BMJ Open

Associations between Insulin Index and Dietary Insulin Load with Cardiometabolic phenotype in the AZAR cohort population: A cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068303
Article Type:	Original research
Date Submitted by the Author:	13-Sep-2022
Complete List of Authors:	faramarzi, elnaz; Tabriz University of Medical Sciences somi, mohammad hossein; Gastroenterology Research Centre of Tabriz University of Medical Sciences Naghibi Irvani, Seyed Sina; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center, Research Institute for Endocrine Science Pourhashem, Nahid; Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences Nourizadeh, Amir Mohammad; Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences
Keywords:	NUTRITION & DIETETICS, DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY, INTERNAL MEDICINE

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Associations between Insulin Index and Dietary Insulin Load with Cardiometabolic phenotype in the AZAR cohort population: A cross-sectional study

Elnaz Faramarzi [1], Ph.D., Prof. Mohammad Hossein Somi, MD [1], Seyed Sina Naghibi Irvani [1] , MD, MPH, MBA, Nahid Pourhashem [1], Amir Mohammad Nourizadeh [1*], MD

[1] Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran.

Order of Authors:

1. Elnaz Faramarzi. Liver and Gastrointestinal Diseases Research center, Tabriz University of Medical Sciences. Email: elnazfaramarzi849@gmail.com

2. Mohammad Hossein Somi. Liver and Gastrointestinal Diseases Research Center of Tabriz university of medical sciences. Tabriz,Iran. Email: mhosseinsina@yahoo.com

3. . Seyed Sina Naghibi Irvani. Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz,Iran. Email: sina.irvani@gmail.com

4. Nahid Pourhashem. . Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz,Iran. Email: npourhashem@yahoo.com

5. Amir Mohammad Nourizadeh. Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran. Email: Nourizadehamirmohammad@gmail.com

*Corresponding Author:

Amir Mohammad Nourizadeh, MD,

Liver and Gastrointestinal Diseases Research Center. Tabriz University of Medical Sciences. Tabriz, Iran. (**Email:** Nourizadehamirmohammad@gmail.com)

ORCID Number: 0000-0001-9206-5327

P.O. Box: 1567812907, **Tel:** +98-914-9979121, **Fax:** +98-413-3845238

(Word count: 4159)

Keywords:

Nutrition and Dietetics/ Diabetes/ Endocrinology/ Internal Medicine

ABSTRACT

Objectives:

Hyperinsulinemia and insulin resistance are proposed as a significant contributor to the evergrowing incidence of unhealthy cardiometabolic phenotypes. (CMPs). This study analyzed the association between dietary insulin load (DIL) and dietary insulin index (DII) with CMPs in AZAR cohort population.

Design:

The current study was a cross-sectional analysis of the AZAR cohort study, beginning in 2014 and continuing to this date.

Setting:

AZAR cohort is a part of an Iranian national screening program named the Persian cohort and involves participants who have lived in the Shabestar region in East-Azarbaijan province, Iran for at least 9 months.

Participants:

A total number of 15006 participants agreed to partake in the study. We excluded participants with missing data (N=9), participants with a daily energy intake lower than 800 kcal (N=7) or higher than 8000 kcal (N=17), and participants with cancer (N=85). Finally, 14888 individuals remained.

Primary and secondary outcome measures:

The gathered information included demographic, dietary, anthropometric, and activity data of the participants.

Results: The findings of the unadjusted model demonstrated that high DIL and DII were associated with decreased odds of unhealthy CMPs. The fourth quartile of DIL had 79% lesser odds for having metabolically unhealthy normal weight (MUHN) phenotype and 63% lesser odds for having metabolically unhealthy obese (MUHO) phenotype compared to those in the first quartile. The same results were observed for DII. mean energy intake of each unhealthy CMP was lower than mean energy intake of the corresponding healthy CMP.

Conclusions: DII and DIL were correlated with a decreased odds ratio of MUHN and MUHO. We suggest that the reason for this observation was an unnoticed lifestyle behavior change in participants with unhealthy CMPs that caused a lower energy intake. Further studies are required to confirm this speculation via taking possible recent lifestyle behavior changes into account.

Article summary:

Strengths and limitations of this study:

- The current study was an analysis of the AZAR cohort study which is a very large population. The final number of participants included was just less than 15,000 individuals.
- In this study, the associations between DII and DIL with four different CMPs were studied for the first time. This model helped us to analyze the data in a more organized fashion.

- The presense of confounders and their effect were considered while analyzing the data.
- Even though the data were analyzed with the consideration of confounding factors, still some of them were not assessed.

Introduction

According to World Health Organization (WHO), over 600 million adults are obese. (1) Metabolic Syndrome (MetS), which is closely associated with obesity, has increased the global burden of cardiovascular diseases, and its prevalence and incidence have significantly risen the past two decades. (2) The incidence of MetS usually agrees with the incidence of obesity. Prevalence of MetS has doubled in 73 countries and has notably increased in others as of 1980. (3)

Even though abdominal obesity is one of the criteria for MetS, MetS doesn't always equal obesity. Some other interesting phenotypes are recently seen more often. Some obese individuals do not have the criteria for MetS. They are called the Metabolically Healthy Obese (MHO). (4) Conversely, some non-obese individuals fulfill the criteria for MetS. They are called the Metabolically Unhealthy Normal Weight (MUHN) or the Metabolically Obese Normal Weight. (5)(6)(7)(8) This calls for classifying individuals into four different cardiometabolic phenotype (CMP) groups and assessing different metabolic factors based on four phenotypes; obese individuals who fulfill MetS criteria, called the Metabolically Unhealthy Obese (MUHO), obese individuals who do not fulfill MetS criteria, called the Metabolically Healthy Obese (MHO), normal weight individuals who fulfill MetS criteria, called the

Metabolically Unhealthy Normal Weight (MUHN), and normal weight individuals who do not fulfill MetS criteria, called the Metabolically Healthy Normal Weight (MHN).

Previous studies show a strong relationship between cardiometabolic status and insulin resistance. (9)(10) The ability of foods to induce postprandial insulin secretion is a significant factor in assessing the effect of individuals' diets on weight gain, hyperlipidemia, and type 2 diabetes. (11) Therefore, it is beneficial to quantify the ability of individuals' diets to induce postprandial insulin secretion. A diet with a high glycemic index (GI) and high Glycemic Load (GL) can lead to increased postprandial insulin secretion, leading to obesity and diabetes. (12)(13) Still, these two Indexes solely measure the effect of carbohydrates in this regard. In addition to carbohydrates, proteins and lipids also increase postprandial insulin secretion. Moreover, proteins enhance the effect of carbohydrates on insulin secretion. This leads to the fact that the amount of carbohydrates in a diet is not accurately proportional to postprandial insulin secretion. (14) A food Insulin Index (II) and Dietary Insulin Load (DIL) have been suggested. II can directly quantify the postprandial insulin response to a test food compared to an isoenergetic portion of a reference food. (11)(14) DIL can be calculated for each individual using II and the energy content of each food they consume. (15) since II and DIL are directly based on insulin response, they are more satisfactory to evaluate hypotheses that connect insulin exposure to cardiometabolic diseases compared to GI and GL.(11)

Some studies have assessed the relation between insulin exposure of diets with MetS and obesity but to the best of our knowledge, no studies have ever structured

and grouped individuals in different CMP classifications and assessed the relation between the insulinemic potential of their diets according to their CMP. Therefore, in this study we try to investigate the association between II and DIL with CMP in AZAR cohort population.

Materials and Methods

Study design and participants

Azar cohort is a prospective population-based study(16) in Iran and a part of a national screening program named prospective epidemiological research studies in Iran (Persian cohort).(17)(18) Its main goal is to investigate the major non-communicable diseases risk factors, including cardiovascular, pulmonary, and renal diseases, diabetes, and cancer. Azar cohort started in October 2014 and is still in progress in East- Azarbaijan province in Northwestern Iran. It is a study of up to 15000 individuals within the range of 35-70 years of age who have lived in the Shabestar region for at least 9 months. Subjects with severe psychiatric or physical illnesses and pregnant women were excluded from the study. This study is explained in greater detail in other studies. (16)(17)(18)

Our cross-sectional study was conducted on the AZAR cohort population. A total number of 15006 individuals agreed to participate. Then, we excluded individuals with missing data (N=9). We excluded individuals who had a daily energy intake lower than 800 kcal (N=7) or higher than 8000 kcal (N=17). Individuals who had cancer were also excluded (N=85). Finally, 14888 individuals remained. The

information included demographic, dietary, anthropometric, and activity data of the participants. All participants filled out a written informed consent form before the study. The Bioethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, approved the study. (Ethics Number: IR.TBZMED.REC.1401.414)

Socioeconomic status of the participants was evaluated by the Wealth Score Index (WSI), calculated by Multiple Correspondence Analysis (MCA). Each participant's WSI was determined by assessing their possession of different permanent property (eg TV, dishwasher, and car), their residence's conditions (eg type of ownership, the number of rooms), and levels of education. Participants were separated into five WSI quintiles, from the lowest WSI to the highest one (1st to 5th quintile, respectively). By using a questionnaire completed by the participants, their daily activity was assessed. We used Metabolic Equivalent of Task (MET) as a criterion for this goal. MET shows the amount of energy consumed by each person based on their weight. For instance, one MET is the amount of oxygen consumed per kilogram of body weight per minute by each resting person, that is 3.5 ml of oxygen. And therefore, four MET equals 16 milliliters of oxygen used per kilogram of body weight per minute. We measured the activity levels of each participant by using this criterion.

Smokers were defined as participants who continuously smoked at least one cigarette per day for more than six months. Ex-smokers were considered as participants who had stopped smoking at least a year before, and non-smokers were considered as participants who had never smoked. Other tobacco smokers were considered as participants who smoked other tobacco products. Participants were

divided into three categories based on their alcohol consumption; non-drinkers (participants who had never consumed alcohol), experienced/ex-drinkers (participants who had experienced alcohol consumption or who had used to drink), and drinkers (participants who regularly consumed alcohol).

Biochemical measurements

Samples of blood were collected from every individual after an overnight fast of 12 hours. Fasting blood sugar (FBS), serum triglyceride (TG), and high-density lipoprotein (HDL) were determined using a commercial kit (Pars Azmoon, Tehran). (17)

Anthropometric measurements

We used a mounted tape for measuring the height to the nearest 1 mm. Weight was measured with light clothing and without using shoes with a Seca scale to the nearest 0.1 kg. BMI was calculated by dividing weight (kg) by the square of height (m) and presented as kg/ m2. The waist circumference (WC) was measured according to NIH guidelines. Female individuals with WC ≥88 cm and male individuals with WC of ≥ 102 cm were considered abdominally obese. (19)

Blood pressure measurements

The blood pressure was measured two times in each arm in the sitting position and according to Persian cohort protocol. (17) The individuals rested for ten minutes between each measurement. The blood pressure of every individual was calculated as the average of the two measurements in each arm.

Cardiometabolic phenotypes and Metabolic syndrome definition

We defined Mets according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATPIII) criteria. (3) According to these criteria, MetS is defined by the presence of three or more of the followings: Fasting blood glucose ≥100 mg/dl; HDL cholesterol less than 40 mg/dl in men or less than 50 mg/dl in women; blood triglycerides ≥ 150 mg/dl or drug treatment for elevated triglycerides; waist circumference greater than 102 cm in men or greater than 88 cm in women; systolic blood pressure ≥130 and/or diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension.

We considered the cut off point for Body Mass Index (BMI) to be 25 kg/m^2. (20)

In this study, we categorized the subjects into four CMPs based on their BMI and the presence of MetS. The categories include:

1. Obese individuals who fulfill MetS criteria, called the Metabolically Unhealthy Obese (MUHO)
2. Obese individuals who do not fulfill MetS criteria, called the Metabolically Healthy Obese (MHO)
3. Normal weight individuals who fulfill MetS criteria, called the Metabolically Unhealthy Normal Weight (MUHN)
4. Normal weight individuals who do not fulfill MetS criteria, called the Metabolically Healthy Normal Weight (MHN)

Measuring DII and DIL

The Food Insulin Index (FII) is the area under the curve of increasing insulin over 2 hours after consumption of a 1000-kJ (239 kcal) portion of a test food divided by the area under the curve after consumption of a 1000-kJ (239 kcal) portion of the reference food. The insulin index for 68 food items was gathered from studies by Holt et al (14), Bao et al (21), and Bell et al (22). The Insulin Index for salt, tea, and coffee was considered zero since the amount of carbohydrate, protein, and fat, and the energy content of these foods is approximately zero. For the rest of the 49 food items that were not included in the food lists of the aforementioned studies, the FII of similar food items considering the similarity of their energy, carbohydrate, protein, fat, and fiber content was used. For instance, both dates and raisins are dried fruits. The energy, carbohydrate, fat, protein, and fiber content of both fruits are comparable to each other. Hence, the insulin index of raisins was used for dates. To calculate DIL, the insulin load of each food was determined using the following formula: Insulin load of a given food = insulin index of that food × energy content per 1 g of that food × amount of that food consumed (g/d). By summing up the insulin load of each food, DIL was obtained for each participant. DII for each participant was then determined by dividing DIL by total energy intake.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 11.5, Chicago, IL) was used for the data analysis. Descriptive statistics were obtained for all study variables and reported as mean ± SD as well as number (percentage) where applicable. $\chi 2$ test was used for comparing nominal qualitative variables in different

Cardiometabolic groups and Kruskal-Wallis test was used for comparing ordinal qualitative variables in different Cardiometabolic groups. One-way ANOVA test was used to compare mean values amongst different Cardiometabolic groups. The multinomial logistic regression analysis was used for estimating crude and adjusted odds ratios (OR) and their corresponding 95% confidence intervals (95% CIs). Mets components (hypertension, high FBS, Hypo-HDL, cholesterolemia, hypertriglyceridemia, and abdominal obesity), Insulin Index, and Dietary Insulin Load were considered independent variables. Each variable was introduced in the model one by one. The effect of confounding factors (age, gender, educational level, marital status, current smoking status, and frame size) was adjusted, and MHN was considered as the reference group. Statistical significance was considered as *P* value <0.05.

Finally, We used the STROBE cross sectional checklist when writing our report.(23)

Results

Participants' characteristics

Table 1 presents the participants' baseline characteristics according to their CMPs and Table 2 presents the same characteristics in both genders. Among the four phenotypes, the MUHO phenotype had the highest proportion of female and married participants. (Table 1). The married participants' ratio was significantly higher in both genders. (Table 2) Education levels regardless of gender, and in female participants were lower in the MUHO phenotype group, (p<0.001) but the education levels in

male participants showed no significant differences. (p< 0.39). Physical activity in both genders was significantly lower in metabolically unhealthy participants (Both MUHN and MUHO). (p<0.001) Assessing the quintiles of WSI in all of the participants (Table 1) and female participants (Table 2) showed that the MUHO were mostly among the 1st quintile of WSI. (p<0.001) whereas in male participants (Table 2), the MUHO phenotype was associated with higher income. (p<0.001) Interestingly, mean energy intake of each unhealthy CMP was lower than mean energy intake of the corresponding healthy CMP. For instance, mean energy intake of MUHN participants was 2850.34±919.82 whereas it was 3109.21±919.32 in MHN participants. Moreover, frequency of alcohol consumption and Smoking was significantly higher in MHN participants than in MUHO participants. (p<0.001) On the other hand, the percentage of secondhand smokers was significantly higher in MUHO participants than in MHN ones, both regardless and according to their gender. (Tables 1 and 2) (p<0.001) The mean values of Age, BMI, and waist circumference showed incremental trends from being in a healthy phenotype (whether normal weight or obese) to an unhealthy phenotype. ($p \leq 0.001$) (Tables 1 and 2). Hip circumference was lower in the MHN than in the MHO and MUHO. (p<0.001)

Relationship between Cardiometabolic Phenotypes and Dietary Insulin Load and Index

The frequency of Insulin load and index quartiles showed a significant decrease from the 1st to 4th quartile in metabolically unhealthy participants (Both MUHN and MUHO) ($p \leq 0.001$).

Unexpectedly, the mean values of Dietary Insulin Index and Dietary Insulin Load showed to be higher in metabolically healthy phenotypes than in unhealthy ones, with the MUHN phenotype being the lowest. ($p<0.001$) In addition, the mean value of energy intake was lower in metabolically unhealthy phenotypes compared to their corresponding healthy phenotypes, with the MUHN consuming the lowest energy intake. ($p<0.001$) (Table 1) This trend was seen both regardless of the participants' gender, (Table 1) and in male or female participants divided. (Table 2)

The findings of the unadjusted model indicated that compared to the 1st DIL quartile, the risks of MUHN and MUHO in the 4th DIL quartile decreased by 0.21 (0.14 - 0.32) and 0.37 (0.33 – 0.43), respectively (Table 3). After adjustment for different intervening factors (ie age, gender, education, MET, and Energy intake), a strong negative correlation was observed between DIL with MUHN. But there were no significant correlations between DIL with MHO and MUHO after the adjustments. (Table3). The aforementioned negative correlation was more obvious in the 4th DIL quartile. In Model 2, the observed odds ratio for MUHN was 0.61 (0.42 – 0.90) in the 2nd DIL quartile, while it was 0.23 (0.12 – 0.47) in the 4th DIL quartile. (Table3).

The findings of the unadjusted model for the DII quartiles indicated that compared to the 1st DII quartile, the risks of MUHN and MUHO in the 4th DII quartile decreased by 0.18 (0.11 - 0.28) and 0.39 (0.34 – 0.45), respectively (Table 3). After adjustment for the same intervening factors as DIL quartiles, a strong negative correlation was observed between DII with MUHN and MUHO. But there was no significant correlation between DII with MHO after the adjustments. (Table3). The

aforementioned negative correlations were more obvious in the 4th DII quartile. In Models 1 and 2, the observed odds ratio for MUHN were 0.59 (0.41 – 0.84) respectively in the 2nd DII quartile, while they were both 0.24 (0.15 – 0.37) in the 4th DII quartile. (Table3).

These models were also run for both male and female participants separately. The results in both genders were overall the same as all participants combined.

Discussion

This cross-sectional study looked into the association between DII and DIL with different CMPs. The findings indicated that there was a significant negative correlation between DII and DIL and MUHN and MUHO phenotypes both before and after considering confounding variables. Our findings demonstrated no significant correlation between DIL and DII and MHO. The prevalence of chronic conditions such as MetS has increased in recent years. (2)(24) Previous studies indicate a significant positive association between insulin resistance and unhealthy cardiometabolic status. (25) One of the main causes of insulin resistance is the tendency towards diets with high insulinemic capability. (21)(26) Thus, it is of great importance to establish a reliable index to demonstrate the insulinemic potential of individuals' diets. Since DII and DIL directly depend on insulin response to food, there has been an increase of attention to these two in evaluating the aforementioned potential. (11)(21) By measuring these two indices in different populations, we can search for an association between these two and different

CMPs and deduce whether we can use DII and DIL to predict the odds of unhealthy CMPs or not. To the best of our knowledge, this is the first study trying to answer this question and evaluate this association in different CMPs. In our study, there was a correlation between unhealthy CMPs and lower DIL and DII values. In addition, high DIL and DII were associated with lower odds of unhealthy CMPs. (both MUHN and MUHO). The trend of odds ratio in metabolically healthy phenotypes was not significant. We can conclude these findings in two different parts.

First, the correlation between lower DIL and DII with unhealthy CMPs can be justified by the fact that the mean energy intake in unhealthy phenotypes was lower than in healthy phenotypes. This finding suggests that the participants with unhealthy phenotypes restricted their energy intake and possibly lowered the insulinemic potential of their diet (ie lowered their DII and DIL) to lose weight and modify their lifestyle behavior. Additionally, our findings demonstrate that alcohol consumption and smoking were also lower in metabolically unhealthy phenotypes. This supports the speculation that participants with unhealthy phenotypes were following a lifestyle modification plan in diet, smoking, and alcohol consumption. This modification could be the reason for lower DII and DIL in unhealthy phenotypes. Therefore, we suggest that measuring DII and DIL cannot be a reliable index for predicting the CMP and the risk of developing chronic diseases. Further studies are needed to take recent lifestyle modifications into account and determine the associations between DII and DIL with CMPs in participants who have not had a recent lifestyle modification, specifically modifications in their diets.

Secondly, the insignificant trend of odds ratio in metabolically healthy phenotypes suggests that insulin resistance may not be easily assessed and predicted by simply measuring indices such as DII and DIL since insulin secretion depends on different components including the participant's diet, neural, and hormonal activity. (27)

In line with our findings, Karimbeiki et al demonstrated that a higher insulinemic effect of diet was not associated with higher rates of obesity. (28) Another study by Anjom-Shojaei et al showed that a high DII of diet was not associated with obesity in men, although it was associated with obesity in women. (15) A cross-sectional study on 262 participants of the Dortmund Nutritional and Anthropometric Longitudinally Designed Study demonstrated that a higher DII and DIL were associated with higher body fat percentage, but not higher BMI. (29) On the other hand, a cross-sectional study conducted on 203 overweight/obese adolescents showed that a diet with higher DII and DIL was associated with higher odds of being in the MUHO group. (30) A cross-sectional study on the Shahidieh cohort demonstrated that a higher DII was associated with higher odds of MetS in women, but no such association was seen in men. (24) moreover, a clinical trial with a Mediterranean diet style was associated with healthier CMPs, lower body weight, lower BMI and fat mass, and lower blood glucose and lipids in children and adolescents with obesity. (31) Approving the aforementioned study, a cross-sectional study on 137 European overweight and obese participants in their puberty, showed that a Mediterranean diet was associated with a lower risk of MUHO phenotype. (32) Another cross-sectional study involving both overweight and

normal-weight Turkish children has demonstrated that breakfast and dinner with higher DII and DIL were associated with a higher odds ratio of being overweight. (33) Two other studies were investigating the correlation between DII and DIL with diabetes, and cardiovascular disease respectively. The first study concluded that a higher DII and DIL of the diet were associated with a higher risk of diabetes, and DIL was a better predictor for diabetes compared to DII. (34) The other study demonstrated that DII and DIL were not associated with the risk of CVD,(35) which is in line with our findings. In the current study, we demonstrated that DII and DIL were strongly correlated with a decreased odds ratio of MUHN and MUHO and that there was no significant correlation between DIL and DII and MHO.

Previous studies suggest several mechanisms for the correlation between DII and DIL with unhealthy CMPs. Insulin secretion can be a result of highly insulinemic diets, which in turn, increases the oxidation of carbohydrates and decreases the oxidation of lipids. Therefore, these diets can cause a surplus in abdominal fat storage, and increase the risk of obesity and unhealthy CMPs. (30) Moreover, high insulinemic diets potentially cause faster carbohydrate digestion and absorption, and higher blood glucose and insulin levels. They also cause a faster drop in the post-prandial blood glucose levels after the surge. (36)(37) This sudden drop in blood glucose can reduce satiety and cause a high-calorie intake of food, resulting in abdominal obesity and unhealthy CMPs. (36)(37) Additionally, High DII and DIL are associated with a higher incidence of insulin resistance and diabetes. (34)(38)

Our study had several strengths. The associations between DII and DIL with four different CMPs were studied for the first time, and these CMPs were organized based on the presence or absence of obesity, and the presence or absence of MetS. This model helped assess the data in a more organized pattern. In addition, the effect of confounding factors was also taken into account while analyzing the data. Another strength of this study was its large population. Our study was conducted on just less than 15000 participants. Nevertheless, there were some limitations during the conduction of this study which should be taken into consideration while evaluating the results. Since this was a cross-sectional study, we could not establish a cause and effect correlation and more prospective studies are needed to establish and assert such causality. Even though the data were analyzed with the confounding factors taken into account, still some confounding factors including dietary habits, psychological factors, parental obesity, and family history of cardiometabolic diseases were not assessed. Finally, considering our findings demonstrated that participants with unhealthy CMPs had lower energy intake and alcohol consumption, and a lower smoking rate, it is presumable that some may have changed their lifestyle behavior. This presumed lifestyle behavior change can be the main reason for DII and DIL being associated with a lower odds ratio of unhealthy CMPs. This finding highlights the importance of considering recent lifestyle behavior change as a confounding factor and further studies are needed to evaluate the association between DII and DIL with different CMPs in participants with no recent lifestyle behavior change or evaluate this association while taking the aforementioned confounding factor into account.

Conclusion

This current cross-sectional study demonstrated that DII and DIL were strongly correlated with a decreased odds ratio of MUHN and MUHO and that there was no significant correlation between DIL and DII and MHO. As mentioned before, we speculate that a lower energy intake in participants with unhealthy cardiometabolic phenotypes, as a result of lifestyle behavior change, was the main reason for this observation. Further studies, specifically with a prospective design, are required to confirm this speculation via assessing the correlation between DII and DIL with different CMPs in participants who have not experienced a recent lifestyle behavior change.

Acknowledgments:

The authors are grateful for the financial support of the liver and gastrointestinal diseases research center, Tabriz University of Medical Sciences. The authors also are deeply indebted to all subjects who participated in this study. We appreciate the contribution by the investigators and the staff of the Azar cohort study. We thank the close collaboration of the Shabestar health center. In addition, we would like to thank the Persian cohort study staff for their technical support. We would like to appreciate the cooperation of the Clinical Research Development Unit of Imam Reza General Hospital, Tabriz, Iran in conducting this research.

Declaration

Ethics approval and consent to participate

This study was approved by the ethic committee of Tabriz University of medical sciences (IR.TBZMED.REC.1401.414)

Funding

This study was supported by the liver and gastrointestinal diseases research center (Grant number700/108 on 14 March 2016), Tabriz University of Medical Sciences. The funder had no role on the study design, data analysis, interpreting and writing the manuscript in this study.

Competing interests

The authors declare that they have no competing interests

Availability of data and materials

The data that support the findings of this study are available from [Vice Chancellor for Research] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [Vice Chancellor for Research]

Author statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar

material has not been and will not be submitted to or published in any other publication before its appearance in the *BMJ open.*

References

1. Collaborators GBD 2015 O. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27.
2. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev. 2015;16(1):1–12.
3. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):1–8.
4. Goday A, Calvo E, Vázquez LA, Caveda E, Margallo T, Catalina-Romero C, et al. Prevalence and clinical characteristics of metabolically healthy obese individuals and other obese/non-obese metabolic phenotypes in a working population: results from the Icaria study. BMC Public Health. 2016;16(1):1–14.
5. Osadnik K, Osadnik T, Lonnie M, Lejawa M, Reguła R, Fronczek M, et al. Metabolically healthy obese and metabolic syndrome of the lean: the importance of diet quality. Analysis of MAGNETIC cohort. Nutr J. 2020;19(1):1–13.
6. Ding C, Chan Z, Magkos F. Lean, but not healthy: the 'metabolically obese, normal-weight'phenotype. Curr Opin Clin Nutr Metab Care. 2016;19(6):408–17.
7. Wang B, Zhuang R, Luo X, Yin L, Pang C, Feng T, et al. Prevalence of metabolically healthy obese and metabolically obese but normal weight in adults worldwide: a meta-analysis. Horm Metab Res. 2015;47(11):839–45.
8. Jung CH, Lee MJ, Kang YM, Jang JE, Leem J, Hwang JY, et al. The risk of incident type 2 diabetes in a Korean metabolically healthy obese population: the role of systemic inflammation. J Clin Endocrinol Metab. 2015;100(3):934–41.
9. Eddy D, Schlessinger L, Kahn R, Peskin B, Schiebinger R. Relationship of insulin resistance and related metabolic variables to coronary artery disease: a mathematical analysis. Diabetes Care. 2009;32(2):361–6.
10. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol. 2013;3(1):1.
11. Nimptsch K, Brand-Miller JC, Franz M, Sampson L, Willett WC, Giovannucci E. Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers. Am J Clin Nutr.

2011;94(1):182–90.

12. Bell SJ, Sears B. Low-glycemic-load diets: impact on obesity and chronic diseases. 2003;
13. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr. 2000;71(6):1455–61.
14. Holt SH, Miller JC, Petocz P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. Am J Clin Nutr. 1997;66(5):1264–76.
15. Anjom-Shoae J, Keshteli AH, Sadeghi O, Pouraram H, Afshar H, Esmaillzadeh A, et al. Association between dietary insulin index and load with obesity in adults. Eur J Nutr. 2020;59(4):1563–75.
16. Farhang S, Faramarzi E, Amini Sani N, Poustchi H, Ostadrahimi A, Alizadeh BZ, et al. Cohort profile: The AZAR cohort, a health-oriented research model in areas of major environmental change in Central Asia. Int J Epidemiol. 2019;48(2):382-382h.
17. Poustchi H, Eghtesad S, Kamangar F, Etemadi A, Keshtkar A-A, Hekmatdoost A, et al. Prospective epidemiological research studies in Iran (the PERSIAN Cohort Study): rationale, objectives, and design. Am J Epidemiol. 2018;187(4):647–55.
18. Eghtesad S, Mohammadi Z, Shayanrad A, Faramarzi E, Joukar F, Hamzeh B, et al. The PERSIAN cohort: providing the evidence needed for healthcare reform. Arch Iran Med. 2017;20(11):691–5.
19. Consultation WHO. Obesity: preventing and managing the global epidemic. World Health Organ Tech Rep Ser. 2000;894:1–253.
20. Somi MH, Nikniaz Z, Ostadrahimi A, Sadat ATE, Faramarzi E. Is normal body mass index a good indicator of metabolic health in Azar cohort population? J Cardiovasc Thorac Res. 2019;11(1):53.
21. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. Am J Clin Nutr. 2011;93(5):984–96.
22. Bell KJ, Petocz P, Colagiuri S, Brand-Miller JC. Algorithms to improve the prediction of postprandial insulinaemia in response to common foods. Nutrients. 2016;8(4):210.
23. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573–7.
24. Sadeghi O, Hasani H, Mozaffari-Khosravi H, Maleki V, Lotfi MH, Mirzaei M. Dietary Insulin Index and dietary insulin load in relation to metabolic syndrome: The Shahedieh cohort study. J Acad Nutr Diet. 2020;120(10):1672–86.
25. Okosun IS, Okosun B, Lyn R, Airhihenbuwa C. Surrogate indexes of insulin resistance and risk of metabolic syndrome in non-Hispanic White, non-

Hispanic Black and Mexican American. Diabetes Metab Syndr Clin Res Rev. 2020;14(1):3–9.
26. Hsieh C-H, Wu C-Z, Hsiao F-C, Lin J-D, Li J-C, Wan H-L, et al. The impact of metabolic syndrome on insulin sensitivity, glucose sensitivity, and acute insulin response after glucose load in early-onset type 2 diabetes mellitus: Taiwan Early-Onset Type 2 Diabetes Cohort Study. Metabolism. 2008;57(11):1615–21.
27. Seino S, Shibasaki T, Minami K. Dynamics of insulin secretion and the clinical implications for obesity and diabetes. J Clin Invest. 2011;121(6):2118–25.
28. Karimbeiki R, Namkhah Z, Alipoor E, Yaseri M, Hosseinzadeh-Attar MJ. The relationship between low-carbohydrate diet score, dietary insulin index and load with obesity in healthy adults. Eat Weight Disord Anorexia, Bulim Obes. 2022;1–10.
29. Joslowski G, Goletzke J, Cheng G, Günther ALB, Bao J, Brand-Miller JC, et al. Prospective associations of dietary insulin demand, glycemic index, and glycemic load during puberty with body composition in young adulthood. Int J Obes. 2012;36(11):1463–71.
30. Hajhashemy Z, Mirzaei S, Asadi A, Akhlaghi M, Saneei P. Association of Dietary Insulin Index and Dietary Insulin Load With Metabolic Health Status in Iranian Overweight and Obese Adolescents. Front Nutr. 2022;9.
31. Velázquez-López L, Santiago-Díaz G, Nava-Hernández J, Muñoz-Torres A V, Medina-Bravo P, Torres-Tamayo M. Mediterranean-style diet reduces metabolic syndrome components in obese children and adolescents with obesity. BMC Pediatr. 2014;14(1):1–10.
32. Arenaza L, Huybrechts I, Ortega FB, Ruiz JR, De Henauw S, Manios Y, et al. Adherence to the Mediterranean diet in metabolically healthy and unhealthy overweight and obese European adolescents: the HELENA study. Eur J Nutr. 2019;58(7):2615–23.
33. Caferoglu Z, Erdal B, Akin L, Kurtoglu S. Breakfast and dinner insulin index and insulin load in relation to overweight in children and adolescents. Eur J Nutr. 2021;60(5):2819–29.
34. Teymoori F, Farhadnejad H, Moslehi N, Mirmiran P, Mokhtari E, Azizi F. The association of dietary insulin and glycemic indices with the risk of type 2 diabetes. Clin Nutr. 2021;40(4):2138–44.
35. Teymoori F, Farhadnejad H, Mirmiran P, Nazarzadeh M, Azizi F. The association between dietary glycemic and insulin indices with incidence of cardiovascular disease: Tehran lipid and glucose study. BMC Public Health. 2020;20(1):1–10.
36. Hellström PM. Satiety signals and obesity. Curr Opin Gastroenterol. 2013;29(2):222–7.
37. Zhu R, Larsen TM, Poppitt SD, Silvestre MP, Fogelholm M, Jalo E, et al. Associations of quantity and quality of carbohydrate sources with subjective appetite sensations during 3-year weight-loss maintenance: Results from the PREVIEW intervention study. Clin Nutr. 2022;41(1):219–30.

38. Mirmiran P, Esfandiari S, Bahadoran Z, Tohidi M, Azizi F. Dietary insulin load and insulin index are associated with the risk of insulin resistance: a prospective approach in tehran lipid and glucose study. J Diabetes Metab Disord. 2015;15(1):1–7.

Table1: General characteristics of participants stratified by cardio metabolic phenotypes

	Cardiometabolic Phenotype				
	MHN(n=2954)	MUHN(n=240)	MHO(n=6870)	MUHO(n=4824)	P value
	N(%)	N(%)	N(%)	N(%)	
Gender					*<0.001
Male	1822(61.7)	106(44.2)	3136(45.6)	1604(33.3)	
Female	1132(38.3)	134(55.8)	3734(54.4)	3220(66.7)	
Marital status					*<0.001
Not married	220(7.4)	20(8.3)	401(5.8)	441(9.1)	
Married	2734(92.6)	220(91.7)	6469(94.2)	4383(90.9)	
Education level					**<0.001
Illiterate	390(132)	60(25)	896(13.1)	1127(23.4)	
Primary school	1040(35.2)	73(30.4)	2745(40)	1955(40.5)	
Diploma	1181(40)	87(36.3)	2562(37.3)	1451(30.1)	
University	341(11.6)	20(8.3)	662(9.6)	289(6)	
Physical activity level (METs¶)					
**<0.001					
Low	821(27.8)	88(36.7)	2110(30.7)	1958(40.6)	
Moderate	852(28.8)	83(34.6)	2353(34.3)	1665(34.5)	
High	1281(43.4)	69(28.7)	2407(35)	1201(24.9)	
Quintiles of wealth index					**<0.001
1 (poorest)	759(25.7)	51(21.3)	1402(20.4)	1232(25.5)	
2	472(16)	39(16.3)	1097(43.6)	909(18.8)	
3	564(19.1)	62(25.8)	1452(21.1)	949(19.7)	
4	598(20.2)	37(15.4)	1570(22.9)	902(18.7)	
5 (richest)	561(19)	51(21.3)	1349(19.6)	832(17.2)	
Current Smoking status					**<0.001
No smoker	1935(65.5)	176(73.3)	5276(76.8)	3922(81.3)	
Ex-Smoker	238(8.1)	17(7.1)	608(8.9)	373(7.7)	
Smoker	728(24.6)	44(18.3)	843(12.3)	451(9.3)	
Smoker other tobacco products(water pipe, hookah,pipe, ..)	53(1.8)	3(1.3)	143(2.1)	78(1.6)	

Secondhand smoking	1261(42.7)	104(43.3)	3205(46.7)	2433(50.4)	*<0.001
Alcohol consumption					**<0.001
No	2567(86.9)	216(90)	6247((90.9)	4452(92.3)	
Experiment	296(10)	17(7.1)	482(7)	276(5.7)	
Limit time (for treatment	3(0.1)	0	7(0.1)	6(0.1)	
Ex-drinker	9(0.3)	0	24(0.3)	8(0.2)	
drinker	79(2.7)	7(2.9)	110(1.6)	82(1.7)	
Insulin load					**<0.001
1th	564(19.1)	97(40.4)	1503(21.9)	1545(32)	
2nd	686(23.2)	64(26.7)	1747(25.4)	1233(25.6)	
3rd	795(26.9)	45(18.8)	1778(25.9)	1105(22.9)	
4th	909(30.8)	34(14.2)	1842(26.8)	941(19.5)	
Insulin index					**<0.001
1th	578(19.6)	97(40.4)	1507(21.9)	1524(31.6)	
2nd	707(23.9)	56(23.3)	1690(24.6)	1272(26.4)	
3rd	762(25.8)	59(24.6)	1831(26.7)	1078(22.3)	
4th	907(30.7)	28(11.7)	1842(26.8)	950(19.7)	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	
Age (years)	48.68±9.75	55.36±9.03	48.06±8.81	52.09±8.98	***<0.001
Height (cm)	165.40±9.51	161.66±9.26	162.36±9.29	160.43±9.27	***<0.001
Weight (kg)	61.86±8.54	61.93±7.94	77.98±11.30	82.23±13.19	***<0.001
Waist circumference (cm)	80.98±7.22	87.21±6.36	94.97±8.83	101.77±9.14	***<0.001
Hip circumference (cm)	95.42±4.86	95.19±4.59	105.94±7.28	108.40±8.61	***<0.001
Dietary insulin index	54.88±19.42	47.95±9.24	53.42±18.46	50.78±16.52	***<0.001
Dietary insulin load	157814.75±84217.19	121546.75±61228. 21	150506.01±80295.64	135191.32±72140.76	***<0.001
Energy intake (kcal)	2830.45±911.30	2476.97±875.68	2768.65±885.93	2611.62±859.49	***<0.001

; ¶METs: metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

Table 2: General characteristics of participants stratified by cardio metabolic phenotypes in both genders

	Cardiometabolic Phenotype				
	MHN (n=1822)	**MUHN (n=106)**	**MHO (n=3136)**	**MUHO(n=1604)**	P value
	N(%)	**N(%)**	**N(%)**	**N(%)**	
Male					
Marital status					*0.01
Not married	34(1.9)	1(0.9)	28(0.9)	16(1)	
Married	1788(98.1)	105(99.1)	3108(99.1)	1588(99)	
Education level					**0.39
Illiterate	171(9.4)	9(8.5)	250(8)	152(9.5)	
Primary school	658(36.1)	34(32.1)	1158(36.9)	591(36.8)	
Diploma	774(42.5)	51(48.1)	1313(41.9)	681(42.5)	
University	218(12)	12(11.3)	413(13.2)	180(11.2)	
Physical activity level (METs¶)					**<0.001
Low	464(25.5)	35(33)	927(29.6)	617(38.5)	
Moderate	334(18.3)	24(22.6)	621(19.8)	340(21.2)	
High	1024(56.2)	47(44.3)	1588(50.6)	647(40.3)	
Quintiles of wealth index					**<0.001
1 (poorest)	409(22.4)	11(10.4)	505(16.1)	259(16.1)	
2	304(16.7)	17(16)	472(15.1)	259(16.1)	
3	351(19.3)	32(30.2)	683(21.8)	347(21.6)	
4	369(20.3)	16(15.1)	702(22.4)	326(20.3)	
5 (richest)	389(21.4)	30(28.3)	774(24.7)	413(25.7)	
Current Smoking status					**<0.001
No smoker	820(45)	44(41.5)	1578(50.3)	745(46.4)	
Ex-Smoker	234(12.8)	15(14.2)	591(18.8)	358(22.3)	
Smoker	718(39.4)	44(41.5)	831(26.5)	434(27.1)	
Smoker other tobacco products(water pipe, hookah,pipe,..)	50(2.7)	3(2.8)	136(4.3)	67(4.2)	
Secondhand smoking	752(41.3)	35(33)	1371(43.7)	722(45)	*0.02
Alcohol consumption					**0.3
No	1442(79.1)	82(77.4)	2552(80.4)	1243(77.5)	
Experiment	290(15.9)	17(16)	476(15.2)	269(16.8)	
Limit time (for treatment	3(0.2)	0	6(0.2)	5(0.3)	
Ex-drinker	9(0.5)	0	22(0.7)	7(0.4)	

drinker	78(4.3)	7(6.6)	110(3.5)	80(29.1)	
Insulin load					**<0.001
1th	166(9.1)	23(21.7)	240(7.7)	200(12.5)	
2nd	358(19.6)	27(25.5)	607(19.4)	338(21.1)	
3rd	553(30.4)	31(29.2)	946(30.2)	472(29.4)	
4th	745(40.9)	25(23.6)	1343(42.8)	594(37)	
Insulin index					**<0.001
1th	250(13.7)	30(28.3)	435(13.9)	313(19.5)	
2nd	404(22.2)	28(26.4)	719(22.9)	439(27.4)	
3rd	518(28.4)	28(26.4)	955(30.5)	424(26.4)	
4th	650(35.7)	20(18.9)	1027(32.7)	428(26.7)	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	
Age (years)	49.71±9.61	55.15±8.85	49.23±9.04	52.01±8.97	***<0.001
Height (cm)	170.61±7.00	169.29±6.35	169.78±6.63	170.35±6.33	***<0.001
Weight (kg)	65.48±7.58	67.76±6.17	82.66±9.94	90.27±11.94	***<0.001
Waist circumference (cm)	82.85±6.95	89.20±5.58	97.82±7.37	105.26±8.33	***<0.001
Hip circumference (cm)	95.58±4.65	96.11±4.09	104.05±5.30	107.11±6.33	***<0.001
Dietary insulin index	56.44±19.27	50.20±9.74	55.38±17.39	53.10±15.33	***<0.001
Dietary insulin load	178265.37±9195 3.88	146325.32±6833 8.32	179204.06±8816 4.46	169201.99±8385 7.36	***<0.001
Energy intake (kcal)	3109.21±919.32	2850.34±919.82	3192.65±931.32	3132.97±961.05	***<0.001
	MHN (n=1132) N(%)	**MUHN (n=134) N(%)**	**MHO (n=3734) N(%)**	**MUHO(n=3220) N(%)**	
Female					
Marital status					*<0.001
Not married	186(16.4)	19(14.2)	373(10)	425(13.2)	
Married	946(83.6)	115(85.8)	3361(90)	2795(86.8)	
Education level					**<0.001
Illiterate	219(19.4)	51(38.1)	646(17.3)	975(30.3)	
Primary school	382(33.8)	39(29.1)	1587(42.5)	1364(42.4)	
Diploma	407(36)	36(26.9)	1249(33.5)	770(23.9)	
University	123(10.9)	8(6)	249(6.7)	109(3.4)	
Physical activity level (METs¶)					**<0.001
Low	357(31.5)	53(39.6)	1183(31.7)	1341(41.6)	
Moderate	518(45.8)	59(44)	1732(46.4)	1325(41.1)	
High	257(22.7)	22(16.4)	819(21.9)	554(17.2)	
Quintiles of wealth index					**<0.001

1 (poorest)	350(30.9)	40(29.9)	897(24)	973(30.2)	
2	168(14.8)	22(16.4)	625(16.7)	650(20.2)	
3	213(18.8)	30(22.4)	769(20.6)	602(18.7)	
4	229(20.2)	21(15.7)	868(23.2)	576(17.9)	
5 (richest)	172(15.2)	21(15.7)	575(15.4)	419(13)	
Current Smoking status					**0.21
No smoker	1115(98.5)	132(98.5)	3698(99)	3177(98.7)	
Ex-Smoker	4(0.4)	2(1.5)	17(0.5)	15(0.5)	
Smoker	10(0.9)	0	12(0.3)	17(0.5)	
Smoker other tobacco products(water pipe, hookah,pipe,..)	3(0.3)	0	7(0.2)	11(0.3)	
Secondhand smoking	509(12.3)	69(51.5)	1834(49.1)	1711(53.1)	*<0.001
Alcohol consumption					**0.65
No	1125(99.4)	134(100)	3725(99.8)	3209(99.7)	
Experiment	6(0.5)	0	6(0.2)	7(0.2)	
Limit time (for treatment	0	0	1(0.	1(0.02)	
Ex-drinker	0	0	2(0.1)	1(0.02)	
drinker	0	0	0	2(0.1)	
Insulin load					**<0.001
1th	398(35.2)	74(55.2)	1263(33.8)	1345(41.8)	
2nd	328(29)	37(27.6)	1140(30.5)	895(27.8)	
3rd	242(21.4)	14(10.4)	832(22.3)	633(19.7)	
4th	164(14.5)	9(6.7)	499(13.4)	347(10.8)	
Insulin index					**<0.001
1th	328(29)	67(50)	1072(28.7)	1211(37.6)	
2nd	303(26.8)	28(20.9)	971(26)	833(25.9)	
3rd	244(21.6)	31(23.1)	876(23.5)	654(20.3)	
4th	257(22.7)	8(6)	815(21.8)	522(16.2)	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	
Age (years)	47.01±9.75	55.52±9.21	47.07±8.49	52.13±8.98	***<0.001
Height (cm)	157.01±6.58	155.63±6.25	156.12±	155.49±5.94	***<0.001
Weight (kg)	56.02±6.54	57.32±5.89	74.04±10.87	78.23±11.90	***<0.001
Waist circumference (cm)	77.97±6.62	85.63±6.52	92.57±9.24	100.03±9.03	***<0.001
Hip circumference (cm)	95.16±5.30	94.45±4.84	107.54±8.27	109.04±9.48	***<0.001
Dietary insulin index	52.35±19.40	46.17±8.44	51.78±19.16	49.62±16.96	***<0.001
Dietary insulin load	124898.66±56090.32	101945.79±46619.43	126403.94±63741.27	118249.36±58585.05	***<0.001

Energy intake (kcal)	2381.77±693.49	2165.50±708.04	2412.56±661.78	2351.92±666.32	***<0.001

; ¶METs: metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

Table3: Association between cardiometabolic phenotype and across quartiles of DIL and DIL scores of Azar cohort population

	Quartiles of DIL				Quartiles of DII			
	1 (n=3711)	2 (n=3730)	3 (n=3725)	4 (3726)	1 (n=3708)	2 (n=3726)	3 (n=3730)	4 (3728)
Q rang	≤99828.05	99828.06-	129348.54-	>171278.61	≤44.43	44.44-48.64	48.65-55.29	>55.30

		129348.53	171278.60					
Crude								
MUHL	Reference	0.54(0.38-0.75)	0.32(0.22-0.47)	0.21(0.14-0.32)	Reference	0.47(0.33-0.66)	0.46(0.32-0.64)	0.18(0.11-0.28)
MHO	Reference	0.95(0.83-1.08)	0.83(0.73-0.95)	0.76(0.67-0.86)	Reference	0.91(0.80-1.04)	0.92(0.81-1.04)	0.77(0.68-0.88)
MUHO	Reference	0.65(0.57-0.75)	0.50(0.44-0.57)	0.37(0.33-0.43)	Reference	0.68(0.59-0.77)	0.53(0.47-0.61)	0.39(0.34-0.45)
MUHL								
Model 1	Reference	0.66(0.46-0.93)	0.45(0.30-0.67)	0.34(0.22-0.53)	Reference	0.59(0.410.84)	0.58(0.41-0.83)	0.24(0.15-0.37)
Model 2	Reference	061(0.42-0.90)	0.38(0.23-0.62)	0.23(0.12-0.47)	Reference	0.57(0.40-0.81)	0.57(0.40-0.82)	0.24(0.15-0.37)
MHO								
Model 1	Reference	1.05(0.91-1.20)	1.03(0.90-1.18)	1.04(0.90-1.20)	Reference	0.97(0.85-1.11)	1.03(0.90-1.17)	0.88(0.78-1.01)
Model 2	Reference	1.01(0.87-1.16)	0.94(0.80-1.09)	0.85(0.74-1.04)	Reference	0.91(0.80-1.04)	0.94(0.82-1.07)	0.80(0.70-0.91)
MUHO								
Model 1	Reference	0.88(0.76-1.01)	0.85(0.74-0.99)	0.80(0.69-0.93)	Reference	0.86(0.75-0.99)	0.74(0.64-0.85)	0.57(0.50-0.66)
Model 2	Reference	0.48(0.38-0.59)	0.65(0.55-0.76)	0.772(0.66-0.89)	Reference	0.77(0.67-0.89)	0.64(0.56-0.74)	0.48(0.42-0.561)
Male					Reference			
Crude								
MUHL	Reference	0.54(0.30-0.97)	0.40(0.23-0.71)	0.24(0.13-0.43)	Reference	0.57(0.33-0.99)	0.45(0.26-0.77)	0.25(0.14-0.46)
MHO	Reference	1.17(0.92-1.48)	1.18(0.94-1.48)	1.24(1.00-1.54)	Reference	1.02(0.83-1.24)	1.06(0.87-1.28)	0.90(0.75-1.09)
MUHO	Reference	0.66(0.52-0.83)	0.70(0.55-0.90)	0.78(0.60-1.01)	Reference	0.86(0.70-1.07)	0.65(0.53-0.80)	0.52(0.42-0.64)
MUHL								
Model 1	Reference	0.56(0.31-1.02)	0.44(0.25-0.79)	0.28(0.15-0.52)	Reference	0.64(0.37-1.11)	0.46(0.27(0.80)	0.27(0.15-0.50)
Model 2	Reference	0.49(0.26-0.92)	0.34(0.17-0.69)	0.17(0.06-0.46)	Reference	0.66(0.38-1.14)	0.50(0.29-0.86)	0.30(0.16-0.55)
MHO								
Model 1	Reference	1.12(0.88-1.42)	1.10(0.88-1.39)	1.16(0.93-1.45)	Reference	0.99(0.81-1.21)	1.01(0.84-1.22)	0.86(0.71-1.03)
Model 2	Reference	1.05(0.82-1.35)	0.98(0.76-1.26)	0.93(0.70-1.24)	Reference	0.98(0.80-1.19)	0.99(0.81-1.20)	0.82(0.68-1)
MUHO								
Model 1	Reference	0.78(0.60-1.01)	0.72(0.56-0.92)	0.70(0.55-0.89)	Reference	0.89(0.72-1.11)	0.65(0.53-0.81)	0.53(0.43-0.65)

Model 2	Reference	0.68(0.52-0.89)	0.55(0.42-0.73)	0.41(0.30-0.57)	Reference	0.89(0.71-1.11)	0.64(0.52-0.80)	0.51(0.41-0.63)
Female								
Crude								
MUHL	Reference	0.60(0.39-0.92)	0.31(0.17-0.56)	0.29(0.14-0.60)	Reference	0.45(0.28-0.72)	0.62((0.39-0.98)	0.15(0.07-0.32)
MHO	Reference	1.09(0.92-1.29)	1.08(0.90-1.30)	0.95(0.77-1.18)	Reference	0.98(0.82-1.17)	1.09(0.91-1.32)	0.97(0.80-1.17)
MUHO	Reference	0.80(0.68-0.95)	0.77(0.64-0.93)	0.62(0.50-0.77)	Reference	0.74(0.62-0.89)	0.72(0.60-0.87)	0.55(0.45-0.66)
MUHL								
Model 1	Reference	0.77(0.50-1.18)	0.43(0.23-0.78)	0.42(0.20-0.88)	Reference	0.55(0.34-0.89)	0.78(0.49-1.25)	0.18(0.08-0.39)
Model 2	Reference	0.66(0.40-1.10)	0.33(0.15-0.70)	0.29(0.11-0.78)	Reference	0.57(0.35-0.92)	0.82(0.51-1.31)	0.19(0.09-0.41)
MHO								
Model 1	Reference	1.06(0.90-1.26)	1.06(0.88-1.28)	0.95(0.6-1.17)	Reference	0.96(0.808-1.15)	1.07(0.89-1.30)	0.95(0.78-1.14)
Model 2	Reference	0.98(0.81-1.19)	0.92(0.73-1.18)	0.77(0.57-1.05)	Reference	0.95(0.8-1.14)	1.06(0.88-1.29)	0.93(0.77-1.13)
MUHO								
Model 1	Reference	0.95(0.80-1.13)	0.96(0.79-1.17)	0.81(0.64-1..01)	Reference	0.84(0.70-1.01)	0.84(0.69-1.02)	0.62(0.51-0.76)
Model 2	Reference	0.78(0.64-0.95)	0.67(0.52-0.86)	0.47(0.34-0.66)	Reference	0.83(0.69-1.00)	0.83(0.68-1.01)	0.60(0.49-0.74)

MHL was considered as a reference group; Model 1: adjusted for age ,gender,education level, WSI ; Model 2 adjusted for age, gender, MET, Energy intake

Adjusted for gender where appropriate

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	7

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	8
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	9
Bias	#9	Describe any efforts to address potential sources of bias	9
Study size	#10	Explain how the study size was arrived at	8
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	12
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	12
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	12
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	12
Participants	#13c	Consider use of a flow diagram	n/a

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	14
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	12
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
Main results	#16b	Report category boundaries when continuous variables were categorized	12
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	20
Generalisability	#21	Discuss the generalisability (external validity) of the study results	20
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

This checklist was completed on 13. September 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Associations between Insulin Index and Dietary Insulin Load with Cardiometabolic phenotype in the AZAR cohort population in northwestern Iran: A cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068303.R1
Article Type:	Original research
Date Submitted by the Author:	13-Jan-2023
Complete List of Authors:	faramarzi, elnaz; Tabriz University of Medical Sciences somi, mohammad hossein; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center Naghibi Irvani, Seyed Sina; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center, Research Institute for Endocrine Science Pourhashem, Nahid; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center Nourizadeh, Amir Mohammad; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY, INTERNAL MEDICINE, NUTRITION & DIETETICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Associations between Insulin Index and Dietary Insulin Load with Cardiometabolic phenotype in the AZAR cohort population in northwestern Iran: A cross-sectional study

Elnaz Faramarzi [1], Ph.D., Prof. Mohammad Hossein Somi, MD [1], Seyed Sina Naghibi Irvani [1], MD, MPH, MBA, Nahid Pourhashem [1], Amir Mohammad Nourizadeh [1*], MD

[1] Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran.

Order of Authors:

1. Elnaz Faramarzi. Liver and Gastrointestinal Diseases Research center, Tabriz University of Medical Sciences. Email: elnazfaramarzi849@gmail.com

2. Mohammad Hossein Somi. Liver and Gastrointestinal Diseases Research Center of Tabriz university of medical sciences. Tabriz, Iran. Email: mhosseinsina@yahoo.com

3. . Seyed Sina Naghibi Irvani. Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran. Email: sina.irvani@gmail.com

4. Nahid Pourhashem. . Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran. Email: npourhashem@yahoo.com

5. Amir Mohammad Nourizadeh. Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran. Email: Nourizadehamirmohammad@gmail.com

*Corresponding Author:

Amir Mohammad Nourizadeh, MD,

Liver and Gastrointestinal Diseases Research Center. Tabriz University of Medical Sciences. Tabriz, Iran. (**Email:** Nourizadehamirmohammad@gmail.com)

ORCID Number: 0000-0001-9206-5327

P.O. Box: 1567812907, **Tel:** +98-914-9979121, **Fax:** +98-413-3845238

(Word count: 4159)

Keywords:

Nutrition and Dietetics/ Diabetes/ Endocrinology/ Internal Medicine

ABSTRACT

Objectives:

Hyperinsulinemia and insulin resistance are proposed as contributors to the incidence of cardiometabolic phenotypes (CMPs) with unhealthy metabolic status. This study analyzed the association between dietary insulin load (DIL) and dietary insulin index (DII) with CMPs in the AZAR cohort population.

Design:

This study was a cross-sectional analysis of the AZAR cohort study, beginning in 2014 and continuing to this date.

Setting:

AZAR cohort is a part of an Iranian screening program named the Persian cohort and involves participants living in the Shabestar region, Iran for at least 9 months.

Participants:

A total of 15006 participants agreed to partake in the study. We excluded participants with missing data (N=15), daily energy intake lower than 800 kcal (N=7) or higher than 8000 kcal (N=17), and cancer (N=85). Finally, 14882 individuals remained.

Primary and secondary outcome measures:

The gathered information included the participants' demographic, dietary, anthropometric, and physical activity data.

Results: The frequency of DIL and DII significantly decreased from the 1st to 4th quartile in metabolically unhealthy participants ($p \leq 0.001$). The mean values of DIL and DII were greater in metabolically healthy participants than in unhealthy ones. ($p<0.001$). The findings of the unadjusted model presented that the risks of unhealthy phenotypes in the 4th DIL quartile decreased by 0.21 (0.14 - 0.32) and 0.37 (0.33 – 0.43) respectively compared to the 1st quartile. The same model showed the same risks for DII decreased by 0.18 (0.11 - 0.28) and 0.39 (0.34 – 0.45) respectively. The results in both genders were the same as all participants combined.

Conclusions: DII and DIL were correlated with a decreased odds ratio of unhealthy phenotypes. We suggest the reason may be either a lifestyle change in metabolically unhealthy participants or elevated insulin secretion not being as detrimental as previously thought. Further studies can confirm these speculations.

Article Summary:

Strengths and limitations of this study:

- The current study was an analysis of the AZAR cohort study which is a very large population. The final number of participants included was just less than 15000 individuals.
- In this study, the associations between DII and DIL with four different CMPs were studied for the first time. This model helped us to analyze the data in a more organized fashion.
- The presence of confounders and their effect were considered while analyzing the data.
- This was a cross-sectional study. Therefore we were unable to establish a cause-and-effect correlation. More prospective studies are needed to investigate and establish such causality.

Introduction

According to World Health Organization (WHO), over 600 million adults are obese. (1) Metabolic Syndrome (MetS), which is closely associated with obesity, has increased the global burden of cardiovascular diseases, and its prevalence and incidence have significantly risen in the past two decades. (2) MetS represents a collection of different metabolic abnormalities. MetS is a pathophysiological, asymptomatic condition characterized by obesity, insulin resistance, hypertension, glycemic abnormalities, and dyslipidemia(3). Although various criteria and definitions have been proposed to describe MetS(3); it is mainly agreed that a combination of three or more of the following constituents should be present: Hypertension, elevated fasting blood glucose, elevated triglycerides, low HDL cholesterol, and large waist circumference. The incidence of MetS usually agrees with the incidence of obesity. The prevalence of MetS has doubled in 73 countries and has notably increased in others as of 1980. (4)

Even though abdominal obesity is one of the criteria for MetS, MetS doesn't always equal obesity. Some other interesting phenotypes are recently seen more often. Some obese individuals do not have the criteria for MetS. They are called the Metabolically Healthy Obese (MHO). (5) Conversely, some non-obese individuals fulfill the criteria for MetS. They are called the Metabolically Unhealthy Normal Weight (MUHN) or the Metabolically Obese Normal Weight. (6)(7)(8)(9) This calls for classifying individuals into four different cardiometabolic phenotypes (CMPs) groups and assessing different metabolic factors based on four phenotypes; obese

individuals who fulfill MetS criteria, called the Metabolically Unhealthy Obese (MUHO), obese individuals who do not fulfill MetS criteria, called the MHO, normal weight individuals who fulfill MetS criteria, called the MUHN, and normal weight individuals who do not fulfill MetS criteria, called the Metabolically Healthy Normal Weight (MHN).

Previous studies show a strong relationship between cardiometabolic status and insulin resistance. (10)(11) The ability of foods to induce postprandial insulin secretion is a significant factor in assessing the effect of individuals' diets on weight gain, hyperlipidemia, and type 2 diabetes. (12) Therefore, it is beneficial to quantify the ability of individuals' diets to induce postprandial insulin secretion. A diet with a high glycemic index (GI) and high Glycemic Load (GL) can lead to increased postprandial insulin secretion, leading to obesity and diabetes. (13)(14) Still, these two Indexes solely measure the effect of carbohydrates in this regard. In addition to carbohydrates, proteins and lipids also increase postprandial insulin secretion. Moreover, proteins enhance the effect of carbohydrates on insulin secretion. This points out that the amount of carbohydrates in a diet is not accurately proportional to postprandial insulin secretion. (15) A food Insulin Index (II) and Dietary Insulin Load (DIL) have been suggested. The II can directly quantify the postprandial insulin response to a test food compared to an isoenergetic portion of a reference food. (12)(15) DIL can be calculated for each individual using II and the energy content of each food they consume. (16) since II and DIL are directly based on insulin

response, they are more satisfactory to evaluate hypotheses that connect insulin exposure to cardiometabolic diseases compared to GI and GL.(12)

Some studies have assessed the relation between insulin exposure of diets with MetS and obesity but to the best of our knowledge, no studies have ever structured and grouped individuals in different CMP classifications and assessed the relation between the insulinemic potential of their diets according to their CMP. Therefore, in this study, we try to investigate the association between II and DIL with CMP in the AZAR cohort population.

Materials and Methods

Study design and participants

AZAR cohort is a prospective population-based study(17) in Iran and a part of a national screening program named prospective epidemiological research studies in Iran (Persian cohort). (18)(19) Its main goal is to investigate the major non-communicable diseases risk factors, including cardiovascular, pulmonary, and renal diseases, diabetes, and cancer. The AZAR cohort started in October 2014 and is still in progress in East- Azarbaijan province in Northwestern Iran. It is a study of up to 15000 individuals within the range of 35-70 years of age who have lived in the Shabestar region for at least 9 months. Subjects with severe psychiatric or physical illnesses and pregnant women were excluded from the study. This study is explained in greater detail in other studies. (17)(18)(19)

Our cross-sectional study was conducted on the AZAR cohort population. A total number of 15006 individuals agreed to participate. Then, we excluded individuals with missing data (N=15). We excluded individuals who had a daily energy intake lower than 800 kcal (N=7) or higher than 8000 kcal (N=17). Individuals who had cancer were also excluded (N=85). Finally, 14882 individuals remained. The information included demographic, dietary, anthropometric, and activity data of the participants. All participants filled out a written informed consent form before the study. The Bioethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, approved the study. (Ethics Number: IR.TBZMED.REC.1401.414)

The socioeconomic status of the participants was evaluated by the Wealth Score Index (WSI), calculated by Multiple Correspondence Analysis (MCA). Each participant's WSI was determined by assessing their possession of different permanent property (eg TV, dishwasher, and car), their residence's conditions (eg type of ownership, the number of rooms), and levels of education. Participants were separated into five WSI quintiles, from the lowest WSI to the highest one (1st to 5th quintile, respectively). The participants' dietary intake was assessed by using a food frequency questionnaire (FFQ) which they were asked to complete. The FFQ was designed as a semi-quantitative, interviewer-administered questionnaire with 130 items, enquiring about participants' usual intake of each food item over the past year. Participants reported their daily, weekly, monthly, or yearly use of each item, as well as the portion consumed each time, based on portion sizes applicable to each item. Actual dishes, cups, and utensils, as well as several portion size models, were

shown to participants for a more precise portion size estimation. In addition, a 64-picture album (20) including standard portions of bread, fruits, and vegetables, was used whenever needed. We used Metabolic Equivalent of Task (MET) as a criterion for this goal. MET shows the amount of energy consumed by each person based on their weight. For instance, one MET is the amount of oxygen consumed per kilogram of body weight per minute by each resting person, that is 3.5 ml of oxygen. And therefore, four MET equals 14 milliliters of oxygen used per kilogram of body weight per minute. We measured the activity levels of each participant by using this criterion.

Smokers were defined as participants who continuously smoked at least one cigarette per day for more than six months. Ex-smokers were considered as participants who had stopped smoking at least a year before, and non-smokers were considered as participants who had never smoked. Other tobacco smokers were considered as participants who smoked other tobacco products. Participants were divided into three categories based on their alcohol consumption; non-drinkers (participants who had never consumed alcohol), experienced/ex-drinkers (participants who had experienced alcohol consumption or who had used to drink), and drinkers (participants who regularly consumed alcohol).

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Biochemical measurements

Samples of blood were collected from every individual after an overnight fast of 12 hours. Fasting blood sugar (FBS), serum triglyceride (TG), and high-density lipoprotein (HDL) were determined using a commercial kit (Pars Azmoon, Tehran). (18)

Anthropometric measurements

We used a mounted tape for measuring the height to the nearest 1 mm. Weight was measured with light clothing and without using shoes with a Seca scale to the nearest 0.1 kg. Body Mass Index (BMI) was calculated by dividing weight (kg) by the square of height (m) and presented as kg/ m^2. The waist circumference (WC) was measured according to NIH guidelines. Female individuals with WC ≥88 cm and male individuals with WC of ≥ 102 cm were considered abdominally obese. (21)

Blood pressure measurements

The blood pressure was measured two times in each arm in the sitting position and according to Persian cohort protocol. (18) The individuals rested for ten minutes between each measurement. The blood pressure of every individual was calculated as the average of the two measurements in each arm.

Cardiometabolic phenotypes and Metabolic syndrome definition

We defined Mets according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATPIII) criteria. (4) According to these criteria, MetS is defined by the presence of three or more of the followings: Fasting blood glucose

≥100 mg/dl or drug treatment for elevated blood glucose; HDL cholesterol less than 40 mg/dl in men or less than 50 mg/dl in women or drug treatment for low HDL; blood triglycerides ≥ 150 mg/dl or drug treatment for elevated triglycerides; waist circumference greater than 102 cm in men or greater than 88 cm in women; systolic blood pressure ≥130 and/or diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension.

We considered the cut-off point for Body Mass Index (BMI) to be 25 kg/m^2 for overweight and obese participants. (22)

In this study, we categorized the subjects into four CMPs based on their BMI and the presence of MetS. The categories include:

1. Obese individuals who fulfill MetS criteria, called the MUHO
2. Obese individuals who do not fulfill MetS criteria, called the MHO
3. Normal-weight individuals who fulfill MetS criteria, called the MUHN
4. Normal-weight individuals who do not fulfill MetS criteria, called the MHN

Measuring DII and DIL

The Food Insulin Index (FII) is the area under the curve of increasing insulin over 2 hours after consumption of a 1000-kJ (239 kcal) portion of a test food divided by the area under the curve after consumption of a 1000-kJ (239 kcal) portion of the reference food. The insulin index for 68 food items was gathered from studies by Holt et al (15), Bao et al (23), and Bell et al (24). The Insulin Index for salt, tea, and coffee was considered zero since the amount of carbohydrates, protein, and fat, and

the energy content of these foods is approximately zero. For the rest of the 49 food items that were not included in the food lists of the aforementioned studies, the FII of similar food items considering the similarity of their energy, carbohydrate, protein, fat, and fiber content was used. For instance, both dates and raisins are dried fruits. The energy, carbohydrate, fat, protein, and fiber content of both fruits are comparable to each other. Hence, the insulin index of raisins was used for dates. To calculate DIL, the insulin load of each food was determined using the following formula: Insulin load of a given food = insulin index of that food × energy content per 1 g of that food × amount of that food consumed (g/d). By summing up the insulin load of each food, DIL was obtained for each participant. DII for each participant was then determined by dividing DIL by total energy intake.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 11.5, Chicago, IL) was used for the data analysis. Descriptive statistics were obtained for all study variables and reported as mean ± SD as well as number (percentage) where applicable. χ2 test was used for comparing nominal qualitative variables in different Cardiometabolic groups and the Kruskal-Wallis test was used for comparing ordinal qualitative variables in different Cardiometabolic groups. A one-way ANOVA test was used to compare mean values amongst different Cardiometabolic groups. The multinomial logistic regression analysis was used for estimating crude and adjusted odds ratios (OR) and their corresponding 95% confidence intervals (95% CIs). Mets components (hypertension, high FBS, Hypo-HDL, cholesterolemia,

hypertriglyceridemia, and abdominal obesity), Insulin Index, and Dietary Insulin Load were considered independent variables. Each variable was introduced in the model one by one. The effect of confounding factors (age, gender, educational level, marital status, current smoking status, and frame size) was adjusted, and MHN was considered as the reference group. Statistical significance was considered as *P* value <0.05.

Finally, We used the STROBE cross-sectional checklist when writing our report. (25)

Results

Participants' characteristics

Table 1 presents the participants' baseline characteristics according to their CMPs and Tables 2 and 3 present the same characteristics in both genders.

Table1: General characteristics of participants stratified by cardiometabolic phenotypes

	Cardiometabolic Phenotype					P value
	MHN(n=2948)	MUHN(n=240)	MHO(n=6870)	MUHO(n=4824)		
	N(%)	N(%)	N(%)	N(%)		
Gender						*<0.001
Male	1820(61.7)	106(44.2)	3136(45.6)	1604(33.3)		
Female	1128(38.3)	134(55.8)	3734(54.4)	3220(66.7)		
Marital status						*<0.001
Not married	218(7.4)	20(8.3)	401(5.8)	441(9.1)		
Married	2730(92.6)	220(91.7)	6469(94.2)	4383(90.9)		
Education level						**<0.001
Illiterate	387(13.1)	60(25)	898(13.1)	1128(23.4)		
Primary school	1040(35.3)	73(30.4)	2747(40)	1956(40.5)		
Diploma	1180(40)	87(36.3)	2562(37.3)	1451(30.1)		

University	341(11.6)	20(8.3)	663(9.7)	289(6)		
Physical activity level (METs¶)						**<0.001
Low	816(27.7)	88(36.7)	2110(30.7)	1958(40.6)		
Moderate	851(28.9)	83(34.6)	2353(34.3)	1665(34.5)		
High	1281(43.5)	69(28.7)	2407(35)	1201(24.9)		
Quintiles of wealth index						**<0.001
1 (poorest)	758(25.7)	51(21.3)	1402(20.4)	1232(25.5)		
2	470(15.9)	39(16.3)	1097(43.6)	909(18.8)		
3	564(19.1)	62(25.8)	1452(21.1)	949(19.7)		
4	597(20.3)	37(15.4)	1570(22.9)	902(18.7)		
5 (richest)	559(19)	51(21.3)	1349(19.6)	832(17.2)		
Current Smoking status						**<0.001
No smoker	1930(65.5)	176(73.3)	5276(76.8)	3922(81.3)		
Ex-Smoker	238(8.1)	17(7.1)	608(8.9)	373(7.7)		
Smoker	727(24.7)	44(18.3)	843(12.3)	451(9.3)		
Smokers of other tobacco products(water pipe, hookah, pipe,..)	53(1.8)	3(1.3)	143(2.1)	78(1.6)		
Secondhand smoking	1256(42.6)	104(43.3)	3205(46.7)	2433(50.4)		*<0.001
Alcohol consumption						**<0.001
No	2561(86.9)	216(90)	6247((90.9)	4452(92.3)		
Experiment	296(10)	17(7.1)	482(7)	276(5.7)		
Limit time (for treatment	3(0.1)	0	7(0.1)	6(0.1)		
Ex-drinker	9(0.3)	0	24(0.3)	8(0.2)		
drinker	79(2.7)	7(2.9)	110(1.6)	82(1.7)		
Insulin load						**<0.001
1th	561(19)	97(40.4)	1503(21.9)	1545(32)		
2nd	685(23.2)	64(26.7)	1747(25.4)	1233(25.6)		
3rd	794(26.9)	45(18.8)	1778(25.9)	1105(22.9)		
4th	908(30.8)	34(14.2)	1842(26.8)	941(19.5)		
Insulin index						**<0.001
1th	577(19.6)	97(40.4)	1507(21.9)	1524(31.6)		
2nd	703(23.8)	56(23.3)	1690(24.6)	1272(26.4)		
3rd	761(25.8)	59(24.6)	1831(26.7)	1078(22.3)		

4th	907(30.7)	28(11.7)	1842(26.8)	950(19.7)		
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**		
Age (years)	48.68±9.75	55.36±9.03	48.06±8.81	52.09±8.98		***<0.001
Height (cm)	165.40±9.51	161.66±9.26	162.36±9.29	160.43±9.27		***<0.001
Weight (kg)	61.86±8.54	61.93±7.94	77.98±11.30	82.23±13.19		***<0.001
Waist circumference (cm)	80.98±7.22	87.21±6.36	94.97±8.83	101.77±9.14		***<0.001
Hip circumference (cm)	95.42±4.86	95.19±4.59	105.94±7.28	108.40±8.61		***<0.001
Dietary insulin index	54.89±19.43	47.95±9.24	53.42±18.46	50.78±16.52		***<0.001
Dietary insulin load	157907.35±84258.16	121546.75±61228.21	150506.01±80295.64	135191.32±72140.76		***<0.001
Energy intake (kcal)	2831.29±911.44	2476.97±875.68	2768.65±885.93	2611.62±859.49		***<0.001

; ¶METs: the metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

Table 2: General characteristics of participants stratified by cardiometabolic phenotypes in male participants

	Cardiometabolic Phenotype				
	MHN (n=1820)	**MUHN (n=106)**	**MHO (n=3136)**	**MUHO(n=1604)**	P value
	N(%)	**N(%)**	**N(%)**	**N(%)**	
Male					
Marital status					*0.01
Not married	34(1.9)	1(0.9)	28(0.9)	16(1)	
Married	1786(98.1)	105(99.1)	3108(99.1)	1588(99)	
Education level					**0.39
Illiterate	170(9.3)	9(8.5)	252(8)	152(9.5)	
Primary school	659(36.2)	34(32.1)	1158(36.9)	591(36.8)	
Diploma	773(42.5)	51(48.1)	1313(41.9)	681(42.5)	
University	218(12)	12(11.3)	413(13.2)	180(11.2)	

Physical activity level (METs¶)					**<0.001
Low	462(25.4)	35(33)	927(29.6)	617(38.5)	
Moderate	334(18.4)	24(22.6)	621(19.8)	340(21.2)	
High	1024(56.3)	47(44.3)	1588(50.6)	647(40.3)	
Quintiles of wealth index					**<0.001
1 (poorest)	408(22.4)	11(10.4)	505(16.1)	259(16.1)	
2	304(16.7)	17(16)	472(15.1)	259(16.1)	
3	351(19.3)	32(30.2)	683(21.8)	347(21.6)	
4	369(20.3)	16(15.1)	702(22.4)	326(20.3)	
5 (richest)	388(21.3)	30(28.3)	774(24.7)	413(25.7)	
Current Smoking status					**<0.001
No smoker	819(45)	44(41.5)	1578(50.3)	745(46.4)	
Ex-Smoker	234(12.8)	15(14.2)	591(18.8)	358(22.3)	
Smoker	717(39.4)	44(41.5)	831(26.5)	434(27.1)	
Smokers of other tobacco products(water pipe, hookah, pipe,..)	50(2.7)	3(2.8)	136(4.3)	67(4.2)	
Secondhand smoking	750(41.2)	35(33)	1371(43.7)	722(45)	*0.02
Alcohol consumption					**0.3
No	1440(79.1)	82(77.4)	2552(80.4)	1243(77.5)	
Experiment	290(15.9)	17(16)	476(15.2)	269(16.8)	
Limit time (for treatment	3(0.2)	0	6(0.2)	5(0.3)	
Ex-drinker	9(0.5)	0	22(0.7)	7(0.4)	
drinker	78(4.3)	7(6.6)	110(3.5)	80(29.1)	
Insulin load					**<0.001
1th	166(9.1)	23(21.7)	240(7.7)	200(12.5)	
2nd	358(19.6)	27(25.5)	607(19.4)	338(21.1)	
3rd	552(30.3)	31(29.2)	946(30.2)	472(29.4)	
4th	744(40.9)	25(23.6)	1343(42.8)	594(37)	
Insulin index					**<0.001
1th	250(13.7)	30(28.3)	435(13.9)	313(19.5)	
2nd	403(22.1)	28(26.4)	719(22.9)	439(27.4)	
3rd	517(28.4)	28(26.4)	955(30.5)	424(26.4)	
4th	650(35.7)	20(18.9)	1027(32.7)	428(26.7)	

	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
Age (years)	49.71±9.61	55.15±8.85	49.23±9.04	52.01±8.97	***<0.001
Height (cm)	170.61±7.00	169.29±6.35	169.78±6.63	170.35±6.33	***<0.001
Weight (kg)	65.48±7.58	67.76±6.17	82.66±9.94	90.27±11.94	***<0.001
Waist circumference (cm)	82.85±6.95	89.20±5.58	97.82±7.37	105.26±8.33	***<0.001
Hip circumference (cm)	95.58±4.65	96.11±4.09	104.05±5.30	107.11±6.33	***<0.001
Dietary insulin index	56.44±19.27	50.20±9.74	55.38±17.39	53.10±15.33	***<0.001
Dietary insulin load	178265.37±91953.88	146325.32±68338.32	179204.06±88164.46	169201.99±83857.36	***<0.0001
Energy intake (kcal)	3109.21±919.32	2850.34±919.82	3192.65±931.32	3132.97±961.05	***<0.001

; ¶METs: the metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

Table 3: General characteristics of participants stratified by cardiometabolic phenotypes in female participants

	Cardiometabolic Phenotype				
	MHN (n=1128)	**MUHN (n=134)**	**MHO (n=3734)**	**MUHO(n=3220)**	
	N(%)	**N(%)**	**N(%)**	**N(%)**	
Female					
Marital status					*<0.001
Not married	184(16.4)	19(14.2)	373(10)	425(13.2)	
Married	944(83.7)	115(85.8)	3361(90)	2795(86.8)	
Education level					**<0.001
Illiterate	217(19.2)	51(38.1)	646(17.3)	976(30.3)	
Primary school	381(33.8)	39(29.1)	1589(42.5)	1365(42.4)	
Diploma	407(36)	36(26.9)	1249(33.5)	770(23.9)	
University	123(10.9)	8(6)	250(6.7)	109(3.4)	
Physical activity level (METs¶)					**<0.001
Low	354(31.4)	53(39.6)	1183(31.7)	1341(41.6)	
Moderate	517(45.8)	59(44)	1732(46.4)	1325(41.1)	
High	257(22.7)	22(16.4)	819(21.9)	554(17.2)	

Quintiles of wealth index					**<0.001
1 (poorest)	350(30.9)	40(29.9)	897(24)	973(30.2)	
2	166(14.8)	22(16.4)	625(16.7)	650(20.2)	
3	213(18.8)	30(22.4)	769(20.6)	602(18.7)	
4	228(20.2)	21(15.7)	868(23.2)	576(17.9)	
5 (richest)	171(15.2)	21(15.7)	575(15.4)	419(13)	
Current Smoking status					**0.21
No smoker	1111(98.5)	132(98.5)	3698(99)	3177(98.7)	
Ex-Smoker	4(0.4)	2(1.5)	17(0.5)	15(0.5)	
Smoker	10(0.9)	0	12(0.3)	17(0.5)	
Smoker other tobacco products(water pipe, hookah, pipe,..)	3(0.3)	0	7(0.2)	11(0.3)	
Secondhand smoking	506(12.3)	69(51.5)	1834(49.1)	1711(53.1)	*<0.001
Alcohol consumption					**0.65
No	1121(99.4)	134(100)	3725(99.8)	3209(99.7)	
Experiment	6(0.5)	0	6(0.2)	7(0.2)	
Limit time (for treatment	0	0	1(0.	1(0.02)	
Ex-drinker	0	0	2(0.1)	1(0.02)	
drinker	1 (0.1)	0	0	2(0.1)	
Insulin load					**<0.001
1th	395(35)	74(55.2)	1263(33.8)	1345(41.8)	
2nd	327(29)	37(27.6)	1140(30.5)	895(27.8)	
3rd	242(21.4)	14(10.4)	832(22.3)	633(19.7)	
4th	164(14.5)	9(6.7)	499(13.4)	347(10.8)	
Insulin index					**<0.001
1th	327(29)	67(50)	1072(28.7)	1211(37.6)	
2nd	300(26.6)	28(20.9)	971(26)	833(25.9)	
3rd	244(21.6)	31(23.1)	876(23.5)	654(20.3)	
4th	257(22.7)	8(6)	815(21.8)	522(16.2)	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	
Age (years)	47.01±9.75	55.52±9.21	47.07±8.49	52.13±8.98	***<0.001
Height (cm)	157.01±6.58	155.63±6.25	156.12±	155.49±5.94	***<0.001

Weight (kg)	56.02±6.54	57.32±5.89	74.04±10.87	78.23±11.90	***<0.001
Waist circumference (cm)	77.97±6.62	85.63±6.52	92.57±9.24	100.03±9.03	***<0.001
Hip circumference (cm)	95.16±5.30	94.45±4.84	107.54±8.27	109.04±9.48	***<0.001
Dietary insulin index	52.35±19.40	46.17±8.44	51.78±19.16	49.62±16.96	***<0.001
Dietary insulin load	124898.66±56090.32	101945.79±46619.43	126403.94±63741.27	118249.36±585855.05	***<0.001
Energy intake (kcal)	2381.77±693.49	2165.50±708.04	2412.56±661.78	2351.92±666.32	***<0.001

; ¶METs: the metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

Among the four phenotypes, the MUHO phenotype had the highest proportion of female and married participants. (Table 1). The married participants' ratio was significantly higher in both genders. (Tables 2 and 3) Education levels regardless of gender, and in female participants were lower in the MUHO phenotype group, ($p<0.001$) but the education levels in male participants showed no significant differences. ($p< 0.39$). Physical activity in both genders was significantly lower in metabolically unhealthy participants (Both MUHN and MUHO). ($p<0.001$) Assessing the quintiles of WSI in all of the participants (Table 1) and female participants (Table 3) showed that the MUHO were mostly among the 1st quintile of WSI. ($p<0.001$) whereas in male participants (Table 2), the MUHO phenotype was associated with higher income. ($p<0.001$) Interestingly, the mean energy intake of each unhealthy CMP was lower than the mean energy intake of the corresponding healthy CMP. For instance, the mean energy intake of MUHN participants was 2850.34±919.82 whereas it was 3109.21±919.32 in MHN participants. Moreover, the frequency of

alcohol consumption and Smoking was significantly higher in MHN participants than in MUHO participants. (p<0.001) On the other hand, the percentage of secondhand smokers was significantly higher in MUHO participants than in MHN ones, both regardless and according to their gender. (Tables 1 and 2) (p<0.001) The mean values of Age, BMI, and waist circumference showed incremental trends from being in a healthy phenotype (whether normal weight or obese) to an unhealthy phenotype. ($p \leq 0.001$) (Tables 1 and 2). Hip circumference was lower in the MHN than in the MHO and MUHO. (p<0.001)

Relationship between Cardiometabolic Phenotypes and Dietary Insulin Load and Index

The frequency of Insulin load and index quartiles showed a significant decrease from the 1st to 4th quartile in metabolically unhealthy participants (Both MUHN and MUHO) ($p \leq 0.001$).

Unexpectedly, the mean values of the Dietary Insulin Index and Dietary Insulin Load showed to be higher in metabolically healthy phenotypes than in unhealthy ones, with the MUHN phenotype being the lowest. (p<0.001) In addition, the mean value of energy intake was lower in metabolically unhealthy phenotypes compared to their corresponding healthy phenotypes, with the MUHN consuming the lowest energy intake. (p<0.001) (Table 1) This trend was seen both regardless of the participants' gender, (Table 1) and in male or female participants divided. (Tables 2 and 3)

The findings of the unadjusted model indicated that compared to the 1st DIL quartile, the risks of MUHN and MUHO in the 4th DIL quartile decreased by 0.21 (0.14 - 0.32) and 0.37 (0.33 – 0.43), respectively (Table 4).

Table4: Association between cardiometabolic phenotype and across quartiles of DIL and DIL scores of Azar cohort population

	Quartiles of DIL				Quartiles of DII			
	1 (n=3711)	2 (n=3730)	3 (n=3725)	4 (3726)	1 (n=3708)	2 (n=3726)	3 (n=3730)	4 (3728)
Q rang	≤99828.05	99828.06-129348.53	129348.54-171278.60	>171278.61	≤44.43	44.44-48.64	48.65-55.29	>55.30
Crude								
MUHN	Reference	0.54(0.38-0.75)	0.32(0.22-0.47)	0.21(0.14-0.32)	Reference	0.47(0.33-0.66)	0.46(0.32-0.64)	0.18(0.11-0.28)
MHO	Reference	0.95(0.83-1.08)	0.83(0.73-0.95)	0.76(0.67-0.86)	Reference	0.91(0.80-1.04)	0.92(0.81-1.04)	0.77(0.68-0.88)
MUHO	Reference	0.65(0.57-0.75)	0.50(0.44-0.57)	0.37(0.33-0.43)	Reference	0.68(0.59-0.77)	0.53(0.47-0.61)	0.39(0.34-0.45)
MUHN								
Model 1	Reference	0.66(0.46-0.93)	0.45(0.30-0.67)	0.34(0.22-0.53)	Reference	0.59(0.410.84)	0.58(0.41-0.83)	0.24(0.15-0.37)
Model2	Reference	061(0.42-0.90)	0.38(0.23-0.62)	0.23(0.12-0.47)	Reference	0.57(0.40-0.81)	0.57(0.40-0.82)	0.24(0.15-0.37)
MHO								
Model1	Reference	1.05(0.91-1.20)	1.03(0.90-1.18)	1.04(0.90-1.20)	Reference	0.97(0.85-1.11)	1.03(0.90-1.17)	0.88(0.78-1.01)
Model2	Reference	1.01(0.87-1.16)	0.94(0.80-1.09)	0.85(0.74-1.04)	Reference	0.91(0.80-1.04)	0.94(0.82-1.07)	0.80(0.70-0.91)
MUHO								
Model1	Reference	0.88(0.76-1.01)	0.85(0.74-0.99)	0.80(0.69-0.93)	Reference	0.86(0.75-0.99)	0.74(0.64-0.85)	0.57(0.50-0.66)
Model2	Reference	0.48(0.38-0.59)	0.65(0.55-0.76)	0.772(0.66-0.89)	Reference	0.77(0.67-0.89)	0.64(0.56-0.74)	0.48(0.42-0.561)
Male								
Crude								

MUHN	Reference	0.54(0.30-0.97)	0.40(0.23-0.71)	0.24(0.13-0.43)	Reference	0.57(0.33-0.99)	0.45(0.26-0.77)	0.25(0.14-0.46)
MHO	Reference	1.17(0.92-1.48)	1.18(0.94-1.48)	1.24(1.00-1.54)	Reference	1.02(0.83-1.24)	1.06(0.87-1.28)	0.90(0.75-1.09)
MUHO	Reference	0.66(0.52-0.83)	0.70(0.55-0.90)	0.78(0.60-1.01)	Reference	0.86(0.70-1.07)	0.65(0.53-0.80)	0.52(0.42-0.64)
MUHN								
Model 1	Reference	0.56(0.31-1.02)	0.44(0.25-0.79)	0.28(0.15-0.52)	Reference	0.64(0.37-1.11)	0.46(0.27(0.80)	0.27(0.15-0.50)
Model2	Reference	0.49(0.26-0.92)	0.34(0.17-0.69)	0.17(0.06-0.46)	Reference	0.66(0.38-1.14)	0.50(0.29-0.86)	0.30(0.16-0.55)
MHO								
Model1	Reference	1.12(0.88-1.42)	1.10(0.88-1.39)	1.16(0.93-1.45)	Reference	0.99(0.81-1.21)	1.01(0.84-1.22)	0.86(0.71-1.03)
Model2	Reference	1.05(0.82-1.35)	0.98(0.76-1.26)	0.93(0.70-1.24)	Reference	0.98(0.80-1.19)	0.99(0.81-1.20)	0.82(0.68-1)
MUHO								
Model1	Reference	0.78(0.60-1.01)	0.72(0.56-0.92)	0.70(0.55-0.89)	Reference	0.89(0.72-1.11)	0.65(0.53-0.81)	0.53(0.43-0.65)
Model2	Reference	0.68(0.52-0.89)	0.55(0.42-0.73)	0.41(0.30-0.57)	Reference	0.89(0.71-1.11)	0.64(0.52-0.80)	0.51(0.41-0.63)
Female								
Crude								
MUHN	Reference	0.60(0.39-0.92)	0.31(0.17-0.56)	0.29(0.14-0.60)	Reference	0.45(0.28-0.72)	0.62((0.39-0.98)	0.15(0.07-0.32)
MHO	Reference	1.09(0.92-1.29)	1.08(0.90-1.30)	0.95(0.77-1.18)	Reference	0.98(0.82-1.17)	1.09(0.91-1.32)	0.97(0.80-1.17)
MUHO	Reference	0.80(0.68-0.95)	0.77(0.64-0.93)	0.62(0.50-0.77)	Reference	0.74(0.62-0.89)	0.72(0.60-0.87)	0.55(0.45-0.66)
MUHN								
Model 1	Reference	0.77(0.50-1.18)	0.43(0.23-0.78)	0.42(0.20-0.88)	Reference	0.55(0.34-0.89)	0.78(0.49-1.25)	0.18(0.08-0.39)
Model2	Reference	0.66(0.40-1.10)	0.33(0.15-0.70)	0.29(0.11-0.78)	Reference	0.57(0.35-0.92)	0.82(0.51-1.31)	0.19(0.09-0.41)
MHO								
Model1	Reference	1.06(0.90-1.26)	1.06(0.88-1.28)	0.95(0.6-1.17)	Reference	0.96(0.808-1.15)	1.07(0.89-1.30)	0.95(0.78-1.14)
Model2	Reference	0.98(0.81-1.19)	0.92(0.73-1.18)	0.77(0.57-1.05)	Reference	0.95(0.8-1.14)	1.06(0.88-1.29)	0.93(0.77-1.13)
MUHO								

Model1	Reference	0.95(0.80-1.13)	0.96(0.79-1.17)	0.81(0.64-1..01)	Reference	0.84(0.70-1.01)	0.84(0.69-1.02)	0.62(0.51-0.76)
Model2	Reference	0.78(0.64-0.95)	0.67(0.52-0.86)	0.47(0.34-0.66)	Reference	0.83(0.69-1.00)	0.83(0.68-1.01)	0.60(0.49-0.74)

MHL was considered as a reference group; Model 1: adjusted for age, gender, education level, WSI; Model 2 adjusted for age, gender, MET, Energy intake. Adjusted for gender where appropriate

After adjustment for different intervening factors (ie age, gender, education, MET, and Energy intake), a strong negative correlation was observed between DIL with MUHN and MUHO. But there were no significant correlations between DIL with MHO after the adjustments. (Table 4). The aforementioned negative correlation was more obvious in the 4th DIL quartile. In Model 2, the observed odds ratio for MUHN was 0.61 (0.42 – 0.90) in the 2nd DIL quartile, while it was 0.23 (0.12 – 0.47) in the 4th DIL quartile. (Table 4).

The findings of the unadjusted model for the DII quartiles indicated that compared to the 1st DII quartile, the risks of MUHN and MUHO in the 4th DII quartile decreased by 0.18 (0.11 - 0.28) and 0.39 (0.34 – 0.45), respectively (Table 4). After adjustment for the same intervening factors as DIL quartiles, a strong negative correlation was observed between DII with MUHN and MUHO. But there was no significant correlation between DII with MHO after the adjustments. (Table 4). The aforementioned negative correlations were more obvious in the 4th DII quartile. In Models 1 and 2, the observed odds ratio for MUHN were 0.59 (0.41 – 0.84) and 0.57(0.40-0.81) respectively in the 2nd DII quartile, while they were both 0.24 (0.15 – 0.37) in the 4th DII quartile. (Table 4).

These models were also run for both male and female participants separately. The results in both genders were overall the same as all participants combined.

Discussion

This cross-sectional study looked into the association between DII and DIL with different CMPs. The findings indicated that there was a significant negative correlation between DII and DIL and MUHN and MUHO phenotypes both before and after considering confounding variables. Our findings demonstrated no significant correlation between DIL and DII and MHO. The prevalence of chronic conditions such as MetS has increased in recent years. (2)(26) Previous studies indicate a significant positive association between insulin resistance and unhealthy cardiometabolic status. (27) One of the main causes of insulin resistance is the tendency towards diets with high insulinemic capability. (23)(28) Thus, it is of great importance to establish a reliable index to demonstrate the insulinemic potential of individuals' diets. Since DII and DIL directly depend on insulin response to food, there has been an increase in attention to these two in evaluating the aforementioned potential. (12)(23) By measuring these two indices in different populations, we can search for an association between these two and different CMPs and deduce whether we can use DII and DIL to predict the odds of unhealthy CMPs or not. To the best of our knowledge, this is the first study trying to answer this question and evaluate this association in different CMPs. In our study, there was a correlation between unhealthy CMPs and lower DIL and DII values. In addition, high DIL and DII were associated with lower odds of unhealthy CMPs. (both MUHN

and MUHO). The trend of odds ratio in metabolically healthy phenotypes was not significant. We can conclude these findings in two different parts.

First, the correlation between lower DIL and DII with unhealthy CMPs can be justified by the fact that the mean energy intake in unhealthy phenotypes was lower than in healthy phenotypes. This finding suggests that the participants with unhealthy phenotypes restricted their energy intake and possibly lowered the insulinemic potential of their diet (ie lowered their DII and DIL) to lose weight and modify their lifestyle behavior. Additionally, our findings demonstrate that alcohol consumption and smoking were also lower in metabolically unhealthy phenotypes. This supports the speculation that participants with unhealthy phenotypes were following a lifestyle modification plan in diet, smoking, and alcohol consumption. This modification could be the reason for lower DII and DIL in unhealthy phenotypes. Therefore, we suggest that measuring DII and DIL cannot be a reliable index for predicting the CMP and the risk of developing chronic diseases. Further studies are needed to take recent lifestyle modifications into account and determine the associations between DII and DIL with CMPs in participants who have not had a recent lifestyle modification, specifically modifications in their diets.

Secondly, the insignificant trend of odds ratio in metabolically healthy phenotypes suggests that insulin resistance may not be easily assessed and predicted by simply measuring indices such as DII and DIL since insulin secretion depends on different components including the participant's diet, neural, and hormonal activity. (29)

In line with our findings, Karimbeiki et al demonstrated that a higher insulinemic effect of diet was not associated with higher rates of obesity. (30) Another study by Anjom-Shojaei et al showed that a high DII of diet was not associated with obesity in men, although it was associated with obesity in women. (16) A cross-sectional study on 262 participants of the Dortmund Nutritional and Anthropometric Longitudinally Designed Study demonstrated that a higher DII and DIL were associated with higher body fat percentage, but not higher BMI. (31) On the other hand, a cross-sectional study conducted on 203 overweight/obese adolescents showed that a diet with higher DII and DIL was associated with higher odds of being in the MUHO group. (32) A cross-sectional study on the Shahidieh cohort demonstrated that a higher DII was associated with higher odds of MetS in women, but no such association was seen in men. (26) moreover, a clinical trial with a Mediterranean diet style was associated with healthier CMPs, lower body weight, lower BMI and fat mass, and lower blood glucose and lipids in children and adolescents with obesity. (33) Approving the aforementioned study, a cross-sectional study on 137 European overweight and obese participants in their puberty, showed that a Mediterranean diet was associated with a lower risk of MUHO phenotype. (34) Another cross-sectional study involving both overweight and normal-weight Turkish children has demonstrated that breakfast and dinner with higher DII and DIL were associated with a higher odds ratio of being overweight. (35) Two other studies were investigating the correlation between DII and DIL with diabetes, and cardiovascular disease respectively. The first study concluded that a higher DII and DIL of the diet were associated with a higher risk of diabetes, and DIL

was a better predictor for diabetes compared to DII. (36) The other study demonstrated that DII and DIL were not associated with the risk of CVD,(37) which is in line with our findings. In the current study, we demonstrated that DII and DIL were strongly correlated with a decreased odds ratio of MUHN and MUHO and that there was no significant correlation between DIL and DII, and MHO.

Previous studies suggest several mechanisms for the correlation between DII and DIL with unhealthy CMPs. Insulin secretion can be a result of highly insulinemic diets, which in turn, increases the oxidation of carbohydrates and decreases the oxidation of lipids. Therefore, these diets can cause a surplus in abdominal fat storage, and increase the risk of obesity and unhealthy CMPs. (32) Moreover, high insulinemic diets potentially cause faster carbohydrate digestion and absorption, and higher blood glucose and insulin levels. They also cause a faster drop in post-prandial blood glucose levels after the surge. (38)(39) This sudden drop in blood glucose can reduce satiety and cause a high-calorie intake of food, resulting in abdominal obesity and unhealthy CMPs. (38)(39) Additionally, High DII and DIL are associated with a higher incidence of insulin resistance and diabetes. (36)(40)

Our study had several strengths. The associations between DII and DIL with four different CMPs were studied for the first time, and these CMPs were organized based on the presence or absence of obesity, and the presence or absence of MetS. This model helped assess the data in a more organized pattern. In addition, the effect of confounding factors was also taken into account while analyzing the data. Another strength of this study was its large population. Our study was conducted on

just less than 15000 participants. Nevertheless, there were some limitations during the conduction of this study which should be taken into consideration while evaluating the results. Since this was a cross-sectional study, we could not establish a cause-and-effect correlation and more prospective studies are needed to establish and assert such causality. Another limitation was recall bias. The most frequently used tool to assess the dietary habits of participants in epidemiological studies is the FFQ, however there is always a recall bias when using this tool. Even though the data were analyzed with the confounding factors taken into account, still some confounding factors including dietary habits, psychological factors, parental obesity, and family history of cardiometabolic diseases were not assessed. We suggest two possible reasons for our observations. First, despite the presumed belief that increased insulin secretion is correlated with increased rates of different metabolic abnormalities, genetic data, as opposed to epidemiological data, propose this correlation to be overrated. Elevated insulin secretion could even be beneficial. (41)(42) Secondly, considering our findings demonstrated that participants with unhealthy CMPs had lower energy intake and alcohol consumption, and a lower smoking rate, it is presumable that some may have changed their lifestyle behavior. This presumed lifestyle behavior change can be the main reason for DII and DIL being associated with a lower odds ratio of unhealthy CMPs. This finding highlights the importance of considering recent lifestyle behavior change as a confounding factor and further studies are needed to evaluate the association between DII and DIL with different CMPs in participants with no recent lifestyle behavior change or evaluate this association while taking the aforementioned confounding factors into

account. Moreover, further studies can observe participants with healthy CMPs and look into possible eventual shifts to unhealthy CMPs. Genetic factors can also be studied to evaluate the correlation between elevated insulin secretion and CMPs.

Conclusion

This current cross-sectional study demonstrated that DII and DIL were strongly correlated with a decreased odds ratio of MUHN and MUHO and that there was no significant correlation between DIL and DII and MHO. As mentioned before, we speculate that a lower energy intake in participants with unhealthy cardiometabolic phenotypes, as a result of lifestyle behavior change, was the main reason for this observation. Further studies, specifically with a prospective design, are required to confirm this speculation by assessing the correlation between DII and DIL with different CMPs in participants who have not experienced a recent lifestyle behavior change.

Acknowledgments:

The authors are grateful for the financial support of the liver and gastrointestinal diseases research center, at Tabriz University of Medical Sciences. The authors also are deeply indebted to all subjects who participated in this study. We appreciate the contribution of the investigators and the staff of the AZAR cohort study. We thank the close collaboration of the Shabestar health center. In addition, we would like to thank the Persian cohort study staff for their technical support. We would like to

appreciate the cooperation of the Clinical Research Development Unit of Imam Reza General Hospital, Tabriz, Iran in conducting this research.

Declaration

Ethics approval and consent to participate

This study was approved by the ethics committee of Tabriz University of medical sciences (IR.TBZMED.REC.1401.414)

Funding

This study was supported by the liver and gastrointestinal diseases research center (Grant number 700/108 on 14 March 2016), Tabriz University of Medical Sciences. The funder had no role in the study design, data analysis, interpretation, and writing the manuscript in this study.

Competing interests

The authors declare that they have no competing interests

Availability of data and materials

The data that support the findings of this study are available from [Vice Chancellor for Research] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [Vice Chancellor for Research]

Authors' contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *BMJ open.* E.F, SS.NI, and AM.N helped with the conception and design of the work. E.F, MH.S, N.P, and AM.N helped with the acquisition and analysis. E.F, MH.S, SS.NI, N.P, and AM.N interpreted the data, and E.F, N.P, and AM.N drafted the work and revised it. All authors have read and approved the manuscript.

References

1. Collaborators GBD 2015 O. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27.
2. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev. 2015;16(1):1–12.
3. Nolan PB, Carrick-Ranson G, Stinear JW, Reading SA, Dalleck LC. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: A pooled analysis. Prev Med reports. 2017;7:211–5.
4. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):1–8.
5. Goday A, Calvo E, Vázquez LA, Caveda E, Margallo T, Catalina-Romero C, et al. Prevalence and clinical characteristics of metabolically healthy obese individuals and other obese/non-obese metabolic phenotypes in a working population: results from the Icaria study. BMC Public Health. 2016;16(1):1–14.
6. Osadnik K, Osadnik T, Lonnie M, Lejawa M, Reguła R, Fronczek M, et al. Metabolically healthy obese and metabolic syndrome of the lean: the

importance of diet quality. Analysis of MAGNETIC cohort. Nutr J. 2020;19(1):1–13.
7. Ding C, Chan Z, Magkos F. Lean, but not healthy: the 'metabolically obese, normal-weight'phenotype. Curr Opin Clin Nutr Metab Care. 2016;19(6):408–17.
8. Wang B, Zhuang R, Luo X, Yin L, Pang C, Feng T, et al. Prevalence of metabolically healthy obese and metabolically obese but normal weight in adults worldwide: a meta-analysis. Horm Metab Res. 2015;47(11):839–45.
9. Jung CH, Lee MJ, Kang YM, Jang JE, Leem J, Hwang JY, et al. The risk of incident type 2 diabetes in a Korean metabolically healthy obese population: the role of systemic inflammation. J Clin Endocrinol Metab. 2015;100(3):934–41.
10. Eddy D, Schlessinger L, Kahn R, Peskin B, Schiebinger R. Relationship of insulin resistance and related metabolic variables to coronary artery disease: a mathematical analysis. Diabetes Care. 2009;32(2):361–6.
11. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol. 2013;3(1):1.
12. Nimptsch K, Brand-Miller JC, Franz M, Sampson L, Willett WC, Giovannucci E. Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers. Am J Clin Nutr. 2011;94(1):182–90.
13. Bell SJ, Sears B. Low-glycemic-load diets: impact on obesity and chronic diseases. 2003;
14. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr. 2000;71(6):1455–61.
15. Holt SH, Miller JC, Petocz P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. Am J Clin Nutr. 1997;66(5):1264–76.
16. Anjom-Shoae J, Keshteli AH, Sadeghi O, Pouraram H, Afshar H, Esmaillzadeh A, et al. Association between dietary insulin index and load with obesity in adults. Eur J Nutr. 2020;59(4):1563–75.
17. Farhang S, Faramarzi E, Amini Sani N, Poustchi H, Ostadrahimi A, Alizadeh BZ, et al. Cohort profile: The AZAR cohort, a health-oriented research model in areas of major environmental change in Central Asia. Int J Epidemiol. 2019;48(2):382-382h.
18. Poustchi H, Eghtesad S, Kamangar F, Etemadi A, Keshtkar A-A, Hekmatdoost A, et al. Prospective epidemiological research studies in Iran (the PERSIAN Cohort Study): rationale, objectives, and design. Am J Epidemiol. 2018;187(4):647–55.
19. Eghtesad S, Mohammadi Z, Shayanrad A, Faramarzi E, Joukar F, Hamzeh B, et al. The PERSIAN cohort: providing the evidence needed for healthcare reform. Arch Iran Med. 2017;20(11):691–5.
20. Ghafarpour M, Kianfar H, Hoshyarrad A BB. Food Album. Natl Nutr Food

Technol Res Institute ISBN 9786005040005.
21. Consultation WHO. Obesity: preventing and managing the global epidemic. World Health Organ Tech Rep Ser. 2000;894:1–253.
22. Somi MH, Nikniaz Z, Ostadrahimi A, Sadat ATE, Faramarzi E. Is normal body mass index a good indicator of metabolic health in Azar cohort population? J Cardiovasc Thorac Res. 2019;11(1):53.
23. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. Am J Clin Nutr. 2011;93(5):984–96.
24. Bell KJ, Petocz P, Colagiuri S, Brand-Miller JC. Algorithms to improve the prediction of postprandial insulinaemia in response to common foods. Nutrients. 2016;8(4):210.
25. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573–7.
26. Sadeghi O, Hasani H, Mozaffari-Khosravi H, Maleki V, Lotfi MH, Mirzaei M. Dietary Insulin Index and dietary insulin load in relation to metabolic syndrome: The Shahedieh cohort study. J Acad Nutr Diet. 2020;120(10):1672–86.
27. Okosun IS, Okosun B, Lyn R, Airhihenbuwa C. Surrogate indexes of insulin resistance and risk of metabolic syndrome in non-Hispanic White, non-Hispanic Black and Mexican American. Diabetes Metab Syndr Clin Res Rev. 2020;14(1):3–9.
28. Hsieh C-H, Wu C-Z, Hsiao F-C, Lin J-D, Li J-C, Wan H-L, et al. The impact of metabolic syndrome on insulin sensitivity, glucose sensitivity, and acute insulin response after glucose load in early-onset type 2 diabetes mellitus: Taiwan Early-Onset Type 2 Diabetes Cohort Study. Metabolism. 2008;57(11):1615–21.
29. Seino S, Shibasaki T, Minami K. Dynamics of insulin secretion and the clinical implications for obesity and diabetes. J Clin Invest. 2011;121(6):2118–25.
30. Karimbeiki R, Namkhah Z, Alipoor E, Yaseri M, Hosseinzadeh-Attar MJ. The relationship between low-carbohydrate diet score, dietary insulin index and load with obesity in healthy adults. Eat Weight Disord Anorexia, Bulim Obes. 2022;1–10.
31. Joslowski G, Goletzke J, Cheng G, Günther ALB, Bao J, Brand-Miller JC, et al. Prospective associations of dietary insulin demand, glycemic index, and glycemic load during puberty with body composition in young adulthood. Int J Obes. 2012;36(11):1463–71.
32. Hajhashemy Z, Mirzaei S, Asadi A, Akhlaghi M, Saneei P. Association of Dietary Insulin Index and Dietary Insulin Load With Metabolic Health Status in Iranian Overweight and Obese Adolescents. Front Nutr. 2022;9.
33. Velázquez-López L, Santiago-Díaz G, Nava-Hernández J, Muñoz-Torres A

V, Medina-Bravo P, Torres-Tamayo M. Mediterranean-style diet reduces metabolic syndrome components in obese children and adolescents with obesity. BMC Pediatr. 2014;14(1):1–10.
34. Arenaza L, Huybrechts I, Ortega FB, Ruiz JR, De Henauw S, Manios Y, et al. Adherence to the Mediterranean diet in metabolically healthy and unhealthy overweight and obese European adolescents: the HELENA study. Eur J Nutr. 2019;58(7):2615–23.
35. Caferoglu Z, Erdal B, Akin L, Kurtoglu S. Breakfast and dinner insulin index and insulin load in relation to overweight in children and adolescents. Eur J Nutr. 2021;60(5):2819–29.
36. Teymoori F, Farhadnejad H, Moslehi N, Mirmiran P, Mokhtari E, Azizi F. The association of dietary insulin and glycemic indices with the risk of type 2 diabetes. Clin Nutr. 2021;40(4):2138–44.
37. Teymoori F, Farhadnejad H, Mirmiran P, Nazarzadeh M, Azizi F. The association between dietary glycemic and insulin indices with incidence of cardiovascular disease: Tehran lipid and glucose study. BMC Public Health. 2020;20(1):1–10.
38. Hellström PM. Satiety signals and obesity. Curr Opin Gastroenterol. 2013;29(2):222–7.
39. Zhu R, Larsen TM, Poppitt SD, Silvestre MP, Fogelholm M, Jalo E, et al. Associations of quantity and quality of carbohydrate sources with subjective appetite sensations during 3-year weight-loss maintenance: Results from the PREVIEW intervention study. Clin Nutr. 2022;41(1):219–30.
40. Mirmiran P, Esfandiari S, Bahadoran Z, Tohidi M, Azizi F. Dietary insulin load and insulin index are associated with the risk of insulin resistance: a prospective approach in tehran lipid and glucose study. J Diabetes Metab Disord. 2015;15(1):1–7.
41. Nguyen A, Khafagy R, Meerasa A, Roshandel D, Paterson AD, Dash S. Insulin Response to Oral Glucose and Cardiometabolic Disease: A Mendelian Randomization Study to Assess Potential Causality. Diabetes. 2022;71(9):1880–90.
42. Dwivedi OP, Lehtovirta M, Hastoy B, Chandra V, Krentz NAJ, Kleiner S, et al. Loss of ZnT8 function protects against diabetes by enhanced insulin secretion. Nat Genet. 2019;51(11):1596–606.

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	7

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	8
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	9
Bias	#9	Describe any efforts to address potential sources of bias	9
Study size	#10	Explain how the study size was arrived at	8
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	12
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	12
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	12
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	12
Participants	#13c	Consider use of a flow diagram	n/a

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	14
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	12
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
Main results	#16b	Report category boundaries when continuous variables were categorized	12
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	20
Generalisability	#21	Discuss the generalisability (external validity) of the study results	20
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

This checklist was completed on 13. September 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Associations between Insulin Index and Dietary Insulin Load with Cardiometabolic phenotype in the AZAR cohort population in northwestern Iran: A cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-068303.R2
Article Type:	Original research
Date Submitted by the Author:	29-Mar-2023
Complete List of Authors:	faramarzi, elnaz; Tabriz University of Medical Sciences somi, mohammad hossein; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center Naghibi Irvani, Seyed Sina; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center, Research Institute for Endocrine Science Pourhashem, Nahid; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center Nourizadeh, Amir Mohammad; Tabriz University of Medical Sciences Liver and Gastrointestinal Diseases Research Center
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY, INTERNAL MEDICINE, NUTRITION & DIETETICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Associations between Insulin Index and Dietary Insulin Load with Cardiometabolic phenotype in the AZAR cohort population in northwestern Iran: A cross-sectional study

Elnaz Faramarzi [1], Ph.D., Prof. Mohammad Hossein Somi, MD [1], Seyed Sina Naghibi Irvani [1], MD, MPH, MBA, Nahid Pourhashem [1], Amir Mohammad Nourizadeh [1*], MD

[1] Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran.

Order of Authors:

1. Elnaz Faramarzi. Liver and Gastrointestinal Diseases Research center, Tabriz University of Medical Sciences. Email: elnazfaramarzi849@gmail.com

2. Mohammad Hossein Somi. Liver and Gastrointestinal Diseases Research Center of Tabriz university of medical sciences. Tabriz, Iran. Email: mhosseinsina@yahoo.com

3. . Seyed Sina Naghibi Irvani. Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran. Email: sina.irvani@gmail.com

4. Nahid Pourhashem. . Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran. Email: npourhashem@yahoo.com

5. Amir Mohammad Nourizadeh. Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences. Tabriz, Iran. Email: Nourizadehamirmohammad@gmail.com

*Corresponding Author:

Amir Mohammad Nourizadeh, MD,

Liver and Gastrointestinal Diseases Research Center. Tabriz University of Medical Sciences. Tabriz, Iran. (**Email:** Nourizadehamirmohammad@gmail.com)

ORCID Number: 0000-0001-9206-5327

P.O. Box: 1567812907, **Tel:** +98-914-9979121, **Fax:** +98-413-3845238

(Word count: 4159)

Keywords:

Nutrition and Dietetics/ Diabetes/ Endocrinology/ Internal Medicine

ABSTRACT

Objectives:

Hyperinsulinemia and insulin resistance are proposed as contributors to the incidence of cardiometabolic phenotypes (CMPs) with unhealthy metabolic status. This study analyzed the association between dietary insulin load (DIL) and dietary insulin index (DII) with CMPs in the AZAR cohort population.

Design:

This study was a cross-sectional analysis of the AZAR cohort study, beginning in 2014 and continuing to this date.

Setting:

AZAR cohort is a part of an Iranian screening program named the Persian cohort and involves participants living in the Shabestar region, Iran for at least 9 months.

Participants:

A total of 15006 participants agreed to partake in the study. We excluded participants with missing data (N=15), daily energy intake lower than 800 kcal (N=7) or higher than 8000 kcal (N=17), and cancer (N=85). Finally, 14882 individuals remained.

Primary and secondary outcome measures:

The gathered information included the participants' demographic, dietary, anthropometric, and physical activity data.

Results: The frequency of DIL and DII significantly decreased from the 1st to 4th quartile in metabolically unhealthy participants ($p \leq 0.001$). The mean values of DIL and DII were greater in metabolically healthy participants than in unhealthy ones ($p<0.001$). The results of the unadjusted model showed that the risks of unhealthy phenotypes in the 4th DIL quartile decreased by 0.21 (0.14 - 0.32) and 0.37 (0.33 – 0.43) respectively compared to the 1st quartile. The same model showed the same risks for DII decreased by 0.18 (0.11 - 0.28) and 0.39 (0.34 – 0.45) respectively. The results in both genders were the same as all participants combined.

Conclusions: DII and DIL were correlated with a decreased odds ratio of unhealthy phenotypes. We suggest the reason may be either a lifestyle change in metabolically unhealthy participants or elevated insulin secretion not being as detrimental as previously thought. Further studies can confirm these speculations.

Article Summary:

Strengths and limitations of this study:

- The current study was an analysis of the AZAR cohort study which is a very large population. The final number of participants included was just less than 15000 individuals.
- In this study, the associations between DII and DIL with four different CMPs were studied for the first time. This model helped us to analyze the data in a more organized fashion.
- The presence of confounders and their effect were considered while analyzing the data.
- This was a cross-sectional study. Therefore we were unable to establish a cause-and-effect correlation. More prospective studies are needed to investigate and establish such causality.

Introduction

The World Health Organization (WHO) has reported that over 600 million adults worldwide are obese (1) Obesity is closely associated with Metabolic Syndrome (MetS), which has increased the global burden of cardiovascular diseases. The prevalence and incidence of MetS have significantly increased in the past two decades. (2) MetS represents a collection of different metabolic abnormalities. MetS is a pathophysiological, asymptomatic condition characterized by obesity, insulin resistance, hypertension, glycemic abnormalities, and dyslipidemia(3). Although various criteria and definitions have been proposed to describe MetS(3), it is generally agreed that a combination of three or more of the following constituents should be present: Hypertension, elevated fasting blood glucose, elevated triglycerides, low HDL cholesterol, and large waist circumference. The incidence of MetS usually correlates with the incidence of obesity. The prevalence of MetS has doubled in 73 countries and has notably increased in others since 1980. (4)

Although abdominal obesity is one of the criteria for MetS, it should be noted that MetS doesn't always equal obesity. In fact, some other interesting phenotypes have recently been seen more often. For instance, some obese individuals do not meet the criteria for MetS. They are called the Metabolically Healthy Obese (MHO). (5) Conversely, some non-obese individuals do fulfill the criteria for MetS. They are called the Metabolically Unhealthy Normal Weight (MUHN) or the Metabolically Obese Normal Weight. (6)(7)(8)(9) This calls for classifying individuals into four different cardiometabolic phenotypes (CMPs) groups and assessing different

metabolic factors based on four phenotypes; obese individuals who fulfill MetS criteria, called the Metabolically Unhealthy Obese (MUHO), obese individuals who do not fulfill MetS criteria, called the MHO, normal weight individuals who fulfill MetS criteria, called the MUHN, and normal weight individuals who do not fulfill MetS criteria, called the Metabolically Healthy Normal Weight (MHN).

Previous studies have shown a strong relationship between cardiometabolic status and insulin resistance. (10)(11) Assessing the effect of individuals' diets on weight gain, hyperlipidemia, and type 2 diabetes requires measuring the ability of foods to induce postprandial insulin secretion. (12) Hence, it is essential to quantify the capability of individuals' diets to induce postprandial insulin secretion. A diet with a high glycemic index (GI) and high Glycemic Load (GL) can increase postprandial insulin secretion, leading to obesity and diabetes. (13)(14) However, these two Indices solely measure the effect of carbohydrates in this regard. In addition to carbohydrates, proteins and lipids also increase postprandial insulin secretion. Moreover, proteins enhance the effect of carbohydrates on insulin secretion. This suggests that the amount of carbohydrates in a diet is not accurately proportional to postprandial insulin secretion. (15) As a result, a food Insulin Index (II) and Dietary Insulin Load (DIL) have been suggested. (13) (15)(16) The II can directly quantify the postprandial insulin response to a test food compared to an isoenergetic portion of a reference food. (12)(15) DIL can be calculated for each individual using II and the energy content of each food they consume. (17) since II and DIL are directly

based on insulin response, they are more satisfactory to evaluate hypotheses that connect insulin exposure to cardiometabolic diseases compared to GI and GL.(12)

Although some studies have assessed the relation between insulin exposure of diets with MetS and obesity, to the best of our knowledge, no studies have ever structured and grouped individuals into different CMP classifications and assessed the relation between the insulinemic potential of their diets according to their CMP. Therefore, in this study, we try to investigate the association between II and DIL with CMP in the AZAR cohort population.

Materials and Methods

Study design and participants

AZAR cohort is a prospective population-based study(18) in Iran and a part of a national screening program named prospective epidemiological research studies in Iran (Persian cohort). (19)(20) The study's main goal is to investigate the major non-communicable diseases risk factors, including cardiovascular, pulmonary, and renal diseases, diabetes, and cancer. The AZAR cohort started in October 2014 and is still in progress in East- Azarbaijan province in Northwestern Iran. The study includes up to 15000 individuals aged between 35-70 years who have lived in the Shabestar region for at least nine months. Subjects with severe psychiatric or physical illnesses and pregnant women were excluded from the study. This study is explained in greater detail in other studies. (18)(19)(20)

Our cross-sectional study was conducted on the AZAR cohort population. A total number of 15006 individuals agreed to participate. We excluded individuals with missing data (N=15). Additionally, individuals with a daily energy intake lower than 800 kcal (N=7) or higher than 8000 kcal (N=17) were also excluded, as well as those who had cancer (N=85). Finally, 14882 individuals remained. The information collected included demographic, dietary, anthropometric, and activity data of the participants. All participants filled out a written informed consent form before the study. The Bioethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, approved the study. (Ethics Number: IR.TBZMED.REC.1401.414)

The socioeconomic status of the participants was evaluated by the Wealth Score Index (WSI), calculated by Multiple Correspondence Analysis (MCA). Each participant's WSI was determined by assessing their possession of different permanent property (eg TV, dishwasher, and car), their residence's conditions (eg type of ownership, the number of rooms), and levels of education. Participants were divided into five WSI quintiles, ranging from the lowest to the highest (1st to 5th quintile, respectively). The participants' dietary intake was assessed using a food frequency questionnaire (FFQ), which they were asked to complete. The FFQ was designed as a semi-quantitative, interviewer-administered questionnaire with 130 items, enquiring about participants' usual intake of each food item over the past year. Participants reported their daily, weekly, monthly, or yearly use of each item, as well as the portion consumed each time, based on portion sizes applicable to each item. Actual dishes, cups, and utensils, as well as several portion size models, were

shown to participants for a more precise portion size estimation. In addition, a 64-picture album (21) including standard portions of bread, fruits, and vegetables, was used whenever needed. We used Metabolic Equivalent of Task (MET) as a criterion for measuring physical activity levels. MET shows the amount of energy consumed by each person based on their weight. For instance, one MET is the amount of oxygen consumed per kilogram of body weight per minute by each resting person, that is 3.5 ml of oxygen. And therefore, four MET equals 14 milliliters of oxygen used per kilogram of body weight per minute. We measured the activity levels of each participant by using this criterion.

Smokers were defined as participants who continuously smoked at least one cigarette per day for more than six months. Ex-smokers were considered as participants who had stopped smoking at least a year before, and non-smokers were considered as participants who had never smoked. Other tobacco smokers were considered as participants who smoked other tobacco products. Participants were divided into three categories based on their alcohol consumption; non-drinkers (participants who had never consumed alcohol), experienced/ex-drinkers (participants who had previously consumed alcohol but had stopped), and drinkers (participants who regularly consumed alcohol).

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Biochemical measurements

Blood samples were collected from every individual after an overnight fast of 12 hours. Fasting blood sugar (FBS), serum triglyceride (TG), and high-density lipoprotein (HDL) were determined using a commercial kit (Pars Azmoon, Tehran). (19)

Anthropometric measurements

We used a mounted tape for measuring the height to the nearest 1 mm. Weight was measured with light clothing and without using shoes with a Seca scale to the nearest 0.1 kg. Body Mass Index (BMI) was calculated by dividing weight (kg) by the square of height (m) and presented as kg/ m^2. The waist circumference (WC) was measured according to NIH guidelines. Female individuals with WC ≥88 cm and male individuals with WC of ≥ 102 cm were considered abdominally obese. (22)

Blood pressure measurements

The blood pressure was measured two times in each arm in the sitting position and according to Persian cohort protocol. (19) The individuals rested for ten minutes between each measurement. The blood pressure of every individual was calculated as the average of the two measurements in each arm.

Cardiometabolic phenotypes and Metabolic syndrome definition

We defined Mets according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATPIII) criteria. (4) According to these criteria, MetS is defined by the presence of three or more of the followings: Fasting blood glucose

≥100 mg/dl or drug treatment for elevated blood glucose; HDL cholesterol less than 40 mg/dl in men or less than 50 mg/dl in women or drug treatment for low HDL; blood triglycerides ≥ 150 mg/dl or drug treatment for elevated triglycerides; waist circumference greater than 102 cm in men or greater than 88 cm in women; systolic blood pressure ≥130 and/or diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension.

We considered the cut-off point for Body Mass Index (BMI) to be 25 kg/m^2 for overweight and obese participants. (23)

In this study, we categorized the subjects into four CMPs based on their BMI and the presence of MetS. The categories include:

1. Obese individuals who fulfill MetS criteria, called the MUHO
2. Obese individuals who do not fulfill MetS criteria, called the MHO
3. Normal-weight individuals who fulfill MetS criteria, called the MUHN
4. Normal-weight individuals who do not fulfill MetS criteria, called the MHN

Measuring DII and DIL

The Food Insulin Index (FII) is a measure of the area under the curve of increasing insulin over 2 hours after consumption of a 1000-kJ (239 kcal) portion of a test food, divided by the area under the curve after consumption of a 1000-kJ (239 kcal) portion of a reference food. The insulin index for 68 food items was collected from studies by Holt et al (15), Bao et al (24), and Bell et al (25). Salt, tea, and coffee were considered to have an insulin index of zero due to their low carbohydrate,

protein, fat, and energy content. For the remaining 49 food items that were not included in the food lists of the aforementioned studies, the FII of similar food items was used taking into account the similarity of their energy, carbohydrate, protein, fat, and fiber content. For example, since both dates and raisins are dried fruits and have comparable nutritional content, the insulin index of raisins was used for dates. To calculate DIL, the insulin load of each food was determined using the following formula: Insulin load of a given food = insulin index of that food × energy content per 1 g of that food × amount of that food consumed (g/d). By summing up the insulin load of each food, DIL was obtained for each participant. DII for each participant was then determined by dividing DIL by total energy intake.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 11.5, Chicago, IL). Descriptive statistics were obtained for all study variables and reported as mean ± SD, as well as number (percentage) where applicable. The $\chi 2$ test was used to compare nominal qualitative variables in different cardiometabolic groups and the Kruskal-Wallis test was used for comparing ordinal qualitative variables in different cardiometabolic groups. A one-way ANOVA test was used to compare mean values amongst different cardiometabolic groups. Multinomial logistic regression analysis was used to estimate crude and adjusted odds ratios (OR) and their corresponding 95% confidence intervals (95% CIs). Mets components (hypertension, high FBS, Hypo-HDL, cholesterolemia, hypertriglyceridemia, and abdominal obesity), Insulin Index, and Dietary Insulin Load

were considered independent variables. Each variable was introduced in the model one by one, and the effect of confounding factors (age, gender, educational level, marital status, current smoking status, and frame size) was adjusted. The MHN group was considered as the reference group. Statistical significance was considered at a *P* value <0.05.

the STROBE cross-sectional checklist was used when writing our report (26).(26)

Results

Participants' characteristics

Table 1 presents the baseline characteristics of participants according to their cardiometabolic phenotypes (CMPs), while Tables 2 and 3 present the same characteristics for both genders.

Table1: General characteristics of participants stratified by cardiometabolic phenotypes

	Cardiometabolic Phenotype					P value
	MHN(n=2948)	MUHN(n=240)	MHO(n=6870)	MUHO(n=4824)		
	N(%)	N(%)	N(%)	N(%)		
Gender						*<0.001
Male	1820(61.7)	106(44.2)	3136(45.6)	1604(33.3)		
Female	1128(38.3)	134(55.8)	3734(54.4)	3220(66.7)		
Marital status						*<0.001
Not married	218(7.4)	20(8.3)	401(5.8)	441(9.1)		
Married	2730(92.6)	220(91.7)	6469(94.2)	4383(90.9)		
Education level						**<0.001
Illiterate	387(13.1)	60(25)	898(13.1)	1128(23.4)		
Primary school	1040(35.3)	73(30.4)	2747(40)	1956(40.5)		
Diploma	1180(40)	87(36.3)	2562(37.3)	1451(30.1)		

University	341(11.6)	20(8.3)	663(9.7)	289(6)		
Physical activity level (METs¶)						**<0.001
Low	816(27.7)	88(36.7)	2110(30.7)	1958(40.6)		
Moderate	851(28.9)	83(34.6)	2353(34.3)	1665(34.5)		
High	1281(43.5)	69(28.7)	2407(35)	1201(24.9)		
Quintiles of wealth index						**<0.001
1 (poorest)	758(25.7)	51(21.3)	1402(20.4)	1232(25.5)		
2	470(15.9)	39(16.3)	1097(43.6)	909(18.8)		
3	564(19.1)	62(25.8)	1452(21.1)	949(19.7)		
4	597(20.3)	37(15.4)	1570(22.9)	902(18.7)		
5 (richest)	559(19)	51(21.3)	1349(19.6)	832(17.2)		
Current Smoking status						**<0.001
No smoker	1930(65.5)	176(73.3)	5276(76.8)	3922(81.3)		
Ex-Smoker	238(8.1)	17(7.1)	608(8.9)	373(7.7)		
Smoker	727(24.7)	44(18.3)	843(12.3)	451(9.3)		
Smokers of other tobacco products(water pipe, hookah, pipe,..)	53(1.8)	3(1.3)	143(2.1)	78(1.6)		
Secondhand smoking	1256(42.6)	104(43.3)	3205(46.7)	2433(50.4)		*<0.001
Alcohol consumption						**<0.001
No	2561(86.9)	216(90)	6247((90.9)	4452(92.3)		
Experiment	296(10)	17(7.1)	482(7)	276(5.7)		
Limit time (for treatment	3(0.1)	0	7(0.1)	6(0.1)		
Ex-drinker	9(0.3)	0	24(0.3)	8(0.2)		
drinker	79(2.7)	7(2.9)	110(1.6)	82(1.7)		
Insulin load						**<0.001
1th	561(19)	97(40.4)	1503(21.9)	1545(32)		
2nd	685(23.2)	64(26.7)	1747(25.4)	1233(25.6)		
3rd	794(26.9)	45(18.8)	1778(25.9)	1105(22.9)		
4th	908(30.8)	34(14.2)	1842(26.8)	941(19.5)		
Insulin index						**<0.001
1th	577(19.6)	97(40.4)	1507(21.9)	1524(31.6)		
2nd	703(23.8)	56(23.3)	1690(24.6)	1272(26.4)		
3rd	761(25.8)	59(24.6)	1831(26.7)	1078(22.3)		

4th	907(30.7)	28(11.7)	1842(26.8)	950(19.7)		
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**		
Age (years)	48.68±9.75	55.36±9.03	48.06±8.81	52.09±8.98		***<0.001
Height (cm)	165.40±9.51	161.66±9.26	162.36±9.29	160.43±9.27		***<0.001
Weight (kg)	61.86±8.54	61.93±7.94	77.98±11.30	82.23±13.19		***<0.001
Waist circumference (cm)	80.98±7.22	87.21±6.36	94.97±8.83	101.77±9.14		***<0.001
Hip circumference (cm)	95.42±4.86	95.19±4.59	105.94±7.28	108.40±8.61		***<0.001
Dietary insulin index	54.89±19.43	47.95±9.24	53.42±18.46	50.78±16.52		***<0.001
Dietary insulin load	157907.35±84258.16	121546.75±61228.21	150506.01±80295.64	135191.32±72140.76		***<0.001
Energy intake (kcal)	2831.29±911.44	2476.97±875.68	2768.65±885.93	2611.62±859.49		***<0.001

; ¶METs: the metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

Table 2: General characteristics of participants stratified by cardiometabolic phenotypes in male participants

	Cardiometabolic Phenotype				
	MHN (n=1820)	**MUHN (n=106)**	**MHO (n=3136)**	**MUHO(n=1604)**	P value
	N(%)	**N(%)**	**N(%)**	**N(%)**	
Male					
Marital status					*0.01
Not married	34(1.9)	1(0.9)	28(0.9)	16(1)	
Married	1786(98.1)	105(99.1)	3108(99.1)	1588(99)	
Education level					**0.39
Illiterate	170(9.3)	9(8.5)	252(8)	152(9.5)	
Primary school	659(36.2)	34(32.1)	1158(36.9)	591(36.8)	
Diploma	773(42.5)	51(48.1)	1313(41.9)	681(42.5)	
University	218(12)	12(11.3)	413(13.2)	180(11.2)	

Physical activity level (METs¶)					**<0.001
Low	462(25.4)	35(33)	927(29.6)	617(38.5)	
Moderate	334(18.4)	24(22.6)	621(19.8)	340(21.2)	
High	1024(56.3)	47(44.3)	1588(50.6)	647(40.3)	
Quintiles of wealth index					**<0.001
1 (poorest)	408(22.4)	11(10.4)	505(16.1)	259(16.1)	
2	304(16.7)	17(16)	472(15.1)	259(16.1)	
3	351(19.3)	32(30.2)	683(21.8)	347(21.6)	
4	369(20.3)	16(15.1)	702(22.4)	326(20.3)	
5 (richest)	388(21.3)	30(28.3)	774(24.7)	413(25.7)	
Current Smoking status					**<0.001
No smoker	819(45)	44(41.5)	1578(50.3)	745(46.4)	
Ex-Smoker	234(12.8)	15(14.2)	591(18.8)	358(22.3)	
Smoker	717(39.4)	44(41.5)	831(26.5)	434(27.1)	
Smokers of other tobacco products(water pipe, hookah, pipe,..)	50(2.7)	3(2.8)	136(4.3)	67(4.2)	
Secondhand smoking	750(41.2)	35(33)	1371(43.7)	722(45)	*0.02
Alcohol consumption					**0.3
No	1440(79.1)	82(77.4)	2552(80.4)	1243(77.5)	
Experiment	290(15.9)	17(16)	476(15.2)	269(16.8)	
Limit time (for treatment	3(0.2)	0	6(0.2)	5(0.3)	
Ex-drinker	9(0.5)	0	22(0.7)	7(0.4)	
drinker	78(4.3)	7(6.6)	110(3.5)	80(29.1)	
Insulin load					**<0.001
1th	166(9.1)	23(21.7)	240(7.7)	200(12.5)	
2nd	358(19.6)	27(25.5)	607(19.4)	338(21.1)	
3rd	552(30.3)	31(29.2)	946(30.2)	472(29.4)	
4th	744(40.9)	25(23.6)	1343(42.8)	594(37)	
Insulin index					**<0.001
1th	250(13.7)	30(28.3)	435(13.9)	313(19.5)	
2nd	403(22.1)	28(26.4)	719(22.9)	439(27.4)	
3rd	517(28.4)	28(26.4)	955(30.5)	424(26.4)	
4th	650(35.7)	20(18.9)	1027(32.7)	428(26.7)	

	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	
Age (years)	49.71±9.61	55.15±8.85	49.23±9.04	52.01±8.97	***<0.001
Height (cm)	170.61±7.00	169.29±6.35	169.78±6.63	170.35±6.33	***<0.001
Weight (kg)	65.48±7.58	67.76±6.17	82.66±9.94	90.27±11.94	***<0.001
Waist circumference (cm)	82.85±6.95	89.20±5.58	97.82±7.37	105.26±8.33	***<0.001
Hip circumference (cm)	95.58±4.65	96.11±4.09	104.05±5.30	107.11±6.33	***<0.001
Dietary insulin index	56.44±19.27	50.20±9.74	55.38±17.39	53.10±15.33	***<0.001
Dietary insulin load	178265.37±91953.88	146325.32±68338.32	179204.06±88164.46	169201.99±83857.36	***<0.0001
Energy intake (kcal)	3109.21±919.32	2850.34±919.82	3192.65±931.32	3132.97±961.05	***<0.001

; ¶METs: the metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

Table 3: General characteristics of participants stratified by cardiometabolic phenotypes in female participants

	Cardiometabolic Phenotype				
	MHN (n=1128)	**MUHN (n=134)**	**MHO (n=3734)**	**MUHO(n=3220)**	
	N(%)	**N(%)**	**N(%)**	**N(%)**	
Female					
Marital status					*<0.001
Not married	184(16.4)	19(14.2)	373(10)	425(13.2)	
Married	944(83.7)	115(85.8)	3361(90)	2795(86.8)	
Education level					**<0.001
Illiterate	217(19.2)	51(38.1)	646(17.3)	976(30.3)	
Primary school	381(33.8)	39(29.1)	1589(42.5)	1365(42.4)	
Diploma	407(36)	36(26.9)	1249(33.5)	770(23.9)	
University	123(10.9)	8(6)	250(6.7)	109(3.4)	
Physical activity level (METs¶)					**<0.001
Low	354(31.4)	53(39.6)	1183(31.7)	1341(41.6)	
Moderate	517(45.8)	59(44)	1732(46.4)	1325(41.1)	
High	257(22.7)	22(16.4)	819(21.9)	554(17.2)	

Quintiles of wealth index					**<0.001
1 (poorest)	350(30.9)	40(29.9)	897(24)	973(30.2)	
2	166(14.8)	22(16.4)	625(16.7)	650(20.2)	
3	213(18.8)	30(22.4)	769(20.6)	602(18.7)	
4	228(20.2)	21(15.7)	868(23.2)	576(17.9)	
5 (richest)	171(15.2)	21(15.7)	575(15.4)	419(13)	
Current Smoking status					**0.21
No smoker	1111(98.5)	132(98.5)	3698(99)	3177(98.7)	
Ex-Smoker	4(0.4)	2(1.5)	17(0.5)	15(0.5)	
Smoker	10(0.9)	0	12(0.3)	17(0.5)	
Smoker other tobacco products(water pipe, hookah, pipe,..)	3(0.3)	0	7(0.2)	11(0.3)	
Secondhand smoking	506(12.3)	69(51.5)	1834(49.1)	1711(53.1)	*<0.001
Alcohol consumption					**0.65
No	1121(99.4)	134(100)	3725(99.8)	3209(99.7)	
Experiment	6(0.5)	0	6(0.2)	7(0.2)	
Limit time (for treatment	0	0	1(0.	1(0.02)	
Ex-drinker	0	0	2(0.1)	1(0.02)	
drinker	1 (0.1)	0	0	2(0.1)	
Insulin load					**<0.001
1th	395(35)	74(55.2)	1263(33.8)	1345(41.8)	
2nd	327(29)	37(27.6)	1140(30.5)	895(27.8)	
3rd	242(21.4)	14(10.4)	832(22.3)	633(19.7)	
4th	164(14.5)	9(6.7)	499(13.4)	347(10.8)	
Insulin index					**<0.001
1th	327(29)	67(50)	1072(28.7)	1211(37.6)	
2nd	300(26.6)	28(20.9)	971(26)	833(25.9)	
3rd	244(21.6)	31(23.1)	876(23.5)	654(20.3)	
4th	257(22.7)	8(6)	815(21.8)	522(16.2)	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	
Age (years)	47.01±9.75	55.52±9.21	47.07±8.49	52.13±8.98	***<0.001
Height (cm)	157.01±6.58	155.63±6.25	156.12±	155.49±5.94	***<0.001

Weight (kg)	56.02±6.54	57.32±5.89	74.04±10.87	78.23±11.90	***<0.001
Waist circumference (cm)	77.97±6.62	85.63±6.52	92.57±9.24	100.03±9.03	***<0.001
Hip circumference (cm)	95.16±5.30	94.45±4.84	107.54±8.27	109.04±9.48	***<0.001
Dietary insulin index	52.35±19.40	46.17±8.44	51.78±19.16	49.62±16.96	***<0.001
Dietary insulin load	124898.66±56090.32	101945.79±46619.43	126403.94±63741.27	118249.36±585855.05	***<0.001
Energy intake (kcal)	2381.77±693.49	2165.50±708.04	2412.56±661.78	2351.92±666.32	***<0.001

; ¶METs: the metabolic equivalent of task

*P value: chi-square test ; ** P value :kruskal –Wallis; *** P value :One Way ANOVA

The ratio of married participants was significantly higher in both genders (Tables 2 and 3). Education levels, regardless of gender, and in female participants, were lower in the MUHO phenotype group (p<0.001), but education levels in male participants showed no significant differences (p<0.39). Physical activity was significantly lower in metabolically unhealthy participants in both genders (both MUHN and MUHO) (p<0.001). Assessing the quintiles of WSI in all participants (Table 1) and female participants (Table 3) showed that the MUHO were mostly among the 1st quintile of WSI (p<0.001), whereas in male participants (Table 2), the MUHO phenotype was associated with higher income (p<0.001). Interestingly, the mean energy intake of each unhealthy CMP was lower than the mean energy intake of the corresponding healthy CMP. For instance, the mean energy intake of MUHN participants was 2850.34±919.82, whereas it was 3109.21±919.32 in MHN participants. Moreover, the frequency of alcohol consumption and smoking was significantly higher in MHN participants than in

MUHO participants (p<0.001). On the other hand, the percentage of secondhand smokers was significantly higher in MUHO participants than in MHN ones, both regardless and according to their gender (Tables 1 and 2) (p<0.001). The mean values of age, BMI, and waist circumference showed incremental trends from being in a healthy phenotype (whether normal weight or obese) to an unhealthy phenotype. ($p \leq 0.001$) (Tables 1 and 2). Hip circumference was lower in the MHN than in the MHO and MUHO. (p<0.001).

Relationship between Cardiometabolic Phenotypes and Dietary Insulin Load and Index:

The frequency of Insulin load and index quartiles showed a significant decrease from the 1st to 4th quartile in metabolically unhealthy participants (Both MUHN and MUHO) ($p \leq 0.001$).

Unexpectedly, the mean values of the Dietary Insulin Index and Dietary Insulin Load showed to be higher in metabolically healthy phenotypes than in unhealthy ones, with the MUHN phenotype being the lowest (p<0.001). In addition, the mean value of energy intake was lower in metabolically unhealthy phenotypes compared to their corresponding healthy phenotypes, with the MUHN consuming the lowest energy intake (p<0.001) (Table 1). This trend was seen both regardless of the participants' gender, (Table 1) and in male or female participants divided (Tables 2 and 3).

The findings of the unadjusted model indicated that compared to the 1st DIL quartile, the risks of MUHN and MUHO in the 4th DIL quartile decreased by 0.21 (0.14 - 0.32) and 0.37 (0.33 – 0.43), respectively (Table 4).

Table4: Association between cardiometabolic phenotype and across quartiles of DIL and DIL scores of Azar cohort population

	Quartiles of DIL				Quartiles of DII			
	1 (n=3711)	2 (n=3730)	3 (n=3725)	4 (3726)	1 (n=3708)	2 (n=3726)	3 (n=3730)	4 (3728)
Q rang	≤99828.05	99828.06-129348.53	129348.54-171278.60	>171278.61	≤44.43	44.44-48.64	48.65-55.29	>55.30
Crude								
MUHN	Reference	0.54(0.38-0.75)	0.32(0.22-0.47)	0.21(0.14-0.32)	Reference	0.47(0.33-0.66)	0.46(0.32-0.64)	0.18(0.11-0.28)
MHO	Reference	0.95(0.83-1.08)	0.83(0.73-0.95)	0.76(0.67-0.86)	Reference	0.91(0.80-1.04)	0.92(0.81-1.04)	0.77(0.68-0.88)
MUHO	Reference	0.65(0.57-0.75)	0.50(0.44-0.57)	0.37(0.33-0.43)	Reference	0.68(0.59-0.77)	0.53(0.47-0.61)	0.39(0.34-0.45)
MUHN								
Model 1	Reference	0.66(0.46-0.93)	0.45(0.30-0.67)	0.34(0.22-0.53)	Reference	0.59(0.410.84)	0.58(0.41-0.83)	0.24(0.15-0.37)
Model2	Reference	061(0.42-0.90)	0.38(0.23-0.62)	0.23(0.12-0.47)	Reference	0.57(0.40-0.81)	0.57(0.40-0.82)	0.24(0.15-0.37)
MHO								
Model1	Reference	1.05(0.91-1.20)	1.03(0.90-1.18)	1.04(0.90-1.20)	Reference	0.97(0.85-1.11)	1.03(0.90-1.17)	0.88(0.78-1.01)
Model2	Reference	1.01(0.87-1.16)	0.94(0.80-1.09)	0.85(0.74-1.04)	Reference	0.91(0.80-1.04)	0.94(0.82-1.07)	0.80(0.70-0.91)
MUHO								
Model1	Reference	0.88(0.76-1.01)	0.85(0.74-0.99)	0.80(0.69-0.93)	Reference	0.86(0.75-0.99)	0.74(0.64-0.85)	0.57(0.50-0.66)
Model2	Reference	0.48(0.38-0.59)	0.65(0.55-0.76)	0.772(0.66-0.89)	Reference	0.77(0.67-0.89)	0.64(0.56-0.74)	0.48(0.42-0.561)
Male								
Crude								

MUHN	Reference	0.54(0.30-0.97)	0.40(0.23-0.71)	0.24(0.13-0.43)	Reference	0.57(0.33-0.99)	0.45(0.26-0.77)	0.25(0.14-0.46)
MHO	Reference	1.17(0.92-1.48)	1.18(0.94-1.48)	1.24(1.00-1.54)	Reference	1.02(0.83-1.24)	1.06(0.87-1.28)	0.90(0.75-1.09)
MUHO	Reference	0.66(0.52-0.83)	0.70(0.55-0.90)	0.78(0.60-1.01)	Reference	0.86(0.70-1.07)	0.65(0.53-0.80)	0.52(0.42-0.64)
MUHN								
Model 1	Reference	0.56(0.31-1.02)	0.44(0.25-0.79)	0.28(0.15-0.52)	Reference	0.64(0.37-1.11)	0.46(0.27(0.80)	0.27(0.15-0.50)
Model2	Reference	0.49(0.26-0.92)	0.34(0.17-0.69)	0.17(0.06-0.46)	Reference	0.66(0.38-1.14)	0.50(0.29-0.86)	0.30(0.16-0.55)
MHO								
Model1	Reference	1.12(0.88-1.42)	1.10(0.88-1.39)	1.16(0.93-1.45)	Reference	0.99(0.81-1.21)	1.01(0.84-1.22)	0.86(0.71-1.03)
Model2	Reference	1.05(0.82-1.35)	0.98(0.76-1.26)	0.93(0.70-1.24)	Reference	0.98(0.80-1.19)	0.99(0.81-1.20)	0.82(0.68-1)
MUHO								
Model1	Reference	0.78(0.60-1.01)	0.72(0.56-0.92)	0.70(0.55-0.89)	Reference	0.89(0.72-1.11)	0.65(0.53-0.81)	0.53(0.43-0.65)
Model2	Reference	0.68(0.52-0.89)	0.55(0.42-0.73)	0.41(0.30-0.57)	Reference	0.89(0.71-1.11)	0.64(0.52-0.80)	0.51(0.41-0.63)
Female								
Crude								
MUHN	Reference	0.60(0.39-0.92)	0.31(0.17-0.56)	0.29(0.14-0.60)	Reference	0.45(0.28-0.72)	0.62((0.39-0.98)	0.15(0.07-0.32)
MHO	Reference	1.09(0.92-1.29)	1.08(0.90-1.30)	0.95(0.77-1.18)	Reference	0.98(0.82-1.17)	1.09(0.91-1.32)	0.97(0.80-1.17)
MUHO	Reference	0.80(0.68-0.95)	0.77(0.64-0.93)	0.62(0.50-0.77)	Reference	0.74(0.62-0.89)	0.72(0.60-0.87)	0.55(0.45-0.66)
MUHN								
Model 1	Reference	0.77(0.50-1.18)	0.43(0.23-0.78)	0.42(0.20-0.88)	Reference	0.55(0.34-0.89)	0.78(0.49-1.25)	0.18(0.08-0.39)
Model2	Reference	0.66(0.40-1.10)	0.33(0.15-0.70)	0.29(0.11-0.78)	Reference	0.57(0.35-0.92)	0.82(0.51-1.31)	0.19(0.09-0.41)
MHO								
Model1	Reference	1.06(0.90-1.26)	1.06(0.88-1.28)	0.95(0.6-1.17)	Reference	0.96(0.808-1.15)	1.07(0.89-1.30)	0.95(0.78-1.14)
Model2	Reference	0.98(0.81-1.19)	0.92(0.73-1.18)	0.77(0.57-1.05)	Reference	0.95(0.8-1.14)	1.06(0.88-1.29)	0.93(0.77-1.13)
MUHO								

Model1	Reference	0.95(0.80-1.13)	0.96(0.79-1.17)	0.81(0.64-1..01)	Reference	0.84(0.70-1.01)	0.84(0.69-1.02)	0.62(0.51-0.76)
Model2	Reference	0.78(0.64-0.95)	0.67(0.52-0.86)	0.47(0.34-0.66)	Reference	0.83(0.69-1.00)	0.83(0.68-1.01)	0.60(0.49-0.74)

MHL was considered as a reference group; Model 1: adjusted for age, gender, education level, WSI; Model 2 adjusted for age, gender, MET, Energy intake. Adjusted for gender where appropriate

After adjustment for different intervening factors (i.e. age, gender, education, MET, and energy intake), a strong negative correlation was observed between DIL and MUHN and MUHO. However, there were no significant correlations between DIL and MHO after the adjustments. (Table 4). The aforementioned negative correlation was more obvious in the 4th DIL quartile. In Model 2, the observed odds ratio for MUHN was 0.61 (0.42 – 0.90) in the 2nd DIL quartile, while it was 0.23 (0.12 – 0.47) in the 4th DIL quartile. (Table 4).

The findings of the unadjusted model for the DII quartiles indicated that compared to the 1st DII quartile, the risks of MUHN and MUHO in the 4th DII quartile decreased by 0.18 (0.11 - 0.28) and 0.39 (0.34 – 0.45), respectively (Table 4). After adjustment for the same intervening factors as DIL quartiles, a strong negative correlation was observed between DII and MUHN and MUHO. However, there was no significant correlation between DII and MHO after the adjustments. (Table 4). The aforementioned negative correlations were more obvious in the 4th DII quartile. In Models 1 and 2, the observed odds ratios for MUHN were 0.59 (0.41 – 0.84) and 0.57 (0.40-0.81), respectively, in the 2nd DII quartile, while they were both 0.24 (0.15 – 0.37) in the 4th DII quartile. (Table 4).

These models were also run for both male and female participants separately. The results in both genders were overall the same as in all participants combined.

Discussion

This cross-sectional study examined the association between DII and DIL and different CMPs. The findings indicated that there is a significant negative correlation between DII and DIL and MUHN and MUHO phenotypes, both before and after considering confounding variables. Our findings demonstrated no significant correlation between DIL and DII and MHO. The prevalence of chronic conditions such as MetS has increased in recent years. (2)(27) Previous studies indicate a significant positive association between insulin resistance and unhealthy cardiometabolic status. (28) One of the main causes of insulin resistance is the tendency towards diets with high insulinemic capability. (24)(29) Thus, it is of great importance to establish a reliable index to demonstrate the insulinemic potential of individuals' diets. Since DII and DIL directly depend on insulin response to food, there has been an increase in attention to these two indices in evaluating the aforementioned potential. (12)(24) By measuring these two indices in different populations, we can search for an association between these two indices and different CMPs and deduce whether we can use DII and DIL to predict the odds of unhealthy CMPs or not. To the best of our knowledge, this is the first study attempting to answer this question and evaluate this association in different CMPs. Our study found a correlation between unhealthy CMPs and lower DIL and DII values. Furthermore, high DIL and DII values were associated with lower odds of

unhealthy CMPs (both MUHN and MUHO). The trend of odds ratio in metabolically healthy phenotypes was not significant. We can conclude these findings in two different ways.

Firstly, the correlation between lower DIL and DII with unhealthy CMPs may be explained by the fact that the mean energy intake in unhealthy phenotypes was lower than in healthy phenotypes. This finding suggests that the participants with unhealthy phenotypes may have restricted their energy intake to lose weight and modify their lifestyle behavior, thereby lowering the insulinemic potential of their diet (i.e., lowering their DII and DIL). Additionally, our findings demonstrate that alcohol consumption and smoking were also lower in metabolically unhealthy phenotypes. This supports the speculation that participants with unhealthy phenotypes were following a lifestyle modification plan that included changes in their diet, smoking, and alcohol consumption. This modification could be the reason for the lower DII and DIL values observed in unhealthy phenotypes. Therefore, we suggest that measuring DII and DIL may not be a reliable index for predicting CMPs and the risk of developing chronic diseases. Further studies are needed to take recent lifestyle modifications into account and determine the associations between DII and DIL with CMPs in participants who have not had a recent lifestyle modification, specifically modifications in their diets.

Secondly, the insignificant trend of odds ratio in metabolically healthy phenotypes suggests that insulin resistance may not be easily assessed and predicted by simply

measuring indices such as DII and DIL since insulin secretion depends on various components, including the participant's diet, neural, and hormonal activity. (30)

In accordance with our findings, Karimbeiki et al demonstrated that a higher insulinemic effect of diet was not associated with increased obesity rates. (31) Anjom-Shojaei et al found in their study that a high DII was not linked to obesity in men, but it was in women. (17) Another cross-sectional study, involving 262 participants of the Dortmund Nutritional and Anthropometric Longitudinally Designed Study, discovered that a higher DII and DIL were correlated with higher body fat percentage, but not a higher BMI. (32) Conversely, a cross-sectional study on 203 overweight/obese adolescents showed that a diet with higher DII and DIL was associated with higher odds of being in the MUHO group. (33) Additionally, a study on the Shahidieh cohort showed that a higher DII was linked with a higher risk of metabolic syndrome in women, but no such connection was found in men (27) In a clinical trial with a Mediterranean-style diet, children and adolescents with obesity exhibited healthier cardiometabolic profiles, lower body weight, lower BMI and fat mass, and lower blood glucose and lipids (34) A cross-sectional study on 137 European overweight and obese adolescents in their puberty also supported the aforementioned study, indicating that a Mediterranean diet was related to a reduced risk of the MUHO phenotype (35) A cross-sectional study conducted on both overweight and normal-weight Turkish children revealed that breakfast and dinner with a higher DII and DIL were associated with a higher odds ratio of being overweight (36) Two other studies were investigating the correlation between DII

and DIL with diabetes, and cardiovascular disease respectively. The first study concluded that a higher DII and DIL of the diet were associated with a higher risk of diabetes, and DIL was a better predictor for diabetes compared to DII. (37) The other study demonstrated that DII and DIL were not associated with the risk of CVD,(38) which is in line with our findings. In the current study, we demonstrated that DII and DIL were strongly correlated with a decreased odds ratio of MUHN and MUHO and that there was no significant correlation between DIL and DII, and MHO.

Previous studies suggest several mechanisms that explain the correlation between DII and DIL with unhealthy CMPs. Highly insulinemic diets can cause insulin secretion, which increases the oxidation of carbohydrates and decreases the oxidation of lipids. This, in turn, leads to excess abdominal fat storage and a higher risk of obesity and unhealthy CMPs. (33) Furthermore, highly insulinemic diets potentially cause faster carbohydrate digestion and absorption, leading to higher blood glucose and insulin levels. They also result in a rapid drop in post-prandial blood glucose levels after the surge, which can reduce satiety and lead to a high-calorie intake of food, causing abdominal obesity and unhealthy CMPs. (39)(40) Finally, high DII and DIL are associated with a higher incidence of insulin resistance and diabetes. (37)(41)

Our study had several strengths. For the first time, we studied the associations between DII and DIL with four different CMPs, which were organized based on the presence or absence of obesity, and the presence or absence of MetS. This model helped assess the data in a more organized pattern. Additionally, we took into

account the effect of confounding factors while analyzing the data. Another strength of this study was its large population, as we conducted our study on just under 15000 participants. However, there were some limitations during the conduction of this study that should be considered while evaluating the results. Since this was a cross-sectional study, we could not establish a cause-and-effect correlation. More prospective studies are needed to establish and assert such causality. Another limitation was recall bias. The most frequently used tool to assess the dietary habits of participants in epidemiological studies is the FFQ. However, there is always a recall bias when using this tool. Even though we analyzed the data with the confounding factors taken into account, still some confounding factors, including dietary habits, psychological factors, parental obesity, and family history of cardiometabolic diseases, were not assessed. We suggest two possible reasons for our observations. First, despite the presumed belief that increased insulin secretion is correlated with increased rates of different metabolic abnormalities, genetic data, as opposed to epidemiological data, suggest that this correlation may be overrated. Elevated insulin secretion could even be beneficial. (42)(43) Secondly, considering our findings demonstrated that participants with unhealthy CMPs had lower energy intake and alcohol consumption, and a lower smoking rate, it is presumable that some may have changed their lifestyle behavior. This presumed lifestyle behavior change can be the main reason for DII and DIL being associated with a lower odds ratio of unhealthy CMPs. This finding highlights the importance of considering recent lifestyle behavior change as a confounding factor, and further studies are needed to evaluate the association between DII and DIL with different CMPs in participants

with no recent lifestyle behavior change or evaluate this association while taking the aforementioned confounding factors into account. Furthermore, further studies can observe participants with healthy CMPs and look into possible eventual shifts to unhealthy CMPs. Genetic factors can also be studied to evaluate the correlation between elevated insulin secretion and CMPs.

Conclusion

This current cross-sectional study demonstrated that DII and DIL were strongly correlated with a decreased odds ratio of MUHN and MUHO. There was no significant correlation between DIL and DII and MHO. As mentioned before, we speculate that a lower energy intake in participants with unhealthy cardiometabolic phenotypes, as a result of lifestyle behavior change, was the main reason for this observation. To better investigate causality and establish the temporal relationship between DII and DIL with different CMPs, further studies are required, specifically with a prospective design. These studies should assess the correlation between DII and DIL with different CMPs in participants who have not undergone recent lifestyle changes, in order to confirm our main speculation.

Acknowledgments:

The authors are grateful for the financial support of the liver and gastrointestinal diseases research center, at Tabriz University of Medical Sciences. The authors also are deeply indebted to all subjects who participated in this study. We appreciate the contribution of the investigators and the staff of the AZAR cohort study. We thank

the close collaboration of the Shabestar health center. In addition, we would like to thank the Persian cohort study staff for their technical support. We would like to appreciate the cooperation of the Clinical Research Development Unit of Imam Reza General Hospital, Tabriz, Iran in conducting this research.

Declaration

Ethics approval and consent to participate

This study was approved by the ethics committee of Tabriz University of medical sciences (IR.TBZMED.REC.1401.414)

Funding

This study was supported by the liver and gastrointestinal diseases research center (Grant number 700/108 on 14 March 2016), Tabriz University of Medical Sciences. The funder had no role in the study design, data analysis, interpretation, and writing the manuscript in this study.

Competing interests

The authors declare that they have no competing interests

Availability of data and materials

The data that support the findings of this study are available from [Vice Chancellor for Research] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are

however available from the authors upon reasonable request and with permission of [Vice Chancellor for Research]

Authors' contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *BMJ open.* E.F, SS.NI, and AM.N helped with the conception and design of the work. E.F, MH.S, N.P, and AM.N helped with the acquisition and analysis. E.F, MH.S, SS.NI, N.P, and AM.N interpreted the data, and E.F, N.P, and AM.N drafted the work and revised it. All authors have read and approved the manuscript.

References

1. Collaborators GBD 2015 O. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27.
2. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev. 2015;16(1):1–12.
3. Nolan PB, Carrick-Ranson G, Stinear JW, Reading SA, Dalleck LC. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: A pooled analysis. Prev Med reports. 2017;7:211–5.
4. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):1–8.
5. Goday A, Calvo E, Vázquez LA, Caveda E, Margallo T, Catalina-Romero C, et al. Prevalence and clinical characteristics of metabolically healthy obese

individuals and other obese/non-obese metabolic phenotypes in a working population: results from the Icaria study. BMC Public Health. 2016;16(1):1–14.
6. Osadnik K, Osadnik T, Lonnie M, Lejawa M, Reguła R, Fronczek M, et al. Metabolically healthy obese and metabolic syndrome of the lean: the importance of diet quality. Analysis of MAGNETIC cohort. Nutr J. 2020;19(1):1–13.
7. Ding C, Chan Z, Magkos F. Lean, but not healthy: the 'metabolically obese, normal-weight'phenotype. Curr Opin Clin Nutr Metab Care. 2016;19(6):408–17.
8. Wang B, Zhuang R, Luo X, Yin L, Pang C, Feng T, et al. Prevalence of metabolically healthy obese and metabolically obese but normal weight in adults worldwide: a meta-analysis. Horm Metab Res. 2015;47(11):839–45.
9. Jung CH, Lee MJ, Kang YM, Jang JE, Leem J, Hwang JY, et al. The risk of incident type 2 diabetes in a Korean metabolically healthy obese population: the role of systemic inflammation. J Clin Endocrinol Metab. 2015;100(3):934–41.
10. Eddy D, Schlessinger L, Kahn R, Peskin B, Schiebinger R. Relationship of insulin resistance and related metabolic variables to coronary artery disease: a mathematical analysis. Diabetes Care. 2009;32(2):361–6.
11. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol. 2013;3(1):1.
12. Nimptsch K, Brand-Miller JC, Franz M, Sampson L, Willett WC, Giovannucci E. Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers. Am J Clin Nutr. 2011;94(1):182–90.
13. Bell SJ, Sears B. Low-glycemic-load diets: impact on obesity and chronic diseases. 2003;
14. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr. 2000;71(6):1455–61.
15. Holt SH, Miller JC, Petocz P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. Am J Clin Nutr. 1997;66(5):1264–76.
16. Bao J, De Jong V, Atkinson F, Petocz P, Brand-Miller JC. Food insulin index: physiologic basis for predicting insulin demand evoked by composite meals. Am J Clin Nutr. 2009;90(4):986–92.
17. Anjom-Shoae J, Keshteli AH, Sadeghi O, Pouraram H, Afshar H, Esmaillzadeh A, et al. Association between dietary insulin index and load with obesity in adults. Eur J Nutr. 2020;59(4):1563–75.
18. Farhang S, Faramarzi E, Amini Sani N, Poustchi H, Ostadrahimi A, Alizadeh BZ, et al. Cohort profile: The AZAR cohort, a health-oriented research model in areas of major environmental change in Central Asia. Int J Epidemiol. 2019;48(2):382-382h.

19. Poustchi H, Eghtesad S, Kamangar F, Etemadi A, Keshtkar A-A, Hekmatdoost A, et al. Prospective epidemiological research studies in Iran (the PERSIAN Cohort Study): rationale, objectives, and design. Am J Epidemiol. 2018;187(4):647–55.
20. Eghtesad S, Mohammadi Z, Shayanrad A, Faramarzi E, Joukar F, Hamzeh B, et al. The PERSIAN cohort: providing the evidence needed for healthcare reform. Arch Iran Med. 2017;20(11):691–5.
21. Ghafarpour M, Kianfar H, Hoshyarrad A BB. Food Album. Natl Nutr Food Technol Res Institute ISBN 9786005040005.
22. Consultation WHO. Obesity: preventing and managing the global epidemic. World Health Organ Tech Rep Ser. 2000;894:1–253.
23. Somi MH, Nikniaz Z, Ostadrahimi A, Sadat ATE, Faramarzi E. Is normal body mass index a good indicator of metabolic health in Azar cohort population? J Cardiovasc Thorac Res. 2019;11(1):53.
24. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. Am J Clin Nutr. 2011;93(5):984–96.
25. Bell KJ, Petocz P, Colagiuri S, Brand-Miller JC. Algorithms to improve the prediction of postprandial insulinaemia in response to common foods. Nutrients. 2016;8(4):210.
26. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147(8):573–7.
27. Sadeghi O, Hasani H, Mozaffari-Khosravi H, Maleki V, Lotfi MH, Mirzaei M. Dietary Insulin Index and dietary insulin load in relation to metabolic syndrome: The Shahedieh cohort study. J Acad Nutr Diet. 2020;120(10):1672–86.
28. Okosun IS, Okosun B, Lyn R, Airhihenbuwa C. Surrogate indexes of insulin resistance and risk of metabolic syndrome in non-Hispanic White, non-Hispanic Black and Mexican American. Diabetes Metab Syndr Clin Res Rev. 2020;14(1):3–9.
29. Hsieh C-H, Wu C-Z, Hsiao F-C, Lin J-D, Li J-C, Wan H-L, et al. The impact of metabolic syndrome on insulin sensitivity, glucose sensitivity, and acute insulin response after glucose load in early-onset type 2 diabetes mellitus: Taiwan Early-Onset Type 2 Diabetes Cohort Study. Metabolism. 2008;57(11):1615–21.
30. Seino S, Shibasaki T, Minami K. Dynamics of insulin secretion and the clinical implications for obesity and diabetes. J Clin Invest. 2011;121(6):2118–25.
31. Karimbeiki R, Namkhah Z, Alipoor E, Yaseri M, Hosseinzadeh-Attar MJ. The relationship between low-carbohydrate diet score, dietary insulin index and load with obesity in healthy adults. Eat Weight Disord Anorexia, Bulim Obes. 2022;1–10.

32. Joslowski G, Goletzke J, Cheng G, Günther ALB, Bao J, Brand-Miller JC, et al. Prospective associations of dietary insulin demand, glycemic index, and glycemic load during puberty with body composition in young adulthood. Int J Obes. 2012;36(11):1463–71.
33. Hajhashemy Z, Mirzaei S, Asadi A, Akhlaghi M, Saneei P. Association of Dietary Insulin Index and Dietary Insulin Load With Metabolic Health Status in Iranian Overweight and Obese Adolescents. Front Nutr. 2022;9.
34. Velázquez-López L, Santiago-Díaz G, Nava-Hernández J, Muñoz-Torres A V, Medina-Bravo P, Torres-Tamayo M. Mediterranean-style diet reduces metabolic syndrome components in obese children and adolescents with obesity. BMC Pediatr. 2014;14(1):1–10.
35. Arenaza L, Huybrechts I, Ortega FB, Ruiz JR, De Henauw S, Manios Y, et al. Adherence to the Mediterranean diet in metabolically healthy and unhealthy overweight and obese European adolescents: the HELENA study. Eur J Nutr. 2019;58(7):2615–23.
36. Caferoglu Z, Erdal B, Akin L, Kurtoglu S. Breakfast and dinner insulin index and insulin load in relation to overweight in children and adolescents. Eur J Nutr. 2021;60(5):2819–29.
37. Teymoori F, Farhadnejad H, Moslehi N, Mirmiran P, Mokhtari E, Azizi F. The association of dietary insulin and glycemic indices with the risk of type 2 diabetes. Clin Nutr. 2021;40(4):2138–44.
38. Teymoori F, Farhadnejad H, Mirmiran P, Nazarzadeh M, Azizi F. The association between dietary glycemic and insulin indices with incidence of cardiovascular disease: Tehran lipid and glucose study. BMC Public Health. 2020;20(1):1–10.
39. Hellström PM. Satiety signals and obesity. Curr Opin Gastroenterol. 2013;29(2):222–7.
40. Zhu R, Larsen TM, Poppitt SD, Silvestre MP, Fogelholm M, Jalo E, et al. Associations of quantity and quality of carbohydrate sources with subjective appetite sensations during 3-year weight-loss maintenance: Results from the PREVIEW intervention study. Clin Nutr. 2022;41(1):219–30.
41. Mirmiran P, Esfandiari S, Bahadoran Z, Tohidi M, Azizi F. Dietary insulin load and insulin index are associated with the risk of insulin resistance: a prospective approach in tehran lipid and glucose study. J Diabetes Metab Disord. 2015;15(1):1–7.
42. Nguyen A, Khafagy R, Meerasa A, Roshandel D, Paterson AD, Dash S. Insulin Response to Oral Glucose and Cardiometabolic Disease: A Mendelian Randomization Study to Assess Potential Causality. Diabetes. 2022;71(9):1880–90.
43. Dwivedi OP, Lehtovirta M, Hastoy B, Chandra V, Krentz NAJ, Kleiner S, et al. Loss of ZnT8 function protects against diabetes by enhanced insulin secretion. Nat Genet. 2019;51(11):1596–606.

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of	7

		recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	8
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	9
Bias	#9	Describe any efforts to address potential sources of bias	9
Study size	#10	Explain how the study size was arrived at	8
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	12
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	12
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	#12e	Describe any sensitivity analyses	12
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	12
Participants	#13b	Give reasons for non-participation at each stage	12
Participants	#13c	Consider use of a flow diagram	n/a

Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	14
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	12
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
Main results	#16b	Report category boundaries when continuous variables were categorized	12
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13
Discussion			
Key results	#18	Summarise key results with reference to study objectives	15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	20
Generalisability	#21	Discuss the generalisability (external validity) of the study results	20
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

This checklist was completed on 13. September 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai