7·0	6·3	6·6	7·1	0·95
Psychological distress	24·2	30·4	26·8	27·1	0·21	26·2	27·0	28·4	26·9	0·90

* Obtained from ANOVA or χ^2 test, where appropriate.

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Table 2. Dietary and nutrient intakes of men and women across quartiles (Q) of dietary insulin load (DIL) and dietary insulin index (DII) (Mean values with their standard errors)

	Quartiles of DIL									Quartiles of DII								
	Q1		Q2		Q3		Q4			Q1		Q2		Q3		Q4		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P**	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P**
Men																		
Food groups (g/d)																		
Fruits	304·8	12·3	264·9	11·4	271·5	11·8	264·6	11·7	<0·001	262·7	11·0	279·5	11·8	314·6	13·6	248·8	10·4	0·001
Vegetables	286·6	7·7	225·2	6·1	216·4	5·5	218·4	6·5	0·05	258·5	7·4	241·5	6·9	237·8	5·8	208·6	6·3	<0·001
Red meat	120·2	2·9	82·4	2·2	71·1	2·2	64·7	2·1	<0·001	109·5	3·1	89·6	2·5	79·6	2·4	59·6	1·8	<0·001
Fish	16·3	1·0	11·6	1·1	8·2	0·5	6·9	0·5	<0·001	14·9	1·0	12·3	1·2	9·3	0·6	6·5	0·5	<0·001
Legume and nuts	75·9	2·5	54·1	2·0	46·8	1·7	49·6	2·4	<0·001	68·5	2·5	59·6	2·2	50·3	1·7	48·0	2·4	<0·001
Whole grains	38·4	3·5	36·6	3·4	41·7	3·4	64·0	5·8	<0·001	30·0	3·0	40·9	3·8	49·6	3·8	60·2	5·6	<0·001
Refined grains	395·9	9·4	344·8	8·8	334·6	9·9	576·6	14·7	<0·001	372·1	9·5	348·1	9·0	376·2	10·4	555·3	15·1	<0·001
Dairy products	315·7	12·4	335·8	16·9	348·9	14·4	392·6	16·0	0·003	284·1	12·0	335·7	15·1	393·7	16·5	379·5	15·7	<0·001
Nutrients																		
Energy (kJ/d)	11 906·8	158·1	9144·5	157·3	8772·1	181·1	11 672·5	187·8	<0·001	10 900·5	188·6	9531·9	175·3	9916·9	179·4	11 141·9	193·3	<0·001
Protein (g/d)	112·6	1·7	84·0	1·5	78·3	1·7	99·7	1·7	<0·001	103·2	2·0	87·8	1·7	88·7	1·7	95·0	1·7	<0·001
Fat (g/d)	136·6	1·8	96·7	1·5	87·1	1·8	92·5	1·6	<0·001	126·5	2·1	101·1	1·8	97·5	1·7	87·7	1·5	<0·001
Carbohydrate (g/d)	300·5	5·0	252·0	5·1	257·6	5·6	395·8	6·7	<0·001	271·1	5·4	262·1	5·4	293·1	5·7	379·3	7·0	<0·001
Dietary fibre (g/d)	24·8	0·4	19·8	0·4	19·6	0·4	26·9	0·5	<0·001	22·1	0·5	21·1	0·5	22·3	0·4	25·6	0·5	<0·001
Women																		
Food groups (g/d)																		
Fruits	379·4	12·2	316·7	11·0	340·5	13·0	337·1	11·1	0·002	337·4	11·7	329·6	11·3	382·1	13·5	324·4	10·7	0·002
Vegetables	293·5	7·2	231·0	5·8	214·8	5·9	223·6	5·9	<0·001	272·4	7·5	237·6	6·1	238·7	6·0	214·2	5·7	<0·001
Red meat	108·4	2·5	72·0	1·7	59·1	1·6	60·1	2·0	<0·001	97·1	2·5	78·6	2·0	69·7	2·1	54·2	1·6	<0·001
Fish	13·8	0·7	9·7	0·5	8·4	0·4	7·8	0·5	<0·001	12·9	0·7	10·4	0·5	9·0	0·5	7·3	0·5	<0·001
Legume and nuts	64·5	1·8	47·9	1·4	43·0	1·5	40·7	1·2	<0·001	60·2	1·9	49·3	1·5	48·4	1·5	38·2	1·2	<0·001
Whole grains	46·8	4·2	33·7	3·1	32·5	2·6	51·5	4·1	<0·001	34·6	3·1	42·1	4·0	39·8	3·0	47·9	4·0	0·07
Refined grains	393·4	9·3	330·5	8·0	309·2	7·5	464·7	11·6	<0·001	355·0	8·8	344·9	8·4	358·1	8·9	439·6	11·5	<0·001
Dairy products	227·2	9·2	321·4	11·0	381·0	12·9	445·0	13·8	0·06	318·7	11·8	328·6	12·2	364·2	12·1	363·0	13·4	0·01
Nutrients																		
Energy (kJ/d)	11 715·2	130·9	8693·9	135·1	8173·0	155·6	10 124·8	165·6	<0·001	10 577·1	160·6	9156·2	154·3	9447·4	160·6	9521·9	161·0	<0·001
Protein (g/d)	104·7	1·4	76·9	1·2	70·9	1·4	86·0	1·4	<0·001	94·8	1·6	81·4	1·4	81·3	1·4	80·9	1·4	<0·001
Fat (g/d)	129·4	1·5	90·1	1·3	78·7	1·4	84·3	1·4	<0·001	118·8	1·7	94·5	1·6	90·4	1·5	78·8	1·3	<0·001
Carbohydrate (g/d)	314·6	4·3	248·3	4·6	248·8	5·1	337·4	5·8	<0·001	279·3	4·9	261·7	4·8	289·5	5·4	318·6	5·8	<0·001
Dietary fibre (g/d)	25·5	0·4	20·0	0·4	19·5	0·4	24·3	0·4	<0·001	22·8	0·4	21·2	0·4	22·3	0·4	23·1	0·4	0·01

* Obtained from ANOVA.

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Table 3. Risk for psychological disorders according to quartiles (Q) of dietary insulin load (DIL) and dietary insulin index (DII) (Odds ratios and 95 % confidence intervals)

	Quartiles of DIL								Quartiles of DII							
		Q2		Q3		Q4				Q2		Q3		Q4		
	Q1	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}	Q1	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
Men																
Depression																
Crude	1	0·66	0·35, 1·24	1·00	0·57, 1·77	0·67	0·36, 1·25	0·44	1	0·81	0·44, 1·48	0·88	0·48, 1·59	0·78	0·42, 1·44	0·50
Model 1*	1	0·83	0·38, 1·77	1·32	0·66, 2·67	0·60	0·28, 1·26	0·39	1	0·89	0·43, 1·83	1·02	0·51, 2·05	0·66	0·32, 1·39	0·37
Model 2†	1	0·74	0·33, 1·66	1·39	0·67, 2·91	0·70	0·32, 1·51	0·74	1	0·52	0·19, 1·42	0·93	0·38, 2·22	0·67	0·27, 1·65	0·58
Model 3‡	1	0·67	0·29, 1·50	1·15	0·53, 2·46	0·64	0·29, 1·40	0·52	1	0·81	0·38, 1·70	0·75	0·34, 1·63	0·77	0·36, 1·66	0·48
Anxiety																
Crude	1	0·60	0·27, 1·35	0·80	0·38, 1·70	0·74	0·34, 1·59	0·57	1	0·77	0·35, 1·68	0·86	0·40, 1·85	0·72	0·32, 1·60	0·49
Model 1	1	0·47	0·16, 1·35	1·02	0·43, 2·39	0·59	0·26, 1·33	0·37	1	0·62	0·24, 1·60	0·96	0·42, 2·20	0·58	0·24, 1·37	0·34
Model 2	1	0·40	0·13, 1·23	0·94	0·38, 2·33	0·70	0·30, 1·64	0·64	1	0·57	0·21, 1·48	0·80	0·32, 1·96	0·66	0·26, 1·67	0·59
Model 3	1	0·41	0·13, 1·31	0·83	0·31, 2·22	0·64	0·25, 1·64	0·51	1	0·59	0·21, 1·64	0·76	0·29, 2·03	0·73	0·28, 1·91	0·60
Psychological distress																
Crude	1	0·74	0·49, 1·11	0·90	0·61, 1·33	0·83	0·56, 1·23	0·56	1	0·79	0·53, 1·18	0·88	0·60, 1·30	0·80	0·53, 1·18	0·36
Model 1	1	0·88	0·55, 1·41	1·23	0·78, 1·94	0·92	0·60, 1·42	0·91	1	0·91	0·58, 1·43	1·13	0·73, 1·74	0·89	0·57, 1·38	0·85
Model 2	1	0·86	0·53, 1·42	1·19	0·74, 1·93	0·99	0·63, 1·55	0·71	1	0·88	0·55, 1·42	1·10	0·69, 1·74	0·94	0·59, 1·48	0·96
Model 3	1	0·80	0·48, 1·34	1·12	0·68, 1·84	0·94	0·59, 1·50	0·87	1	0·87	0·53, 1·42	1·02	0·63, 1·66	0·93	0·58, 1·50	0·95
Women																
Depression																
Crude	1	1·46	0·96, 2·22	1·49	0·98, 2·26	1·50	0·99, 2·27	0·06	1	1·05	0·69, 1·58	1·25	0·84, 1·87	1·33	0·90, 1·98	0·09
Model 1	1	1·35	0·84, 2·15	1·36	0·84, 2·19	1·55	0·99, 2·44	0·07	1	1·00	0·64, 1·55	1·20	0·78, 1·84	1·38	0·91, 2·10	0·07
Model 2	1	1·46	0·89, 2·40	1·46	0·89, 2·41	1·81	1·13, 2·90	0·02	1	1·07	0·67, 1·71	1·32	0·84, 2·07	1·60	1·03, 2·48	0·02
Model 3	1	1·42	0·86, 2·36	1·47	0·88, 2·44	1·84	1·14, 2·96	0·01	1	1·09	0·68, 1·76	1·32	0·83, 2·09	1·65	1·05, 2·58	0·01
Anxiety																
Crude	1	1·04	0·61, 1·78	1·16	0·68, 1·97	1·03	0·60, 1·77	0·80	1	0·88	0·51, 1·50	0·93	0·55, 1·58	1·01	0·60, 1·69	0·92
Model 1	1	0·79	0·44, 1·43	0·91	0·51, 1·64	0·95	0·54, 1·66	0·94	1	0·79	0·45, 1·38	0·86	0·50, 1·48	0·97	0·57, 1·65	0·98
Model 2	1	0·80	0·43, 1·49	0·88	0·47, 1·64	1·08	0·60, 1·95	0·65	1	0·78	0·44, 1·40	0·87	0·49, 1·54	1·08	0·62, 1·88	0·68
Model 3	1	0·86	0·45, 1·63	0·93	0·48, 1·78	1·21	0·66, 2·22	0·42	1	0·86	0·47, 1·56	0·87	0·48, 1·58	1·19	0·67, 2·11	0·51
Psychological distress																
Crude	1	1·37	1·01, 1·84	1·15	0·85, 1·55	1·16	0·86, 1·57	0·58	1	1·04	0·77, 1·40	1·11	0·83, 1·50	1·03	0·76, 1·39	0·72
Model 1	1	1·33	0·96, 1·85	1·13	0·81, 1·59	1·18	0·86, 1·62	0·57	1	1·00	0·73, 1·36	1·11	0·81, 1·51	1·03	0·75, 1·40	0·68
Model 2	1	1·32	0·94, 1·85	1·10	0·78, 1·57	1·22	0·88, 1·70	0·44	1	0·99	0·71, 1·37	1·10	0·80, 1·52	1·06	0·76, 1·46	0·57
Model 3	1	1·35	0·95, 1·92	1·14	0·80, 1·63	1·26	0·90, 1·77	0·35	1	1·01	0·72, 1·42	1·11	0·80, 1·54	1·09	0·78, 1·52	0·49

* Model 1: adjusted for age and energy intake.
† Model 2: additionally adjusted for marital status, education, family size, smoking status, physical activity, home ownership, diabetes mellitus, dietary supplement use and antipsychotic medications.
‡ Model 3: further controlled for BMI.

Table 4. Risk for psychological disorders according to quartiles (Q) of dietary insulin load (DIL) and dietary insulin index (DII) (Odds ratios and 95 % confidence intervals)

	Quartiles of DIL								Quartiles of DII							
		Q2		Q3		Q4				Q2		Q3		Q4		
	Q1	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}	Q1	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
Under university																
Depression																
Crude	1	1·08	0·66, 1·75	1·11	0·68, 1·80	1·21	0·75, 1·95	0·42	1	0·84	0·51, 1·36	0·93	0·58, 1·49	1·05	0·66, 1·67	0·72
Adjusted model*	1	0·99	0·52, 1·87	1·08	0·57, 2·07	1·40	0·78, 2·49	0·20	1	0·93	0·52, 1·68	1·03	0·58, 1·85	1·27	0·72, 2·22	0·34
Anxiety																
Crude	1	1·02	0·58, 1·79	0·82	0·45, 1·48	0·66	0·35, 1·23	0·15	1	0·81	0·46, 1·43	0·69	0·38, 1·24	0·62	0·34, 1·14	0·10
Adjusted model	1	0·94	0·44, 2·00	0·74	0·32, 1·69	0·87	0·41, 1·81	0·59	1	0·80	0·40, 1·60	0·66	0·31, 1·37	U0·80)	0·39, 1·62	0·44
Psychological distress																
Crude	1	1·59	1·04, 2·42	1·59	1·04, 2·42	1·50	0·98, 2·29	0·35	1	0·76	0·52, 1·10	0·91	0·63, 1·31	0·74	0·51, 1·08	0·24
Adjusted model	1	0·88	0·54, 1·41	0·97	0·59, 1·59	1·03	0·66, 1·60	0·74	1	0·76	0·48, 1·19	1·04	0·67, 1·61	0·90	0·58, 1·39	0·98
University graduated																
Depression																
Crude	1	1·15	0·71, 1·86	1·20	0·74, 1·93	1·28	0·80, 2·05	0·29	1	1·17	0·72, 1·90	1·31	0·81, 2·10	1·33	0·83, 2·14	0·19
Adjusted model	1	1·30	0·73, 2·32	1·31	0·73, 2·32	1·52	0·88, 2·64	0·15	1	1·27	0·73, 2·23	1·32	0·76, 2·28	1·54	0·90, 2·64	0·11
Anxiety																
Crude	1	0·87	0·43, 1·78	1·32	0·69, 2·52	1·31	0·68, 2·50	0·24	1	0·88	0·43, 1·79	1·32	0·69, 2·53	1·32	0·69, 2·51	0·23
Adjusted model	1	0·83	0·37, 1·83	1·28	0·61, 2·66	1·31	0·65, 2·64	0·26	1	0·88	0·41, 1·88	1·24	0·61, 2·53	1·35	0·67, 2·69	0·26
Psychological distress																
Crude	1	1·27	0·93, 1·72	1·10	0·80, 1·50	1·23	0·90, 1·67	0·34	1	1·12	0·82, 1·53	1·07	0·78, 1·46	1·16	0·86, 1·58	0·39
Adjusted model	1	1·41	0·98, 2·02	1·15	0·79, 1·66	1·29	0·91, 1·84	0·33	1	1·21	0·85, 1·71	1·06	0·74, 1·51	1·22	0·86, 1·72	0·40

* Adjusted model: adjusted for age, sex, BMI, energy intake, marital status, education, family size, smoking status, physical activity, home ownership, diabetes mellitus, dietary supplement use and antipsychotic medications.

Table 5. Regression coefficients for the relationship between dietary insulin load (DIL) and dietary insulin index (DII) and scores of psychological disorders
(*β*-Coefficients and 95 % confidence intervals)

	DIL			DII		
	β	95 % CI	*P*	*β*	95 % CI	*P*
Men						
Depression						
Crude	−0·003	−0·11, 0·005	0·43	−0·01	−0·03, 0·01	0·26
Model 1*	−0·002	−0·01, 0·007	0·66	−0·004	−0·02, 0·02	0·72
Model 2†	0·001	−0·008, 0·009	0·84	0·003	−0·02, 0·02	0·83
Model 3‡	<0·001	−0·009, 0·008	0·93	−0·002	−0·02, 0·02	0·88
Anxiety						
Crude	−0·008	−0·01, 0·001	0·06	−0·02	−0·04, −0·002	0·03
Model 1	−0·009	−0·01, 0·001	0·05	−0·02	−0·04, 0·002	0·06
Model 2	−0·006	−0·01, 0·002	0·15	−0·01	−0·04, 0·007	0·14
Model 3	−0·005	−0·01, 0·004	0·23	−0·01	−0·04, 0·009	0·21
Psychological distress						
Crude	<0·001	−0·006, 0·006	0·99	−0·003	−0·02, 0·01	0·72
Model 1	0·001	−0·005, 0·008	0·69	0·004	−0·01, 0·02	0·70
Model 2	0·003	−0·004, 0·009	0·43	0·006	−0·01, 0·02	0·49
Model 3	0·003	−0·004, 0·01	0·37	0·006	−0·01, 0·02	0·51
Women						
Depression						
Crude	0·003	−0·006, 0·01	0·55	0·009	−0·01, 0·03	0·44
Model 1	0·003	−0·007, 0·01	0·58	0·01	−0·01, 0·03	0·41
Model 2	0·002	−0·007, 0·01	0·67	0·01	−0·01, 0·03	0·33
Model 3	0·004	−0·006, 0·01	0·40	0·01	−0·008, 0·04	0·18
Anxiety						
Crude	0·002	−0·008, 0·01	0·70	−0·001	−0·02, 0·02	0·96
Model 1	0·002	−0·009, 0·01	0·68	0·003	−0·02, 0·03	0·85
Model 2	0·002	−0·008, 0·01	0·65	0·007	−0·02, 0·03	0·60
Model 3	0·005	−0·006, 0·01	0·38	0·01	−0·01, 0·04	0·36
Psychological distress						
Crude	0·009	0·001, 0·01	0·02	0·02	0·001, 0·04	0·05
Model 1	0·01	0·001, 0·01	0·02	0·02	0·002, 0·04	0·03
Model 2	0·009	0·001, 0·01	0·02	0·02	0·002, 0·04	0·03
Model 3	0·01	0·002, 0·01	0·01	0·02	0·005, 0·04	0·01

* Model 1: adjusted for age and energy intake.
† Model 2: additionally adjusted for marital status, education, family size, smoking status, physical activity, home ownership, diabetes mellitus, dietary supplement use and antipsychotic medications.
‡ Model 3: further controlled for BMI.

no association between dietary GI and GL during pregnancy and postpartum depression among 865 Japanese women[38]. Additionally, an Australian cross-sectional study reported a positive correlation between dietary GI (but not GL) and depressive symptoms assessed by the Mental Health Index in 1981 adults (≥55 years of age)[39]. Likewise, in a meta-analysis, Salari-Moghaddam *et al.*[40] found a significant effect of a high-GL diet on depression based on data from clinical trials, while no relationship was found between dietary GI and GL and odds of depression summarising published cross-sectional studies. As mentioned, all these studies have focused on dietary GI and GL and nothing is available about DIL and DII and risk of depression. To address the insulin hypothesis more directly, it may be more suitable to use food energy, as the constant, allowing all foods, not just those with sufficient carbohydrate content, to be investigated. In this method, all dietary components and their metabolic interactions could be considered[41]. Additionally, as the aetiological hypothesis addressing the risk of psychological disorders is primarily related to hyperinsulinaemia, therefore using other dietary surrogate measures for the insulin responses such as GI, GL or total carbohydrate intake is indirect and conceptually suboptimal[7]. Hence, we used novel dietary insulin scores to quantify directly the postprandial insulin response. In addition, using DIL and DII is of more significance given that several dietary factors such as fructose, certain amino acids and fatty acids as well as gastrointestinal hormones such as gastric inhibitory peptide, glucagon and cholecystokinin are known to mediate postprandial insulin secretion[42]. Thus, protein- and fat-rich foods might lead to substantial insulin secretion despite producing relatively small blood glucose responses[43,13]. However, some other variables, such as cooking methods, which might interact with the stimulatory effect of glucose, should not be ignored.

In the present study, we reached a sex difference in the relationship between DII and DIL and psychological disorders. The reason for this finding is unclear; however, it might be explained, at least in part, by the influence of gonadal steroids on mood[44,45]. Another reason for this sex disparity might be the difference in the accuracy of reported dietary intakes between men and women. Previous studies have shown that actual food choices[46], self-reported preferences for foods[47] and the accuracy of reported dietary intakes[48] are different between men and women.

The underlying aetiology of the association between dietary insulin indices and depressive symptoms remains unclear; however, several probable mechanisms have been given. Insulin regulation through dietary factors might influence mood disorders as reported by experimental and human studies[9,10,49]. For instance, in a rat model, inactivation of the insulin receptor in the hypothalamus results in systemic insulin resistance, dyslipidaemia as well as depressive-like behaviour[50]. In addition, it has been suggested that consumption of a high glycaemic diet might also lead to insulin resistance which is in turn linked to a pattern of volumetric and neurocognitive repercussions that are highly similar to those reported in individuals suffering from major depression[51]. Another path by which such diets might contribute to depression is their influence on chronic inflammation[52].

The present study has several strengths. As far as we know, this is the first study examining the association between dietary insulin indices and psychological disorders. Additionally, its large sample size of adults, including either sex, should also be considered. Furthermore, in order to reach an independent association between DII and DIL and psychological disorders, we controlled the analyses for several potential confounders such as dietary supplements. Sex-stratified analysis along with the use of a validated FFQ for dietary assessment is among other strengths of the present study. However, the present study had several limitations. The design of our study was cross-sectional, which prohibits us from inferring causality. Therefore, further prospective studies are needed to confirm our findings. In addition, despite the use of a validated FFQ for dietary assessment, some degree of measurement errors and misclassification may have occurred. This is also the case about the outcome of interest and anthropometric indicators in the present study. Even though a significant correlation between self-reported and measured data on different variables was revealed in our validation study, some sort of errors might also occur in this case. In addition, given that no biochemical parameters were measured, some undiagnosed participants with different chronic diseases might be included in the present study[53]. Furthermore, some sort of co-linearity might have occurred in the last model after adjusting for BMI. However, most previous studies have shown a significant association between obesity and mental disorders[54]. In addition, based on our previous publication, DII was also significantly associated with obesity[55]. This is why we adjusted for BMI in an additional model to reach an independent association. Additionally, due to the limited number of foods with a tested FII value, for foods that were not available in the database, we used the values for similar foods.

In conclusion, adherence to a diet with a high DIL as well as high DII was associated with greater odds of depression in women, but not in men. However, such findings were not seen for anxiety and psychological distress. Further studies, in particular with a prospective design, in other populations are required to confirm these findings.

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None of the authors has any conflicts of interest to declare.

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