British Journal of Nutrition (2019), 121, 773–781
doi:10.1017/S0007114518003872

Associations between dietary insulin load with cardiovascular risk factors and inflammatory parameters in elderly men: a cross-sectional study

Hadis Mozaffari[1], Nazli Namazi[2], Bagher Larijani[3], Pamela J. Surkan[4] and Leila Azadbakht[1,2,5]*

[1]*Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, 141556117 Tehran, Iran*
[2]*Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, 1411713137 Tehran, Iran*
[3]*Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, 1411713137 Tehran, Iran*
[4]*Department of International Health, John Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA*
[5]*Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Science, 81746 73461 Isfahan, Iran*

(Submitted 4 April 2018 – Final revision received 20 November 2018 – Accepted 3 December 2018)

Abstract

Given the limited research on dietary insulin load (DIL), we examined DIL in relation to cardiovascular risk factors and inflammatory biomarkers in elderly men. For the present cross-sectional study, we recruited 357 elderly men. Dietary intake was assessed using FFQ. DIL was estimated by multiplying the insulin index of each food by its energy content and frequency of consumption and then summing the final value of all food items. After adjustment for covariates, a significant positive association was observed between high DIL with fasting blood sugar (FBS) levels (OR: 7·52; 95 % CI 3·38, 16·75; $P=0·0001$) and high-sensitive C-reactive protein (hs-CRP) (OR: 3·03; 95 % CI 1·54, 5·94; $P=0·001$). However, there was no association between high DIL and BMI (OR: 1·43; 95 % CI 0·75, 2·75; $P=0·27$), serum TAG level (OR: 0·82; 95 % CI 0·26, 2·59; $P=0·73$), HDL-cholesterol (OR: 2·03; 95 % CI 0·79, 5·23; $P=0·13$) and fibrinogen (OR: 1·57; 95 % CI 0·80, 3·06; $P=0·18$). Overall, elderly men with high DIL had higher FBS and hs-CRP levels than those with low DIL. Future studies are needed to clarify the association between DIL and other cardiovascular risk factors in both men and women.

Key words: **Dietary insulin load: Cardiovascular risks: Inflammation: Elderly**

CVD is the most common cause of death in the world[1]. Approximately one third of deaths are related to CVD[1]. In 2010, the prevalence of CVD among individuals over 65 years old was 19·8 % in the USA[2].

Older people are at higher risk of obesity[3]. Obesity with insulin resistance is associated with hyperinsulinaemia[4] and hyperinsulinaemia can lead to dyslipidaemia[5], high blood pressure[6] and inflammation[7]. Moreover, obesity in the elderly can increase inflammatory parameters that lead to dyslipidaemia and insulin resistance[3].

The potential use of diet to induce postprandial insulin secretion is likely to be critical for managing dyslipidaemia, weight gain and inflammation[8–12]. Although evidence has been accumulating regarding specific dietary factors and insulin resistance[13–15], dietary indices that examine the overall dietary patterns may be more informative. Dietary insulin load (DIL) is an example of one such index[16].

The insulin index represents the insulin response to isoenergetic components of foods in comparison to a reference food (glucose or white bread)[17]. Insulin index is based on postprandial insulin secretion that is evoked through mixed meals[17]. This index takes into account not only carbohydrate-containing foods but also high-fat, high-protein foods and their interactions[18]. Given that insulin index is based on insulin secretion, a link between insulin exposure and propensity to chronic diseases might exist[11,19]. DIL is another dietary index that is estimated through multiplying the reported insulin index value of each food by its energy content and the frequency of consumption of each food[16].

A Finnish study with 22 years of follow-up demonstrated that insulin was a suitable predictor of coronary disease[20]. Limited research exists on the association between insulin indices and CVD risk factors, with existing literature lacking systematic

Abbreviations: DIL, dietary insulin load; FBS, fasting blood sugar; hs-CRP, high-sensitive C-reactive protein; SES, socio-economic status.

* **Corresponding author:** L. Azadbakht, fax +98 2188984861, email azadbakhtleila@gmail.com

evaluation across studies focusing on the same risk factors. Mirmiran *et al.*[16] showed an inverse association between DIL and insulin resistance. Nimptsch *et al.*[11] also found an inverse association between DIL and HDL-cholesterol and a positive association between DIL and TAG, particularly among obese individuals. In a prospective study by Joslowski *et al.*[21], DIL was associated with body fat mass, while no relation to BMI was observed.

Elderly subjects might be more at the risk for insulin resistance due to their body compositions and metabolic profiles,[3] calling for the examination of the association between the DIL and cardiovascular risk factors in this population. Moreover, men are at higher risk of CVD compared with women[22]. Research shows that CVD develops approximately 7–10 years earlier in men compared with women[23]. Due to the limited studies on DIL and its association with cardiovascular biomarkers, our aim was to examine the association between DIL and cardiovascular risk factors in elderly men.

Methods

Study population

To date, little attention has been paid to men, especially the elderly men, so we prioritised this group in our study. In this cross-sectional study, we used clustered random sampling to select men referred to ten health centres in southern Tehran, Iran (March to August 2017). To calculate the number of men to be sampled from each health centre, the total population served by each centre was represented proportionally in the calculated sample size (*n* 313). We included men over the age of 60 years who were not already adhering to specific diets. Men were excluded if they had any malignant disease such as cancer. Moreover, we excluded subjects from our analyses with under- and overreported total energy intake (<3347 and >17573 kJ/d)[24]. High-sensitive C-reactive protein (hs-CRP) was considered the main dependent variable for calculating the sample size[25]. For the sample size calculation, we defined $\alpha = 0{\cdot}05$, $d = 4\,\%$ and the effect size = 1·5. Finally, based on hs-CRP values, we determined that 313 individuals were needed. However, to compensate for potential exclusion of participants due to under- and overreporting of total energy intake, 365 subjects were selected for inclusion. After exclusion of participants who under- and overreported the total energy intake (*n* 8), 357 remained in the analysis. Therefore, under- and overreported total energy intake was the only reason for exclusion. Written informed consent was obtained from all participants. Ethical approval for this protocol was given by the National Institute for Medical Research Development (grant and ethics number: 965430).

Dietary assessment

Participants' usual dietary intake was obtained using a 168-item semi-quantitative FFQ through face-to-face interviews with a trained nutritionist. The validity and reliability of this questionnaire has been previously reported to be adequate[26]. Participants were asked to report on average frequencies of their food consumption on a daily, weekly or monthly basis. The portion size of each food was translated from household measures into grams. An adapted version of NUTRITIONIST IV modified for Iranian foods (version 7.0; N-Squared Computing) was used to calculate mean energy and nutrient intakes[25,27,28].

Calculation of dietary insulin load. The insulin index of each food was extracted for analysis (based on methods outlined in Kirstine Bell's thesis)[29]. Insulin index was defined as the AUC representing insulin (during 120 min) in response to intake of approximately a 1000 kJ portion of the test food, which then was divided by the area below the curve after consumption of an isoenergetic reference food[17]. The average value of DIL for each study participant during the previous year was computed using FFQ data. In this fashion, the insulin index value of each food item was multiplied by its energy content and also by the frequency of consumption. Finally, all food item values were summed. The formula used was as follows:

$$\text{Insulin load of food} = \sum(\text{Insulin index of food} \times \text{energy content of food (kcal/serving)} \times \text{frequency of consumption (serving of food/d)})$$

Biochemical assessment

For each subject, a single venous blood sample was taken after 12 h of fasting. Serum concentrations for fasting blood sugar (FBS), lipid profiles including total cholesterol, LDL-cholesterol, HDL-cholesterol and TAG were quantified using commercial enzymatic reagents (Pars Azmoon). Insulin serum levels were measured using the ELISA method (ELISA; Diagnostic Biochem Canada, Inc.). hs-CRP concentrations were assessed using an ultrasensitive latex-enhanced immunoturbidimetric assay (Randox Laboratory Ltd). Serum levels of inflammatory biomarkers were determined using the ELISA method (Boster Biological Technology for IL-6 and TNF-α). We used the Clauss clotting method that involves recording the rate of fibrinogen conversion to fibrin in the presence of thrombin. Insulin resistance and insulin sensitivity were assessed using the homoeostasis model assessment for insulin resistance (HOMA-IR)[30] and the quantitative insulin-sensitivity check index (QUICKI)[31], respectively.

Anthropometric assessment

Anthropometric indices (body weight, height and waist circumference) were measured by a trained nutritionist. Body weight was measured using calibrated digital scales (SECA 813; Seca) after participants had removed their shoes and any heavy clothes. Body weight was reported within 100 g of precision. Height was measured using a tape metre (with measurement

precision of 0·5 cm), while participants were standing against a wall and their shoulders were in a normal position. Waist circumference was measured at the narrowest point between the inferior rib and iliac crest over light clothing without applying pressure to the body. It was recorded to the nearest 0·5 cm. BMI was calculated as body weight in kg divided by height in m^2.

Assessment of other variables

Blood pressure was measured twice while participants were in a seated position for 10 min. Participants waited at least 30 s between the first and second measurements. The average of the two readings was used as the final blood pressure. Socio-economic status (SES) was assessed using a questionnaire that has been validated and is reliable in the Iranian population and that was developed for measuring SES and its association with health outcomes[32]. A total standardised score for all participants was computed (using factor analysis and a summary index), then its compliance with a normal summary index was also examined using a Kappa test. This questionnaire consists of questions about educational level, participant job, car or house ownership, having modern appliances, number of family members and trips inside or outside the country during the last year. The reported correlation of these parameters with the total score was 0·87. In the current study, participant SES was described for each category of DIL based on the calculated total scores.

Statistical analysis

The Kolmogorov–Smirnov test and histogram curves were used to examine whether variables had normal distributions. Parameters with normal distributions were presented as means and standard deviations. We categorised participant characteristics, dietary intake, anthropometric indices and biochemical parameters based on the median DIL scores. Basic participant characteristics were provided for the total population and each category of DIL. To investigate the differences in characteristics between categories of DIL, χ^2 (qualitative variables) and independent t tests (quantitative variables) were used. Dietary intakes within categories of DIL were compared using ANCOVA to adjust for daily energy intake. The levels of anthropometric measures, and biochemical parameters within categories of DIL were compared using independent t tests in crude models and ANCOVA in adjusted models. To assess the association between DIL and cardiometabolic risk factors, binary logistic crude and adjusted regression models were used. In the adjusted models, we controlled for a wide range of confounders (model 1: energy intake, marital status, SES and smoking; model 2: energy intake, marital status, SES, smoking, disease status, anti-diabetic drugs, thyroid drugs and heart disease drugs). The low category of DIL was considered the reference group and high and low categories were compared to predict the risk of CVD. Glycaemic control parameters and lipid profiles were considered primary outcomes, while inflammatory biomarkers were considered secondary outcomes. All statistical analyses were performed using SPSS software (version 18; SPSS Inc.). $P<0·05$ was considered statistically significant.

Results

The mean age of participants (n 357) was 64·96 years. General participant characteristics in the two DIL categories are represented in Table 1. A larger percentage of participants in the high category were married ($P=0·003$), had lower education levels ($P=0·009$), were non-smokers ($P=0·0001$), had no disease ($P=0·02$), did not use anti-diabetic drugs ($P=0·02$), thyroid drugs ($P=0·001$) or drugs for heart disease ($P=0·0001$).

Participant dietary intakes in each DIL category are represented in Table 2. Participants in the high DIL category had higher consumption of energy ($P=0·0001$), carbohydrates ($P=0·0001$), fruits ($P=0·002$), vegetables ($P=0·006$), meats ($P=0·04$) and grains ($P=0·0001$), compared with those in the low category. However, participants who were in the high category of DIL had lower fat ($P=0·02$) and oil consumption ($P=0·0001$).

Participants' anthropometric measurements and biochemical markers are displayed in Table 3. With regard to blood pressure, participants in the high DIL category had higher systolic blood pressure ($P=0·004$), insulin ($P=0·0001$), HOMA-IR ($P=0·005$) and hs-CRP ($P=0·04$) levels compared with participants in the low category. However, the differences between anthropometric measurements, glycaemic parameters, lipid profiles, liver enzymes and inflammatory biomarkers did not significantly differ between elderly men classified in the low and high DIL categories.

OR and 95 % CI for cardiovascular risk factors by medians of DIL are provided in Table 4. In subjects who had diets with high DIL, serum levels of FBS were 7·52 times greater than those with low DIL (OR: 7·52; 95 % CI 3·38, 16·75; $P=0·0001$). Moreover, subjects with high DIL showed 3·03 times greater hs-CRP levels than those with low DIL (OR: 3·03; 95 % CI 1·54, 5·94; $P=0·001$). No associations were found between high DIL and BMI (OR: 1·43; 95 % CI 0·75, 2·75; $P=0·27$), serum levels of TAG (OR: 0·82; 95 % CI 0·26, 2·59; $P=0·73$), HDL-cholesterol (OR: 2·03; 95 % CI 0·79, 5·23; $P=0·13$) or fibrinogen (OR: 1·57; 95 % CI 0·80, 3·06; $P=0·18$).

Discussion

In the present cross-sectional study, DIL was positively associated with serum levels of FBS and hs-CRP. However, there was no association between DIL and BMI or between DIL and lipid profiles. To the best of our knowledge, this is the first study, in which glycaemic parameters, lipid profile and also inflammatory biomarkers were investigated to provide better insight into the association between DIL and CVD risk factors in elderly men.

DIL is an indicator that adequately reflects insulin secretion of the whole diet, rather than a single nutrient[18]. In the field of nutritional epidemiology, DIL is a suitable indicator to examine the link between insulin exposure and the development of metabolic diseases[11,19]. Apart from carbohydrates, dietary protein and fat can affect insulin secretion[33–35]. Therefore, macronutrients might act synergistically to increase insulin secretion and reduce blood glucose levels[33–36]. White bread, potato, skim milk, low-fat ice

British Journal of Nutrition

Table 1. General participant characteristics and median dietary insulin loads (DIL)
(Numbers and percentages; mean values and standard deviations)

		DIL median			
		Low category		High category	
	Total (*n* 357)	*n* 164		*n* 193	
Variables	*n* %	*n*	%	*n*	%	*P**
Age (years)						0·45
Mean	64·9	65·2		64·7		
SD	6·5	6·7		6·3		
Weight (kg)						0·29
Mean	72·1	72·8		71·6		
SD	10·2	9·6		10·7		
Socio-economic status†						0·12
Mean	13·0	13·1		12·9		
SD	1·6	1·8		1·3		
Marital status						
Married	344 96	164	100	180	93	0·003
Single/divorced	13 4	0	0	13	7	
Educational status						
Illiterate/ <high school	334 94	150	91	184	95	0·009
High school diploma	15 4	6	4	9	5	
University education	8 2	8	5	0	0	
Smoking						
Yes	62 83	31	19	31	16	0·0001
No	295 17	133	81	162	84	
Disease						
Yes	114 32	64	39	50	26	0·02
No	243 68	100	61	143	74	
Diabetes						
Yes	19 5	12	7	7	4	0·09
No	338 95	152	93	186	96	
Anti-diabetic drug						
Yes	71 20	31	19	40	21	0·02
No	286 80	133	81	153	79	
Lipid lowering drug						
Yes	48 13	16	10	32	17	0·17
No	309 87	148	90	161	83	
Diuretic drug						
Yes	21 6	2	1	19	10	0·35
No	336 94	162	99	174	90	
Thyroid drug						
Yes	10 3	0	0	10	5	0·001
No	347 97	164	100	183	95	
Heart disease drug						
Yes	64 18	14	9	50	26	0·0001
No	293 82	150	91	143	74	

* Calculated using χ^2 tests and *t* tests for qualitative and quantitative variables, respectively.
† Socio-economic status; minimum: 10, maximum: 18.

cream or yogurt, melon, fruit juice, canned fruits, jam, chocolate and jelly beans are examples of food items with high insulin index[29].

Associations between dietary insulin indices and metabolic features such as glycaemic status, lipid profile, inflammatory biomarkers and body composition have been addressed only in limited studies and results have been inconsistent[11,16,21]. Moreover, documented associations between diet and disease in young adults cannot be generalised to the elderly due to the differences in the grade of systematic inflammation as well as differences in the quantity and distribution of fat mass[3]. In addition, men are at higher risk of CVD compared with women[22]. Research suggests that CVD develops approximately 7–10 years earlier in men *v.* women[23].

In the present study, DIL was not associated with BMI. These findings are consistent with a prospective study conducted by Joslowski *et al.*[21]. This study found that high intake of dietary insulin index (DII) (45 compared with 39) or DIL (362

Table 2. Energy-adjusted dietary intakes and medians of dietary insulin load (DIL) (Mean values and standard deviations)

	DIL median*				
	Low category		High category		
	n 164		*n* 193		
Variables	Mean	SD	Mean	SD	*P*†
Energy (kJ/d)	7130	1347	10615	2167	0·0001
Protein (g/d)	83·74	19·32	82·51	20·97	0·56
Fat (g/d)	62·91	15·48	58·95	16·80	0·02
Carbohydrate (g/d)	326·26	39·16	343·98	42·50	0·0001
Cholesterol (mg/d)	182·67	88·96	188·28	96·53	0·57
SFA (mg/d)	16·52	5·88	17·22	6·38	0·29
MUFA (mg/d)	18·04	6·27	17·98	6·80	0·92
PUFA (mg/d)	13·39	3·45	12·27	3·75	0·005
Fibre (g/d)	5·91	2·56	6·48	2·50	0·06
Vitamin B_9 (μg/d)	403·58	98·43	382·45	106·81	0·05
Vitamin B_1 (mg/d)	1·59	0·25	1·44	0·27	0·0001
Vitamin B_6 (mg/d)	1·89	0·38	1·82	0·41	0·13
Vitamin C (mg/d)	214·03	83·84	227·34	90·97	0·15
Vitamin A (RAE/d)	1342·31	510·84	1412·61	554·34	0·21
Ca (mg/d)	1539·90	635·90	1465·46	690·05	0·29
Mg (mg/d)	318·38	72·83	320·52	70·03	0·79
K (mg/d)	3957·62	933·76	4170·79	1013·27	0·04
Zn (mg/d)	9·48	3·20	8·91	3·74	0·11
Fe (mg/d)	13·19	2·94	11·66	3·19	0·0001
Fruit (g/d)	357·97	179·58	426·89	175·70	0·002
Vegetables (g/d)	359·97	201·98	427·17	197·65	0·006
Meat (g/d)	70·93	41·85	80·96	40·97	0·04
Grain (g/d)	314·22	163·20	411·76	159·73	0·0001
Dairy products (g/d)	612·57	401·66	643·82	393·08	0·51
Oil (g/d)	65·28	41·08	35·32	40·28	0·0001

RAE, retinol activity equivalents.
* All the variables, except energy, were adjusted for energy intake.
† Calculated using multivariate ANCOVA.

compared with 321) during puberty (among healthy subjects) was not associated with BMI in young adulthood[21]. However, Chaput *et al.*[37] showed that high insulin secretion can predict weight gain in adulthood. In Chaput *et al.*'s study, adults with the highest level of insulin concentration and with the lowest level of dietary fat gained approximately 4·5 kg more weight after 6 years of follow-up compared with those with the lowest levels of insulin and dietary fat[37]. It has been demonstrated that high insulin secretion due to high consumption of insulinogenic foods during a long period can result in the development of fat mass[21] and insulin resistance[16]. Following insulin resistance, the risk of obesity can increase[38]. Moreover, high insulin concentrations can suppress lipolysis and stimulate glucose uptake, which in turn enhances lipogenesis in adipocytes[39].

Regarding glycaemic control, a significant positive association was observed between DIL and FBS concentrations. Although high secretion of insulin can result in lower FBS levels, it seems that prolonged consumption of foods with high insulin index causes β-cell dysfunction[11]. This condition subsequently can lead to insulin resistance and increased serum glucose levels.

We found no association between DIL and HDL-cholesterol concentrations. In the study by Nimptsch *et al.*, they observed an inverse association between DIL (≥858 compared with <648) and HDL-cholesterol. However, after stratification by BMI, DIL was no longer associated with HDL-cholesterol levels in normal (BMI <25 kg/m^2) and overweight (BMI = 25–29·9 kg/m^2) subjects. However, an inverse association remained among obese (BMI ≥30 kg/m^2) subjects[11]. A reason why we failed to observe any association between DIL and HDL-cholesterol might be due to the overall low mean BMI of our participants (approximately 25·4 kg/m^2).

It appears that the inverse association between DIL and HDL-cholesterol found by Nimptsch *et al.*, especially in obese subjects, is due to the high insulin resistance in this group. A possible mechanism is that an insulinogenic diet aggravates insulin secretion, which in turn may lead to insulin resistance in the long-term, as was observed in the study by Mirmiran *et al.*[16] (DIL ≥1097 compared with <794 was associated with a 69 % increase in the risk of insulin resistance). Based on previous research, insulin resistance and disturbance of glycaemic control is associated with lower HDL-cholesterol serum levels[40]. Moreover, studies have revealed that high carbohydrate consumption is associated with low serum levels of HDL-cholesterol[41,42]. In the present study, no association was found between DIL and serum TAG levels. However, in a study conducted by Nimptsch *et al.*[11], a significant positive association between dietary insulin indices (DII: ≥46·2 compared with <38·3; DIL: ≥858 compared with <648) and TAG concentration was observed in all BMI categories, particularly in the obese.

Table 3. Medians of dietary insulin load (DIL) by anthropometric indices, biochemical markers and blood pressure (Mean values and standard deviations)

	DIL median				
	Low category		High category		
	n 164		*n* 193		
Variables	Mean	SD	Mean	SD	*P**
BMI (kg/m^2)					
Crude†	24·83	2·72	26·10	3·30	0·001
Model 1‡	25·70	3·50	25·06	3·61	0·16
Model 2§	25·49	3·50	25·24	3·61	0·57
WC (cm)					
Crude†	96·64	7·57	95·71	9·34	0·30
Model 1‡	96·76	9·78	95·61	10·13	0·36
Model 2§	96·26	9·78	96·04	10·13	0·86
SBP (mmHg)					
Crude†	120·64	10·42	130·10	10·76	0·008
Model 1‡	120·58	10·69	130·15	10·80	0·01
Model 2§	120·53	10·69	130·20	10·80	0·004
DBP (mmHg)					
Crude†	70·70	8·50	70·90	7·20	0·01
Model 1‡	70·78	8·40	70·83	8·30	0·63
Model 2§	70·80	8·40	70·81	8·30	0·92
Insulin (pmol/l)					
Crude†	58·33	28·95	64·93	38·91	0·07
Model 1‡	54·79	39·37	67·77	41·45	0·01
Model 2§	51·73	37·70	70·41	39·51	0·0001
HOMA-IR					
Crude†	2·32	1·25	2·37	1·67	0·75
Model 1‡	2·14	1·69	2·51	1·25	0·09
Model 2§	2·02	1·57	2·62	1·66	0·005
QUICKI					
Crude†	0·34	0·03	0·35	0·03	0·30
Model 1‡	0·35	0·05	0·35	0·04	0·91
Model 2§	0·35	0·03	0·34	0·04	0·21
TAG (mmol/l)					
Crude†	1·47	0·36	1·47	0·47	0·94
Model 1‡	1·50	0·49	1·44	0·51	0·30
Model 2§	1·49	0·49	1·45	0·51	0·49
HDL-C (mmol/l)					
Crude†	1·24	0·21	1·30	0·23	0·01
Model 1‡	1·30	0·24	1·25	0·26	0·12
Model 2§	1·29	0·23	1·25	0·24	0·18
LDL-C (mmol/l)					
Crude†	2·39	0·55	2·51	0·53	0·03
Model 1‡	2·44	0·60	2·46	0·63	0·83
Model 2§	2·44	0·57	2·46	0·59	0·71
TC (mmol/l)					
Crude†	4·43	0·70	4·68	0·59	0·0001
Model 1‡	4·49	0·68	4·62	0·71	0·13
Model 2§	4·50	0·60	4·61	0·63	0·14
hs-CRP (μg/ml)					
Crude†	1·65	0·87	1·94	0·88	0·002
Model 1‡	1·75	0·96	1·86	0·97	0·39
Model 2§	1·67	0·96	1·92	0·97	0·04
Fibrinogen (g/l)					
Crude†	2·82	0·52	2·67	0·40	0·002
Model 1‡	2·75	0·53	2·74	0·55	0·86
Model 2§	2·73	0·53	2·75	0·55	0·84
IL-6 (pg/ml)					
Crude†	6·49	0·74	6·46	0·74	0·75
Model 1‡	6·45	0·84	6·49	0·83	0·70
Model 2§	6·45	0·84	6·49	0·83	0·70
TNF-*α* (pg/ml)					
Crude†	0·72	0·08	0·72	0·07	0·78
Model 1‡	0·72	0·09	0·72	0·09	0·73
Model 2§	0·72	0·09	0·72	0·09	0·75

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homoeostasis model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index; TC, total cholesterol; hs-CRP, high-sensitive C-reactive protein.

* Calculated using *t* tests for the crude model and ANCOVA in the adjusted models.

† Crude: not adjusted for any variables.

‡ Model 1: this model was adjusted for energy intake, marital status (which includes educational level), socio-economic status and smoking.

§ Model 2: this model was adjusted for energy intake, marital status, socio-economic status (which includes educational level), smoking, disease, anti-diabetic drugs, thyroid drugs and heart disease drugs.

Table 4. Crude and multivariable OR and 95 % CI in medians of dietary insulin load (DIL) (Odds ratios and 95 % confidence intervals)

	DIL median			
	Low category	High category		
		n 193		
Variables	*n* 164	OR	95 % CI	*P**
Overweight and obese (BMI >25 g/m^2)				
Crude†	1	0·88	0·58, 1·34	0·56
Model 1‡	1	1·64	0·88, 3·06	0·11
Model 2§	1	1·43	0·75, 2·75	0·27
FBS (>5·55 mmol/l)				
Crude†	1	4·64	2·90, 7·44	0·0001
Model 1‡	1	5·69	2·78, 11·63	0·0001
Model 2§	1	7·52	3·38, 16·75	0·0001
TAG (>1·69 mmol/l)				
Crude†	1	1·78	0·80, 3·92	0·15
Model 1‡	1	0·72	0·23, 2·22	0·57
Model 2§	1	0·82	0·26, 2·59	0·73
HDL-cholesterol (<1·03 mmol/l)				
Crude†	1	0·55	0·30, 0·99	0·04
Model 1‡	1	2·02	0·85, 4·77	0·10
Model 2§	1	2·03	0·79, 5·23	0·13
hs-CRP (>2 mg/l)				
Crude†	1	1·92	1·25, 2·93	0·003
Model 1‡	1	1·97	1·08, 3·59	0·02
Model 2§		3·03	1·54, 5·94	0·001
Fibrinogen (>2·85 g/l)				
Crude†	1	0·54	0·35, 0·83	0·005
Model 1‡	1	1·43	0·76, 2·69	0·26
Model 2§	1	1·57	0·80, 3·06	0·18

FBS, fasting blood sugar; hs-CRP, high-sensitive C-reactive protein.
* Calculated using logistic regression.
† Crude: not adjusted for any variables.
‡ Model 1: the model was adjusted for energy intake, marital status, socio-economic status (which includes educational level) and smoking.
§ Model 2: the model was adjusted for energy intake, marital status, socio-economic status (which includes educational level), smoking, disease, anti-diabetic drugs, thyroid drugs and heart disease drugs.

In the present study, we did not find an association between DIL and fibrinogen levels. However, there was a positive relationship between high DIL and serum levels of hs-CRP. In contrast to our study, Nimptsch *et al.* failed to find any association between dietary insulin indices (DII: ≥46·2 compared with <38·3; DIL: ≥858 compared with <648) and inflammatory biomarkers including IL-6 and C-reactive protein (CRP). In another study, hyperglycaemia was associated with increased levels of inflammatory biomarkers (OR for CRP: 1·33; for IL-6: 1·51 and TNF-α: 1·14)[43]. Under normal conditions, the pro-inflammatory effects of glucose are controlled by the anti-inflammatory action of insulin[44]. However, in the current study, high levels of FBS in participants with high DIL (who might have reduced insulin secretion due to older age), might be an explanation for increased levels of hs-CRP.

Our failure to find relationships with a number of biomarkers may be due to several limitations. The cross-sectional design of the study prevents us from making causal inferences. Therefore, prospective studies are needed to evaluate these associations over longer periods. Second, since our study only included men, the results are not generalisable to the both sexes. Third, in this study basal insulin secretion was assessed by taking fasting insulin samples. However, DII is based on postprandial insulin secretion. Fourth, in addition to dietary factors that affect the insulin levels, it is important to consider multiple other factors that determine insulin levels such as physical activity [45,46], anthropometric characteristics and genetic predisposition[47–49]. Fifth, the insulin index values for foods were derived from a study that was conducted in young lean students whose insulin responses are relatively different from elderly and obese subjects[17]. However, according to a validation study, the positive link between insulin index and TAG concentrations is expected to be stronger among overweight subjects[11]. This suggests that the insulin index would also be applicable in heavier subjects. Sixth, using an FFQ as a retrospective dietary assessment tool might cause misclassification. Despite our best effort to control for major confounders, some additional confounders may not have been accounted for or residual confounding may remain. One such confounder might be recent changes in body weight as it has been shown to be associated with CVD risk factors[50–52], particularly incidence and remission of insulin resistance[51].

The current study has several strengths. First, limited research is available on the association between insulin indices and cardiovascular risk factors. Second, not all published studies have comprehensively taken into account different cardiovascular risk factors. However, in the present study, glycaemic parameters, lipid profile and also inflammatory biomarkers

were investigated to provide better insight into the association between DIL and CVD risk factors. Third, as little information is available about dietary patterns and indices such as DIL in the elderly, attention to this group is critical. Fourth, the elderly are at higher risk of insulin resistance, therefore examining the association between dietary insulin indices and cardiovascular risk factors is important.

Conclusion

In this cross-sectional study, DIL was positively associated with serum FBS and hs-CRP levels. However, no association was observed between DIL and BMI or lipid profiles. More research is needed to elucidate the association between DIL and other cardiovascular risk factors and to understand potential differences by sex.

Acknowledgements

The authors thank the subjects who participated in the study.

This study was funded by the National Institute for Medical Research Development (grant no. 965430). The National Institute for Medical Research had no role in the design, analysis or writing of this article.

H. M., N. N. and L. A. designed the study. H. M., N. N., B. L., P. J. S. and L. A. contributed to the statistical analysis, interpretation of the data and to the drafting of the manuscript. The final version of the manuscript was approved by all authors before submission.

The authors declare that there are no conflicts of interest.

References

1. Pagidipati NJ & Gaziano TA (2013) Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. *Circulation* **127**, 749–756.
2. Centers for Disease Control and Prevention (2011) Prevalence of coronary heart disease–United States, 2006–2010. *MMWR Morb Mortal Wkly Rep* **60**, 1377–1381.
3. Guarner V & Rubio-Ruiz ME (2015) Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. *Interdiscip Top Gerontol* **40**, 99–106.
4. Nagasaki K, Hara H, Ogawa J, *et al.* (1986) Relationship between hyperinsulinemia and risk factors of atherosclerosis. *Jpn J Med* **25**, 270–277.
5. Haffner SM, Fong D, Hazuda HP, *et al.* (1988) Hyperinsulinemia, upper body adiposity, and cardiovascular risk factors in non-diabetics. *Metabolism* **37**, 338–345.
6. Fournier AM, Gadia MT, Kubrusly DB, *et al.* (1986) Blood pressure, insulin, and glycemia in nondiabetic subjects. *Am J Med* **80**, 861–864.
7. Dandona P, Aljada A & Bandyopadhyay A (2004) Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* **25**, 4–7.
8. Hensrud DD (2004) Diet and obesity. *Curr Opin Gastroenterol* **20**, 119–124.
9. Galland L (2010) Diet and inflammation. *Nutr Clin Pract* **25**, 634–640.
10. Mekki K, Bouzidi-bekada N, Kaddous A, *et al.* (2010) Mediterranean diet improves dyslipidemia and biomarkers in chronic renal failure patients. *Food Funct* **1**, 110–115.
11. Nimptsch K, Brand-Miller JC, Franz M, *et al.* (2011) Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers. *Am J Clin Nutr* **94**, 182–190.
12. Setorki M, Nazari B, Asgary S, *et al.* (2011) Anti atherosclerotic effects of verjuice on hypocholesterolemic rabbits. *Afr J Pharm Pharmacol* **5**, 1038–1045.
13. Pereira MA, Jacobs DR Jr, Pins JJ, *et al.* (2002) Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr* **75**, 848–855.
14. Pereira MA, Jacobs DR Jr, Van Horn L, *et al.* (2002) Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. *JAMA* **287**, 2081–2089.
15. Zhang Z-F, Lu J, Zheng Y-L, *et al.* (2013) Purple sweet potato color attenuates hepatic insulin resistance via blocking oxidative stress and endoplasmic reticulum stress in high-fat-diet-treated mice. *J Nutr Biochem* **24**, 1008–1018.
16. Mirmiran P, Esfandiari S, Bahadoran Z, *et al.* (2015) 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* **15**, 23.
17. Holt S, Miller J & Petocz P (1997) An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. *Am J Clin Nutr* **66**, 1264–1276.
18. Bao J, de Jong V, Atkinson F, *et al.* (2009) Food insulin index: physiologic basis for predicting insulin demand evoked by composite meals. *Am J Clin Nutr* **90**, 986–992.
19. Bao Y, Nimptsch K, Meyerhardt J, *et al.* (2010) Dietary insulin load, dietary insulin index, and colorectal cancer. *Cancer Epidemiol Biomarkers Prev* **19**, 3020–3026.
20. Pyörälä K, Savolainen E, Kaukola S, *et al.* (1985) Plasma insulin as coronary heart disease risk factor: relationship to other risk factors and predictive value during 91/2-year follow-up of the Helsinki policemen study population. *J Intern Med* **218**, 38–52.
21. Joslowski G, Goletzke J, Cheng G, *et al.* (2012) Prospective associations of dietary insulin demand, glycemic index, and glycemic load during puberty with body composition in young adulthood. *Int J Obes* **36**, 1463–1471.
22. Weidner G (2000) Why do men get more heart disease than women? An international perspective. *J Am Coll Health* **48**, 291–294.
23. Maas A & Appelman Y (2010) Gender differences in coronary heart disease. *Neth Heart J* **18**, 598–603.
24. Saraf-Bank S, Haghighatdoost F, Esmaillzadeh A, *et al.* (2017) Adherence to healthy eating index-2010 is inversely associated with metabolic syndrome and its features among Iranian adult women. *Eur J Clin Nutr* **71**, 425–430.
25. Fard NRP, Karimi M, Baghaei MH, *et al.* (2015) Dairy consumption, cardiovascular risk factors and inflammation in elderly subjects. *ARYA Atheroscler* **11**, 323–331.
26. Mirmiran P, Esfahani FH, Mehrabi Y, *et al.* (2010) Reliability and relative validity of an FFQ for nutrients in the Tehran Lipid and Glucose Study. *Public Health Nutr* **13**, 654–662.
27. Azadbakht L, Kimiagar M, Mehrabi Y, *et al.* (2007) Dietary soya intake alters plasma antioxidant status and lipid peroxidation in postmenopausal women with the metabolic syndrome. *Br J Nutr* **98**, 807–813.
28. Esmaillzadeh A & Azadbakht L (2011) Different kinds of vegetable oils in relation to individual cardiovascular risk factors among Iranian women. *Br J Nutr* **105**, 919–927.
29. Bell K (2014) Clinical Application of the Food Insulin Index to Diabetes Mellitus. PhD thesis, University of Sydney, School of Molecular and Microbial Bioscience. http://hdl.handle.net/2123/11945 (accessed February 2019).

30. Matthews D, Hosker J, Rudenski A, *et al.* (1985) Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419.
31. Katz A, Nambi SS, Mather K, *et al.* (2000) Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* **85**, 2402–2410.
32. Garmaroudi GR & Moradi A (2010) Socio-economic status in Iran: a study of measurement index. *PAYESH* **9**, 137–144.
33. Collier GR, Greenberg GR, Wolever TM, *et al.* (1988) The acute effect of fat on insulin secretion. *J Clin Endocrinol Metab* **66**, 323–326.
34. Gannon MC, Nuttall FQ, Neil BJ, *et al.* (1988) The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. *Metab Clin Exp* **37**, 1081–1088.
35. Gannon MC, Nuttall FQ, Westphal SA, *et al.* (1993) The effect of fat and carbohydrate on plasma glucose, insulin, C-peptide, and triglycerides in normal male subjects. *J Am Coll Nutr* **12**, 36–41.
36. Azadbakht L & Esmaillzadeh A (2009) Soy-protein consumption and kidney-related biomarkers among type 2 diabetics: a crossover, randomized clinical trial. *J Ren Nutr* **19**, 479–486.
37. Chaput J-P, Tremblay A, Rimm EB, *et al.* (2008) A novel interaction between dietary composition and insulin secretion: effects on weight gain in the Quebec Family Study. *Am J Clin Nutr* **87**, 303–309.
38. McKeigue P, Shah B & Marmot M (1991) Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* **337**, 382–386.
39. Ludwig DS, Majzoub JA, Al-Zahrani A, *et al.* (1999) High glycemic index foods, overeating, and obesity. *Pediatrics* **103**, E26.
40. Reaven GM (1988) Role of insulin resistance in human disease. *Diabetes* **37**, 1595–1607.
41. Liu S, Manson JE, Stampfer MJ, *et al.* (2001) Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr* **73**, 560–566.
42. Rock CL, Flatt SW, Thomson CA, *et al.* (2004) Plasma triacylglycerol and HDL cholesterol concentrations confirm self-reported changes in carbohydrate and fat intakes in women in a diet intervention trial. *J Nutr* **134**, 342–347.
43. De Rekeneire N, Peila R, Ding J, *et al.* (2006) Diabetes, hyperglycemia, and inflammation in older individuals: the Health, Aging and Body Composition Study. *Diabetes Care* **29**, 1902–1908.
44. Esposito K, Marfella R & Giugliano D (2003) Stress hyperglycemia, inflammation, and cardiovascular events. *Diabetes Care* **26**, 1650–1651.
45. Steele RM, Brage S, Corder K, *et al.* (2008) Physical activity, cardiorespiratory fitness, and the metabolic syndrome in youth. *J Appl Physiol* **105**, 342–351.
46. Fedewa MV, Gist NH, Evans EM, *et al.* (2014) Exercise and insulin resistance in youth: a meta-analysis. *Pediatrics* **133**, e163–e174.
47. Strawbridge RJ, Dupuis J, Prokopenko I, *et al.* (2011) Genome–wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type 2 diabetes. *Diabetes* **60**, 2624–2634.
48. Manning AK, Hivert M-F, Scott RA, *et al.* (2012) A genome–wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. *Nat Genet* **44**, 659–669.
49. Wang J, Wu Z, Li D, *et al.* (2012) Nutrition, epigenetics, and metabolic syndrome. *Antioxid Redox Signaling* **17**, 282–301.
50. Alnasir FA & Masuadi EM (2006) The effect of loss of body weight on lipid profile in overweight individuals. *Saudi Med J* **27**, 687–692.
51. Chang Y, Sung E, Yun KE, *et al.* (2013) Weight change as a predictor of incidence and remission of insulin resistance. *PLOS ONE* **8**, e63690.
52. Vasunilashorn S (2013) Retrospective reports of weight change and inflammation in the US National Health and Nutrition Examination Survey. *J Obes* **2013**, 601534.