The Association Between Dietary Glycemic and Insulin Indices with Incidence of Cardiovascular Disease: Tehran Lipid and Glucose Study

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Abstract

Background The aim of this study was to investigate the association of dietary insulin index (II), insulin load (IL), glycemic index (GI), and glycemic load (GL) with risk of cardiovascular disease (CVD) outcomes among adults.

Methods This cohort study was conducted within the framework of the Tehran Lipid and Glucose Study on 2198 subjects, aged ≥19 years, who were followed-up for a mean of 4.7 years. Dietary GI, GL, II, IL were calculated using a food frequency questionnaire at baseline. Multivariate Cox proportional hazard regression models, adjusted for potential confounders, were used to estimate risk of CVD across quartiles of dietary insulin and glycemic indices.

Results Mean±SD age of the study population (44.9% men) was 38.3±13.4 years. During an average of 2406 ± 417 person-years of follow-up, 76 (3.5%) new cases of CVD were ascertained. The Mean±SD of II, IL, GI, and GL of participants were 51.7±6.5, 235.8±90.2, 61.9±7.8, and 202.2±78.1, respectively. After adjusting for age, sex, smoking, physical activity, daily energy intake, body mass index, diabetes, and hypertension, the hazard ratio (HR) of the highest quartile of dietary GL was 2.77 (95%CI:1.00-7.69, P for trend:0.033) compared with the lowest one. However, there was no significant association between dietary GI, II, IL and risk for CVD incident.

Conclusions Our findings suggest that high GL diet can increase the incidence of CVD, whereas high dietary II and IL was not associated with risk of CVD among adults.

Introduction

Cardiovascular disease (CVD) is the main cause of death worldwide and known as one of the sustainable challenge in human development [1]. The main risk factors of CVD are obesity, hypertension, dyslipidemia, hyperglycemia, and insulin resistance (IR) [2, 3], which all are affected by dietary intakes. Several studies show associations of low fiber diet with overweight and IR, high sodium intake with hypertension, high saturated fatty acids with hypercholesterolemia and atherosclerosis, diet rich in refined grain and simple sugar with hyperglycaemia and IR [4–6].

Glycemic indices, including glycemic index (GI) and glycemic load (GL) commonly used for estimation of insulinogenic effects of foods. The GI indicates the rate of increasing blood sugar (BS) after consumption of carbohydrate content of food compared with reference foods including glucose or white bread [7]. However, serum response of glucose is not necessarily in accordance with insulin response. Although insulin response almost induced by carbohydrates, other nutrients such as dietary protein and fats can affect insulin secretion. Protein rich foods or some fats can induce the insulin response; also dietary protein augments the insulin response after consuming the carbohydrate foods [8].

Based on the concept of insulinogenic effects of foods with chronic disease, recently insulin indices (IIs) of foods including dietary insulin index (II) and insulin load (IL) have been introduced, which can predicts
the overall insulin load of the main part of diet; consequently estimates the odds of being hyperinsulinemia. IIs directly predicts the insulin demand evoked by composite meals including isoenergetic portions of single foods (1000 kJ) compared with 1000 KJ of glucose or white bread [8, 9]. As IIs computes based on the calorie content of foods, rather than glycemic indices, which are determined based on carbohydrate food content, it also provide ability for assessing the insulin response induces by low or free carbohydrate foods.

The review of literature and findings of meta-analysis of observational studies indicates direct association between GI, GL with CVD risk factors such as increased low density lipoprotein-cholesterol (LDL-C) and diabetes; however findings about incident CVD is not definite, and it seems to be a risk factor of CVD among women, not for men [10, 11].

Studies which investigated the relation of insulin indices and CVD risk factors are scare and their findings are controversial [12–15]. In study by Nimptsch et al, II was related with higher triglycerides (TGs) and lower high density lipoprotein-cholesterol (HDL-C) and showed no association with BS and C-reactive protein (CRP) [15]. Whereas, IL indicated no association with TGs, HDL-C, and obesity, however, positive association with fasting blood glucose (FBS) and CRP in another study [14]. Also, IIs were associated with greater odds of obesity and IR [12, 13].

Regarding the well-known association between IR and compensatory hyperinsulinemia with early atherosclerosis and consequently risk of CVD [16], and also predictive potential of IIs for determining the insulin response, assessing the relation between IIs and development of CVD may give us more practical information about diet therapy for preventing the risk of CVD among adults. To our knowledge no previous study assessed the relation between IIs and risk of incident CVD, we aimed to first, investigate the association of dietary II, IL, GI, and GL with risk of incident CVD among adult participants of the Tehran Lipid and Glucose Study (TLGS).

**Material And Methods**

**Study participants**

The present study was conducted within the framework of the TLGS, which conducted to determine the risk factors for non-communicable diseases among a representative urban population of Tehran, including 15 005 participants aged ≥ 3 years. The TLGS is an ongoing population-based prospective study initiated in 1999 (baseline phase) and its data are being collected prospectively at 3 y intervals; details of the TLGS have been reported previously [17].

In the third phase of the TLGS (2006–08), among 12 523 participants, 3652 were randomly selected for dietary assessment. After excluding participants with incomplete data (n = 187), among 2915 subjects aged ≥ 19 years participants with a history of myocardial infarction, stroke, and cancer (n = 40), those who reported daily energy intakes outside the range of 800–4200 kcal/ day (n = 163), those on specific diets (n = 376), and pregnant and lactating women (n = 52) were excluded; some individuals fell into more
than one exclusion category. Finally, 2362 participants were followed until March 2012, with a mean period of 4.7 years from the baseline examination. After excluding the participants who were missed to follow up (n = 164), final analyses was conducted on 2198 adults.

**Clinical and biologic measurements**

The data on demographic variables, medical histories, medication, and smoking habits were collected using pretested questionnaires during a face to face interview by trained interviewers. Subjects who smoke cigarettes daily or occasionally considered as smokers. Body weight were measured and recorded while subjects were wearing light clothing, without shoes, using a digital scale with an accuracy of 100 gr. Heights were measured in a standing position without shoes, while the shoulders were in normal alignment, using a stadiometer with a minimum measurement of 0.1 cm. Body mass index (BMI) were computed as weight (kg) divided by height (m$^2$). We measured arterial Blood pressure (BP) manually using a mercury sphygmomanometer and Korotkoff sound technique; twice on the right arm with a minimum interval of 30 seconds and the average was considered as the final pressure.

After 12 h to 14 h of overnight fasting, blood samples were taken and were centrifuged within 30–45 min of collection. On the day of blood collection, all blood analyses were performed at the TLGS research laboratory. Samples were analysed using the Selectra 2 autoanalyzer (Vital Scientific, Spankeren, The Netherlands). Fasting plasma glucose levels were measured with glucose oxidase using an enzymatic colorimetric method. Inter- and intra-assay coefficient variations were both 2.2% for fasting plasma glucose levels. The 2-hour oral glucose tolerance test were done using a 82.5 g of glucose monohydrate solution (equivalent to 75 g anhydrous glucose) which administered orally to subjects, aged > 20 years, except for those with diabetes and taking medication. These analyses were performed using commercial kits (Pars Azmoon, Tehran, Iran).

**Dietary assessment**

Dietary intakes of study population over the previous year were assessed using a valid and reliable 168-semi-quantitative food frequency questionnaire (FFQ) [18]. Trained dieticians, with at least 5 years’ experience in TLGS, during face-to-face interview asked participants to designate their consumption frequency for each food item on a daily, weekly or monthly basis during the previous year. Portion sizes of consumed foods, reported in household measures were then converted to grams. Using the United States Department of Agriculture (USDA) food composition table (FCT), energy and nutrients content were computed. Local food items that were not available in USDA FCT, was analysed using The Iranian FCT.

**Glycemic indices**

For each carbohydrate-containing food, GI is defined as the area under the blood glucose response curve over two hours after eating the food relative to that after consuming the equivalent amount of carbohydrate as glucose or white bread. The GI value of each food item was obtained from the international table of GI and from the publication that lists the GI of Iranian foods [19, 20].
Dietary GI = [(carbohydrate content of each food item) × (number of servings/d) × (GI) / total daily carbohydrate intake].

Dietary GL = (carbohydrate content of each food item) × (number of servings/d) × (GI)

**Insulin indices**

Measurement of insulin indices including II and IL were conducted using the published data of three previous studies by Jennie C Brand-Miller in the University of Sydney [8, 9, 21].

In calculation of insulin index (II), postprandial plasma insulin response after consumption of each food compares with a reference food including glucose or white bread. The insulin index value was calculated by dividing the area under the insulin response curve for 1000 kJ (239 kcal) of an each food by the area under the insulin response curve for 1000 kJ (239 kJ) of the reference food [8]. We matched the food items of our FFQ with previous food items which their II were calculated previously by Jennie C Brand-Miller et al.

Then, the total dietary insulin load (IL) of whole diet during the past year for each of study population by multiplying the insulin index value of each food by the total energy intake contributed by that food and summing values for all food items reported as follows [22]:

Dietary IL = \[\sum (\text{insulin index of food} \times \text{energy content of food (kcal/serving)} \times \text{frequency of consumption (servings of food/d)})\].

The dietary II of whole diet was calculated by dividing the dietary IL by the total energy intake as follows [22]:

Dietary II = \[\frac{\text{Dietary insulin load}}{\sum (\text{energy content of food (kcal/serving)} \times \text{frequency of consumption (servings of food/d)})}\]

**Physical activity assessment**

Physical activity measured using A Modifiable Activity Questionnaire (MAQ), which previously modified and validated among Iranians [23]. Individuals were asked to report and identify the frequency and time spent on activities of light, moderate, hard, and very hard intensity during the past 12 months, according to a list of common activities of daily life; physical activity levels were expressed as metabolic equivalent hours per week (MET-h/wk).

**Definitions**

The details about data collection of CVD outcomes in the TLGS have been provided in the previous reports [24, 25]. We defined the cardiovascular disease as any coronary heart disease (CHD) events, stroke, or CVD death (definite fatal myocardial infarction (MI), definite fatal CHD, and definite fatal stroke) [26]. Coronary heart disease-related events included cases of definite MI (diagnostic ECG and biomarkers), probable MI (positive ECG findings, cardiac symptoms or signs, and missing biomarkers; or...
positive ECG findings and equivocal biomarkers), and angiographic confirmed CHD. Stroke was considered as a new neurological deficit that lasted at least 24 h. History of CVD was considered as previous ischemic heart disease and/or cerebrovascular accidents.

We used JNC8 criteria for determining of hypertension as: systolic blood pressure (SBP) ≥ 140, or diastolic blood pressure (DBP) ≥ 90, or taking antihypertensive medications in subjects, aged < 60 years and SBP ≥ 150, or DBP ≥ 90 or taking antihypertensive medications in subjects, aged > 60 years [27].

Diabetes mellitus was defined as a fasting blood glucose of 126 mg/dl and higher, 2-hour blood glucose of 200 mg/dl and higher, or being on anti-diabetic medication [28].

**Statistical analysis**

All statistical analyses were performed using the Statistical Package for Social Sciences (Version 15.0; SPSS, Chicago, IL). The normality of the variables was assessed using histogram charts and Kolmogorov–Smirnov analysis. Participants were categorized based on quartiles of II, IL, GI, and GL. Presentation the baseline characteristics among subjects were reported according to quartiles of IL and GL; as the mean ± SD or median (interquartile) and percentages for continuous and categorical variables, respectively.

To test the trend of qualitative and quantitative variables across quartiles of IL and GL (as median value in each quartile), Chi-square and linear regression were used, respectively.

Time to event was determined as time to end of follow-up (censored cases) or time to having an event, whichever occurred first. We censored participants at the time of death due to non-CVD causes, at the time of leaving the district, or study follow-up end time of March 2014. The association between II, IL, GI, and GL with incident CVD were evaluated using Cox proportional hazard regression models and hazard ratios (HRs) and 95% confidence interval (CI) was reported. We also adjusted the potential confounders including age, sex, BMI, physical activity, smoking, diabetes, and hypertension, and daily energy intake in Cox regression models. P-values < 0.05 were considered to be statistically significant.

**Result**

Mean ± SD age and BMI of participants at baseline (44.9% men) were 38.3 ± 13.4 years and 26.6 ± 4.8 Kg/m², respectively. During an average of 2406 ± 417 person-year of follow-up, 76 (3.5%) new cases of CVD were ascertained. The mean ± SD of II, IL, GI, and GL of participants were 51.7 ± 6.5, 235.8 ± 90.2, 61.9 ± 7.8, and 202.2 ± 78.1, respectively.

Across quartiles of IL, participants were more likely to be male, physically active, smokers, having hypertension, and had higher dietary intakes of energy, refined grain, carbohydrate, and fiber. However, they had lower age and lower intakes of fruit and vegetable, red and processed meat, nut and legume, fat, and protein. There were no significant trend in other baseline characteristics across quartiles of IL (Table 1).
Table 1
Baseline characteristics among 2198 participants of Tehran Lipid and Glucose Study based on quartiles of dietary insulin load

| Characteristic            | Q1 (n = 549) | Q2 (n = 550) | Q3 (n = 549) | Q4 (n = 550) | P for trend |
|---------------------------|--------------|--------------|--------------|--------------|------------|
| **Insulin Load**          |              |              |              |              |            |
| Load                      | 137 ± 26     | 196 ± 14     | 250 ± 17     | 359 ± 67‡    | < 0.001    |
| Index                     | 48.6 ± 6.4   | 50.6 ± 6.2   | 52.6 ± 5.7   | 55.0 ± 5.9‡  | < 0.001    |
| Age (years)               | 39.2 ± 13.4  | 38.3 ± 13.2  | 38.7 ± 13.2  | 37.1 ± 13.5‡ | < 0.05     |
| Male (%)                  | 27.1         | 36.9         | 52.8         | 62.5‡        | < 0.001    |
| Body mass index (kg/m²)   | 26.8 ± 4.8   | 26.6 ± 4.6   | 26.6 ± 4.9   | 26.3 ± 4.9   | NS         |
| Physical activity (MET_h/week) | 23.6 (9.3–46.1) | 23.4 (10.4–47.8) | 24.3(10.4–50.7) | 24.8(10.9–55.5) ‡ | < 0.001 |
| Current smoker (%)        | 9.8          | 10.9         | 13.3         | 14.2*        | < 0.05     |
| Diabetes and pre-diabetes (%) | 12.0        | 10.5         | 12.9         | 8.7          | NS         |
| Hypertension (%)          | 8.1          | 7.7          | 9.5          | 12.6‡        | < 0.01     |
| **Dietary intakes**       |              |              |              |              |            |
| Energy (kcal)             | 1521 ± 396   | 2019 ± 371   | 2430 ± 434   | 3095 ± 529‡  | < 0.001    |
| Fruit and vegetable (serving/d/10 00 Kcal) | 3.0 ± 1.6 | 2.8 ± 1.4 | 2.6 ± 1.3 | 2.1 ± 1.1‡ | < 0.001 |
| Refined grain (serving/d/10 00 Kcal) | 2.0 ± 1.1 | 2.1 ± 1.0 | 2.3 ± 1.1 | 2.8 ± 15‡ | < 0.001 |

Data are presented as the mean ± SD or as the median (25–75 IQR) for continuous variables and as percentages for categorical variables.
| Characteristic                                      | Q1 (n = 549) | Q2 (n = 550) | Q3 (n = 549) | Q4 (n = 550) | P for trend |
|---------------------------------------------------|--------------|--------------|--------------|--------------|------------|
| Red and processed meat (serving/wk/1000 Kcal)     | 2.2 (1.3–3.8)| 2.3 (1.3–3.7)| 2.1 (1.3–3.4)| 2.0 (1.1–3.4)*| < 0.05     |
| Nut and legume (serving/wk/1000 Kcal)             | 0.99 (0.59–1.69)| 0.96 (0.57–1.60)| 0.97 (0.58–1.65)| 0.87 (0.48–1.46)*| < 0.05     |
| Carbohydrate (% of energy)                        | 54.9 ± 7.4   | 56.3 ± 6.8   | 57.9 ± 6.3   | 60.1 ± 6.7‡  | < 0.001    |
| Fat (% of energy)                                 | 33.9 ± 7.4   | 32.5 ± 6.6   | 31.1 ± 6.2   | 28.7 ± 6.3‡  | < 0.001    |
| Protein (% of energy)                             | 13.8 ± 2.6   | 13.8 ± 2.3   | 13.4 ± 2.1   | 13.3 ± 2.2‡  | < 0.001    |
| Fiber (g/1000 Kcal)                               | 14.9 ± 5.6   | 15.6 ± 5.5   | 16.6 ± 6.9   | 18.1 ± 8.2‡  | < 0.001    |

Data are presented as the mean ± SD or as the median (25–75 IQR) for continuous variables and as percentages for categorical variables.

Individuals in the highest quartile of GL were more likely to be male, smoker, and being more physically active, and had higher dietary intakes of energy, refined grain, carbohydrate, and fiber. However, across the quartiles of GL, age, intakes of fruit and vegetable, red and processed meat, fat, and protein decreased. There were no significant trend across quartiles of GL for BMI, hypertension, diabetes and pre-diabetes, and dietary intakes of nut and legume (Table 2).
Table 2
Baseline characteristics among 2198 participants of Tehran Lipid and Glucose Study based on quartiles of glycemic load

| Characteristic | Q1 (n = 549) | Q2 (n = 550) | Q3 (n = 550) | Q4 (n = 549) | P for trend |
|---------------|-------------|-------------|-------------|-------------|-------------|
| **Glycemic load** |             |             |             |             |             |
| Load          | 117 ± 22    | 167 ± 12    | 214 ± 16    | 309 ± 59‡   | < 0.001     |
| Index         | 58.4 ± 7.8  | 60.8 ± 7.0  | 62.3 ± 6.8  | 66.2 ± 7.5‡ | < 0.001     |
| Age (years)   | 39.2 ± 13.8 | 38.9 ± 13.1 | 38.0 ± 13.0 | 37.1 ± 13.6‡| < 0.01      |
| Male (%)      | 28.1        | 39.8        | 48.5        | 63.0‡        | < 0.001     |
| Body mass index (kg/m2) | 26.9 ± 4.9  | 26.6 ± 4.6  | 26.5 ± 5.0  | 26.3 ± 4.7  | NS          |
| Physical activity (MET_h/week) | 23.6(8.9–45.3) | 23.8(9.1–47.1) | 24.5(11.4–52.1) | 24.3(11.3–55.1) † | < 0.01 |
| Current smoker (%) | 9.7        | 10.2        | 14.5        | 13.8*        | < 0.05      |
| Diabetes and pre-diabetes (%) | 13.3        | 10.9        | 10.4        | 9.7          | NS          |
| Hypertension (%) | 9.5        | 7.3         | 10.2        | 10.8         | NS          |
| **Dietary intakes** |             |             |             |             |             |
| Energy (kcal) | 1522 ± 386  | 2012 ± 373  | 2430 ± 431  | 3103 ± 524‡ | < 0.001     |
| Fruit and vegetable (serving/d/10 00 Kcal) | 2.8 ± 1.5   | 2.7 ± 1.3   | 2.7 ± 1.4   | 2.3 ± 1.3‡  | < 0.001     |
| Refined grain (serving/d/10 00 Kcal) | 1.9 ± 1.0   | 2.1 ± 1.0   | 2.3 ± 1.1   | 3.0 ± 1.5‡  | < 0.001     |

Data are presented as the mean ± SD or as the median (IQR) for continuous variables and as percentages for categorical variables.
The association of II, IL, GI, and GL with incidence of CVD are presented in Table 3. There were no significant association of II, IL, GI, and GL with risk of incident CVD after 4.7 years of follow-up based on the age and sex adjusted model. However, in the fully adjusted model for potential confounders including age, sex, BMI, physical activity, smoking, diabetes, and hypertension, and daily energy intake, the HR of incidence of CVD in participants who were in the highest quartile of GL was 2.67 (95% CI: (1.00-7.69), \( P \) for trend = 0.033) compared to those in the lowest one. In the final adjusted model, other indices showed no significant association with medium to large effect sizes for increasing the risk of incident CVD; the HR(95% CI) of incident CVD for II, IL, and GI were 1.24 (0.65–2.33), 2.08 (0.70–6.19), and 1.55 (0.80–2.99), respectively in the highest compared to the lowest quartile.
## Table 3
Relative risk and 95% CI of cardiovascular disease by dietary insulin and glycemic scores in the Tehran Lipid and Glucose Study, 2006–2011

| Quartiles | Insulin Index | Insulin Load | Glycemic Index |
|-----------|---------------|--------------|---------------|
|          | P for trend   |              |               |
| Q1        | Q2            | Q3           | Q4            |
|           |               |              |               |
| Median score | 44.3  | 50.0   | 53.8  | 58.9  |
| CVD/Total | 15/549 | 17/550 | 15/549 | 29/550 |
| person-years | 3660.2 | 3605.2 | 3623.0 | 3578.8 |
| Incidence rate (10,000 person year) | 40.9 (24.6–67.8) | 47.0 (29.2–75.7) | 41.3 (24.9–68.5) | 80.9 (56.2–116.4) |
| Crude model | 1.00 (ref) | 1.15 (0.57–2.31) | 1.01 (0.49–2.07) | 1.98 (1.06–3.69) | 0.033 |
| Model 1 | 1.00 (ref) | 1.01 (0.50–2.04) | 0.66 (0.32–1.35) | 1.10 (0.58–2.08) | 0.840 |
| Model 2 | 1.00 (ref) | 1.16 (0.57–2.36) | 0.69 (0.33–1.45) | 1.24 (0.65–2.33) | 0.638 |

| Median score | 142.6 | 196.0 | 248.5 | 340.6 |
| CVD/Total | 15/549 | 18/550 | 22/549 | 21/550 |
| person-years | 3643.2 | 3643.5 | 3630.9 | 3550.1 |
| Incidence rate (10,000 person year) | 41.1 (24.7–68.1) | 49.3 (31.0–78.2) | 60.4 (39.8–91.8) | 59.0 (38.5–90.5) |
| Crude model | 1.00 (ref) | 1.19 (0.60–2.37) | 1.47 (0.76–2.83) | 1.41 (0.73–2.75) | 0.279 |
| Model 1 | 1.00 (ref) | 1.26 (0.63–2.50) | 1.20 (0.61–2.35) | 1.38 (0.71–2.71) | 0.386 |
| Model 2 | 1.00 (ref) | 1.52 (0.71–3.27) | 1.69 (0.71–3.77) | 2.08 (0.70–6.19) | 0.238 |

| Median score | 53.0 | 59.9 | 64.4 | 70.6 |

*Cox proportional hazard regression models were used to estimate relative risks (RR) and 95% confidence interval (CI)*
### Glycemic Load

| Quartiles | P for trend |
|-----------|-------------|
| Q1  | Q2  | Q3  | Q4  |
| CVD/Total | 18/550 | 24/549 | 15/549 | 19/550 |
| person-years | 3587.6 | 3603.9 | 3644.7 | 3629.6 |
| Incidence rate (10,000 person year) | 50.0 (31.5–79.5) | 66.4 (44.5–99.2) | 41.0 (24.7–68.1) | 52.2 (33.3–81.9) |
| Crude model | 1.00 (ref) | 1.34 (0.72–2.47) | 0.82 (0.41–1.64) | 1.05 (0.55–2.00) |
| Model 1 | 1.00 (ref) | 1.30 (0.70–2.41) | 0.87 (0.43–1.73) | 1.27 (0.66–2.43) |
| Model 2 | 1.00 (ref) | 1.32 (0.71–2.46) | 0.97 (0.48–1.97) | 1.55 (0.80–2.99) |

*Cox proportional hazard regression models were used to estimate relative risks (RR) and 95% confidence interval (CI)*

In a subsample of participants with dysglycemia (n = 243), we observed that those who were in the highest vs the lowest quartile of II, IL, GI, and GL had higher risk of CVD with HR(95% CI) of (1.20 (0.43–3.32), P for trend = 0.610), (5.59 (0.96–32.55), P for trend = 0.046), (3.24 (0.96–11.00), P for trend = 0.097), and (5.66 (1.08–29.61), P for trend = 0.029), respectively.

**Discussion**
The current study provided evidence that the highest score of dietary GL was significantly associated with an increased risk of CVD, independent of potential confounding factors including age, sex, BMI, physical activity, smoking, diabetes, hypertension, and daily energy intake in Tehranian adults. However, there was no significant association between dietary GI, II, and IL score and the risk of CVD in adults.

In the last decade, meta-analyses and review reports summarized the association of GI and GI with risk of cardiovascular events [10, 11, 29]; our findings are comparable with results of these previously published studies conducted on adult population which reported high dietary GL and GI were associated with increased risk of CVD events, specifically for women. Three reviews have suggested that gender may significantly modified the association of dietary GL and GI with risk of CVD outcomes [10, 11, 29]. Xiang-yu et al revealed that high dietary GL and GI are related with a 23% and 13% increased risk of CVD events, respectively. This estimated risk of GL and GI for men were lower than women. This dose–response meta-analysis has been found an increased risk of CVD events by 18% per 50 unit increment of GL of diet [10]. Also, based on findings of two previously published reviews, diet with high GL and GI significantly increased CVD events risk in women but not in men [11, 29]. The Knopp et al study reports that increase in triacylglycerol and the decrease in high-density lipoprotein cholesterol concentration in response to a high glycemic diet are greater in women than in men, which can caused differences in results between men and women [30].

Iranians consume more than 55% of energy from carbohydrate, which is higher than the amounts consumed in most western countries [31]. Our population have high carbohydrate intakes with plant sources such as refined grain, rice, and potato [32, 33]. Therefore, in our study, white rice and bread especially white bread were the major contributors of dietary GL and GI; these food items have high carbohydrates content and low amount of fiber which can play a possible role in development of cardiometabolic risk factors. However, higher adherence to low GL diet which is characterised by high consumption of whole-grain bread, fruits, vegetables, and legumes with high fibre content, if combined with lower consumption of white bread and rice could be have protective role in decreasing CVD risk [34, 35].

Although insulin response almost induced by carbohydrates, other nutrients such as dietary protein and fats can affect insulin secretion. Protein rich foods or some fats can induce the insulin response; also dietary protein augments the insulin response after consuming the carbohydrate foods [8]. Recently, pprevious reports declared that dietary II and IL can be more applicable to assess the effect of insulin exposure in development of non-communicable chronic diseases than other factors such as GI, GL, or total carbohydrate intake; because, II is directly based on the insulin response and this index could directly quantifies the insulin secretion in response to the carbohydrate and protein rich foods [36]. Despite the lack of longitudinal study on the association of dietary II and IL with CVD, several studies with reported controversial findings on association of dietary II or IL with cardiovascular risk factors, including hyperglycemia, insulin resistance, obesity, high level of CRP, and dyslipidemia [12–15]. The Nimptsch et al study have shown that dietary II was directly associated with low HDL-C and high triglycerides levels in obese individuals; however, there are no association between dietary II and IL and LDL-C, CRP, and
biomarkers of glycemic control [15]. In a cohort study in the framework of TLGS, dietary II and IL has been mentioned as independent dietary risk factors for risk of insulin resistance [13]. Also, a cross-sectional study has reported that the high II of diet was associated with higher odds of obesity among women, but not in men [12]. Furthermore, Mozaffari et al. has indicated adherence to a diet with a high IL was positively related with serum FBS and hs-CRP levels. However, no association was reported between high dietary IL and BMI or lipid profiles [14].

This is the first study that assessed the association of dietary II and IL with the incidence of CVD events and showed that there is no significant association between these insulin indices scores with risk of CVD. Our failure to find significant association of dietary II and IL with risk of CVD may be due to some reasons. First, due to lack of dietary insulin data, some food items of FFQ such as some fruits or vegetables were not included in the final dietary II and IL scoring, which could be effective on this association. Second, in the current study, individuals in highest quartile of dietary IL have higher intakes of fiber and lower intakes of fat compared to those in the lowest one; in addition to the influencing on calculated dietary IL score, these nutritional factors can also be have modifying effect on the association between insulin indices and development of CVD, independently in the form of a healthy diet. Third, the insulin index values of food items were derived from a report which was conducted on young lean students whose insulin responses can be relatively different from our adult and elderly participants [8]. Fourth, the incidence rate of CVD events in participants in the fourth quartile of the IL was significantly higher than those in lowest quartile (Q4: 59.0 per 10000 person-years vs. Q1: 41.1 per 10000 person-years). This significant difference in incidence rate of CVD was also observed in participants based on quartiles of GL (Q4: 69.9 per 10000 person-years vs. Q1: 49.8 per 10000 person-years). However, the low power of study due to low sample size and limited number of CVD cases in each quartile of IL has been led to provide non-significant finding in our study.

A subgroup analysis in this prospective cohort study on 243 individuals with dysglycemia revealed that dietary pattern with high GL and IL can be related strongly with increased risk of CVD in high risk participants. Previously reported that, the most of individuals with dysglycemia have both hyperinsulinemia and insulin resistance and they are prone to CVD outcomes such as coronary heart disease and stroke. Therefore, a dietary pattern with high GL and IL is likely to be associated with an increased risk of insulin resistance, atherogenesis, and subsequently an increased risk of CVD [37].

Some reports suggest supporting mechanisms and pathways which can explain a beneficial association between these indices with risk of CVD incident. The beneficial effect of low GL or GI diets on reducing cardio-metabolic risk factors, including total cholesterol, LDL-C, TGs, BMI, plasminogen activator inhibitor-1 concentrations have been reported previously [38, 39]. Also, high dietary GI was associated with higher plasma levels of TNF-α, IL-6, and CRP [39, 40]. Furthermore, after consuming high-GI foods with the same amount of carbohydrate, blood glucose concentration increases and stimulates insulin release. The chronically increased insulin demand may eventually leads to the destruction of pancreatic β cell, and, as a consequence, impaired glucose tolerance. Also, high-GI diets can directly increase insulin resistance through their effect on glycemia and free fatty acids [41]. Some reports suggested the potential
mechanisms through which dietary II and IL might influence CVD risk factors. High II of diet may increase risk of obesity by stimulating more insulin secretion, which can reduce fat oxidation and increase carbohydrate oxidation, causing increase fat storage [42]. Also, high dietary IL and II can be linked to β-cell dysfunction and increasing insulin resistance with influencing on insulin secretion [13].

The current study is subject to some limitations; the Iranian food composition table was incomplete and the USDA nutrient databank was mostly used for dietary analyses. Also, despite adjusting of a wide variety of variables in our analysis, the confounding effect of some unknown or unmeasured residual confounding may have occurred. Despite these limitations, to date, this is the first study that assessed the association of dietary II and IL with the incidence of CVD conducted in the Middle East and North Africa (MENA) region. Prospective setting, the long duration of follow-up, and the use of a valid and reliable food-frequency and physical activity questionnaire were other strengths of current study.

In conclusion, the findings of current population-based cohort study provide evidence that a dietary pattern with a higher GL were associated with increased risk of CVD; however, there was no association between dietary GI, II, and IL and the risk for CVD. Further observational studies with long-term follow up are required to address the role of diet with high II and IL in the development of CVD outcomes and its potential mechanisms.

**Abbreviations**

BMI  
Body mass index  
BS  
blood sugar  
CI  
confidence interval  
CHD  
coronary heart disease  
CRP  
C-reactive protein  
CVD  
cardiovascular disease  
DBP  
diastolic blood pressure  
FBS  
fasting blood glucose  
FCT  
food composition table  
FFQ  
food frequency questionnaire
Declarations

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Authors' contributions

FT, GA, and PM conceptualized and designed the study. FT, HF, MN drafted the initial manuscript; FT and HF analyzed and interpreted the data; PM and FA supervised the project; all authors have read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

Written informed consent was obtained from all participants. The study protocol was approved by the ethics research committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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