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ORIGINAL CONTRIBUTION

Association between glycemic index, glycemic load, and fructose with insulin resistance: the CDC of the Canary Islands study

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Abstract
Background The involvement of carbohydrates in triggering insulin resistance (IR) remains a source of controversy.
Aim of the study To study the relation between glycemic index (GI), glycemic load (GL), and fructose with insulin resistance in a predominantly rural population in the Canary Islands.
Methods Cross-sectional study carried out in 668 nondiabetic people aged 18–75. IR was estimated with serum glucose and C-peptide (HOMA2-IR). Nutrient intakes were obtained from a validated food frequency questionnaire. ANOVA was used to analyze nutrient distribution across quartiles of HOMA2-IR. Four multivariate nutrient density models (dependent variable: log-transformed HOMA2-IR) which differed only in the kinds of carbohydrates included were tested (Model 1: carbohydrates; Model 2: GI and then GL; Model 3: free fructose, other simple sugars and starch; Model 4: total fructose, remaining sugars and starch).
Results There was no association between GI and IR. There was a direct association between GL ($P < 0.001$), fructose (free [$P = 0.001$], total [$P = 0.013$]), energy intake ($P < 0.001$), fruit fiber (<0.001), and glucose ($P = 0.003$) with IR. There was an inverse association between cereal ($P = 0.008$) and vegetable fiber ($P < 0.001$) and IR. Multivariate models corroborated the association of carbohydrates, GL, fructose, vegetable fiber, and energy intake with IR. The association between GL and IR disappeared when Model 2 was adjusted by total fructose intake.
Conclusions There was a direct association between fructose intake and IR. There was no relationship between GI and IR. Although a direct association of GL with IR was detected, it was attributable to the consumption of fructose.

Keywords Insulin resistance · Glycemic index · Glycemic load · Fructose · Dietary fiber · Energy intake

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Introduction

In recent decades, the prevalence of chronic noncommunicable disorders such as obesity, diabetes, and cardiovascular disease has increased in wealthy countries [1]. However, it remains unclear which specific aspects of nutrition have a determining influence on the appearance of elevated rates of obesity. The involvement of carbohydrates in triggering obesity and diabetes currently remains a source of controversy. Glycemic index (GI), a measure of the glycemic response to carbohydrate-containing foods, and glycemic load (GL), a measure of both carbohydrate quality and quantity, have been suggested as dietary factors involved in the appearance of type 2 diabetes mellitus [2–5] and coronary disease [6]. Several cross-sectional studies that have analyzed the relationship between GI, GL and insulin resistance (IR) or metabolic

syndrome have yielded contradictory results [7–10] but most of them have found that a high fiber content in the diet was associated with lower IR [7–9]. Mc Keown et al. found that low IR was specifically associated with consumption of cereal fiber, but not fruit or vegetable fiber [8], and Schulze et al. found that the risk of type 2 diabetes was low in women who consumed more cereal and vegetable fiber [2]. Moreover, several studies have observed a clear association between the consumption of soft drinks and metabolic syndrome and diabetes [11–13]. This may be explained by a higher fructose intake from high-fructose ingredients such as corn syrup added to beverages and foods, and the resulting weight gain [14], dyslipidemia and insulin resistance [15]. Few studies, however, have analyzed the association between fructose and insulin resistance in human beings. The Inter 99 Study found an inverse association [8], whereas others suggested a direct relation [13, 16].

The Canary Islands have a higher prevalence of obesity (28 vs. 23%) and type 2 diabetes (11 vs. 6.2%) than continental Spain [17, 18]. The incidence of diabetes in the Canary Islands is not known, but varies in other autonomous communities in Spain from 8 to 10 cases per 1,000 inhabitants per year in the north [19, 20] to 19 per 1,000 inhabitants per year in the south [21]. The ENCA study found a prevalence of IR (as measured with HOMA) in the Canary Islands of 27.2% [22].

Accordingly, the present study was designed to investigate the relationship between GI, GL, and fructose with IR in a sample of the Canary Islands population.

Methods

Study population

The participants in this cross-sectional study were the first 773 individuals enrolled as part of the "CDC of the Canary Island" study (CDC stands for *c*ancer, diabetes and *c*ardiovascular disease), described elsewhere [17]. One pregnant women, 98 participants who identified themselves as having a diagnosis of diabetes, 4 people who stated their energy intake was less than 800 calories/day, and 3 participants with missing values were excluded from the present study, so the final sample size was 668 participants. The total sample of the CDC study ($n = 6{,}729$) was recruited between 2000 and 2005 inclusive; all participants were chosen randomly from the census of health care system affiliates in the seven Canary Islands (age 18–75 years), since public health care covers 99% of the population, and the participation rate was 70%. The 668 participants in the study reported here reside on the islands of El Hierro, La Gomera, and Tenerife and are mainly from rural settings. On average, they were 6.5 years older than the complete CDC study population, with no difference in body mass index (BMI) (27.8 vs. 27.7 kg/m^2) or waist circumference (90.4 vs. 90.3 cm). The study was approved by the Bioethics Committee of the Nuestra Señora de La Candelaria University Hospital.

Measures

All participants underwent physical examination, and a blood sample was obtained from each individual. Participants were weighed (kg) and measured (cm) in light clothing after removing their footwear. Waist circumference was measured at a point halfway between the lowest rib and the iliac crest with the subject breathing normally, and hip circumference was measured at the level of the greater trochanters of both femurs. Heart rate and blood pressure were also recorded, the latter as the mean of two values obtained 5 min apart with the participant seated. Fasting samples of venous blood were drawn and serum aliquots were stored at −80 °C. Blood glucose concentration was recorded for all participants within 24 h after blood was obtained; measurements were made with a Hitachi® 917 autoanalyzer.

Because of cost-efficiency considerations, one aliquot of serum was thawed only for the first 773 individuals enrolled in the study. This aliquot was used to measure the serum concentration of C-peptide. Enzyme-linked immunosorbent assay techniques were used to determine C-peptide (Biosource®, ng/mL, intraassay coefficient of variation 6.3%, interassay coefficient of variation 4.7%). Insulin resistance was estimated from fasting serum glucose and C-peptide concentrations with a computer-based Homeostasis Model Assessment system (HOMA2-IR) provided by the Oxford Centre for Diabetes Endocrinology & Metabolism (http://www.dtu.ox.ac.uk/homa). This model is considered valid for the type of study reported here [23].

The CDC Questionnaire (available at: http://www.icic.es/cuestionario-CDC/docs/encuesta_CDC.pdf) was used to obtain information on social, educational, occupational, and economic variables, personal and family history of disease, use of medication, smoking and eating habits and physical activity. Dietary habits were explored with a food frequency questionnaire (FFQ) which estimated the consumption of 138 food items with 125 closed-response items and 7 open-response items to obtain information about 13 additional food items. This questionnaire has been validated in Spain for adult Canary Island population [24]. The FFQ was validated for food groups and nutrients by determining correlations with mean values obtained from three 24-h recalls. For nutrients, the correlation coefficients, adjusted by calory intake, ranged from 0.248 for

proteins to 0.601 for vitamin C. Mean daily intakes of each food were determined by converting frequencies of consumption to 24-h equivalents. These figures were multiplied by the amount of food per portion, expressed in grams, to obtain daily intakes in grams. Values taken from the food composition tables published by Mataix et al. [25] were adjusted according to the edible portion and weight loss during cooking to convert food intakes to nutrient intakes. Then, the total daily intake of each nutrient was obtained by adding intakes contributed by each food. Mean daily intakes were thus estimated for calories, proteins, fats, carbohydrates, and alcohol. Nutrient density (amount in grams per 1,000 calories – 4,184 kJ – consumed per day) was estimated for nutrients. The amount of alcohol consumed in grams was adjusted to 1,000 calories per day (alcohol density). Daily physical activity (weekly average during the preceding year) was estimated as the sum of work-related, leisure-related, and other activities and was expressed in metabolic equivalents (MET). Participants were considered sedentary if they devoted fewer than 25 (women) or 30 min (men) per day to leisure activities that consumed at least 4 MET [26].

Glycemic index, glycemic load, sugars, and starch

The GI for each food was obtained from the International Table published in 2002 [27], with the scale for glucose. Gofio, a porridge made from toasted cereal flour consumed widely in the Canary Islands, was assigned a GI of 72, halfway between that of its main ingredients corn flour and wheat flour. When more than one GI was found for the same food item, we assigned the value that best reflected the most common cooking or serving technique in the Canary Islands (potato stew, boiled rice, ripe banana, etc.) when no cooking method was specified. The mean GI for each participant was found by totalling the products of the digestible carbohydrate content per serving for each item, multiplied by the average number of servings of that food per day, multiplied by their GI. This product was divided by the total daily intake of digestible carbohydrates. The average dietary GL for each participant was calculated the same way except that the product was divided by 100 instead of by the total amount of carbohydrates consumed per day. Glycemic load was adjusted to 1,000 calories consumed per day (GL density).

To calculate the consumption of fructose, glucose, sucrose, lactose, and starch, the USDA National Nutrient Database for Standard Reference (http://www.nal.usda.gov/fnic/foodcomp/search/) was used. Total fructose was estimated by summing free fructose plus 50% fructose integrated in sucrose. The nutritional densities of these sugars and for starch were also calculated.

Statistical analysis

The results are reported as the mean ± standard deviation or as proportions with 95% confidence intervals. Student's *t* test was used for bivariate comparisons of continuous variables, and continuous and categorical variables were compared with analysis of variance. Pearson's correlation coefficients between GI, GL, carbohydrates, sugars, and starch were calculated. To determine whether there was a linear association between quartiles of HOMA2-IR and the nutritional density of nutrients, we used linear regression analysis that included age, sex, and nutritional density as independent variables and quartiles of HOMA2-IR as the dependent variable. Associations between qualitative variables were sought with Pearson's Chi-squared test. A multivariate nutrient density model [28] was used to determine the associations between IR (with log-transformed HOMA2-IR value as the dependent variable) and the other factors studied here. Linear regression was used, retaining in the model BMI, waist circumference and age as known determinants of IR. Backward regression analysis was used for all other factors studied here. As explanatory variables, we included nutrient density of carbohydrates, fats (MUFA, PUFA, and SFA), proteins, vegetable fiber, cereal fiber, fruit fiber and starchy-pulse fiber, alcohol density, energy intake adjusting for other potential confounding factors such as smoking, daily physical exercise, and family history of diabetes mellitus (Model 1). A second model was run with first GI and then GL density instead of carbohydrates (Model 2). Another model was run with fructose, glucose, lactose, sucrose, and starch instead of carbohydrates (Model 3). A fourth model was tested with total fructose and the sum of the remaining of simple sugars (50% glucose from sucrose included) and starch instead of carbohydrates (Model 4). The results of these analyses are reported as nonstandardized linear regression coefficients and their 95% confidence intervals, and as standardized regression coefficients (SB).

A sample size of 668 individuals to estimate regression coefficients with magnitude of at least 0.012 ensured a potency of at least 85% for two-tailed hypothesis testing with a significance level of 0.05. All statistical analyses were done with SPSS v. 15.0 software.

Results

The population of participants consumed a mean of 290.7 ± 118.4 g/day carbohydrates and 23.50 ± 12.1 g/day fiber. Mean GI was 51.0 ± 9.8 and mean GL was 146.4 ± 60.8. The mean daily consumption of the different sugars in grams was as follows: free fructose 48.6 ± 31.0, free glucose 31.5 ± 20.1, sucrose 52.9 ± 28.8, lactose

29.9 ± 23.1, and starch 65.4 ± 43. The daily intake of total fructose was 74.7 ± 41.7 g. Macronutrients contributed the following proportions of total energy intake: carbohydrates 51%, fats 33.7%, and proteins 15.3%. Table 1 summarizes the general characteristics of the sample and its distribution across quartiles of IR; only age and anthropometric measures presented significant association with IR.

Table 2 shows the distribution of nutritional variables adjusted for age and sex according to IR quartiles. This analysis shows a direct association of IR with energy intake, total fiber, GL, GL density, free fructose nutrient density (ND), glucose ND, and total fructose ND. When total fiber was stratified into its components, only fruit fiber maintained a direct association with IR, whereas the fiber from vegetables and cereals showed an inverse association with IR.

Table 3 presents correlation coefficients between GI, GL, carbohydrates, sugars, and starch. Glycemic load correlated strongly with fructose and sucrose. Table 4 summarizes the results with each of the four models used to test the associations found in the univariate analysis. Regression analysis confirmed all associations except the one between IR and fruit fiber. Cereal intakes were associated with IR only in the model that included GL. Glucose intake was not associated with IR in Models 3 or 4. The association between waist circumference and IR was not statistically significant although there was a tendency toward an inverse association (regression coefficient −0.007; $P = 0.116$ in model 4D). Model 2 (Table 4) was also tested with mean daily GI instead of GL density, but this variable was not retained. When model 2 was adjusted including total fructose as an independent variable, GL density was not retained.

Discussion

Our results show that consumption of carbohydrates was directly associated with IR. This association appears to be tied to GL and fructose. The observed relationship between GL and IR seems to be a consequence of the association of fructose (free and from sucrose) with GL. On the other hand, the intake vegetable fiber was inversely associated with IR.

Concerning fiber, previous studies found an inverse association between fiber and IR [7–9]. In our study

Table 1 Insulin resistance (HOMA2-IR) by quartiles and factors analyzed

	Sample ($n = 668$)	HOMA2-IR by quartile				*P*
		Quartile 1 (<1.8)	Quartile 2 (1.8–2.79)	Quartile 3 (2.8–4.39)	Quartile 4 (≥4.4)	
Sex						
Men	319 (48)	75 (23)	71 (22)	97 (30)	76 (24)	0.419
Women	349 (52)	89 (26)	82 (24)	86 (25)	92 (26)	
Age (years)	47.7 ± 12.7	43 ± 12.9	44 ± 12.2	51 ± 12.8	52 ± 10.6	<0.001
Body mass index	27.9 ± 4.9	27.1 ± 4.9	27 ± 7.7	28.2 ± 4.9	28.7 ± 4.7	<0.05
Waist circumference (cm)	90.3 ± 12.7	88.5 ± 12.8	88.7 ± 13	91.5 ± 12.7	92.3 ± 12	<0.05
Waist/Hip ratio	0.95 ± 0.08	0.92 ± 0.08	0.93 ± 0.1	0.97 ± 0.06	0.98 ± 0.05	<0.001
Systolic blood pressure (mm Hg)	125.2 ± 21.5	121.6 ± 21.3	124.9 ± 22	127.5 ± 21.8	126.3 ± 20.9	0.074
Diastolic blood pressure (mm Hg)	79.7 ± 11.4	78.3 ± 11.9	80.7 ± 12.2	79.4 ± 11.1	80.4 ± 10.2	0.229
Current smoker						
No	518 (77.5)	124 (24)	116 (22)	147 (28)	131 (25)	0.643
Yes	150 (22.5)	40 (27)	37 (25)	36 (24)	37 (25)	
Family history of diabetes mellitus						
No	479 (71.7)	123 (26)	103 (22)	135 (28)	118 (25)	0.409
Yes	189 (28.3)	41 (22)	50 (27)	48 (25)	50 (27)	
Sedentary lifestyle						
Yes	421 (68.5)	101 (24)	101 (24)	120 (29)	99 (24)	0.484
No	247(31.5)	63 (26)	52 (21)	63 (26)	69 (28)	
Weekly average MET/day[a]	32.7 ± 8.7	34.1 ± 9.4	31.8 ± 8.1	32.4 ± 8.4	32.4 ± 8.7	0.086

The data are expressed as observed frequencies and percentages or as the mean ± standard deviation as appropriate

MET metabolic equivalents, *ND* nutrient density

[a] During the preceding year

Table 2 Insulin resistance (HOMA2-IR) by quartiles and nutritional factors analyzed

	Sample (*n*) (668)	HOMA2-IR by quartile				*P**
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Energy intake(kJ/day)	9,613 ± 3,315	8,650 ± 3,255	9,632 ± 3,526	9,720 ± 3,127	10,403 ± 3,319	<0.001
ND carbohydrates	126.6 ± 24.8	122.3 ± 23.5	125.9 ± 26.9	126.8 ± 25.0	131.2 ± 23.1	0.094
Glycemic index	51.0 ± 9.8	50.1 ± 9.20	52.0 ± 10.2	51.0 ± 10.2	50.5 ± 9.4	0.430
Glycemic load	146.4 ± 60.8	126.1 ± 59.3	147.6 ± 62.6	148.2 ± 57.4	162.7 ± 59.3	<0.001
Glycemic load D	63.6 ± 15.7	60.6 ± 14.3	64.7 ± 16.3	63.8 ± 14.8	65.4 ± 13.1	0.062
ND total fructose	32.1 ± 12.3	29.4 ± 11.3	31.6 ± 14.0	32.1 ± 12.2	34.9 ± 11.3	0.013
ND free fructose	20.7 ± 9.9	18.5 ± 9.4	19.9 ± 10.5	21.1 ± 9.6	23.1 ± 9.4	0.001
ND sucrose	23.1 ± 10.0	22.4 ± 9.2	24.1 ± 11.8	22.2 ± 10.0	23.7 ± 8.9	0.467
ND glucose	13.4 ± 6.4	12.1 ± 5.9	12.9 ± 6.7	13.6 ± 6.4	15.0 ± 6.3	0.003
ND lactose	13.2 ± 9.9	13.7 ± 11.2	11.2 ± 6.4	14.0 ± 11.7	13.8 ± 9.1	0.502
ND starch	27.7 ± 14.6	26.5 ± 16.3	29.2 ± 14.8	28.0 ± 14.9	27.2 ± 11.9	0.684
ND total fiber	10.2 ± 3.6	9.2 ± 3.2	9.9 ± 3.8	10.4 ± 3.6	11.1 ± 3.3	0.006
ND vegetable fiber	1.4 ± 1.2	1.7 ± 1.7	1.5 ± 1.2	1.2 ± 0.8	1.2 ± 0.9	<0.001
ND cereal fiber	1.3 ± 1.0	1.4 ± 1.0	1.4 ± 1.1	1.2 ± 0.9	1.1 ± 0.6	0.008
ND fruit fiber	4.7 ± 3.1	3.8 ± 3.0	4.4 ± 3.5	5.0 ± 3.0	5.6 ± 2.9	<0.001
ND starchy-pulse fiber	1.0 ± 0.5	0.9 ± 0.5	1.0 ± 0.5	1.1 ± 0.5	1.1 ± 0.5	0.153
ND proteins	39.8 ± 7.6	39.5 ± 7.9	39.3 ± 8.3	39.5 ± 7.3	40.9 ± 7.1	0.324
ND Fats	37.3 ± 8.3	39.1 ± 9.1	37.5 ± 8.5	37.1 ± 7.9	35.8 ± 7.4	0.158
ND SFA	9.8 ± 3.3	10.4 ± 3.4	9.9 ± 3.4	9.8 ± 3.3	9.2 ± 2.8	0.185
ND MUFA	15.0 ± 4.5	16.0 ± 5.1	15.0 ± 4.7	14.8 ± 4.2	14.4 ± 3.9	0.083
ND PUFA	5.6 ± 2.1	5.7 ± 2.6	5.6 ± 2.1	5.6 ± 2.1	5.4 ± 1.8	0.402

D density, *ND* nutrient density, *SFA* saturated fats, *MUFA* monounsaturated fats, *PUFA* polyunsaturated fats

* Adjusted by sex and age

Table 3 Pearson's Correlation coefficients between nutrient densities of simple sugars and starch and carbohydrates, glycemic load and glycemic index

	Carbohydrates	Glycemic load	Glycemic index
Total fructose	0.669**	0.505**	–0.108*
Free fructose	0.595**	0.308**	–0.253**
Glucose	0.621**	0.358**	–0.229**
Sucrose	0.479**	0.630**	0.222**
Lactose	0.115*	0.065	–0.055
Starch	0.130**	0.390**	0.308**

* $P < 0.05$; ** $P < 0.001$

population, we found an inverse relationship between vegetable fiber and IR. Although we were surprised by this because in the initial univariate analysis we observed a direct association between fruit fiber and IR, this association disappeared in the multivariate models. These results suggest that it is carbohydrates, specifically fructose consumption, that are related to IR and that the association observed in the univariate analysis between total fiber or fruit fiber and IR was due to the interaction between the latter and fructose.

We found that proteins were associated with increased IR. To our knowledge, no previous epidemiological studies have specifically related protein consumption with IR. However, Wolever et al. reported an association between protein intake and the incidence of diabetes in the Native North American population [29]. Subsequent studies confirmed the relationship between meat intake and the incidence of type 2 diabetes [30, 31]. Experimental studies have shown that a constant high dietary intake of protein of 1.87 g kg^{-1} day^{-1} during 6 months stimulates the secretion of glucagon and insulin [32].

Except for age, energy intake was the variable that showed the strongest association with IR in the multivariate models. Several authors have documented the relationship between higher energy intake and IR in earlier studies [33, 34]. However, these studies were experimental in nature, and as was the case for proteins, we found no population studies that reported a direct relationship between calorie intake and IR.

Although we found no relationship between IR and GI, GL was related to IR. A noteworthy aspect of this finding is that our GL values were higher than in other reports (e.g., 146 vs. 131 in the Framingham Offsprings Study, 130 for a

Table 4 Multiple linear regression models with log-HOMA2-IR as the dependent variable

	B (95% CI)	SB
Model 1		
Age	0.013 (0.008; 0.018)	0.223
Energy intake (kJ/1,000)	0.046 (0.028; 0.063)	0.207
ND protein	0.008 (0.001; 0.016)	0.086
ND vegetable fiber	−0.058 (−0.104; −0.012)	−0.095
MET/day	−0.007 (−0.014; −0.001)	−0.075
ND carbohydrates	0.003 (0.001; 0.005)	0.107
BMI	0.025 (0.004; 0.045)	0.160
Waist circumference	−0.007 (−0.015; 0.001)	−0.122
Model 2		
Age	0.014 (0.010; 0.019)	0.244
Energy intake (kJ/1,000)	0.041 (0.024; 0.058)	0.186
ND protein	0.009 (0.001; 0.016)	0.089
ND vegetable fiber	−0.054 (−0.099; −0.008)	−0.088
ND cereal fiber	−0.064 (−0.125; −0.002)	−0.091
MET/day	−0.007 (−0.013; −0.0003)	−0.078
GL density	0.005 (0.001; 0.009)	0.099
BMI	0.024 (0.003; 0.044)	0.155
Waist circumference	−0.007 (−0.015; 0.001)	−0.124
Model 3		
Age	0.014 (0.009; 0.019)	0.240
Energy intake (kJ/1,000)	0.039 (0.022; 0.056)	0.179
ND protein	0.007 (−0.0001; 0.014)	0.073
ND vegetable fiber	−0.069 (−0.115; −0.023)	−0.113
MET/day	−0.007 (−0.013; −0.001)	−0.082
ND free fructose	0.007 (0.001; 0.013)	0.107
BMI	0.021 (0.001; 0.042)	0.139
Waist circumference	−0.006 (−0.014; 0.002)	−0.106
Model 4		
Age	0.013 (0.009; 0.018)	0.243
Energy intake (kJ/1,000)	0.043 (0.025; 0.060)	0.194
ND protein	0.008 (0.001; 0.015)	0.092
ND vegetable fiber	−0.061 (−0108; −0.015)	−0.100
MET/day	−0.007 (−0.014; −0.001)	−0.084
ND total fructose	0.005 (0.001; 0.010)	0.090
BMI	0.022 (0.001; 0.043)	0.143
Waist circumference	−0.007 (−0.015; 0.002)	−0.111

Model 1 Rest of included variables: ND of saturated, monounsaturated, and polyunsaturated fats, ND starch fiber, ND fruit fiber, cereal fiber, alcohol density and gender, family history of diabetes and current smoking status. *Model 2* Rest of included variables: same as model 1 except carbohydrates. *Model 3* Rest of included variables: glucose, lactose, sucrose, starch and the same as model 1 except carbohydrates. *Model 4* Rest of included variables: glucose (including glucose from sucrose), lactose, and starch instead of carbohydrates. All other variables included models 1, 2, 3, and 4 were removed from the final model since they were not significantly associated ($P < 0.05$)

BMI body mass index, *GL* glycemic load, *MET* metabolic equivalents, *ND* nutrient density, *SB* standardized β coefficient

Dutch population, and 128 in the IRAS study) [7, 9, 10]. In fact, ours is the only study to date that found an association between GL and IR. Glycemic load depends not only on the type but also on the amount of carbohydrates consumed, and fructose and sucrose are also associated with higher GL. Mean cereal consumption by our study population was 110 g/day (data not shown), a figure well below the 200–400 g/day intake recommended by the Spanish Community Nutrition Society [35]. The low cereal consumption and high fruit intake detected in our study have been described before in the Canary Islands population [36]; accordingly, both the high GL and its association with IR can be explained by the high consumption of sucrose and fructose (both abundant in fruit).

The association observed between fructose intake and IR has been described by other authors. In the Inter 99 study, the association was inverse, a finding attributed to the protective effect of fruit and vegetables, the food items that provide most of this sugar [8]. However, this study did not investigate food items such as soft drinks, juice, selected sweets and pastries, and some relatively new low-fat and fructose-rich food products; fructose consumption was low among the participants in the Inter 99 study at less than 10 g/day of free fructose. In our study, the intake of fructose (48.6 g/day of free fructose and 74.7 g/day of total fructose) was also higher than in the USA general population (54.7 g/day of total fructose) [37]. Moreover, our results are similar to those of the Nurses' Health Study, which found that C-peptide levels increased with both free and total fructose consumption or with increasing GL [16]. Our findings for fructose are also consistent with results published by Sartorelli et al., who observed a relationship between free fructose intake (21.6 g/day) and impaired glucose tolerance in a population of Japanese Brazilians with a high risk of diabetes [13]. However, these authors found no association between fruit intake and impaired glucose tolerance. The mechanisms that relate high-fructose consumption to IR may be based on the increase in de novo lipogenesis, blood triglycerides, and liver IR [38]. Although high-fructose consumption has not been shown to produce muscular IR, a fructose-rich diet has been shown to increase stearoyl-CoA desaturase-1 and glucose transporter-4 and to decreases peroxisomal proliferator-activated receptor-gamma coactivator-1 alpha in muscles, which may be early markers of IR [39].

In the population we studied, fruit consumption and consequently fructose intake were high. This probably reflects the eminently rural nature of the sample we studied. Among the earliest participants enrolled in the CDC study, 82.5% were from the islands of El Hierro and La Gomera, the smallest and least-populated of the Canary Islands. On these islands, farming is still widespread, either as regular work or as a leisure-time activity.

Eating fruit as part of a regular diet is highly recommended, but we believe that excessive fruit consumption, as in this population, may undermine the benefits of fruit fiber because of fructose overload. The recommended optimum consumption of fruit and vegetables for the Spanish population is more than 400 and 300 g/day, respectively [40]. In our Canary Island population sample, mean fruit consumption was 684 g/day and mean vegetable consumption was 202 g/day (data not shown). The recommended optimum consumption of fructose has not been established for healthy people; however, obesity and diabetes rates were low when total fructose intake was in the range of 25–40 g/day [41], and mean fructose consumption in our sample was above these figures. High levels of fruit consumption (foods with a low GI) and low cereal consumption (foods with a higher GI) may account for the low mean GI in our study population.

An unexpected finding was the lack of association between waist circumference and IR in the multivariate models. Two factors may explain this result. First, the relatively small sample size may have favored beta (type II) error, making statistically significant differences undetectable. Second, fructose intakes more than 25% above the recommended energy requirement in people with overweight or obesity could favor the accumulation of intra-abdominal fat [42]. An interaction between fructose intake and waist circumference in our multivariate models may explain why the regression coefficient was negative.

A limitation of this study that should be taken into account is its cross-sectional design, which means that we cannot adduce causality to any of the associations we observed. Nevertheless, the relationship between fructose intake and IR seems plausible from experimental studies [42]. Moreover, since our population is predominantly rural, people consume fructose mainly from natural foods, a source which should be considered when our results are compared to those for other populations that consume fructose mainly from food or beverage additives such as corn syrup, as is the case in most urban western societies. We found no relationship between sugar-sweetened beverages (or fructose in these products) and IR (data not shown). A further limitation is the lack of information on the amounts of different sugars (glucose, fructose, galactose, sucrose, and starch) in Spanish foods—a situation that led us to use the USDA National Nutrient Database). Finally, the CDC-FFQ, like most similar instruments, was not developed with glycemic index or fructose intake estimation in mind. However, the FFQ was designed to minimize random within-person variation by assessing the average long-term diet, and this is important when dietary data are used to assess diet–disease associations [43].

We conclude that although we found no relationship between GI and IR in this Canary Islands population, we documented a direct association between GL and fructose intake with IR. Nevertheless, the association between GL and IR appears to be a reflection of the relationship between fructose (free or sucrose-derived) and GL.

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Conflict of interest statement The authors state that they have no conflict of interest.

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