Original Article

Relationships between Serum Resistin and Fat Intake, Serum Lipid Concentrations and Adiposity in the General Population

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***Aims*: The serum resistin level is associated with the incidence of ischemic heart disease in the general population. We analyzed the associations between serum resistin and fat intake, serum lipid concentrations and adiposity in the general population.**

***Methods*: A cross-sectional study of 6,637 randomly recruited adults was conducted. The resistin levels were measured in thawed aliquots of serum using an enzyme immunoanalysis technique.**

***Results*: The resistin level exhibited a positive nonparametric correlation with saturated fat intake ($p<0.001$) and an inverse correlation with adherence to the Mediterranean diet ($p<0.001$), monounsaturated fat intake ($p<0.05$), total serum cholesterol ($p<0.001$), non-HDL cholesterol ($p<0.001$), LDL cholesterol ($p<0.001$), body mass index ($p<0.001$), waist circumference ($p<0.001$) and the waist/height ratio ($p<0.001$). An elevated resistin concentration (fifth quintile) was associated with adherence to the Mediterranean diet (OR=0.82 $CI_{95\%}$=0.71-0.93), saturated fat intake (OR=1.34 $CI_{95\%}$=1.16-1.56), monounsaturated fat intake (OR=0.88 $CI_{95\%}$=0.78-0.99), a total cholesterol level of ≥200 mg/dL (OR=0.81 $CI_{95\%}$=0.72-0.91), a low HDL cholesterol level (OR=0.84 $CI_{95\%}$=0.76-0.93), a high non-HDL cholesterol level (OR=0.84 $CI_{95\%}$=0.72-0.99), a high LDL cholesterol level (OR=0.82 $CI_{95\%}$=0.70-0.97) and a waist/height ratio of ≥0.55 (OR=0.76 $CI_{95\%}$=0.67-0.85). The multivariate models corroborated the positive associations between the resistin level and saturated fat intake ($p<0.001$) and serum triglycerides ($p=0.004$) and the inverse associations between the resistin level and adherence to the Mediterranean diet ($p=0.002$), total serum cholesterol ($p<0.001$) and cholesterol fractions and the waist/height ratio ($p=0.02$).**

***Conclusions*: In the general population, the serum resistin level is associated with fat intake: positively with saturated fat intake and inversely with monounsaturated fat intake. As a consequence, the resistin level is also inversely associated with adherence to the Mediterranean diet. In addition, the resistin level is inversely associated with the serum cholesterol level and adiposity.**

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Key words: Resistin, Fat intake, Lipids, Adiposity, Population

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Introduction

Resistin is a proinflammatory protein formed from 108 amino acids; the gene that encodes resistin is located on chromosome 19. This cytokine was discovered in 2001 and has been proposed to be a poten-

tial marker of the link between obesity and diabetes[1]. Although it plays this role in mice, resistin is synthesized in this species primarily in adipose tissue; this is not the case in humans. In our species, resistin is synthesized primarily by mononuclear cells outside adipose tissue, and its production is associated with the expression of proinflammatory mediators, such as TNF-α, IL-1 and IL-6[2-4].

The proinflammatory activity of this cytokine is thus related to the development of atherosclerosis and is associated with the occurrence of ischemic heart disease and stroke in patients[5, 6] and the general population[7], as well as mortality from heart disease[8]. More specifically, resistin promotes the formation of foam cells[9] in which cholesterol crystals trigger the process of inflammation by activating an inflammasome component, termed NOD-like receptor P3[10]. Inflammasomes have been defined as intracytoplasmic, multiprotein "scaffolding" components in which the enzyme caspase-1 functions via IL-1 and IL-18 production[11] in the process of atherogenesis and the induction of insulin resistance and obesity[10, 12]. However, the relationship between resistin and adipose tissue remains unclear; although the resistin levels are increased in obese patients with a history of myocardial infarction[13], they are not decreased in obese patients who lose weight[14]. The evidence available to date regarding the relationship between resistin and adiposity in humans thus remains inconclusive[15].

It is well known that a decreased dietary intake of saturated fat and a decreased serum lipid concentration following treatment with statins reduce the levels of markers of inflammation in patients with atherosclerotic plaque[16]. However, very few studies have analyzed the relationship between the resistin and serum lipid levels in large samples drawn from the general population[17], and we were unable to locate any studies designed to investigate the relationship between resistin and fat intake or any particular type of dietary pattern.

The aim of the present study was therefore to investigate the association between the serum resistin concentration and fat intake, serum lipid levels and anthropometric indices of adiposity in the general population.

Subjects and Methods

The participants of this study were drawn from the CDC de Canarias cohort (CDC is an acronym for cardiovascular, diabetes and cancer), which included individuals randomly selected from the general population of the Canary Islands (Spain) between 2000 and 2005 and constitutes a representative sample of the adult population. The methodology used for this analysis has been reported previously[18]. Briefly, the participation rate was 70%, and all recruited participants (n=6,729; age range 18-75 years) were interviewed in order to obtain information about their personal and family antecedents regarding health and lifestyle (diet, physical activity, smoking, alcohol consumption, etc.). All participants provided their informed consent to take part in the study, which was approved by the Clinical Research Ethics Committee of Hospital Universitario Nuestra Señora de la Candelaria. Each participant underwent a physical examination during which anthropometric indices were recorded. For the current analysis, we used the parameters of waist circumference (in cm), body mass index (BMI, in kg/m^2) and the waist/height ratio. Venous blood samples were obtained after at least 10 hours of abstention from food and liquids. The samples were centrifuged *in situ* (room temperature, 2,000 rpm for 10 minutes) and transported daily to the hospital for lipid measurement within 24 hours. The serum samples were frozen at −80℃ until measurement of the resistin concentrations.

The lipid levels were measured with a Hitachi 917 autoanalyzer, and the results were recorded as the serum concentration in mg/dL. When the level of triglycerides was <300 mg/dL, the level of low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula. The level of non-high-density lipoprotein (Non-HDL-C=total cholesterol minus HDL-C) was measured to compensate for the inaccuracy of the Friedewald equation in calculating LDL when triglycerides are elevated[19].

The resistin concentrations were measured in thawed aliquots of serum using an enzyme immunoanalysis technique (ng/mL, Bio-Vendor®, Heidelberg, Germany; interassay coefficient of variation, 7.72%; intra-assay variation, 3.22%). In order to calculate the coefficients of variation, serum samples from 600 patients seen at the Immunology Unit of our hospital were pooled weekly. Aliquots from this pool were stored at −80℃ until use. The serum resistin concentrations were measured in 32 aliquots to determine the intra-assay coefficient of variation and in 42 aliquots to measure the interassay coefficient of variation.

In order to obtain information regarding dietary habits, we used a food frequency questionnaire validated for our study population[20]. The intake of saturated and monounsaturated fatty acids was estimated and expressed in g/day and adjusted for nutrient density (g/1,000 calories)[21]. In order to analyze the tradi-

Table 1. Summary (mean ± SD) of the variables evaluated in this study and the results of between-sex comparisons

	Total $n=6637$	Women $n=3757$	Men $n=2880$	p
Serum resistin (ng/mL)	5.88 ± 2.33	6.06 ± 2.41	5.63 ± 2.18	< 0.001
Age (years)	42.91 ± 12.77	42.91 ± 12.78	42.92 ± 12.75	0.975
Adherence to Mediterranean diet	4.74 ± 1.59	4.54 ± 1.57	5.00 ± 1.57	< 0.001
Daily calorie intake	1983.52 ± 297.17	1808.07 ± 179.50	2214.81 ± 261.12	< 0.001
Saturated fat intake (g/day)	28.32 ± 6.04	26.19 ± 4.71	31.12 ± 6.43	< 0.001
Mono-unsaturated fat intake (g/day)	32.27 ± 5.75	29.43 ± 3.83	36.02 ± 5.71	< 0.001
Total serum cholesterol (mg/dL)	202.88 ± 41.51	201.93 ± 40.74	204.12 ± 42.46	0.034
HDL cholesterol (mg/dL)	51.12 ± 13.45	54.71 ± 13.19	46.43 ± 12.31	< 0.001
Non-HDL cholesterol (mg/dL)	151.78 ± 42.51	147.23 ± 41.41	157.71 ± 43.21	< 0.001
LDL cholesterol (mg/dL)	127.64 ± 36.33	125.70 ± 35.78	130.21 ± 36.90	< 0.001
Triglycerides (mg/dL)	122.38 ± 91.38	108.32 ± 80.01	140.71 ± 101.48	< 0.001
Body mass index (kg/m^2)	27.42 ± 5.03	27.35 ± 5.55	27.51 ± 4.25	0.182
Waist circumference (cm)	90.79 ± 13.47	87.19 ± 13.76	95.47 ± 11.51	< 0.001
Waist/Height ratio	0.55 ± 0.11	0.54 ± 0.13	0.55 ± 0.08	< 0.001

The mean values of women and men were compared using *t*-tests.

tional Mediterranean diet, which we studied as a dietary pattern of a low saturated fat intake, we considered the following food groups: cereals, fruits and nuts, vegetables, potatoes and legumes, olive oil, fish, dairy products, meat, sugar and sweets and alcoholic beverages. Adherence to the Mediterranean diet was measured by adapting the scale proposed by Trichopoulou *et al.*[22] A value of 0 or 1 was assigned to each of the 10 indicated components using the sex-specific median as the cutoff value. With respect to beneficial components, individuals whose consumption was below the median were assigned a value of 0, while those whose consumption was at or above the median were assigned a value of 1. Regarding detrimental components, individuals whose consumption was below the median were assigned a value of 1, while those whose consumption was at or above the median were assigned a value of 0. For ethanol, a value of 1 was assigned to men who consumed between 10 and 50 g/day of alcohol and women who consumed between 5 and 25 g/day of alcohol. Therefore, the total adapted score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 10 (maximal adherence).

Statistical Analysis

Continuous variables are summarized as the mean ± standard deviation for comparisons between sexes using Student's *t*-test. The serum resistin and triglyceride concentrations were log transformed before comparison. In order to determine the bivariate associations between the resistin level and each of the other study variables, we used Spearman's rank correlation coefficient (rho) as a nonparametric test, and a trend analysis was performed between the serum resistin quintiles (Q) and the studied variables.

The strength of the bivariate associations for correlated variables was determined based on the upper quintile (Q_5) of the resistin level for each sex as an indicator of exposure to elevated resistin. The remaining variables were categorized according to accepted criteria (based on expert consensus) for exposure to risk: total cholesterol ≥ 200 mg/dL, LDL cholesterol ≥ 160 mg/dL, HDL cholesterol ≤ 40 mg/dL in men and ≤ 50 in women, BMI ≥ 25 kg/m^2 and waist/height ratio ≥ 0.55. For triglycerides, non-HDL cholesterol and saturated and monounsaturated fat intake (stratified by sex), we used the fifth quintile as a cutoff point. Based on the literature[22, 23], we assumed that individuals in the two upper quintiles (Q_4 and Q_5) of the indicator of adherence possessed dietary habits consistent with the Mediterranean diet. The results of these associations are reported as odds ratios (ORs) and 95% confidence intervals ($CI_{95\%}$).

For the multivariate analyses, we fitted two linear models with the resistin concentration (ng/mL) as the dependent variable using two sets of independent variables. In model A, the independent variables were sex, age, waist/height ratio, adherence to the Mediterranean diet, total cholesterol and triglycerides. In model B, adherence to the Mediterranean diet was replaced with saturated and monounsaturated fatty acid intake, and total cholesterol was replaced with HDL and non-HDL cholesterol. This model was also adjusted by

Table 2. Association between the resistin concentration and the serum lipid levels, fat intake and anthropometric indices

	Quintiles Resistin					p^*
	Q_1 ($n=1347$)	Q_2 ($n=1325$)	Q_3 ($n=1320$)	Q_4 ($n=1323$)	Q_5 ($n=1322$)	
Age (years)	46.11 ± 12.69	43.93 ± 12.74	41.64 ± 12.98	41.76 ± 12.50	41.06 ± 12.23	< 0.001
Adh. Mediterranean diet	4.86 ± 1.56	4.73 ± 1.55	4.79 ± 1.61	4.69 ± 1.61	4.63 ± 1.61	< 0.001
Daily calorie intake	1968.08 ± 300.77	1967.37 ± 288.50	1989.28 ± 304.31	1989.31 ± 295.05	2003.88 ± 295.81	0.001
Saturated fat intake (g/day)	27.41 ± 5.96	27.69 ± 5.78	28.66 ± 6.09	28.71 ± 5.96	29.16 ± 6.21	< 0.001
Unsaturat. fat intake (g/day)	31.99 ± 5.67	32.09 ± 5.60	32.54 ± 5.94	32.28 ± 5.76	32.46 ± 5.77	0.028 §
Total cholesterol (mg/dL)	209.37 ± 42.39	205.14 ± 41.18	199.39 ± 40.32	201.86 ± 40.88	198.54 ± 41.84	< 0.001
HDL cholesterol (mg/dL)	52.99 ± 14.03	50.84 ± 13.37	51.11 ± 12.76	50.73 ± 13.24	49.87 ± 13.64	< 0.001
Non-HDL cholest. (mg/dL)	156.42 ± 43.42	154.23 ± 42.85	148.32 ± 41.15	151.23 ± 42.15	148.65 ± 42.41	< 0.001
LDL cholesterol (mg/dL)	132.43 ± 36.97	129.52 ± 36.49	124.99 ± 34.91	126.97 ± 36.07	124.23 ± 36.60	< 0.001
Triglycerides (mg/dL)	121.73 ± 106.89	126.77 ± 92.45	118.03 ± 82.08	121.20 ± 80.18	124.17 ± 92.41	0.760
Body mass index (kg/m^2)	27.77 ± 4.73	27.47 ± 5.05	27.22 ± 4.85	27.44 ± 5.25	27.20 ± 5.21	0.007 §
Waist circumference (cm)	91.83 ± 12.89	91.10 ± 13.75	90.07 ± 12.95	90.71 ± 13.71	90.21 ± 13.98	< 0.001
Waist/Height ratio	0.56 ± 0.15	0.55 ± 0.91	0.54 ± 0.09	0.54 ± 0.11	0.53 ± 0.11	< 0.001

* p for trend between the serum resistin quintiles (Q) and the studied variables. § Not significant following Bonferroni correction.

replacing non-HDL cholesterol with LDL cholesterol and replacing nutrient intake (g/day) with nutrient density (g/1,000 calories) with and without daily calorie intake. All calculations were performed using the SPSS© version 19 software program in Spanish, and graphs were generated with the R v. 2.10 program (R Foundation for Statistical Computing).

Results

The resistin levels were measured in 6,637 participants. **Table 1** shows the values for all variables studied in both sexes. The resistin levels were lower in men (**Table 1**), and the cutoff point for the upper quintile (Q_5) used as the reference value for an elevated resistin concentration was 6.5 ng/mL in men and 7.1 ng/mL in women.

The serum resistin concentration exhibited a significant ($p<0.001$) nonparametric correlation with age (rho = −0.148), adherence to the Mediterranean diet (rho = −0.068), saturated fat intake (rho = 0.060), total cholesterol level (rho = −0.097), LDL cholesterol level (rho = −0.091), non-HDL cholesterol level (rho = −0.085), BMI (rho = −0.059) and waist/height ratio (rho = −0.092). With the exception of triglycerides, there were significant associations between the serum resistin quintiles and the studied variables (**Table 2**).

The categorization of the variables for intake, serum lipids and anthropometric indices yielded an increased OR for an elevated resistin concentration between 8% and 34% and a decreased OR between 4% and 24% in the bivariate analysis (**Fig. 1**).

The multivariate analysis (**Table 3**) showed that the first of the two multiple linear regression models (A) confirmed the associations reported above for age, adherence to the Mediterranean diet, total cholesterol, serum triglycerides and the waist/height ratio. The second model (B) further corroborated the associations between the resistin level and saturated and monounsaturated fatty acid intake and the HDL and non-HDL cholesterol levels. Replacing non-HDL cholesterol with LDL cholesterol in model B did not modify the associations shown in **Table 3**, yielding a coefficient of −0.035 for LDL cholesterol ($p=0.010$). Likewise, replacing saturated and monounsaturated fatty acid intake with nutrient density did not modify the previous associations. Although BMI, waist circumference and total calorie intake were also included in both models, these variables were not retained in the multivariate analysis.

Discussion

This study showed that, in the general population, the serum resistin level is positively associated with saturated fat intake and inversely associated with monounsaturated fat intake. These relationships explain the inverse association observed between the resistin levels and adherence to the Mediterranean diet. We also found an inverse association between this cytokine and non-HDL cholesterol and corroborated the associations between serum resistin and

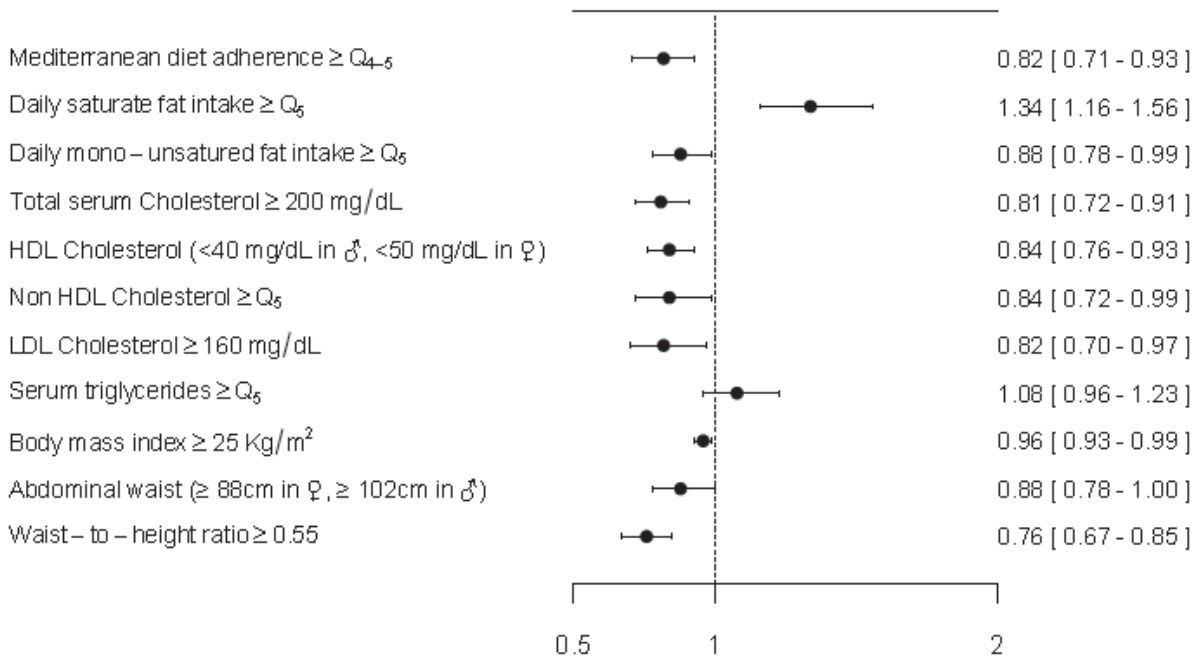

Fig. 1. Forest plot of the bivariate associations between the studied variables and an elevated resistin concentration (Q_5).

The numbers in the Figure are ORs [$CI_{95\%}$].

serum total cholesterol and its HDL and LDL fractions. In addition, we observed a positive association between this cytokine and triglycerides. The waist/height ratio was the only anthropometric index to exhibit evidence of an inverse relationship between the resistin level and adiposity.

To our knowledge, this is the largest sample in which the serum resistin concentrations have been measured and the first report of a well-documented relationship between the resistin level and fat intake in the general population. Although some correlations were apparently weak, it should be noted that these associations reflect changes in the serum concentration of a cytokine per 1-mg/dL variation in a lipid fraction or per 1-g/day differences in fat intake. Despite the present study's cross-sectional design, it is unreasonable to assume that resistin modifies an individual's diet. Moreover, the dietary intake was recorded before the resistin concentrations were measured. In individuals who follow a Western dietary pattern, eating can be considered to induce proinflammatory processes[24]. We therefore suggest that this dietary pattern, which is characterized by the intake of foods rich in saturated fat and poor in monounsaturated fat, favors the induction of inflammation and stimulates the production of resistin. In contrast, the Mediterranean diet, which is low in saturated fat and rich in monounsaturated fat, whose cardiovascular benefits have been well documented[25], reduces the resistin concentration. Against this background, hypocaloric diets are known to lower the concentrations of biomarkers of inflammation and adipokines[26]. However, the Mediterranean diet reduces inflammation without decreasing calorie intake[27], a finding that is also consistent with our observation that the resistin concentration is unrelated to calorie intake. We are aware of at least one earlier study (in a smaller sample) that failed to find an association between the resistin concentration and fat intake[28]; however, this result is likely attributable to insufficient statistical power as well as the fact that specific types of fat in the diet were not analyzed separately.

With regard to the inverse association between resistin and total cholesterol and its HDL and LDL fractions, our results are consistent with earlier findings in a cohort of 1,508 individuals 45 to 74 years of age[17]. We also found that the resistin level is associated with the non-HDL cholesterol level, a finding not previously reported in the literature. The inverse relationship between resistin and cholesterol can be attributed, at least in part, to the ability of resistin to sequester serum lipids and store them in macrophages[29]. However, the actions of HDL cholesterol counteract the effects of resistin, as the former has anti-inflammatory properties[30, 31] and is able to decrease the lipid

Table 3. Multivariate linear regression models corroborating the associations between the resistin concentration and fat intake, the serum lipid levels and adiposity in a general population

A: Linear regression model (n=6637)		
Dependent variable: RESISTIN (ng/mL)	Standardized regression coefficient	p
Sex: male	−0.096	<0.001
Age (years)	−0.086	<0.001
Adherence to Mediterranean diet	−0.038	0.002
Serum cholesterol (mg/dL)	−0.065	<0.001
Triglycerides (mg/dL)	0.073	<0.001
Waist/Height ratio	−0.032	0.018
B: Linear regression model (n=6637)		
Dependent variable: RESISTIN (ng/mL)	Standardized regression coefficient	p
Sex: male	−0.082	<0.001
Age (years)	−0.095	0.009
Saturated fat intake (g/day)	0.131	<0.001
Mono-unsaturated fat intake (g/day)	−0.148	<0.001
HDL cholesterol	−0.068	<0.001
Non-HDL cholesterol (mg/dL)	−0.047	0.004
Triglycerides (mg/dL)	0.050	0.004
Waist/Height ratio	−0.035	0.020

Compared to model A, model B did not include adherence to the Mediterranean diet (replaced with saturated and monounsaturated fatty acid intake) or total cholesterol (replaced with HDL and non-HDL cholesterol).

burden via reverse cholesterol transport[32, 33].

The positive association observed between resistin and triglycerides in this study is not consistent with the findings of earlier authors. This discrepancy may be attributable to differences in the degrees of fatty acid saturation within the triglyceride molecule, as a consequence of dietary differences between the different populations studied to date[34]. A further explanation may lie in differences between studies in terms of measurement techniques, hours of abstention from food before blood sample collection and other technical aspects. Moreover, markedly different populations have been used in different studies. For example, the present study is based on a sample of the general population, whereas other studies have focused on patients with metabolic syndrome[35] or myocardial infarction[36]. Some experimental studies have documented an increase in the serum resistin concentration during the postprandial period[37], a phenomenon that may be explained by the increase in triglycerides following food intake, consistent with the positive association between resistin and triglycerides observed in this study.

In the broader context, the relationships between resistin and lipids can be viewed as part of the process of inflammation. In patients with diseases that arise from pathogenic processes primarily associated with inflammation, the serum lipid levels are often decreased, possibly in relation to the accumulation of lipids in macrophages as a result of the actions of resistin[29]. This view is compatible with the observation of elevated resistin levels in patients with inflammatory diseases, such as rheumatoid arthritis, as the onset of arthritis is known to be preceded by a decrease in the levels of serum lipids[38] and an increase in the levels of proinflammatory cytokines[39]. This same line of reasoning can be invoked to explain why the serum lipid levels are increased in patients with rheumatoid arthritis who receive anti-inflammatory treatment[40].

A final consideration is that the inverse association between the resistin level and waist/height ratio raises a new point for discussion in the effort to elucidate the relationship between this cytokine and adiposity. The waist/height ratio is considered to reflect the cardiovascular risk due to excess adiposity more accurately than BMI[41, 42]. One study[17] described a positive relationship between the resistin concentration and waist circumference in a large sample of the adult population; however, the authors did not adjust this index for height, and this potential limitation may introduce bias due to the comparison of a variable (waist circumference) that is smaller in women with a variable (resistin) that is larger in women. Excellent

reviews have raised doubts regarding the relationship between resistin and adiposity[15]. In our sample - the largest general population sample studied to date - all indices of adiposity exhibited a negative association with the resistin concentration, although only the waist/height ratio remained significant according to a multivariate analysis. Adipose tissue thus does not appear to play a role in the production of this protein. Consequently, the role of resistin as an adipokine in humans may need to be reexamined. It is possible that adiposity and resistin generate cardiovascular risks via different pathways.

One limitation of this study is its cross-sectional design, which does not allow us to establish causal relationships, only associations between variables. However, the likely unidirectional nature of the association between diet and serum resistin, together with available knowledge regarding the association between diet and serum lipid concentrations, favor the direction of association observed between the resistin level and these parameters. The main strength of our study lies in our use of a large sample drawn randomly from the general population.

In conclusion, the serum resistin concentration was found to be positively associated with saturated fat intake and inversely associated with monounsaturated fat intake. As a consequence, adherence to the Mediterranean diet was also inversely associated with the resistin concentration. With regard to the serum lipid levels, the resistin concentration was inversely associated with total cholesterol and its fractions and positively associated with triglycerides. The only anthropometric index that exhibited a significant association was abdominal adiposity, which was inversely associated with serum resistin.

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Disclosures

None.

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