BMJ Open

Associations between Insulin Index and dietary insulin load with cardiometabolic phenotype in the AZAR cohort population in north-western Iran: a cross-sectional study

Elnaz Faramarzi, Mohammad Hossein Somi, Seyed Sina Naghibi Irvani, Nahid Pourhashem, Amir Mohammad Nourizadeh

To cite: Faramarzi E, Somi MH, Naghibi Irvani SS, *et al*. Associations between Insulin Index and dietary insulin load with cardiometabolic phenotype in the AZAR cohort population in north-western Iran: a cross-sectional study. *BMJ Open* 2023;**13**:e068303. doi:10.1136/bmjopen-2022-068303

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068303).

Received 13 September 2022
Accepted 04 April 2023

Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, East Azerbaijan, Iran (the Islamic Republic of)

Correspondence to
Dr Amir Mohammad Nourizadeh; Nourizadehamirmohammad@gmail.com

ABSTRACT

Objectives Hyperinsulinaemia and insulin resistance are proposed as contributors to the incidence of cardiometabolic phenotypes (CMPs) with unhealthy metabolic status. This study analysed 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 The AZAR cohort is a part of an Iranian screening programme named the Persian cohort and involves participants living in the Shabestar region, Iran for at least 9 months.

Participants A total of 15 006 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, 14 882 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 first to fourth quartiles in metabolically unhealthy participants (p≤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 fourth DIL quartile decreased by 0.21 (0.14–0.32) and 0.37 (0.33–0.43), respectively, compared with the first 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 OR 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.

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 dietary insulin index and dietary insulin load with four different cardiometabolic phenotypes were studied for the first time. This model helped us to analyse the data in a more organised fashion.
⇒ The presence of confounders and their effect were considered while analysing 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 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 characterised by obesity, insulin resistance, hypertension, glycaemic abnormalities and dyslipidaemia.[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 (TGs), low high-density lipoprotein (HDL) cholesterol and large waist circumference (WC). The incidence of MetS usually correlates with the incidence of obesity. The prevalence of MetS has doubled

Table 1 General characteristics of participants stratified by cardiometabolic phenotypes

Cardiometabolic phenotype	MHN (n=2948)	MUHN (n=240)	MHO (n=6870)	MUHO (n=4824)	
	N (%)	N (%)	N (%)	N (%)	P value
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
Non-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)	
Limited 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
First	561 (19)	97 (40.4)	1503 (21.9)	1545 (32)	
Second	685 (23.2)	64 (26.7)	1747 (25.4)	1233 (25.6)	
Third	794 (26.9)	45 (18.8)	1778 (25.9)	1105 (22.9)	
Fourth	908 (30.8)	34 (14.2)	1842 (26.8)	941 (19.5)	
Insulin Index					**<0.001
First	577 (19.6)	97 (40.4)	1507 (21.9)	1524 (31.6)	
Second	703 (23.8)	56 (23.3)	1690 (24.6)	1272 (26.4)	
Third	761 (25.8)	59 (24.6)	1831 (26.7)	1078 (22.3)	
Fourth	907 (30.7)	28 (11.7)	1842 (26.8)	950 (19.7)	
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**	

Continued

Table 1 Continued

Cardiometabolic phenotype	MHN (n=2948)	MUHN (n=240)	MHO (n=6870)	MUHO (n=4824)	
	N (%)	N (%)	N (%)	N (%)	P value
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	157 907.35±84 258.16	121 546.75±61 228. 21	150 506.01±80 295.64	135 191.32±72 140.76	***<0.001
Energy intake (kcal)	2831.29±911.44	2476.97±875.68	2768.65±885.93	2611.62±859.49	***<0.001

*P value: χ^2 test ; ** P value: Kruskal–Wallis; *** P value: One-way analysis of variance.
MET, metabolic equivalent of task; MHN, Metabolically Healthy Normal Weight; MHO, Metabolically Healthy Obese; MUHN, Metabolically Unhealthy Normal Weight; MUHO, Metabolically Unhealthy Obese.

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 fulfil the criteria for MetS. They are called the Metabolically Unhealthy Normal Weight (MUHN) or the Metabolically Obese Normal Weight.[6–9] This calls for classifying individuals into four different cardiometabolic phenotype (CMP) groups and assessing different metabolic factors based on four phenotypes; obese individuals who fulfil MetS criteria, called the Metabolically Unhealthy Obese (MUHO), obese individuals who do not fulfil MetS criteria, called the MHO, normal weight individuals who fulfil MetS criteria, called the MUHN, and normal weight individuals who do not fulfil 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, hyperlipidaemia 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 glycaemic index (GI) and high glycaemic 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 with 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 with 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 insulinaemic 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

The AZAR cohort is a prospective population-based study[18] in Iran and is part of a national screening programme named the Prospective Epidemiological Research Studies in Iran (Persian cohort).[19 20] The study's main goal is to investigate the major non-communicable disease risk factors, including cardiovascular, pulmonary and renal diseases, diabetes, and cancer. The AZAR cohort started in October 2014 and is still in progress in the East Azarbaijan province in northwestern Iran. The study includes up to 15 000 individuals aged between 35 years and 70 years 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.[18–20]

Our cross-sectional study was conducted on the AZAR cohort population. A total number of 15 006 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

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)	
	N (%)	N (%)	N (%)	N (%)	P value
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
Non-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)	
Limited 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
First	166 (9.1)	23 (21.7)	240 (7.7)	200 (12.5)	
Second	358 (19.6)	27 (25.5)	607 (19.4)	338 (21.1)	
Third	552 (30.3)	31 (29.2)	946 (30.2)	472 (29.4)	
Fourth	744 (40.9)	25 (23.6)	1343 (42.8)	594[37]	
Insulin Index					**<0.001
First	250 (13.7)	30 (28.3)	435 (13.9)	313 (19.5)	
Second	403 (22.1)	28 (26.4)	719 (22.9)	439 (27.4)	
Third	517 (28.4)	28 (26.4)	955 (30.5)	424 (26.4)	
Fourth	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

Continued

Table 2 Continued

Cardiometabolic phenotype	MHN (n=1820)	MUHN (n=106)	MHO (n=3136)	MUHO (n=1604)	
	N (%)	N (%)	N (%)	N (%)	P value
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	178 265.37±91 953.88	146 325.32±68 338.32	179 204.06±88 164.46	169 201.99±83 857.36	***<0.0001
Energy intake (kcal)	3109.21±919.32	2850.34±919.82	3192.65±931.32	3132.97±961.05	***<0.001

*P value: χ^2 test ; ** P value: Kruskal-Wallis test; *** P value: one-way analysis of variance.
MET, metabolic equivalent of task; MHN, Metabolically Healthy Normal Weight; MHO, Metabolically Healthy Obese; MUHN, Metabolically Unhealthy Normal Weight; MUHO, Metabolically Unhealthy Obese.

those who had cancer (n=85). Finally, 14 882 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 socioeconomic status of the participants was evaluated by the Wealth Score Index (WSI), calculated by multiple correspondence analysis. Each participant's WSI was determined by assessing their possession of different types of permanent property (eg, TV, dishwasher and car), the condition of their residence (eg, type of ownership, the number of rooms) and education level. Participants were divided into five WSI quintiles, ranging from the lowest to the highest (first to fifth 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 semiquantitative, 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 the 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, 1 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. Therefore, 4 MET equals 14 milliliters of oxygen used per kilogram of body weight per minute. We measured the activity level of each participant using this criterion.

Smokers were defined as participants who continuously smoked at least one cigarette per day for more than 6 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 each individual after an overnight fast of 12 hours. Fasting blood sugar (FBS), serum TG and 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 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 WC was measured according to National Institutes of Health (NIH) guidelines. Female individuals with WC≥88 cm and male individuals with WC≥102 cm were considered abdominally obese.[22]

Blood pressure measurements

Blood pressure was measured two times in each arm in the sitting position and according to the Persian cohort protocol.[19] The individuals rested for 10 minutes between each measurement. The blood pressure of every individual was calculated as the average of the two measurements in each arm.

Definitions of CMP and MetS

We defined MetS according to the National Cholesterol Education Programme's Adult Treatment Panel III report criteria.[4] According to these criteria, MetS is defined by the presence of three or more of the following: fasting

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
Non-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)	
Smokes 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)	
Limited 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
First	395[35]	74 (55.2)	1263 (33.8)	1345 (41.8)	
Second	327[29]	37 (27.6)	1140 (30.5)	895 (27.8)	
Third	242 (21.4)	14 (10.4)	832 (22.3)	633 (19.7)	
Fourth	164 (14.5)	9 (6.7)	499 (13.4)	347 (10.8)	
Insulin Index					**<0.001
First	327[29]	67(50)	1072 (28.7)	1211 (37.6)	
Second	300 (26.6)	28 (20.9)	971[26]	833 (25.9)	
Third	244 (21.6)	31 (23.1)	876 (23.5)	654 (20.3)	
Fourth	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

Continued

Table 3 Continued

	Cardiometabolic phenotype				
	MHN (n=1128)	MUHN (n=134)	MHO (n=3734)	MUHO (n=3220)	
	N (%)	N (%)	N (%)	N (%)	
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	124 898.66±56 090.32	101 945.79±46 619.43	126 403.94±63 741.27	118 249.36±58 585.05	***<0.001
Energy intake (kcal)	2381.77±693.49	2165.50±708.04	2412.56±661.78	2351.92±666.32	***<0.001

*P value: χ^2 test; ** P value: Kruskal-Wallis; *** P value: one-way analysis of variance.
MET, metabolic equivalent of task; MHN, Metabolically Healthy Normal Weight; MHO, Metabolically Healthy Obese; MUHN, Metabolically Unhealthy Normal Weight; MUHO, Metabolically Unhealthy Obese.

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 TGs≥150 mg/dL or drug treatment for elevated TGs; WC greater than 102 cm in men or greater than 88 cm in women; systolic blood pressure≥130 mm Hg and/or diastolic blood pressure≥85 mm Hg or antihypertensive drug treatment in a patient with a history of hypertension.

We considered the cut-off point for BMI to be 25 kg/m^2 for overweight and obese participants.[23]

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

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

Measuring DII and DIL

The 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 II 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 II 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 fibre content. For example, since both dates and raisins are dried fruits and have comparable nutritional content, the II 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 = II of that food × energy content per 1 g of that food × amount of that food consumed (g/day). By summing up the insulin load of each food, DIL was obtained for each participant. Dietary Insulin Index (DII) for each participant was then determined by dividing DIL by the total energy intake.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS, V.11.5, Chicago, Illinois, USA). Descriptive statistics were obtained for all study variables and reported as mean±SD, as well as number (percentage) where applicable. The χ^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 analysis of variance test was used to compare mean values among different cardiometabolic groups. Multinomial logistic regression analysis was used to estimate crude and adjusted ORs and their corresponding 95% CIs. MetS components (hypertension, high FBS, hypo-HDL, cholesterolaemia, hypertriglyceridaemia and abdominal obesity), II and DIL 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 value of p<0.05.

We used the Strengthening the reporting of observational studies (STROBE) cross-sectional checklist when writing our report.[26]

RESULTS

Participants' characteristics

Table 1 presents the baseline characteristics of participants according to their CMPs, while tables 2 and 3 present the same characteristics for both genders.

The ratio of married participants was significantly higher in both genders (tables 2 and 3). Education

Table 4 Association between cardiometabolic phenotype and 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	≤99 828.05	99 828.06–129348.53	129 348.54–171278.60	>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)

Continued

Table 4 Continued

Quartiles of DIL				Quartiles of DII			
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)

Metabolically Healthy Lean (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.
DII, Dietary Insulin Index; DIL, dietary insulin load; MET, metabolic equivalent of task; MHO, Metabolically Healthy Obese; MUHN, Metabolically Unhealthy Normal Weight; MUHO, Metabolically Unhealthy Obese; WSI, Wealth Score Index.

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 first 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 WC showed incremental trends from being in a healthy phenotype (whether normal weight or obese) to an unhealthy phenotype (p≤0.001) (tables 1 and 2). Hip circumference was lower in the MHN than in the MHO and MUHO (p<0.001).

Relationship between CMPs and DIL and DII

The frequency of insulin load and index quartiles showed a significant decrease from the first to fourth quartiles in metabolically unhealthy participants (both MUHN and MUHO) (p≤0.001).

Unexpectedly, the mean values of DII and DIL were seen 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 with their corresponding healthy phenotypes, with the MUHN consuming the lowest energy intake (p<0.001) (table 1). This trend was seen 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 with the first DIL quartile, the risks of MUHN and MUHO in the fourth DIL quartile decreased by 0.21 (0.14–0.32) and 0.37 (0.33–0.43), respectively (table 4).

After adjustment for different intervening factors (ie, 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 fourth DIL quartile. In Model 2, the observed OR for MUHN was 0.61 (0.42–0.90) in the second DIL quartile, while it was 0.23 (0.12–0.47) in the fourth DIL quartile (table 4).

The findings of the unadjusted model for the DII quartiles indicated that compared with the first DII quartile, the risks of MUHN and MUHO in the fourth 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 fourth DII quartile. In Models 1 and 2, the observed ORs for MUHN were 0.59 (0.41–0.84) and 0.57 (0.40–0.81), respectively, in the second DII quartile, while they were both 0.24 (0.15–0.37) in the fourth 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 insulinaemic capability.[24 29] Thus, it is of great importance to establish a reliable index to demonstrate the insulinaemic 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 OR in metabolically healthy phenotypes was not significant. We can conclude these findings in two different ways.

First, 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 behaviour, thereby lowering the insulinaemic potential of their diet (ie, 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.

Second, the insignificant trend of the ORs 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, and neural and hormonal activity.[30]

In accordance with our findings, Karimbeiki *et al* demonstrated that a higher insulinaemic effect of diet was not associated with increased obesity rates.[31] Anjom-Shoaei *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 MetS 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 OR 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 with 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 OR 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 insulinaemic 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 insulinaemic diets potentially cause faster carbohydrate digestion and absorption, leading to higher blood glucose and insulin levels. They also result in a rapid drop in postprandial 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 organised based on the presence or absence of obesity, and the presence or absence of MetS. This model helped assess the data in a more organised pattern. Additionally, we took into account the effect of confounding factors while analysing the data. Another strength of this study was its large population, as we conducted our study on just under 15 000 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 analysed the data taking into account the confounding factors, some confounding factors, including dietary habits, psychological factors, parental obesity and family history of cardiometabolic diseases, were still 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 over-rated. Elevated insulin secretion could even be beneficial.[42 43] Second, 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 behaviour. This presumed lifestyle behaviour change can be the main reason for DII and DIL being associated with a lower OR of unhealthy CMPs. This finding highlights the importance of considering recent lifestyle behaviour 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 behaviour 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 OR 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 CMPs, as a result of lifestyle behaviour 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.

Acknowledgements The authors thank all subjects who participated in this study. The authors also thank the investigators and the staff of the AZAR cohort study for thier contribution. The authors also thank the Shabestar health center for their close collaboration and the Persian cohort study staff for their technical support. The authors also thank the Clinical Research Development Unit of Imam Reza General Hospital, Tabriz, Iran for their cooperation in conducting this research.

Contributors 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 *BMJ Open*. EF, SSNI and AMN helped with the conception and design of the work. EF, MHS, NP and AMN helped with the acquisition and analysis. EF, MHS, SSNI, NP and AMN interpreted the data, and EF, NP and AMN drafted the work and revised it. All authors have read and approved the manuscript. AMN acts as the guarantor for this manuscript.

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 Iranian Ministry of Health and Medical Education has contributed to the funding used in the PERSIAN Cohort through Grant no. 700/534. The funder had no role in the study design, data analysis, interpretation, and writing of the manuscript.

Competing interests None declared.

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

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

Ethics approval This study involves human participants and was approved by the Bioethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran, (Ethics Number: IR.TBZMED.REC.1401.414). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. 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].

ORCID iDs
Seyed Sina Naghibi Irvani http://orcid.org/0000-0002-4566-7402
Amir Mohammad Nourizadeh http://orcid.org/0000-0001-9206-5327

REFERENCES

1 Collaborators GBD. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;377:13–27.
2 O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev* 2015;16:1–12.
3 Nolan PB, Carrick-Ranson G, Stinear JW, *et al*. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: a pooled analysis. *Preventive Medicine Reports* 2017;7:211–5.
4 Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep* 2018;20:12.
5 Goday A, Calvo E, Vázquez LA, *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;16:248.
6 Osadnik K, Osadnik T, Lonnie M, *et al*. Metabolically healthy obese and metabolic syndrome of the lean: the importance of diet quality. analysis of magnetic cohort. *Nutr J* 2020;19:19.
7 Ding C, Chan Z, Magkos F. Lean, but not healthy: the "metabolically obese, normal-weight" phenotype. *Curr Opin Clin Nutr Metab Care* 2016;19:408–17.
8 Wang B, Zhuang R, Luo X, *et al*. Prevalence of metabolically healthy obese and metabolically obese but normal weight in adults worldwide: a meta-analysis. *Horm Metab Res* 2015;47:839–45.
9 Jung CH, Lee MJ, Kang YM, *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;100:934–41.
10 Eddy D, Schlessinger L, Kahn R, *et al*. Relationship of insulin resistance and related metabolic variables to coronary artery disease: a mathematical analysis. *Diabetes Care* 2009;32:361–6.
11 Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. *Compr Physiol* 2013;3:1–58.
12 Nimptsch K, Brand-Miller JC, Franz M, *et al*. Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers. *Am J Clin Nutr* 2011;94:182–90.
13 Bell SJ, Sears B. Low-glycemic-load diets: impact on obesity and chronic diseases. *Crit Rev Food Sci Nutr* 2003;43:357–77.
14 Liu S, Willett WC, Stampfer MJ, *et al*. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *The American Journal of Clinical Nutrition* 2000;71:1455–61.
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;66:1264–76.
16 Bao J, de Jong V, Atkinson F, *et al*. Food insulin index: physiologic basis for predicting insulin demand evoked by composite meals. *Am J Clin Nutr* 2009;90:986–92.
17 Anjom-Shoae J, Keshteli AH, Sadeghi O, *et al*. Association between dietary insulin index and load with obesity in adults. *Eur J Nutr* 2020;59:1563–75.
18 Farhang S, Faramarzi E, Amini Sani N, *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;48:382–382h.
19 Poustchi H, Eghtesad S, Kamangar F, *et al*. Prospective epidemiological research studies in iran (the PERSIAN cohort study): rationale, objectives, and design. *Am J Epidemiol* 2018;187:647–55.
20 Eghtesad S, Mohammadi Z, Shayanrad A, *et al*. The PERSIAN cohort: providing the evidence needed for healthcare reform. *Arch Iran Med* 2017;20:691–5.
21 Ghafarpour M, Kianfar H, Hoshyarrad A BB. *Natl nutr food technol res institute*ISBN 9786005040005.
22 WHO Consultation. Obesity: preventing and managing the global epidemic. *World Health Organ Tech Rep Ser* 2000;894:1–253.
23 Somi MH, Nikniaz Z, Ostadrahimi A, *et al*. Is normal body mass index a good indicator of metabolic health in azar cohort population? *J Cardiovasc Thorac Res* 2019;11:53–60.
24 Bao J, Atkinson F, Petocz P, *et al*. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. *Am J Clin Nutr* 2011;93:984–96.
25 Bell KJ, Petocz P, Colagiuri S, *et al*. Algorithms to improve the prediction of postprandial insulinaemia in response to common foods. *Nutrients* 2016;8:210.
26 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573.
27 Sadeghi O, Hasani H, Mozaffari-Khosravi H, *et al*. Dietary insulin index and dietary insulin load in relation to metabolic syndrome: the shahedieh cohort study. *J Acad Nutr Diet* 2020;120:1672–86.
28 Okosun IS, Okosun B, Lyn R, *et al*. Surrogate indexes of insulin resistance and risk of metabolic syndrome in non-hispanic white, non-hispanic black and mexican american. *Diabetes Metab Syndr* 2020;14:3–9.
29 Hsieh C-H, Wu C-Z, Hsiao F-C, *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;57:1615–21.
30 Seino S, Shibasaki T, Minami K. Dynamics of insulin secretion and the clinical implications for obesity and diabetes. *J Clin Invest* 2011;121:2118–25.
31 Karimbeiki R, Namkhah Z, Alipoor E, *et al*. The relationship between low-carbohydrate diet score, dietary insulin index and load with obesity in healthy adults. *Eat Weight Disord* 2022;27:3341–50.
32 Joslowski G, Goletzke J, Cheng G, *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;36:1463–71.
33 Hajhashemy Z, Mirzaei S, Asadi A, *et al*. 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, *et al*. Mediterranean-style diet reduces metabolic syndrome components in obese children and adolescents with obesity. *BMC Pediatr* 2014;14:175.
35 Arenaza L, Huybrechts I, Ortega FB, *et al*. Adherence to the Mediterranean diet in metabolically healthy and unhealthy overweight and obese European adolescents: the Helena study. *Eur J Nutr* 2019;58:2615–23.
36 Caferoglu Z, Erdal B, Akin L, *et al*. Breakfast and dinner insulin index and insulin load in relation to overweight in children and adolescents. *Eur J Nutr* 2021;60:2819–29.
37 Teymoori F, Farhadnejad H, Moslehi N, *et al*. The association of dietary insulin and glycemic indices with the risk of type 2 diabetes. *Clin Nutr* 2021;40:2138–44.
38 Teymoori F, Farhadnejad H, Mirmiran P, *et al*. The association between dietary glycemic and insulin indices with incidence of cardiovascular disease: tehran lipid and glucose study. *BMC Public Health* 2020;20:1496.
39 Hellström PM. Satiety signals and obesity. *Curr Opin Gastroenterol* 2013;29:222–7.
40 Zhu R, Larsen TM, Poppitt SD, *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. *Clinical Nutrition* 2022;41:219–30.
41 Mirmiran P, Esfandiari S, Bahadoran Z, *et al*. 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;15:23.
42 Nguyen A, Khafagy R, Meerasa A, *et al*. Insulin response to oral glucose and cardiometabolic disease: a Mendelian randomization study to assess potential causality. *Diabetes* 2022;71:1880–90.
43 Dwivedi OP, Lehtovirta M, Hastoy B, *et al*. Loss of znt8 function protects against diabetes by enhanced insulin secretion. *Nat Genet* 2019;51:1596–606.