Association between the Dietary Inflammatory Index with gallstone disease: finding from Dena PERSIAN cohort

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ABSTRACT
Objective The Dietary Inflammatory Index (DII) is a documented nutritional tool for assessing diet-induced inflammation that has been linked to various diseases' outcomes. The association between DII and gallstone disease (GSD) is yet to be explored. The objective of this study was to examine the association between DII and GSD.
Design This cross-sectional study was conducted using the baseline phase data of the Dena PERSIAN cohort. The analysed data included demographic information, lifestyle variables, body mass index, diabetes and fatty liver history, and laboratory test results. The 113-item Food Frequency Questionnaire was used to estimate the dietary intake of participants and quantify the inflammatory potential of the individual's diet. DII score was analysed as a continuous and quartiles variables. Univariable and multivariate logistic regressions were used to investigate the relationship between GSD and DII scores.
Results Out of 3626 individuals entering the study, 173 (4.77%) had GSD. The median DII was −0.08 (IQR=0.18). In the unadjusted model, the odds of having GSD were significantly higher in the first and second quartiles of DII (anti-inflammatory diet) than in higher quartiles (proinflammatory diet). In the adjusted model, the odds of having GSD in the third and fourth quartiles of DII scores compared with the first quartile were OR=0.59 (95% CI 0.36 to 0.95) and OR 0.51 (95% CI 0.30 to 0.84), respectively.
Conclusion The results of this study suggest that a proinflammatory diet is associated with a reduced chance of GSD. However, longitudinal studies are needed to examine the causal association.

INTRODUCTION
Gallstone disease (GSD) is a common gastrointestinal tract disease and a major cause of hospital admissions due to gastrointestinal tract disease and a major cause of healthcare systems. For these reasons, GSD can be considered an important public health issue.

Prevalence and clinical manifestations

- Gallstones can be classified into two categories: cholesterol gallstones and pigment gallstones. Cholesterol gallstones, which make up more than 70% of gallstone cases, are commonly associated with obesity and other factors affecting cholesterol concentration in the bile.13 Pigment gallstones, however, are more associated with biliary infections and haemochromatosis.14 15

- The risk factors for GSD include old age, female sex, ethnicity, pregnancy, family history, sedentary lifestyle, obesity and weight gain.7 Diet is a major lifestyle factor that plays a vital role in countries, 2.5–10% in African populations and 3.1–6.1% in Asian people.2 6 7 However, in Iran, the prevalence of GSD is less than 1%.8

- Roughly 3%–8% of GSD patients suffer from complications, such as cholecystitis, gallstone ileus, pancreatitis, empyema and gallbladder perforation.9–11 Thus, the management of GSD could be expensive and impose a considerable burden on a budget of healthcare systems. For these reasons, GSD can be considered an important public health issue.

- Gallstones can be classified into two categories: cholesterol gallstones and pigment gallstones. Cholesterol gallstones, which make up more than 70% of gallstone cases, are commonly associated with obesity and other factors affecting cholesterol concentration in the bile.13 Pigment gallstones, however, are more associated with biliary infections and haemochromatosis.14 15 The risk factors for GSD include old age, female sex, ethnicity, pregnancy, family history, sedentary lifestyle, obesity and weight gain.7 Diet is a major lifestyle factor that plays a vital role in

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ The association of the Dietary Inflammatory Index (DII) with some diseases has been investigated in recent years but here is no information for the association between DII and gallstones in the previous studies.

WHAT THIS STUDY ADDS
⇒ DII was lower in patients with a history of gallstone disease (GSD).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Since, this is the first study to investigate this relationship, further studies are needed to clarify the role of the inflammatory diet on GSD.
GSD causal network. Various studies have shown a link between GSD and dietary factors such as high-calorie intake, low consumption of fiber-rich foods, vegetables and fruits, hypertriglyceridaemia, and high consumption of refined carbohydrates and polysaturated and mono-unsaturated fats.\textsuperscript{116}

Inflammation can also play a role in the formation of gallstones.\textsuperscript{17,19} The studies that have examined the association between inflammation and the risk of gallstones\textsuperscript{11,15} have shown a significant correlation between circulating inflammatory biomarkers and inflammatory proteins measured in bile.\textsuperscript{20} Some inflammation-related conditions, such as obesity, diabetes and infections (eg, Helicobacter pylori), are also linked with an increased risk of cholesterol gallstones.\textsuperscript{21–23} Given the proinflammatory/anti-inflammatory potentials of certain dietary patterns and foods, they could be associated with GSD via this pathway. The Dietary Inflammatory Index (DII) is validated based on various inflammatory biomarkers such as C reactive protein (CRP), tumour necrosis factor (TNF-\(\alpha\)) and interleukins (IL) and quantifying the inflammatory capacity of diets. This index estimates the inflammatory potential of diets based on the intake of foods with inflammatory or anti-inflammatory effects.\textsuperscript{24} Studies have shown a link between high DII and diseases including cardiovascular disease, cancer and metabolic syndrome, and also increased risk of neuropsychiatric disorders.\textsuperscript{25–28} While there is no direct evidence of a link between GSD and DII, since there is an association between inflammation and gallstones, it is reasonable to expect a link between GSD and the proinflammatory potential of diets. No study has investigated the effect of dietary inflammatory capacity on the development of gallstones. Therefore, this is the first study to investigate the relationship between dietary inflammation as indicated by DII and the incidence of GSD in a large population from Dena PERSIAN Cohort in Iran.

**DATA AND METHODS**

**Participants**

This cross-sectional study was performed using the baseline phase data of the Dena PERSIAN cohort. The Dena PERSIAN cohort is a subcohort of the PERSIAN Cohort Study, which has been ongoing since 2018 to assess the risk factors for non-communicable diseases in Iran.\textsuperscript{29} The Dena cohort comprises all people aged 35–70 years old who live in urban and rural areas of Dena County (Sisakht region) near the city of Yasuj, excluding those incapable of attending interviews due to physical/mental disabilities.

**Measurements**

The collected demographic information included age, sex and level of education (based on the number of successful school years). Body mass index (BMI) was obtained by dividing weight in kilograms by the square of height in metres. For lifestyle variables including smoking, alcohol, tobacco and drug use, data were collected by yes/no questions. Smoking was defined as the use of at least 100 cigarettes in a lifetime. Alcohol use was defined as the consumption of approximately 200 mL of beer or 45 mL of alcohol once a week for at least 6 months. Tobacco use was defined as the use of tobacco in the form of Naas, hookah, pipe or snuff once a week for at least 6 months. Drug use was defined as the use of illegal drugs once a week for at least 6 months. The participants’ history of GSD (as the dependent variable) and history of diabetes and fatty liver disease (the factors most strongly associated with gallstone according to the literature) were also collected. This was done by asking the participants whether they had ever been diagnosed with any of these diseases by a physician and whether they were taking medication or being treated for any of these conditions. The collected laboratory data included cholesterol (Chol), triglyceride (Tg), low-density lipoprotein and high-density lipoprotein (HDL) in milligrams per deciliter of blood (mg/dL).

**Dietary assessment**

This study used a validated 113-item Food Frequency Questionnaire (FFQ) plus a 127-item FFQ questionnaire for indigenous foods.\textsuperscript{30} The participants were asked to report the frequency and portions of food items they have consumed on a daily, weekly, monthly and annual basis over the past year. All portion sizes or household sizes were converted to grams per day. The energy and nutrient content of foods were then calculated using the software Nutritionist IV (V.7.0).

**Calculating DII**

The method of calculating DII has been explained in detail in many studies,\textsuperscript{24} 26 but in short, it is determined based on 45 dietary parameters that affect inflammation. This index has been validated for the Iranian population.\textsuperscript{31} Essentially, DII quantifies the inflammatory potential of macronutrients, micronutrients and other dietary substances based on the ratio of proinflammatory cytokines to anti-inflammatory factors. DII has been developed by conducting an extensive literature review of the evidence published from 1950 to 2010 on the relationship between nutrients and inflammation and then giving scores of +1, −1 or 0 to nutrients depending on whether they increase, decrease or not change six inflammatory markers including IL-10, IL-6, IL-4, IL-1\(\beta\), CRP and TNF-\(\alpha\) to create a database of standard global mean and SD of the intake of nutrient parameters. To calculate DII, the intake of each food parameter must be subtracted from the corresponding global mean, and the result must be divided by the global SD to obtain the Z score, which must then be converted to a percentile-based score. This value must then be multiplied by the inflammatory effect score of the food parameter to obtain the DII score of that food parameter. Finally, DII scores obtained for different food parameters must be summed to obtain the
total DII score. The total DII score of a person can vary between −8.87 and 7.98.21

This study used 34 out of 45 food parameters of DII, including alcohol, magnesium, vitamin A, vitamin B12, unsaturated fatty acids (MUFA), vitamin C, vitamin B6, niacin and vitamin D, beta-carotene, n3 fatty acid. Vitamin E, caffeine, n6 fatty acids, zinc, carbohydrates, onions, black or green tea, cholesterol, protein, trans fats, energy, polyunsaturated fatty acids (PUFA), pepper, iron, riboflavin, garlic, total fat, saffron, thiamine, fibre, saturated fats, selenium and folic acid.

Statistical analysis
Data analysis was performed using the software Stata V.16. Mean and SD and frequency and percentage were used to describe quantitative and qualitative variables, respectively. Since the DII variable was not normally distributed, median and IQR were reported for it. DII was analysed as a continuous variable, in quartiles and as a binary variable (with a cut-off point set at zero). In this study, DII values were in the range of −0.40 to 1.43.

Independent sample t-test and $\chi^2$ test were used to determine the difference between basic variables in two study groups.

Because of the binary nature of the outcome (GSD or not GSD), the analysis was performed by logistic regression. First, a univariable logistic regression model was fitted separately for each variable to identify the confounding variables. The variables with $p\leq0.2$ were chosen for use in the multivariable regression model. This multivariate logistic regression model was fitted with all the variables that met the said condition in the univariate regression analysis. In the multivariable regression model, the significance level was $p\leq0.05$.32 It should be noted that a separate set of regression models were developed for each state of DII (continuous, quartile, binary).

The measure used in the logistic regression of this study is the OR. For variables with more than one level, the lowest level was considered the reference for OR calculation.

RESULTS
The total number of participants who entered the study was 3626. The mean age of participants was 50.16 (SD=9.71). The sample consisted of 57% female, and the rest were male. BMI was 30.07 kg/m² in people with gallstones and 27.74 kg/m² in healthy people. The percentage of smokers, alcohol users, tobacco users and drug users in participants were 24.41%, 6.32%, 26.87% and 10.33%, respectively. A higher percentage of people in the GSD group were smokers, alcohol users and drug users than in the healthy group, but tobacco use was more prevalent in the healthy group. The prevalence of diabetes and fatty liver was significantly higher in the GSD group than in the healthy group. Among laboratory indicators, only the mean Tg and HDL were higher in the GSD group than in the healthy group. Table 1 shows the demographic and lifestyle characteristics, medical history and laboratory records of the participants divided by GSD and healthy individuals.

Table 2 shows the DII scores of participants in quartile, continuous and binary forms. The total median DII score was −0.08, with an IQR of 0.18. The median DII score was lower in the GSD group than in the healthy group (+0.11 vs −0.08). The percentage of people with GSD decreased from 36.42 in the first quartile to 18.50 in the fourth. Approximately 70% of participants had a negative DII score, and about 30% had a positive DII score (table 2).

Table 3 shows DII was lower in patients with a past history of GSD. In the crude model, people in higher quartiles have significantly lower GSD odds than those in the first quartile. The adjusted model’s OR was significant for the third and fourth quartiles. Specifically, the OR for GSD was 41% and 49% lower for people in the third and fourth quartiles than for those in the first quartile. When DII was treated as a continuous variable, it was found that each unit increase in DII decreased the odds of having GSD by 75% after adjustment for confounding factors ($p=0.03$). The logistic regression model lost significance when DII was treated as a binary variable.

DISCUSSION
This study investigated the hypothesis of an association between GSD and DII. In this large cross-sectional study of 3626 people, we found that dietary intake of factors associated with a proinflammatory state was associated with a reduced odds of a prior history of GSD. Since this relationship has not been investigated in any previous study, it is impossible to compare these results directly with other findings.

Several studies have examined the effect of inflammatory factors on the formation of gallstones. In one of these studies, Liu et al investigated the relationship between circulating inflammatory proteins and gallostones, finding four ILs, including IL-6, IL-10, IL-12 and IL-13 are associated with an increased risk of gallstones.14 Since IL-6 and IL-10 are inflammatory markers used in the calculation of DII, it is responsible to expect a direct relationship between DII and the formation of gallstones. CRP is also one of the inflammatory biomarkers used to calculate DII. In a study by Shabanzadeh et al on the relationship between metabolic biomarkers and GSD, the results showed a direct relationship between CRP and GSD with OR=1.03.23 This relationship was also observed in the Tong Liu cohort study,3 while the result obtained from our study is in contrast to what would be expected.

A few studies have been performed on the association of dietary micronutrients and macronutrients with GSD. In a survey by Davidović et al, only a high-energy diet predicted GSD development.1 A study by Tsai et al showed that the high intake of polyunsaturated and monounsaturated fatty acids in an otherwise balanced diet is associated with a reduced risk of GSD in men.16 Consistent with these findings, our study found that people with GSD had...
a higher BMI than people without GSD, which may be due to high fat intake in these patients. The association between high fat intake and obesity and inflammation has been confirmed in various studies, which suggests that a proinflammatory diet may be able to predict GSD.33–35

The reason for the inconsistency of our results with the existing evidence could be that our study was cross-sectional research where the temporal order of causes and effects was not taken into account. In other words, while people may change their diet after developing

### Table 1 Characteristics of demographic, lifestyle, medical history and laboratory measurements participants in DENA Persian cohort (n=3626)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Range/category</th>
<th>Gallstone No (%) (n=173)</th>
<th>Healthy No (%) (n=3453)</th>
<th>Total No (%) (n=3626)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>Range: 35–70</td>
<td>54.53±9.52</td>
<td>49.95±9.68</td>
<td>50.16±9.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>142 (82.08)</td>
<td>1926 (55.79)</td>
<td>2068 (57.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>31 (17.92)</td>
<td>1526 (44.21)</td>
<td>1557 (43.0)</td>
<td></td>
</tr>
<tr>
<td>YOS (mean±SD)</td>
<td>Range: 0–22</td>
<td>5.6±5.2</td>
<td>7.8±5.5</td>
<td>7.70±5.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI† (mean±SD)</td>
<td>Range: 15.70–54.86</td>
<td>30.07±4.96</td>
<td>27.74±5.01</td>
<td>27.85±5.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>24 (13.95)</td>
<td>860 (24.93)</td>
<td>884 (24.41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>148 (86.05)</td>
<td>2589 (75.07)</td>
<td>2737 (75.59)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Yes</td>
<td>5 (2.91)</td>
<td>224 (6.49)</td>
<td>229 (6.32)</td>
<td>0.071</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>167 (97.01)</td>
<td>3225 (93.51)</td>
<td>3392 (93.68)</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>Yes</td>
<td>58 (33.77)</td>
<td>915 (26.53)</td>
<td>973 (26.87)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>114 (66.23)</td>
<td>2534 (73.47)</td>
<td>2648 (73.13)</td>
<td></td>
</tr>
<tr>
<td>Drug use</td>
<td>Yes</td>
<td>8 (4.65)</td>
<td>366 (10.61)</td>
<td>374 (10.33)</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>164 (95.35)</td>
<td>3083 (89.39)</td>
<td>3247 (89.67)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>46 (26.59)</td>
<td>412 (11.94)</td>
<td>458 (12.63)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>127 (73.41)</td>
<td>3040 (88.06)</td>
<td>3167 (87.37)</td>
<td></td>
</tr>
<tr>
<td>Fatty liver</td>
<td>Yes</td>
<td>78 (45.09)</td>
<td>677 (19.61)</td>
<td>755 (20.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>95 (54.91)</td>
<td>2775 (80.39)</td>
<td>1870 (79.17)</td>
<td></td>
</tr>
<tr>
<td>Chol (mean±SD)</td>
<td>Range: 80–345</td>
<td>177.07±37.60</td>
<td>179.84±36.46</td>
<td>179.69±36.52</td>
<td>0.273</td>
</tr>
<tr>
<td>Tg (mean±SD)</td>
<td>Range: 33–1755</td>
<td>162.73±90.17</td>
<td>157.32±101.2</td>
<td>157.55±100.71</td>
<td>0.425</td>
</tr>
<tr>
<td>LDL (mean±SD)</td>
<td>Range: 22.60–254.60</td>
<td>96.91±31.44</td>
<td>101.83±32.33</td>
<td>101.53±32.31</td>
<td>0.034</td>
</tr>
<tr>
<td>HDL (mean±SD)</td>
<td>Range: 18–140</td>
<td>51.0±10.74</td>
<td>49.20±9.93</td>
<td>49.29±9.10</td>
<td>0.031</td>
</tr>
</tbody>
</table>

* A significant level for variables of age, years of schools, BMI, Chol, Tg, LDL and HDL was obtained from independent sample t-test. Also, χ² test was used for variables of sex, smoking, alcohol, tobacco, drug use, diabetes and fatty liver.
† Per kilograms/metre².
BMI, body mass index; Chol, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Tg, triglyceride; YOS, years of school.

### Table 2 Characteristics of DII of the participants in the DENA Persian cohort (n=3626)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Range/category</th>
<th>Gallstone No (%) (n=173)</th>
<th>Healthy No (%) (n=3453)</th>
<th>Total No (%) (n=3626)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DII quartile</td>
<td>Range: −0.4 to −0.16</td>
<td>63 (36.42)</td>
<td>867 (25.11)</td>
<td>930 (25.65)</td>
</tr>
<tr>
<td></td>
<td>Range: −0.16 to −0.08</td>
<td>43 (24.85)</td>
<td>898 (26.0)</td>
<td>941 (25.95)</td>
</tr>
<tr>
<td></td>
<td>Range: −0.08 to 0.02</td>
<td>35 (20.23)</td>
<td>845 (24.47)</td>
<td>880 (24.27)</td>
</tr>
<tr>
<td></td>
<td>Range: 0.02 to 1.43</td>
<td>32 (18.50)</td>
<td>843 (24.42)</td>
<td>875 (24.13)</td>
</tr>
<tr>
<td>DII (median (IQR))</td>
<td>Range: −0.4 to 1.43</td>
<td>−0.11 (0.18)</td>
<td>−0.08 (0.18)</td>
<td>−0.08 (0.18)</td>
</tr>
<tr>
<td>Binary DII</td>
<td>&lt; 0</td>
<td>131 (75.72)</td>
<td>2407 (69.71)</td>
<td>2538 (70.0)</td>
</tr>
<tr>
<td></td>
<td>≥ 0</td>
<td>42 (24.28)</td>
<td>1046 (30.29)</td>
<td>1088 (30.0)</td>
</tr>
</tbody>
</table>

DII, Dietary Inflammatory Index.

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This change will not be reflected in the results of cross-sectional research. Thus, studies of new cases or follow-ups will provide more reliable results. Another critical point in investigating the relationship between DII and diseases is adjusting diet-related confounding factors, nutritional factors that affect the mechanism of inflammation but are not included in the calculation of the DII; It can significantly affect the relationship between this indicator and the investigated outcome. In our study, none of these nutritional confounding factors were analysed.

Another point to consider regarding our study was the limited range of DII in participants, as most of them had similar diets and DII scores. This was reflected in the fact that the highest DII score obtained in this study was 1.43, whereas other studies have obtained DII scores as high as 7.98. In other words, all individuals in our study were in the middle of the DII score range, and none were at either end of this spectrum, meaning that they did not have a highly proinflammatory or highly anti-inflammatory diet. This limitation should be considered in the generalisability of the study results to other populations.

One of the strengths of our study was the identification of patients from a general population, which allows for the inclusion of different types of patients in terms of severity of the disease, as opposed to sampling from clinics and hospitals, which leads to the enrolment of more severe cases. The major limitation of our study was the use of the baseline phase data of the Dena Persian cohort study, which made it impossible to perform a longitudinal analysis of the data.

CONCLUSION

The results of our study suggest that a proinflammatory diet is associated with a reduced history of GSD. However, since this is the first study to investigate this relationship, further case–control and cohort studies with adjustments for diet-related confounders are needed to confirm or reject this conclusion and examine the causality of this relationship.

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The ethics committee approved the study of Yasouj University of Medical Sciences with the code IR.YUMS.REC.1400.186. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. No data are available.

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