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# Higher dietary insulin index is directly associated with the odd of kidney stones

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**Kidney stones or Nephrolithiasis are the most common health condition associated with the urinary system. Dietary factors stand as important factors in the occurrence and development of kidney stones. This study aimed to examine the potential link between dietary insulin index (DII) and dietary insulin load (DIL) with prevalence of kidney stones. This cross-sectional study was conducted among adults aged 30 to 75 years in the Shahedieh district of Yazd, Iran, over the period of 2015–2016. DII and DIL were calculated using a validated semi-quantitative food-frequency questionnaire and mathematical formula. Diagnosis of kidney stones is made on the basis of information obtained from self-reported questionnaire (Yes/ No). To explore the association between DII and DIL with the odds of kidney stones, logistic regression was employed in crude and adjusted models. A total of 4,829 participants were included in this study. Individuals in the last quartile of DIL had 214% higher odds of kidney stones in the crude model (OR: 2.14, 95% CI: 1.62–2.83; P-trend < 0.001); this association was remained significant after adjustments for confounding variables (OR: 1.44, 95% CI: 1.04–1.97; P-trend: 0.019). There was a direct significant relationship between DII and odds of kidney stones among third and forth quartiles of DII (OR: 1.52, 95% CI: 1.16–1.98, P-trend = 0.002); but this association disappeared for adjusted models. Higher DII and DIL were associated with an increased odd of renal stones. Large longitudinal study is required to clarify these associations.**

**Keywords** Nephrolithiasis, Kidney stones, Dietary insulin load, Dietary insulin index, Hyperinsulinemia

Nephrolithiasis, or kidney stones, is one of the most common conditions that affects the urinary system, and its prevalence and recurrence rates are steadily rising worldwide[1]. This condition can be linked to a higher likelihood of developing chronic kidney disease (CKD)[2] and end-stage renal disease (ESRD)[3] and incurring substantial healthcare expenses[4]. The formation of kidney stones is an intricate and multifaceted process that involves both intrinsic elements (age, sex, and inheritance) and external factors[1,5], such as climate[6], nutrition[7], and medication[8]. Among all the external factors, diet and dietary factors stand as important factors in the occurrence and development of kidney stones[9].

One of the aspects of diet is the induced insulin, which is stimulated by the food consumed. Postprandial hyperglycaemia and the resulting hyperinsulinemia are known to contribute to the onset of several chronic conditions, including cardiovascular disease[10], diabetes, and metabolic syndrome[11]. The dietary insulin index (DII) is a new method for classifying foods based on how they affect insulin levels after a meal, compared to a reference food (similar to the glycaemic index, which uses glucose or white bread)[12]. Likewise, the dietary insulin load (DIL) is another measure that calculates the impact of a food on insulin levels by multiplying its DII value, energy content, and consumption frequency[13]. Prior research has demonstrated a correlation between DII and DIL with an increased likelihood of developing insulin resistance[14] and metabolic syndrome[13]. Furthermore, researchers have investigated and recognized the relationships between metabolic syndrome, insulin resistance with kidney stones[15,16]. Nonetheless, the potential correlation between DII and DIL with kidney stones has not been previously investigated. To the best of our knowledge. Its first study to examine the association between DII and DIL with prevalence of kidney stones.

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# Materials and methods

## Participants and study design

This is a cross-sectional analysis of the Shahedieh cohort study, which is a component of the large PERSIAN cohort study being carried out in several parts of Iran. The primary objective of the PERSIAN cohort research was to ascertain the possible risk variables associated with noncommunicable diseases among Iranian participants. This cohort study has been carried out by researchers from local institutions in collaboration with the Ministry of Health and Medical Education. Prior publication has provided comprehensive details on the study's design, participants, and methods of data collection for the PERSIAN cohort[17]. To summarize, the Shahedieh cohort study commenced in the Shahedieh district of Yazd, Iran, over the period of 2015–2016. Initially, a letter of invitation was dispatched to 10,194 adult individuals who satisfied the specified requirements and resided in the Shahedieh area. 9,983 people willingly enrolled in the cohort trial. The inclusion criteria for this study were individuals who were of Iranian heritage, aged between 30 and 75 years, and had been living in the Shahedieh region for at least 9 months every year. Individuals were sent an invitation to the healthcare facility located in the Shahedieh area for the purpose of gathering data. The participants were instructed to come in a condition of fasting in order to gather biological samples. Following the collection of a blood sample from each participant, trained interviewers acquired the necessary data on sociodemographic variables, physical activity, and nutritional consumption.

Participants who were missing data for food intake ($n=177$), as well as those who under- or over-reported calorie intake beyond the usual range of energy intake (800-4,200 kcal/d; $n=3{,}025$), were eliminated after combining the information. Consequently, out of the original 9,983 participants, a total of 4,829 individuals were ultimately considered in the final analysis. Written informed permission was obtained from all individuals. The Shahedieh cohort research received approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences, located in Yazd, Iran.

## Dietary assessment

The individuals' dietary intakes were evaluated using a 120-item semi-quantitative food frequency questionnaire (FFQ), which inquired about their dietary habits throughout the previous year. This FFQ, which was specifically designed to assess long-term dietary consumption, was validated for the adult population in Iran[18]. FFQs were completed by trained interviewers during a face-to-face interview. The participants were asked two types of questions regarding each food item: (1) the frequency of food consumption (number of times per month, week, or day the food was consumed) in the previous year, and (2) the amount of the food that was typically consumed each time (portion size based on the standard serving sizes commonly consumed by Iranians). The stated intakes were converted to grams per day using household estimates of the ingested items. The daily nutrient consumptions for each person were estimated by applying the United States Department of Agriculture's (USDA) national nutrient databank. The Nutritionist IV program (First Databank, San Bruno, CA, USA - modified for Iranian foods) was utilized to compute nutritional intakes[19].

## DII and DIL

The food insulin index (FII) is a mathematical formula used to rate different meals based on their effect on insulin levels. It calculates the increase in insulin levels over a two-hour period after consuming a 1000-kJ amount of the test food, compared to the increase in insulin levels after consuming a 1000-kJ portion of the reference food. The FII for each calorie-containing food was obtained from FFQ data using data published by Professor Jennie Brand-Miller of the University of Sydney, Australia[20]. In order to determine DIL, we initially approximated the insulin load of each item by employing the subsequent equation: Insulin load of a given food = insulin index of that food × amount of that food consumed (g/d) × energy content per 1 g of that food (g/d)[21]. DIL for each individual was determined by adding up the insulin load of all food items ingested over the course of the last year. Subsequently, the DII for each participant was calculated by dividing the DIL by their total calorie intake.

$$IL_{ave} = \sum_{a=1}^{n} II_a \times Energy_a \times Frequency_a$$

$$II_{ave} = \frac{\sum_{a=1}^{n} (II_a \times Energy_a \times Frequency_a)}{\sum_{a=1}^{n} (Energy_a \times Frequency_a)}$$

## Anthropometric assessment

The anthropometric indices were measured in accordance with standard protocol and by trained investigator. Weight was measured using a digital scale (SECA, model 755, Germany) in a state of minimum clothing without shoes to the nearest 100 g. Standing height was assessed using a conventional stadiometer, with the exclusion of footwear, to the closest 0.5 cm. The Body Mass Index (BMI) was computed by dividing the weight in kilograms by the square of the height in meters. In order to minimize any potential inaccuracies or distortions in the measurements, anthropometric data were collected in the morning and after the individual had abstained from eating.

## Biochemical assessment

Each participant in a condition of fasting (10–12 h of fasting) provided 25 mL of blood using Vacutainers (Greiner Bio-One International GmbH, Kremsmunster, Austria). The blood was subjected to centrifugation and divided into several portions, which were then labeled and stored in freezers at a temperature of -70 °C. Aside from the preserved samples, a small quantity of blood was utilized to quantify fasting blood glucose (FBG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels. The enzymatic colorimetric technique was employed to quantify FBG. TG levels were quantified using enzymatic colorimetric assays involving glycerol phosphate. The determination of HDL-C contents involved the precipitation of apo B-containing lipoproteins using phosphotungstic acid. The enzymatic reagents provided by Pars Azmoon, located in Tehran, Iran, were used for all measurements. These reagents were utilized in conjunction with an autoanalyzer system (Selectra E) manufactured by Vitalab in Holliston, the Netherlands.

### Physical activity and other assessment

The International Physical Activity Questionnaire was administered to each participant through a face-to-face interview in order to assess their level of physical activity. The International Physical Activity Questionnaire yielded data that was reported as metabolic equivalents per week (MET/min/week). Diagnosis of kidney stones is made on the basis of information obtained from self-reported questionnaire (Yes/ No). Moreover, data regarding age, gender (male or female), marital status (single, married, widowed or discovered), education level (lower than high school, high school, diploma and associated diploma, bachelors, masters, and higher), history of chronic disease (yes or no), supplement use, and smoking history (never smoker, current smoker, ex-smoker) were obtained through a pretested questionnaire administered during an in-person interview.

### Statistical analysis

Individuals were classified into groups based on the quartile thresholds of the DII and DIL scores. The one-way analysis of variance was employed to evaluate variations in quantitative variables across quartiles of DII and DIL. Similarly, the chi-square test was utilized to evaluate the distribution of categorical variables among quartiles of DII and DIL. To explore the association between DII and DIL with odds of kidney stones, logistic regression was conducted in crude and adjusted models. In the first model, adjustments were made for age, gender, and energy intake. The second model underwent additional modifications to account for BMI. The final model additionally incorporated the history of chronic disease (yes/no); marital status (single, married, widow, or discovered); education level (lower than high school, high school, diploma and associated diploma, bachelors, masters, and higher); supplement use; smoking history (never smoker, current smoker, ex-smoker); physical activity level (MET/min/week); and intakes of dietary EPA, DHA, and fiber (continues, g/d). In all models, participants in the lowest quartiles of DIL and DII were designated as the reference group. The statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL), and in all results, the significance level was determined as $p < 0.05$.

## Results

The mean ± SD for the BMI and age of the study population were 27.73 ± 7.52 kg/m2 and 45.34 ± 8.61 years, respectively. The mean ± SD score for DII and DIL were 59.17 ± 6.15 and 107.41 ± 52.92, respectively. General characteristics and biochemical parameters of participants across quartiles of DIL and DII are presented in Tables 1 and 2. Except for BMI, there were significant differences for age, gender, physical activity, level of education, smoking status, marriage status, and serum concentrations of FBG, TG, TC, LDL-C, HDL-C, AST and ALT among the quartiles of DIL. Furthermore, among DII quartiles, significant differences were observed regarding age, gender, physical activity, level of education, smoking status, marriage status, and serum concentrations of FBG, TG, HDL-C, AST and ALT.

Dietary Food groups and nutrient intakes of study participants across quartiles of DIL and DII are shown in Tables 3 and 4. Compared with those in the first quartiles, individuals in the last quartiles of DIL consumed more energy, protein, carbohydrate, total fat, saturated fatty acid, cholesterol, iron, sodium, vitamin B12 and B9, red meat, processed meat, dairy, and refined grain, as well as a lower intake of vegetables, fruits, legumes, nuts, whole grains, eggs, fish, calcium, zinc, potassium, vitamin E, vitamin D, vitamin C, folate, caffeine, and fiber. Also, people in the highest quartile compared to the lower quartile of DII had a higher intake of carbohydrates, caffein, refined grain, and egga, as well as a lower intake of energy, protein, total fat, saturated fatty acid, cholesterol, iron, sodium, vitamin B12 and B9, red meat, processed meat, dairy, vegetables, fruits, legumes, nuts, whole grains, fish, calcium, zinc, potassium, vitamin E, vitamin D, vitamin C, folate, and fiber.

Multivariable-adjusted odds ratios (ORs) and 95% CI for kidney stones across quartiles of DII and DIL are shown in Table 5. There was evidence of increased odds of kidney stones for the subjects in the highest compared to the lowest quartile of the DIL (OR = 2.14, 95% CI 1.62–2.83; P-trend < 0.001). These associations were remained significant in all adjusted models (final adjustment model: OR = 1.44, 95% CI 1.0-1.97; P-trend = 0.019). There was a direct significant relationship between DII and odds of kidney stones among third and forth quartiles of DII (OR: 1.52, 95% CI: 1.16–1.98, P-trend = 0.002); but this association disappeared for adjusted models.

## Discussion

To the best of our knowledge, the current study is the first to investigate the associations between DII and DIL with odds of kidney stones in a substantial population-based cohort study. Direct associations were observed between higher DII and DIL with odds of renal stones.

According to our search, no study has been done to investigate and find the relationship between DII/DIL and kidney stones. However, there are other approaches to investigate findings related to this relationship. For instance, prior research has demonstrated that a reduced intake of fruits and vegetables[22–24] and an increased consumption of meat[25] and processed food (specifically animal derivatives) are linked to a higher risk of developing kidney stones[26]. In a study conducted by Turney et al.[27], individuals who did not consume meat (specifically fish eaters and vegetarians) or consumed less than 50 g/day of meat experienced a significant reduction in the risk of kidney stones. This reduction ranged between 30% and 50% compared to meat-eaters who consumed 100 g/day or more of total meat products. Overall, their findings indicated that the consumption of red meat and poultry

| Variables | | Quartiles of DIL | | | | P |
|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | |
| Age (years) | | 47.78(9.48) | 45.50(8.53) | 44.49(8.17) | 44.35(8.02) | < 0.001 |
| Gender | Male | 225(25.3%) | 449(38.4%) | 701(52.8%) | 1030(73.0%) | < 0.001 |
| | Female | 863(74.7%) | 721(61.6%) | 626(47.2%) | 381(27.0%) | |
| BMI (kg/m2) | | 28.09(5.03) | 27.60(4.70) | 27.80(7.45) | 27.58(10.53) | 0.397 |
| Physical activity (Met/min/week) | | 938.17(912.17) | 918.71(910.81) | 893.51(916.16) | 880.29 (850.12) | < 0.001 |
| Insulin load | | 54.58(6.43) | 57.47(5.44) | 59.68(5.03) | 63.00(4.85) | < 0.001 |
| Insulin index | | 48.36(9.73) | 74.65(7.25) | 105.57(10.89) | 173.47(43.08) | < 0.001 |
| Education | Lower than high school | 167(18.8%) | 137 (11.7%) | 81(6.1%) | 82(5.8%) | < 0.001 |
| | High school | 446(50.2%) | 567(48.5%) | 617(46.5%) | 707(50.2%) | |
| | Diploma and associated diploma | 164(18.5%) | 280(23.9%) | 336(25.3%) | 343(24.4%) | |
| | Bachelors | 93(10.5%) | 163(13.9%) | 258(19.4%) | 243(17.3%) | |
| | Masters and higher | 18(2.0%) | 23(2.0)% | 35(2.6%) | 33(2.3%) | |
| Smoking status | Never smoker | 773(90.6%) | 965(85.2%) | 1015(78.5%) | 912(66.6%) | < 0.001 |
| | Current smoker | 52(6.1%) | 115(10.2%) | 199(15.4%) | 321(23.4%) | |
| | Ex-smoker | 28(3.3%) | 53(4.7%) | 80(6.2%) | 137(10.0%) | |
| Marriage status | Single | 4(0.5%) | 8 (0.7%) | 5(0.4%) | 7(0.5%) | < 0.001 |
| | Married | 842(94.8%) | 1130(96.6%) | 1296(97.7%) | 1387(98.3%) | |
| | Widowed or divorced | 42(4.7%) | 32(2.7%) | 29(2.0%) | 17(1.2%) | |
| Biochemical parameters | | | | | | |
| FBG (mg/dl) | | 97.40(24.81) | 96.03(32.20) | 94.56(19.67) | 95.10(19.05) | 0.043 |
| TG (mg/dl) | | 144.68(78.79) | 150.37(92.51) | 159.73(97.54) | 171.07(113.80) | < 0.001 |
| TC (mg/dl) | | 195.19(67.98) | 189.24(36.70) | 189.95(38.16 | 192.28(40.44) | 0.015 |
| LDL-C (mg/dl) | | 110.84 (64.00) | 105.09(29.86) | 106.63(30.55) | 109.37 (30.41) | 0.003 |
| HDL-C (mg/dl) | | 56.26(12.80) | 54.70(12.32) | 52.34(11.98) | 50.31(10.94) | < 0.001 |
| AST (U/L) | | 17.93(7.38) | 19.16(10.40) | 19.25(8.03) | 20.58(8.65) | < 0.001 |
| ALT (U/L) | | 19.44(16.33) | 22.03(17.63) | 23.09(16.83) | 26.19(18.39) | < 0.001 |

**Table 1**. General characteristics of study participants across quartiles of Dietary insulin load. *BMI* body mass index, *MET* metabolic equivalent, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low density lipoprotein-cholestrol, *HDL-C* high density lipoprotein-cholestrol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase . Data are presented as mean (standard deviation (SD)) or number (percent). [a] Obtained from ANOVA or Chi-square test, where appropriate.

is linked to a higher risk of developing kidney stones. Furthermore, an investigation carried out by Taylor et al.[28] revealed that following a DASH-style diet, which includes eating a lot of fruits and vegetables, some low-fat dairy products, and not much animal protein (but a lot of plant protein from legumes and nuts), significantly lowers the risk of developing kidney stones. Similarly, in another prospective cohort study conducted by Leone et al.[29], a higher level of adherence to a Mediterranean dietary pattern, which is characterized by a low intake of meat and a focus on plant-based foods, had similar protective effects and was related to a decreased risk of developing nephrolithiasis. Interestingly, our research found that those in the bottom quartiles of the DIL had a similar dietary pattern, with a lower intake of red meat, processed meat, dairy products, and refined grains, and a higher intake of fruits, vegetables, legumes, nuts, whole grains, fish, and eggs. Besides, the results of the study conducted by Meschi et al.[30] support the notion that eliminating fruits and vegetables from the diet of healthy individuals results in a decrease in the excretion of potassium, magnesium, citrate, and oxalate in urine while simultaneously increasing the levels of calcium and ammonium. These alterations increase the levels of calcium oxalate and calcium phosphate in the urine.

Our results regarding dairy products align with a previous investigation that suggested individuals with calcium oxalate dehydrate (COD) stones had notably greater consumption of dairy products compared to the control group[31]. Dairy products are commonly regarded as foods that are abundant in calcium. Nevertheless, we did not detect an elevated calcium intake among those who consumed a greater quantity of dairy products compared to those who consumed a lesser amount. The presence of extra substances in some dairy products, like cured cheese and flavored or sweetened yogurts, such as fats, salt, and added sugars, can explain the association between dairy products and risk[31]. There is strong evidence to support the association between salt consumption and an increased risk of hypercalciuria, which in turn leads to the occurrence or recurrence of nephrolithiasis[32]. Furthermore, a recent study has shown that a greater proportion of energy consumed from added sugars is strongly linked to a higher occurrence of kidney stones[33].

Another potential mechanism that might account for our result is the presence of insulin resistance and hyperinsulinemia. A study conducted by Cupisti et al.[34] demonstrated that insulin resistance might potentially contribute to the production of calcium stones by decreasing the excretion of urine citrate. It has been proposed

| Variables | | Quartiles of DII Q1 | Q2 | Q3 | Q4 | P |
|---|---|---|---|---|---|---|
| Age (years) | | 48.99(9.94) | 47.42(9.32) | 47.83(9.54) | 49.74(9.82) | < 0.001 |
| Gender | Male | 645(34.1%) | 916(44.4%) | 1086(51.4%) | 1134(54.4%) | < 0.001 |
| | Female | 1247(65.9%) | 1148(55.6%) | 1028(48.6%) | 950(45.6%) | |
| BMI (kg/m2) | | 29.00(5.12) | 28.60(6.73) | 28.61(9.07)) | 27.97(4.98) | 0.397 |
| Physical activity (Met/min/week) | | 927.81 (907.17) | 912.52(902.32) | 898.59 (912.97) | 888.32 (887.22) | < 0.001 |
| Insulin load | | 62.46(26.76) | 87.41(35.16) | 111.11(46.91) | 136.72(62.14) | < 0.001 |
| Insulin index | | 49.91(3.84) | 56.62(1.30) | 60.76(1.14) | 66.35(3.58) | < 0.001 |
| Education | Lower than high school | 609(32.2%) | 615(29.8%) | 659(31.2%) | 700(33.6%) | < 0.001 |
| | High school | 298 (15.8%) | 363(17.6%) | 340(16.1%) | 327(15.7%) | |
| | Diploma and associated diploma | 354(18.7%) | 429(20.8%) | 447(21.2%) | 384(18.4%) | |
| | Bachelors | 232(12.3%) | 303(14.7%) | 321(15.2%) | 220(10.6%) | |
| | Masters and higher | 36(1.9%) | 56(2.7%) | 38(1.8%) | 29(1.4%) | |
| Smoking status | Never smoker | 1597(85.6%) | 1653(81.5%) | 1615(78.0%) | 1493(73.1%) | < 0.001 |
| | Current smoker | 150(8.0%) | 236(11.6%) | 282(13.6%) | 370(18.1%) | |
| | Ex-smoker | 119(6.4%) | 138(6.8%) | 174(8.4%) | 179(8.8%) | |
| Marriage status | Single | 7(0.4%) | 6(0.3%) | 5(0.2%) | 12(0.6%) | 0.012 |
| | Married | 1786(94.4%) | 1995(96.7%) | 2024(95.7%) | 1978(94.9%) | |
| | Widowed or divorced | 99 (5.2%) | 63(3.1%) | 85(4.0%) | 94(4.5%) | |
| Biochemical parameters | | | | | | |
| FBG (mg/dl) | | 115.18(52.06) | 107.64(42.86) | 104.05(37.19) | 103.15(33.57) | < 0.001 |
| TG (mg/dl) | | 160.11(93.28) | 162.82(102.00) | 168.27(100.02) | 174.34(113.00) | < 0.001 |
| TC (mg/dl) | | 189.18(55.24) | 189.46(42.27) | 190.59(40.60) | 191.15(41.53) | 0.468 |
| LDL-C (mg/dl) | | 103.65(50.42) | 105.05(32.51) | 105.73(31.71) | 105.97(32.74) | 0.220 |
| HDL-C (mg/dl) | | 54.28(12.62) | 53.31(12.28) | 52.38(12.18) | 51.92(11.91) | < 0.001 |
| AST (U/L) | | 18.50(9.25) | 19.37(8.81) | 19.73(8.90) | 19.47(8.42) | < 0.001 |
| ALT (U/L) | | 18.50(9.25) | 19.37(8.81) | 19.73(8.90) | 19.47(8.42) | < 0.001 |

**Table 2**. General characteristics of study participants across quartiles of Dietary insulin index. *BMI* body mass index, *MET* metabolic equivalent, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low density lipoprotein-cholestrol, *HDL-C* high density lipoprotein-cholestrol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase . Data are presented as mean (standard deviation (SD)) or number (percent). [a] Obtained from ANOVA or Chi-square test, where appropriate.

that the reduced excretion of citrate in individuals with insulin resistance may be attributed to a malfunction in the generation of renal ammonium or alterations in the transport processes of sodium, potassium, and hydrogen ions in the renal tubules[35,36]. Individuals with insulin resistance exhibit elevated levels of plasma free fatty acids. These fatty acids can penetrate the cells of the proximal tubule and disrupt the utilization of glutamine. The utilization of free fatty acids by proximal tubule cells as an alternative metabolic substrate result in a reduction in ammoniagenesis and glutamine utilization[37–39]. Additionally, in vitro studies that demonstrated insulin's capacity to promote the production of ammonium from L-glutamine in the kidneys show that insulin resistance can directly impede the process of ammoniagenesis[40,41]. Insulin may also contribute to the function of the Na/K exchanger in the proximal renal tubule, which is responsible for transporting or trapping ammonium ions in the tubular lumen[42]. Therefore, individuals with insulin resistance or hyperinsulinemia may have a reduced capacity to eliminate ammonia, resulting in the production of very acidic urine[36], which is the primary risk factor for the development of uric acid stones[43] and some form of calcium oxalate stones[44]. Additionally, this condition has the potential to disrupt the renal citrate metabolism[34], leading to a reduction in urine citrate levels—a substantial determinant in the development of calcium stones[45].

The strengths of this study include the large sample size, the validated dietary assessment method, the adjustment for potential confounders, and the use of novel indicators of dietary insulin. However, this study also has some limitations that should be acknowledged. First, the dietary intake data were based on self-reported FFQs, which may be subject to measurement error and recall bias. Second, the causal relationship between DIL and kidney stones cannot be established due to the observational nature of the study. Therefore, other studies are needed to confirm our findings. Third, no Iranian foods have undergone analysis for the FII. Consequently, there can be a little discrepancy between the FII of the test items listed as references and the actual foods consumed by the participants in the research. Due to the unavailability of the FII for 41% of food items in the FFQ in the reference lists, the insulin index of similar foods was utilized. Hence, it is advisable to use caution when interpreting the results of this study. In addition, future studies should determine the insulin index of Iranian foods. Fourth, the homogeneous characteristics of the study population, which consisted of one regional population, might limit the generalizability of the findings. Furthermore, the study population was

| Variables | Quartiles of DIL Q1 | Q2 | Q3 | Q4 | *P* |
|---|---|---|---|---|---|
| Food groups (g/day) | | | | | |
| Fruits | 488.68(339.56) | 459.56(335.78) | 395.11(240.27) | 333.51(221.17) | < 0.001 |
| Vegetables | 242.32(130.38) | 232.18(132.68) | 213.15(112.42) | 181.96(95.43) | < 0.001 |
| Red meat | 25.74(19.19) | 33.67(23.02) | 39.53(27.38) | 45.79(38.93) | < 0.001 |
| Processed meat | 0.35(1.21) | 0.84(3.20) | 0.96(2.73) | 1.87(5.63) | < 0.001 |
| Dairy product | 154.12(114.31) | 186.23(128.41) | 201.95(150.43) | 224.66(175.42) | < 0.001 |
| Legumes | 40.88(30.86) | 36.44(31.51) | 32.38(23.54) | 25.16(18.50) | < 0.001 |
| Nut | 25.28(41.03) | 19.45(29.92) | 16.58(25.34) | 10.80(18.68) | < 0.001 |
| Whole grains | 906.18(591.66) | 589.22(529.55) | 371.60(438.82) | 192.25(280.51) | < 0.001 |
| Refined grains | 206.65(88.45) | 330.97(108.29) | 472.55(151.68) | 816.55(326.34) | < 0.001 |
| Fish | 7.02(9.48) | 6.20(7.74) | 5.22(5.88) | 3.92(5.53) | < 0.001 |
| Eggs | 36.73(26.45) | 30.73(21.81) | 25.79(18.98) | 21.22(15.90) | < 0.001 |
| Nutrients | | | | | |
| Energy (Kcal/d) | 3360.15(1591.21) | 3155.75(1319.80) | 3304.23(1050.85) | 4113.86(944.33) | < 0.001 |
| Protein (g/d) | 122.11(62.46) | 110.39(51.39) | 112.65(40.10) | 138.36(36.74) | < 0.001 |
| Fat (g/d) | 88.46(31.76) | 90.91(31.50) | 97.97(30.80) | 114.97(32.79) | < 0.001 |
| Carbohydrate (mg/d) | 556.96(297.38) | 504.11(242.58) | 521.95(188.74) | 667.13(164.33) | < 0.001 |
| Cholesterol | 202.88(87.37) | 250.44(109.03) | 290.85(121.63) | 337.23(147.33) | < 0.001 |
| SFA (g/d) | 25.26(8.31) | 26.89(8.43) | 29.55(9.27) | 34.62(10.59) | < 0.001 |
| Calcium (mg/d) | 1398.35(494.45) | 1175.83(459.48) | 1122.06(474.27) | 1170.80(532.54) | < 0.001 |
| Iron (mg/d) | 33.16(20.69) | 27.24(16.45) | 26.64(11.99) | 33.94(9.92) | < 0.001 |
| Sodium (mg/d) | 6483.43(3327.46) | 5534.41(2747.74) | 5516.59(2317.11) | 6784.41(2135.69) | < 0.001 |
| Zinc(mg/d) | 24.29(7.68) | 19.36(7.94) | 19.25(10.17) | 21.83(12.21) | < 0.001 |
| potassium(mg/d) | 5400.36(1551.80) | 4558.94(1550.14) | 4322.48(1618.56) | 4422.00(1833.32) | < 0.001 |
| Vitamin B12 (mcg/d) | 3.40(2.18) | 4.34(2.48) | 5.03(3.64) | 5.67(3.15) | < 0.001 |
| Vitamin E (mg/d) | 21.87(9.14) | 18.15(10.04) | 18.95(8.81) | 17.85(8.08) | < 0.001 |
| Folate (mcg/d) | 692.13(329.12) | 658.03(267.19) | 683.37(212.45) | 846.89(213.54) | < 0.001 |
| Vitamin D (mcg/d) | 1.28(1.13) | 1.12(0.90) | 1.00(0.80) | 0.85(0.75) | < 0.001 |
| Vitamin C (mg/d) | 136.37(87.15) | 127.90(82.62) | 112.38(63.68) | 90.50(53.81) | < 0.001 |
| Caffein (mg/d) | 184.57(185.70) | 134.25(98.21) | 120.97(89.55) | 107.11(86.75) | < 0.001 |
| Dietary fibre (g/day) | 67.25(43.71) | 52.82(34.52) | 49.96(25.77) | 62.48(21.95) | < 0.001 |

**Table 3**. Dietary food groups and nutrients intakes of study participants across quartiles of Dietary insulin load. *SFA* saturated fatty acid. Data are presented as mean ± standard deviation (SD). [a] Obtained from ANOVA.

from a specific region in Iran, which may limit the generalizability of findings to other populations with different dietary habits and genetic backgrounds. Finally, due to financial limitations due to the large sample size of the study, we were not able to investigate urinary metabolites and also investigate the type of stones.

## Conclusion

In conclusion, this study suggests that higher DIL, but not DII, is associated with an increased odds of kidney stones, independent of potential confounders. This finding implies that the insulin potential of the diet may be an important modifiable risk factor or even a predictor of kidney stones. So that, ,the effects of DII and DIL remain an active area of research with the potential to represent modifiable risk factors and to play a role in prevention and management strategies. Further prospective studies are needed to confirm this association and to elucidate the underlying mechanisms.

| Variables | Quartiles of DII | | | | P |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | |
| Food groups (g/day) | | | | | |
| Fruits | 481.19(321.96) | 452.96(309.58) | 435.53(301.75) | 391.04(322.92) | < 0.001 |
| Vegetables | 249.88(152.62) | 236.68(132.18) | 225.39(129.56) | 205.79(118.06) | < 0.001 |
| Red meat | 33.89(29.95) | 36.49(28.38) | 36.38(28.76) | 32.72(26.09) | < 0.001 |
| Processed meat | 0.85(4.02) | 1.15(5.14) | 0.86(2.71) | 0.76(2.60) | 0.007 |
| Dairy product | 195.39(144.28) | 195.14(142.10) | 196.34(155.20) | 181.23(143.21) | 0.002 |
| Legumes | 33.41(28.42) | 33.51(25.65) | 33.68(26.51) | 31.65(25.77) | 0.047 |
| Nut | 17.94(28.62) | 17.46(27.68) | 17.12(29.44) | 15.51(29.01) | 0.043 |
| Whole grains | 835.91(586.33) | 572.62(547.64) | 436.19(513.99) | 398.40(507.42) | < 0.001 |
| Refined grains | 285.62(165.07) | 411.77(231.31) | 527.64(305.68) | 577.66(371.34) | < 0.001 |
| Fish | 5.70(7.10) | 6.08(8.19) | 5.60(7.41) | 4.27(7.05) | < 0.001 |
| Eggs | 25.78(22.68) | 27.68(20.95) | 27.87(21.35) | 25.84(22.48) | 0.001 |
| Nutrients | | | | | |
| Energy (Kcal/d) | 3608.02(1447.35) | 3288.00(1264.61) | 3385.23(1249.98) | 3588.78(1288.41) | < 0.001 |
| Protein (g/d) | 129.55(57.04) | 115.32(48.51) | 117.90(46.76) | 120.02(47.85) | < 0.001 |
| Fat (g/d) | 104.60(34.50) | 96.20(32.60) | 94.94(33.15) | 93.26(32.45) | < 0.001 |
| Carbohydrate (mg/d) | 576.11(269.63) | 521.45(227.94) | 546.06(220.56) | 601.85(234.03) | < 0.001 |
| Cholesterol | 260.58(130.45) | 270.14(124.88) | 268.70(127.19) | 247.05(134.79) | < 0.001 |
| SFA (g/d) | 30.83(10.21) | 28.81(9.59) | 28.44(9.94) | 27.22(9.57) | < 0.001 |
| Calcium (mg/d) | 1290.02(517.57) | 1183.24(484.70) | 1216.67(500.47) | 1211.03(509.32) | < 0.001 |
| Iron (mg/d) | 33.17(18.91) | 28.13(15.25) | 29.13(14.09) | 30.86(14.51) | < 0.001 |
| Sodium (mg/d) | 6495.39(3106.19) | 5712.20(2686.00) | 5847.86(2536.28) | 6263.11(2632.23) | < 0.001 |
| Zinc(mg/d) | 22.75(11.30) | 19.86(9.55) | 20.48(9.23) | 21.27(9.43) | < 0.001 |
| potassium(mg/d) | 5020.32(1841.54) | 4589.78(1665.62) | 4645.83(1687.49) | 4700.71(1739.64) | < 0.001 |
| Vitamin B12 (mcg/d) | 4.43(2.66) | 4.63(2.95) | 4.70(3.14) | 4.23(2.66) | < 0.001 |
| Vitamin E (mg/d) | 19.63(8.58) | 18.54(8.46) | 18.69(8.72) | 19.36(9.84) | < 0.001 |
| Folate (mcg/d) | 742.41(300.92) | 691.74(264.30) | 714.64(259.20) | 725.49(266.94) | < 0.001 |
| Vitamin D (mcg/d) | 1.17(1.03) | 1.07(0.88) | 1.01(0.95) | 0.81(0.66) | < 0.001 |
| Vitamin C (mg/d) | 129.12(84.96) | 123.89(73.11) | 121.72(76.80) | 108.06(89.68) | < 0.001 |
| Caffein (mg/d) | 111.60(91.75) | 122.15(97.31) | 135.52(99.07) | 194.10(187.66) | < 0.001 |
| Dietary fibre (g/day) | 67.10(40.53) | 54.34(32.19) | 55.40(29.69) | 59.72(30.59) | < 0.001 |

**Table 4**. Dietary food groups and nutrients intakes of study participants across quartiles of Dietary insulin index. *SFA* saturated fatty acid. Data are presented as mean ± standard deviation (SD). [a] Obtained from ANOVA.

| | Quartiles of score | | | | P-trend |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | |
| DII | | | | | |
| Case/Total | 93/968 | 148/1224 | 170/1330 | 180/1307 | |
| Crude | 1.00 (Ref) | 1.30(0.98–1.71) | 1.40(1.07–1.83) | 1.52(1.16–1.98) | 0.002 |
| Model 1* | 1.00 (Ref) | 1.20(0.90–1.59) | 1.19(0.90–1.57) | 1.20(0.91–1.58) | 0.263 |
| Model 2 † | 1.00 (Ref) | 1.20(0.90–1.59) | 1.19 (0.90–1.57) | 1.21(0.92–1.59) | 0.250 |
| Model 3 ‡ | 1.00 (Ref) | 1.18(0.89–1.58) | 1.19(0.89–1.58) | 1.22(0.94–1.63) | 0.227 |
| DIL | | | | | |
| Case/Total | 74/903 | 119/1169 | 169/1332 | 229/1425 | |
| Crude | 1.00 (Ref) | 1.26(0.92–1.71) | 1.62(1.21–2.16) | 2.14(1.62–2.83) | < 0.001 |
| Model 1* | 1.00 (Ref) | 1.15(0.84–1.58) | 1.34(0.99–1.81) | 1.57(1.16–2.12) | 0.001 |
| Model 2 † | 1.00 (Ref) | 1.15(0.84–1.58) | 1.33(0.98–1.81) | 1.56(1.15–2.11) | 0.001 |
| Model 3 ‡ | 1.00 (Ref) | 1.10(0.81–1.52) | 1.23(0.90–1.69) | 1.44(1.04–1.97) | 0.019 |

**Table 5**. Odds ratio (95% CI) and 95% confidence interval (CI) for kidney stones according to Quartiles of Dietary insulin index (DII) and dietary insulin load (DIL). *Model 1: adjusted for age, gender, and intake of energy. †Model 2: adjusted for model 1 and BMI. ‡ Model 3: adjusted for model 2 and history of chronic disease (yes/no); marital status (single, married, widow or discovered); education level (lower than high school, high school, Diploma and associated diploma, Bachelors, Masters and higher); Supplements and drug use, smoking history (never smoker, current smoker, ex-smoker); physical activity level (MET/min/week); intakes of dietary EPA, DHA, water, and fiber (continues, g/d).

## Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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## Author contributions

NM and D.F, contributed to write the manuscript. D.F., MH.S were responsible for the literature search and data collection. M.HS. was responsible for data analysis and interpretation of data. …SSKH.supervised the study and contributed to the conception, design, statistical analyses, data interpretation, and drafting of the article. Final approval of the article before submission was performed by all authors.

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## Declarations

## Competing interests

The authors declare no competing interests.

## Ethics approval and consent to participate

The study adhered to the ethical standard outlined in the Declaration of Helsinki for conducting medical research with human beings. The study received ethical approval from the ethics committee of Shahid Sadoughi University of Medical Science (IR.SSU.SPH.REC.1397.161). All participants also provided written informed consent prior to the collection of data.

## Additional information

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