Accepted Manuscript

THE DIETARY INFLAMMATORY INDEX AND INSULIN RESISTANCE OR METABOLIC SYNDROME IN YOUNG ADULTS

Carolina Carvalho

PII: S0899-9007(18)30378-2
DOI: https://doi.org/10.1016/j.nut.2018.07.014
Reference: NUT 10287

To appear in: *Nutrition*

Received date: 15 May 2018
Revised date: 10 July 2018
Accepted date: 25 July 2018

Please cite this article as: Carolina Carvalho , THE DIETARY INFLAMMATORY INDEX AND INSULIN RESISTANCE OR METABOLIC SYNDROME IN YOUNG ADULTS, *Nutrition* (2018), doi: https://doi.org/10.1016/j.nut.2018.07.014

THE DIETARY INFLAMMATORY INDEX AND INSULIN RESISTANCE OR METABOLIC SYNDROME IN YOUNG ADULTS

Corresponding author. Dr Carolina Carvalho, Federal University of Maranhão, Federal Institute of Maranhão, Rua Barão de Itapari, 155, 65020-070 São Luís, Maranhão, Brazil.Phone: +55(98) 982386515, E-mail: carolcarvalho91@gmail.com

HIGHLIGHTS

- The mean of DII among Brazilian young adults was high.
- The subjects of the study were exposed a very inflammatory diet.
- No was found an association between DII and insulin resistance or metabolic syndrome.

ABSTRACT

Objective: To assess the association between the inflammatory potential of diet, as measured by the Dietary Inflammatory Index (DII®), and insulin resistance (IR) or metabolic syndrome (MS). **Research Methods & Procedures:** A cross-sectional study (nested within a cohort) was conducted on 2017 adults aged 23 to 25 years in Ribeirão Preto, Brazil. Food consumption was assessed using a validated food frequency questionnaire. DII scores were calculated from 35 available food parameters. IR was determined from the classification of homeostatic model assessment (HOMA) values (≥2.7uU mL-1). MS was diagnosed based on the Joint Interim Statement (JIS) criterion. The association of DII score with IR or MS was determined by Poisson regression analysis. The variables included in the multivariable model were selected from Directed Acyclic Graphs (DAG). **Results**: The diet of the young adults studied showed a high inflammatory potential, with a mean DII score of +1.10 (range: -4.69 to +5.28). The prevalence of MS was 12.2% and RI 12.3%; both were higher in males. The correlation between DII and HOMA-IR values was -0.038 (p=0.09). The DII was not associated with IR or MS in either sex. **Conclusion**: Although the association between DII and the outcomes was not detected in this sample, the study demonstrated that the diets of

these young adult Brazilians had a high inflammatory potential when compared with other studies. Future studies, preferably utilizing longitudinal designs, are recommended.

Key-words: Dietary Inflammatory Index; Metabolic Syndrome; Insulin Resistance; Young Adults; Food consumption;

LIST OF ABBREVIATIONS

ANOVA: Variance analysis

BMI: Body mass index

BRAMS: Brazilian Metabolic Syndrome Study

CI: Confidence Interval

CRP: C-reactive protein

DAG: Directed acyclic graph

DII: Dietary inflammatory index

FFQ: Food Frequency Questionnaire

HDI: Human development index

HDL-c: High density lipoprotein cholesterol

HOMA: Homeostatic model assessment

HPLC: High performance liquid chromatography

IL-10: Interleukin–10

IL-1β: Interleukin–1β

IL-4: Interleukin–4

IL-6: Interleukin–6

IPAQ: International Physical Activity Questionnaire

IR: Insulin resistance

JIS: Joint Interim Statement

METs: Metabolic Equivalent of Task

MS: Metabolic syndrome

MUFA: Monounsaturated fatty acids

NCDD: Noncommunicable diseases and disorders

NHANES: National Health and Nutrition Examination Survey

OR: Odds Ratio

PR: Prevalence Ratio

PUFA: polyunsaturated fatty acids

SD: Standard deviation

SEASONS: Seasonal Variation of Blood Cholesterol Study

TNF-α: Tumor necrosis factor-α

WHO: World Health Organization

INTRODUCTION

The worldwide increase in the prevalence of noncommunicable diseases and disorders (NCDD) has motivated studies searching for the causes of these diseases in order to identify preventive measures.

Insulin resistance (IR) is a metabolic disorder characterized by reduced sensitivity to the action of insulin on tissues [1]. Several studies have indicated a role of chronic inflammation in the pathogenesis of IR [2-4]. In turn, IR is considered to be one of the most important causative factors of metabolic syndrome (MS), acting as a link to all others metabolic abnormalities that characterize this condition [2, 5].

MS consists of a set of changes including disorders of glucose metabolism, abdominal obesity, dyslipidemia and increased blood pressure [6]. Chronic inflammation also interferes

with the genesis of MS, acting via IR and abdominal obesity [7-9]. Thus, a chronic inflammatory state may be a common cause of the development of IR and MS.

Several studies have suggested a role of diet in the regulation of chronic inflammation [5, 10-14]. The release of anti-inflammatory cytokines may be stimulated according to diet composition, contributing to the prevention of NCDD[5, 10-14]. The Dietary Inflammatory Index (DII®) has been created in order to characterize the inflammatory potential of the diet [15]. The DII is a score obtained from individual food intake based on the pro- or anti-inflammatory properties of foods, nutrients or food constituents with evidence showing an effect on inflammatory markers [16].

Some studies have explored the association between DII and MS; however, the results are still inconclusive [17-21]. One cohort study has demonstrated the existence of an association between DII and the development of MS [20]. However, three cross-sectional studies [17, 18, 22] and two other cohort studies [19, 21] have not detected this association. IR is considered to be one of the main precursors of MS; however, the association between DII and IR has received little attention and the relationship is still unclear. One study with a cross-sectional design [22] and another cohort study [19], using the current DII, were conducted and did not detect any association. On the other hand, van Woudenbergh et al.[23], using an adapted DII, demonstrated an association of DII with IR, also in a cross-sectional study. All of these studies investigated these outcomes in older adults, including the elderly. However, it is known that deterioration of the quality of the diet of the population, as well as the onset of NCDD, are occurring increasingly earlier [24, 25].

Thus, we hypothesized that a pro-inflammatory diet may promote an inflammatory state, which could lead to the occurrence of cardiovascular risk factors such as IR and MS even in younger individuals in Brazil. There are few studies about this association in middle-income countries such as Brazil and the nutrition transition is known to occur in different

ways across high-, middle-, and low-income countries [26]. It is well known that dietary factors can interact with aspects of socioeconomic status [27] and Brazil is known to have concentrations of food insecurity and poor dietary quality with a transition toward processed foods that may exacerbate problems with IR and MS[28-30]. Thus, the objective of the present study was to assess the diet inflammatory potential and the association of DII with IR or MS in a population of young Brazilian adults.

MATERIALS AND METHODS

Study population

A cross-sectional study was conducted on 2017 young adults aged 23 to 25 years who are part of the fourth follow-up period of the cohort study entitled "Epidemiological-social study of perinatal health in Ribeirão Preto, São Paulo, Brazil", carried out from 2002 to 2004.

The city of Ribeirão Preto, located 320 km from the capital of the state of São Paulo, in the southeast region of Brazil (the richest in the country), had 527.733 inhabitants in 2003. It is one of the most developed cities in the country with a monthly per capita income of R$ 1070.28 (U$$ 339.09) and a human development index (HDI) of 0.733 in 2000 [31, 32].

A total of 9067 liveborns delivered at all the hospitals in Ribeirão Preto between June 1978 and May 1979 were evaluated in the first part of the study, representing 98% of all births. Children whose families did not reside in the municipality (2094 babies) and twins (146 babies) were excluded, resulting in a total of 6827 newborns [33].

Of these, 343 died before completing 20 years of age. Thus, 6484 subjects were potentially eligible in the fourth phase of the study. The search for these subjects was based on the records of the Unified Health System and of private health plans, as well as on contacts obtained during the second and third phases of the study, permitting us to locate 5665 adults. For data collection, the city of Ribeirão Preto was divided into four regions

according to family head income. Next, it was decided to interview one third of the potentially eligible subjects, corresponding to 2161 individuals. Thus, one of each three subjects belonging to the cohort in each region was invited to participate in the follow-up. In instances when the subject refused to participate in the study or was not located, the next participant on the list was contacted. There were 209 refusals, 34 deaths after 20 years of age, 31 subjects who were not interviewed because they were in jail, and 431 subjects who did not attend the interview. Thus, a total of 2063 adults were evaluated [33].

The sample size was calculated considering the prevalence of the studied outcomes of 13%, accuracy of 1% and the design effect of 2.0. The sample size required for a 99% confidence level was 987 individuals.

Two participants were excluded from the study because they did not fill out the Food Frequency Questionnaire (FFQ). An additional 44 participants were excluded because their energy intake was outside the ±3 standard deviation (SD) limit. Thus the final study sample consisted of 2017 adults aged 23 to 25 years. More details about the study are available elsewhere [33].

This study was approved by the ethics committee of the Faculdade de Medicina de Ribeirão Preto (n^{o} 7606/99) and performed in accordance with the ethical standards. All participants gave their informed consent prior to their inclusion in the study.

Food intake and DII calculation

The DII was used to assess the inflammatory potential of the diet [16] The DII is a score that ranges from low values (minimum ≈ -8) that represent an anti-inflammatory diet to high values (maximum ≈ +8) that indicate a proinflammatory diet. This index was created based on an extensive literature review in order to assess the effect of food parameters (foods/nutrients) on the inflammatory markers Interleukin–1β (IL-1β), Interleukin–4 (IL-4),

Interleukin–6 (IL-6), Interleukin–10 (IL-10), Tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP). The score of the inflammatory effect of each of 45 food parameter identified in the search was calculated on the basis of this review[16].

In order to avoid obtaining arbitrary values due to the use of crude food intake quantities with different measuring units, a regionally representative database was created with the food intake representative of the populations of 11 countries (USA, Bahrain, Australia, Denmark, India, Japan, Zealand, Taiwan, South Korea, Mexico, UK). The food intake data of the present study were standardized on the basis of the mean and standard deviation of each food parameter of the DII originating from this database. The standardized values of each food parameter were then converted to centered percentiles and multiplied by their respective inflammatory effect scores calculated from the literature review regarding the DII, resulting in the final DII for each food parameter. Finally, the total DII was calculated from the sum of the final DII value for each food parameter. More details about the method for the calculation of the DII can be obtained from the study of Shivappa et al. [16].

Food intake of the study sample was assessed using a 75-item FFQ validated for the Japanese-Brazilian community of São Paulo, with food of Japanese origin being excluded. The reproducibility of the FFQ and the relative validity were evaluated by repeated administration at one-month interval and by comparison with dietary intake obtained from four three-day weighed dietary records, respectively[34]. Participants were asked to refer to their habitual dietary intake during the 12 months preceding data collection [35].

The food intake data were evaluated based on tables of national food composition such as the Survey of Family Budgets and the Brazilian Table of Food Composition (TACO in the Portuguese acronym). In order to assess some DII parameters that were not available in Brazilian tables, such as caffeine and alcohol, we used the North American food composition

table (United States Department of Agriculture – USDA). In view of unavailable quantitation of flavonoids in the above tables, we consulted the study by Santos[36].

In this study, a total of 35 food parameters were used to calculate the DII: folic acid, monounsaturated fatty acids, polyunsaturated fatty acids, alcohol, caffeine, carbohydrates, black tea, cholesterol, energy, iron, fibers, flavonol, flavones, isoflavones, flavonones, flavon-3-ol, anthocyanidins, saturated fat, total fat, trans fat, magnesium, niacin, omega-3, omega-6, proteins, riboflavin, selenium, thiamine, vitamins A, B6, B12, C, D, E, and zinc. The food parameters oregano, rosemary, onion, garlic, ginger, saffron, curcumin, pepper, beta-carotene and eugenol were not included because they were not part of the FFQ used in the study or in the food composition tables or both.

The DII was categorized into tertiles. Negative DII values indicate that the diet has a low inflammatory potential and positive values indicate a high inflammatory potential [16].

2.3 Metabolic syndrome and insulin resistance

A blood sample was collected from each participant aseptically by a doctor or nursing technician after a fast of at least 12 hours. Fasting glycemia was determined by the GOD /PAP human diagnostic colorimetric enzymatic method (Chronolab AG, Zug, Switzerland). Fasting insulin was measured by radioimmunoassay (insulin kit, DPC, Los Angeles, CA, USA). Total cholesterol, HDL cholesterol and triglycerides were determined by an enzymatic colorimetric method using the Dade Behring XPand apparatus (Dade Behring, Liederbach, Germany) and reagents of Dade Behring Dimension clinical chemistry[33]. More details about the techniques used to obtain these measurements have been described by Barbieri et al[33].

The diagnosis of MS was established according to the Joint Interim Statement (JIS) criterion based on the presence of at least three of the following criteria: 1) fasting glucose

≥100 mg/dL; 2) blood pressure ≥130 mmHg or ≥85 mmHg; 3) HDL-c <40 mg/dL for men and <50 mg/dL for women; 4) triglycerides ≥150 mg/dL; 5) waist circumference ≥90 cm for men and ≥80 cm for women [37].

Insulin resistance was determined by HOMA-IR using the formula: HOMA-IR = Insulin (μU/mL) x (glycemia mg/dL÷18)÷22.5. An IR diagnosis was considered when HOMA-IR was > 2.7 [38].

2.4 Co-variables

The level of physical activity over the last week was determined using the International Physical Activity Questionnaire (IPAQ)[39]. The IPAQ was validated for use in Brazilians adults by means a movement sensor Computer Science & Applications and the reproducibility was determined seven days later. The subjects were classified as sedentary, sufficiently active and active [40].

The daily total energy value and alcohol consumption were calculated using the information from the FFQ and the amount of kilocalories consumed per day (kcal / day) was calculated. Alcohol intake was expressed in grams consumed per day. Family income, schooling, smoking and sex were obtained using semi-structured questionnaires.

The directed acyclic graph (DAG) was used to select the confounding factors that would be included in the adjusted analysis. The DAG is a causal diagram that illustrates theoretical models by graphically representing relationships between variables and by applying heuristic rules. This method was used because it permits selection of the variables that need to be adjusted in the analysis in order to minimize the magnitude of confounding bias; it also helps to avoid over-adjustment of the variables[41, 42].

Figure 1 illustrates the DAG representing the DII as the exposure variable and MS and IR as outcomes. The factors causing MS and IR were considered to be the same, so that it

is possible to assume a single DAG for these two outcomes [6]. IR is considered to be an event that precedes the development of MS[6, 9], so that it would act as a mediator in the relationship between DII and MS, requiring no adjustment in the analysis. Again, for the study of the association between DII and IR it is not necessary to adjust for MS, because MS is a consequence of IR. In the present study, obesity was measured by means of the body mass index (BMI) and was not included in the adjustment because it is not correct to adjust for a variable that mediates the outcomes under study.

Based on the proposed DAG, the minimum set of variables needed to be adjusted for the control of confounding included: age (years), family income in multiples of the month minimum wage (tertiles) and schooling (0-4, 5-8, 9-11 and ≥12 years).

Statistical analysis

The data were analyzed statistically using Stata® software, version 14.0. The distribution of the variables was described using boxplot graphs, a histogram and by examining kurtosis and asymmetry values. According to their distribution, the variables were presented as means or medians followed by standard deviation and range.

Due to the occurrence of follow-up losses inverse probability of selection weighting was performed. The purpose of this procedure is to reestablish the initial composition of the sample at the baseline. The groups that had lower follow-up rates were given higher weights whereas groups with higher follow-up rates were given lower weights.

The socioeconomic, lifestyle and metabolic variables were compared within tertiles of the DII using the chi-square test. ANOVA was used to compare the means and the nonparametric Kruskal-Wallis test was used to compare the medians. To evaluate the variables distribution, we analyze boxplots and histograms, values of skewness and kurtosis, and applied the Shapiro Wilk test.

The nutrients, HOMA-IR and family income that did not show normal distribution were transformed into logarithms or square root values. After this, the nutrients were adjusted for energy by the residual method [43]. After the analysis, the variables were converted to their original units of measurement, for the purpose of presenting the results.

The correlation between DII and HOMA-IR values was determined using the Pearson correlation test and the association of DII with IR or MS was determined using Poisson regression with robust variance. In the multivariate analysis, the variables pointed out by DAG were included for confounding control and selection bias. The analysis of the association between DII and isolated components of MS (blood pressure, waist circumference, triglycerides and HDL) also was performed. The level of significance was set at 0.05 in all analyses.

This study was approved by the Research Ethical Committee under the protocol number 7606/99 and all participants signed a written consent form and received a copy for their records.

RESULTS

The mean age of the subjects under study was 23.9 years and 53.1% were women. Their DII ranged from -4.69 to 5.28, with a mean of +1.10. The mean values were +0.74 (±1.72) for men and +1.42 (±1.83) for women. The overall prevalence of IR was 12.3%; 14.1% for men and 10.7% for women. The prevalence of MS was 12.2%; 18.9% for men and 6.3% for women.

Table 1 presents the socioeconomic, lifestyle and metabolic characteristics by DII tertile according to sex. Among men, there was a higher proportion of active individuals ($p<0.001$) in the lowest DII tertile (anti-inflammatory) and individuals with lower levels of education ($p=0.012$) in the second tertile. Among women, the prevalence of sedentary

lifestyle (p<0.001) was higher among those who belonged to the higher DII tertile (pro-inflammatory).

The mean daily intake of the food parameters used in calculating the DII is presented in Table 2. Among men, higher consumption of the food parameters was observed in subjects in the lowest (most anti-inflammatory) DII tertile, except for total (p<0.001), saturated (p<0.001), trans (p<0.001) and monounsaturated fatty acids (p<0.001). Similarly, among women, most of the dietary parameters were most consumed by those belonging to the lowest DII tercile, except total (p<0.001), saturated (p<0.001), trans (p=0.025) and monounsaturated fat (p<0.001), which were most consumed in the higher DII (pro-inflammatory) tercile.

The correlation between DII and HOMA-IR values was r= -0.005 (p=0.87) for men and r= -0.040 (p=0.19) for woman. Adjusted analysis for confounding variables did not reveal an association of the increase in DII with insulin resistance among men (PR=0.98; 95%CI=0.89-1.08, p=0.76) or women (PR=0.96; 95%CI=0.87-1.07, p=0.48). Similarly, the increase in DII was not associated with MS among men (PR=0.98; 95%CI=0.91-1.07, p=0.67) or women (PR=1.05; 95%CI=0.91-1.20, p=0.53) (Table 3). The DII and the isolated components of SM also were not associated (data not shown).

DISCUSSION

No association was detected in the present study between DII scores and IR or MS among young adults. However, comparing with other studies that investigated the relation between DII and metabolic outcomes [17, 19, 20, 22, 44] the mean DII score was high in this sample.

Only one cohort study detected an association between DII and MS among French subjects, who were 48.9 years of age, on average, and who were followed up over a mean period of 12.4 years [20]. All other studies [17, 18, 22], with a cross-sectional design and

conducted on significantly older populations than the present one, did not detect an association. Similarly, Alkerwi et al.[22], in a study of Luxembourg adults, did not detect a significant association between DII and IR. Van Woudenbergh et al[23], using an adapted DII, detected the presence of an association between DII and IR in sample of adult, including elderly Dutch subjects. However, we would like to point out that the adaptations made in the DII used by Van Woudenbergh et al [23], such as the exclusion of some foods that were present in the original DII and the adjustment of nutrients according to energy before calculating the final DII, impair a comparison with the present study.

The prevalence of MS in the present study was lower (12.2%) than in other studies that evaluated the association of this outcome with the DII. Alkerwi et al. [22], studying a sample of adults and the elderly, with a mean age of 44 years, found a prevalence of 26.2%. In Poland, Sokol et al. [17] found a prevalence of 30% of MS among adults and the elderly from 45 to 64 years. It should be considered that these studies studied populations older than those in the present study, which helps explain the higher prevalence.

The no association of DII with MS and IR in our study may be related to the fact that risk factors for chronic diseases act over a long period of time until they culminate in the development of the disease [45, 46]. Therefore, it is possible that the effect of a pro-inflammatory diet in promoting these outcomes has not yet had time to manifest itself.

The occurrence of these diseases in the sample studied may be associated with several other mechanisms, besides diet, that influence the occurrence of inflammation and may also cause these outcomes [47, 48].

Originally, the DII was validated in a sample of US subjects with a mean age of 49 years in the Seasonal Variation of Blood Cholesterol Study (SEASONS)[15]. Subsequently, it was validated in three additional populations in the U.S.: in the Women's Health Initiative[49], in a population of African-Americans in South Carolina [18] and in the

NHANES [50]. It also was subjected to construct validation in three studies conducted among adults in Europe (i.e., in Belgium [51] and France [44]) and among children in Greece, Germany, Belgium, France, Austria, and Spain [44, 52]. When testing the validity of this index in a population of adults and elderly people in Luxembourg, Alkerwi et al. [22] did not detect an association between C-reactive protein levels and DII scores; the only study to date in which a statistically significant association was not observed. Without access to data on inflammatory markers for validation in the present study we could not verify its validity in this population.

DII scores in the current sample ranged from -4.69 to +5.28, with a mean of +1.07, indicating the proinflammatory characteristic of the diet. This result indicates that the diet is harmful to health, with the predominance of food parameters that promote inflammation. In the original validation study [15], DII scores ranged from -5.3 to +4.3, with a mean of +0.84, thus revealing a lower inflammatory potential than that observed in the present sample. Among all the studies that evaluated MS and IR as outcomes, the present one showed the most proinflammatory mean value. It has been demonstrated that the food intake of younger people, characterized by high consumption of saturated fat, sodium, sugar and low consumption of whole foods, fruits and vegetables, is less healthy than that of older people [53-56]. This may help explain the more proinflammatory diet observed in the present sample.

Regarding the high mean DII of the sample, it should be pointed out that the 10 parameters not estimated were of an anti-inflammatory nature. Despite this, many of the non-estimated parameters are foods used as seasonings, consumed in lesser amounts in the diet, such as turmeric, saffron and rosemary. The difficulty in quantifying these parameters is common in studies that use the FFQ as the assessment method, because spices are not normally listed in the questionnaire [15].

The present study has some limitations. First, its cross-sectional design does not allow for establishing a temporal relationship between the independent variables and the outcomes analyzed. Indeed, reverse causation may obscure a real association. The effect of diet on the occurrence of chronic outcomes is more likely to be evidenced in studies with longitudinal design. Second, the DII consists of 45 food parameters, but only 35 were used in the present study because some parameters were not included in the FFQ or were not available in the food composition tables. However, studies that did not assess parameters similar to those missing in the present study have suggested that the reduction in the number of parameters does not compromise the discriminatory potential of the DII [15, 49]. Nevertheless, the FFQ is commonly used to assess the association between dietary intake and NCDD because it evaluates the habitual food intake of the sample [57].

Despite its weaknesses, the present study has strengths that require mention. These include its large sample size and the population-based representation. The use of the DAG for the construction of the theoretical model, and the use of the backdoor criterion to select a minimal set of adjustments for confounding factors, thus preventing unnecessary adjustment in multivariable analysis. Additionally, this was the first study to assess the association of the DII with IR or MS in young subjects of a middle-income country, like Brazil. Even though it did not demonstrate such an association, it revealed that the average diet of the young subjects studied has a high inflammatory potential, when compared with other studies. Future studies, preferably utilizing longitudinal designs, are recommended to further test the hypothesis that diet-associated inflammation is associated with IR or MS.

ACKNOWLEDGMENTS

The authors thank the participants, the staff and the funding agencies.

FUNDING

This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo [Grant numbers 00/09508-7] and the Conselho Nacional de Desenvolvimento Científico e Tecnológico.

CONFLICT OF INTEREST

Declarations of interest: none

DISCLOSURE

JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. NS is an employee of CHI.

REFERENCES

[1] Zeyda M, Stulnig TM. Obesity, inflammation, and insulin resistance--a mini-review. Gerontology. 2009;55:379-86.
[2] Laakso M. Is Insulin Resistance a Feature of or a Primary Risk Factor for Cardiovascular Disease? Curr Diab Rep. 2015;15:105.
[3] Wieser V, Moschen AR, Tilg H. Inflammation, cytokines and insulin resistance: a clinical perspective. Arch Immunol Ther Exp (Warsz). 2013;61:119-25.
[4] Zhao L, Fu Z, Wu J, Aylor KW, Barrett EJ, Cao W, et al. Inflammation-induced microvascular insulin resistance is an early event in diet-induced obesity. Clin Sci (Lond). 2015;129:1025-36.
[5] Riccardi G, Giacco R, Rivellese AA. Dietary fat, insulin sensitivity and the metabolic syndrome. Clin Nutr. 2004;23:447-56.
[6] Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med. 2011;9:48.

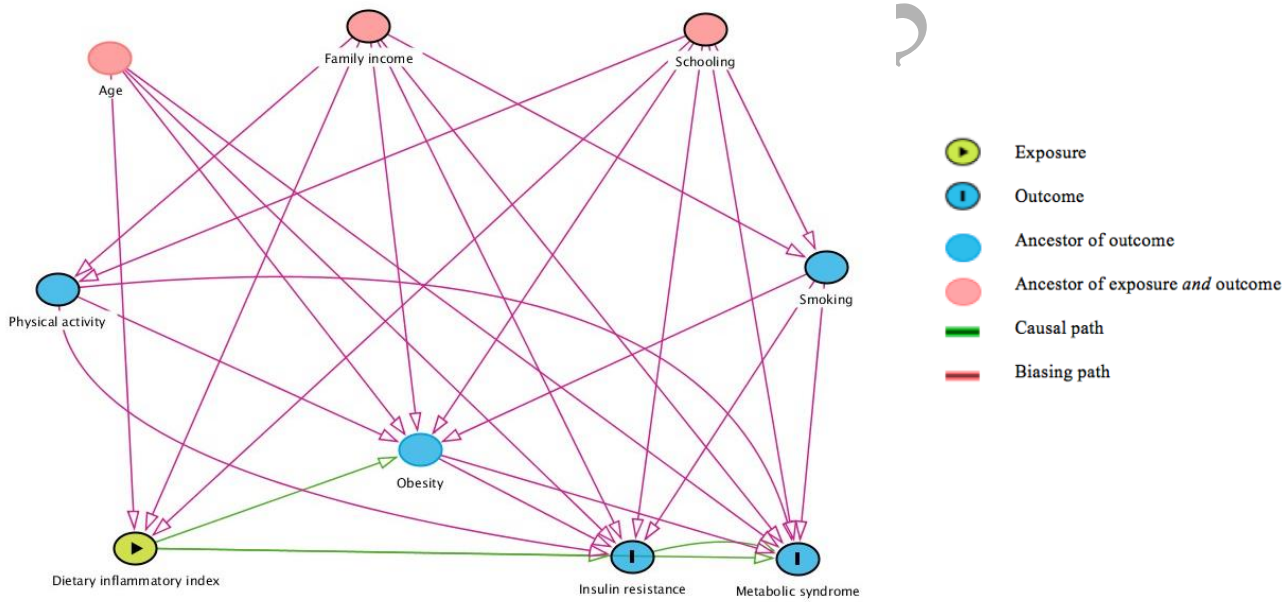
[7] Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105:141-50.
[8] Farooq W, Farwa U, Khan FR. The metabolic syndrome and inflammation: role of insulin resistance and increased adiposity. Oman Med J. 2015;30:100-3.
[9] Zuliani G, Volpato S, Galvani M, Ble A, Bandinelli S, Corsi AM, et al. Elevated C-reactive protein levels and metabolic syndrome in the elderly: The role of central obesity data from the InChianti study. Atherosclerosis. 2009;203:626-32.
[10] Azadbakht L, Esmaillzadeh A. Red meat intake is associated with metabolic syndrome and the plasma C-reactive protein concentration in women. J Nutr. 2009;139:335-9.
[11] Babio N, Bullo M, Basora J, Martinez-Gonzalez MA, Fernandez-Ballart J, Marquez-Sandoval F, et al. Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. Nutr Metab Cardiovasc Dis. 2009;19:563-70.
[12] Estruch R. Anti-inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. Proc Nutr Soc. 2010;69:333-40.
[13] Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. J Am Coll Cardiol. 2006;48:677-85.
[14] Lorente-Cebrian S, Costa AG, Navas-Carretero S, Zabala M, Martinez JA, Moreno-Aliaga MJ. Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. J Physiol Biochem. 2013;69:633-51.
[15] Shivappa N, Steck SE, Hurley TG, Hussey JR, Yunsheng MA, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public Health Nutr. 2014;17:1825-33.
[16] Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17:1689-96.
[17] Sokol A, Wirth MD, Manczuk M, Shivappa N, Zatonska K, Hurley TG, et al. Association between the dietary inflammatory index, waist-to-hip ratio and metabolic syndrome. Nutr Res. 2016;36:1298-303.
[18] Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, et al. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. J Occup Environ Med. 2014;56:986-9.
[19] Sen S, Rifas-Shiman SL, Shivappa N, Wirth MD, Hebert JR, Gold DR, et al. Associations of prenatal and early life dietary inflammatory potential with childhood adiposity and cardiometabolic risk in Project Viva. Pediatr Obes. 2017.
[20] Neufcourt L, Assmann KE, Fezeu LK, Touvier M, Graffouillere L, Shivappa N, et al. Prospective association between the dietary inflammatory index and metabolic syndrome: findings from the SU.VI.MAX study. Nutr Metab Cardiovasc Dis. 2015;25:988-96.
[21] Pimenta AM, Toledo E, Rodriguez-Diez MC, Gea A, Lopez-Iracheta R, Shivappa N, et al. Dietary indexes, food patterns and incidence of metabolic syndrome in a Mediterranean cohort: The SUN project. Clin Nutr. 2015;34:508-14.
[22] Alkerwi A, Shivappa N, Crichton G, Hebert JR. No significant independent relationships with cardiometabolic biomarkers were detected in the Observation of Cardiovascular Risk Factors in Luxembourg study population. Nutr Res. 2014;34:1058-65.
[23] van Woudenbergh GJ, Theofylaktopoulou D, Kuijsten A, Ferreira I, van Greevenbroek MM, van der Kallen CJ, et al. Adapted dietary inflammatory index and its association with a summary score for low-grade inflammation and markers of glucose metabolism: the Cohort study on Diabetes and Atherosclerosis Maastricht (CODAM) and the Hoorn study. Am J Clin Nutr. 2013;98:1533-42.

[24] Saneei P, Hashemipour M, Kelishadi R, Esmaillzadeh A. The Dietary Approaches to Stop Hypertension (DASH) diet affects inflammation in childhood metabolic syndrome: a randomized cross-over clinical trial. Ann Nutr Metab. 2014;64:20-7.
[25] Pettitt DJ, Talton J, Dabelea D, Divers J, Imperatore G, Lawrence JM, et al. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for diabetes in youth study. Diabetes Care. 2014;37:402-8.
[26] Popkin BM. The shift in stages of the nutrition transition in the developing world differs from past experiences! Public Health Nutr. 2002;5:205-14.
[27] Hinnig PF, Monteiro JS, de Assis MAA, Levy RB, Peres MA, Perazi FM, et al. Dietary Patterns of Children and Adolescents from High, Medium and Low Human Development Countries and Associated Socioeconomic Factors: A Systematic Review. Nutrients. 2018;10.
[28] Rodrigues LP, Carvalho RC, Maciel A, Otanasio PN, Garavello ME, Nardoto GB. Food Insecurity in Urban and Rural Areas in Central Brazil: Transition from Locally Produced Foods to Processed Items. Ecol Food Nutr. 2016;55:365-77.
[29] Conde WL, Monteiro CA. Nutrition transition and double burden of undernutrition and excess of weight in Brazil. Am J Clin Nutr. 2014;100:1617S-22S.
[30] Monteiro CA, Mondini L, de Souza AL, Popkin BM. The nutrition transition in Brazil. Eur J Clin Nutr. 1995;49:105-13.
[31] PNUD. Ranking IDHM Municípios 2000. 2000.
[32] IBGE. Estimativas de população - 2003. 2003.
[33] Barbieri MA, Bettiol H, Silva AA, Cardoso VC, Simoes VM, Gutierrez MR, et al. Health in early adulthood: the contribution of the 1978/79 Ribeirao Preto birth cohort. Braz J Med Biol Res. 2006;39:1041-55.
[34] Cardoso MA, Kida AA, Tomita LY, Stocco PR. Reproducibility and validity of a food frequency questionnaire among women of Japanese ancestry living in Brazil. Nutrition Research. 2001;21:725-33.
[35] Molina MC, Bettiol H, Barbieri MA, Silva AAM, Conceição SIO, Dos-Santos JE. Food consumption by young adults living in Ribeirão Preto, SP, 2002/2004. Brazilian Journal of Medical and Biological Research. 2007;40:1257-66.
[36] Santos NC. Tabela Brasileira de Composição de Alimentos (TBCA-USP): dados de flavonóides. São Paulo: Universidade de São Paulo; 2009.
[37] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-5.
[38] Geloneze B, Vasques AC, Stabe CF, Pareja JC, Rosado LE, Queiroz EC, et al. HOMA1-IR and HOMA2-IR indexes in identifying insulin resistance and metabolic syndrome: Brazilian Metabolic Syndrome Study (BRAMS). Arq Bras Endocrinol Metabol. 2009;53:281-7.
[39] IPAQ. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ). (Updated Nov 2005). [http://www.ipaq.ki.se/dloads/IPAQ LS Scoring Protocols
Nov05.pdf. . 2006.
[40] Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al. Questionário Internacional De Atividade Física (Ipaq): Estupo de validade e reprodutibilidade no Brasil. . Revista Brasileira de Atividade Física & Saúde 2001;6:13.
[41] Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22:745.

[42] Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10:37-48.
[43] Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. 1997;65:1220S-8S; discussion 9S-31S.
[44] Julia C, Assmann KE, Shivappa N, Hebert JR, Wirth MD, Hercberg S, et al. Long-term associations between inflammatory dietary scores in relation to long-term C-reactive protein status measured 12 years later: findings from the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) cohort. Br J Nutr. 2017;117:306-14.
[45] Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31:285-93.
[46] Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001;161:1581-6.
[47] Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444:860-7.
[48] Kelishadi R, Mirghaffari N, Poursafa P, Gidding SS. Lifestyle and environmental factors associated with inflammation, oxidative stress and insulin resistance in children. Atherosclerosis. 2009;203:311-9.
[49] Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, et al. Construct validation of the dietary inflammatory index among postmenopausal women. Ann Epidemiol. 2015;25:398-405.
[50] Shivappa N, Wirth MD, Hurley TG, Hebert JR. Association between the dietary inflammatory index (DII) and telomere length and C-reactive protein from the National Health and Nutrition Examination Survey-1999-2002. Mol Nutr Food Res. 2017;61.
[51] Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. Br J Nutr. 2015;113:665-71.
[52] Shivappa N, Hebert JR, Marcos A, Diaz LE, Gomez S, Nova E, et al. Association between dietary inflammatory index and inflammatory markers in the HELENA study. Mol Nutr Food Res. 2017;61.
[53] Jaime PC, Stopa SR, Oliveira TP, Vieira ML, Szwarcwald CL, Malta DC. Prevalência e distribuição sociodemográfica de marcadores de alimentação saudável, Pesquisa Nacional de Saúde, Brasil 2013. Epidemiologia e Serviços de Saúde. 2015;24:267-76.
[54] Souza AdM, Pereira RA, Yokoo EM, Levy RB, Sichieri R. Alimentos mais consumidos no Brasil: Inquérito Nacional de Alimentação 2008-2009. Revista de Saúde Pública. 2013;47:190s-9s.
[55] Andrade SC, Previdelli AN, Cesar CL, Marchioni DM, Fisberg RM. Trends in diet quality among adolescents, adults and older adults: A population-based study. Prev Med Rep. 2016;4:391-6.
[56] Tek; NA, Yildiran; H, Akbulut; G, Bilici; S, Koksal; E, Karadag; MG, et al. Evaluation of dietary quality of adolescents using Healthy Eating Index. Nutr Res Pract. 2011;5:6.
[57] Fisberg RM, Marchioni DML, Colucci ACA. Avaliação do consumo alimentar e da ingestão de nutrientes na prática clínica. Arquivos Brasileiros de Endocrinologia & Metabologia. 2009;53:617-24.

FIGURE LEGENDS

Figure 1. Directed acyclic graph illustrating the relationship between Dietary Inflammatory Index and Insulin Resistance or Metabolic Syndrome.



***Preference for color: online only**

TABLES

Table 1. Socioeconomic, metabolic and lifestyle characteristics according to the tertiles of the Dietary Inflammatory Index (DII) for each sex, Ribeirão Preto, 2002-2004.

	TERTILES OF DII									
		MEN				WOMEN				
	Total	**T1**	**T2**	**T3**	**p – value**	**Total**	**T1**	**T2**	**T3**	**p – value***
DII (score mean)	957	-0.96	1.11	2.94	<0.01	1060	-0.93	1.19	3.17	<0.01
Standard deviation		0.93	0.49	0.71			0.95	0.51	0.81	
BMI (kg/m^2 mean)	954	24.89	24.88	25.22	0.62	1056	23.88	23.50	23.65	0.67
Standard deviation		4.39	4.31	4.45			4.97	5.30	4.91	
Family income[*] (mean)	798	4.45	4.85	5.06	0.18	836	4.38	4.41	5.25	0.06
Standard deviation		5.20	5.39	4.65			5.44	5.30	5.91	
Schooling (years) (%)					0.01					0.68
≥12	312	35.2	32.2	32.6		385	24.3	31.0	44.7	
9-11	490	42.6	34.4	23.1		520	28.2	33.9	37.9	
5-8	130	42.6	39.1	18.4		125	29.3	31.7	39.1	
0-4	25	28.0	58.1	13.8		30	23.4	36.7	39.9	
Physical activity (%)					<0.01					<0.01
Active	400	43.1	37.7	19.3		221	34.7	31.3	34.1	
Sufficiently acive	156	43.3	35.5	21.2		232	34.1	31.8	34.0	
Sedentary	400	34.9	33.0	32.1		602	21.3	33.9	44.8	
Smoking (%)					0.37					0.42
No	767	40.5	34.2	25.3		914	26.2	32.6	41.2	
Yes	190	37.0	39.9	23.2		146	30.8	33.7	35.5	
HDL-c (%)					0.27					0.98
Normal	584	37.8	36.0	26.2		596	27.1	32.4	40.5	
Low	373	43.0	34.4	22.6		464	26.7	33.1	40.2	
Triglycerides (%)					0.07					0.08
Normal	797	38.0	36.7	25.3		939	26.5	32.2	41.3	

High	150	48.4	28.3	23.3		103	31.6	38.8	29.6	
Glycemia (%)					0.66					0.38
Normal	905	40.1	35.3	24.6		1022	26.7	32.9	40.4	
High	48	33.7	36.8	29.5		22	39.8	23.0	37.2	
Blood pressure (%)					0.71					0.86
Normal	562	39.4	36.5	24.1		990	26.8	32.6	40.6	
High	394	40.6	33.8	25.6		68	27.8	35.1	37.1	
Waist circumference (%)					0.50					0.58
Normal	607	41.0	35.4	23.6		760	26.2	33.6	40.2	
High	350	37.7	35.3	27.0		300	28.8	30.5	40.7	
Insulin resistance (%)					0.23					0.59
No	808	39.2	36.7	24.1		924	26.7	32.6	40.7	
Yes	134	43.1	28.7	28.2		110	30.5	33.6	35.9	
Metabolic syndrome (%)					0.75					0.58
No	766	39.2	36.0	24.8		969	26.9	32.5	40.6	
Yes	180	41.8	33.0	25.2		67	24.5	38.8	36.7	

DII, Dietary Inflammatory Index; BMI, Body mass index; HDL-C, High density lipoprotein. * Difference between tertiles. Significance for values p<0.05.

Table 2. Distribution of food parameters into DII tertiles according to sex, Ribeirão Preto, 2002-2004.

	TERTILES OF DII							
	MEN				WOMEN			
	MEAN				MEAN			
Nutrients	**T1**	**T2**	**T3**	**p-value**	**T1**	**T2**	**T3**	**p-value**
Energy (kcal/kg/day)	38.71	30.87	24.19	<0.01	42.19	34.80	26.81	<0.01
Carbohydrates (g)	287.60	283.60	276.98	0.01	296.70	290.51	284.90	<0.01
Proteins (g)	90.90	88.98	85.20	<0.01	88.32	85.66	83.10	<0.01
Total fat (g)	65.32	67.95	72.57	<0.01	62.43	66.36	69.99	<0.01
Saturated fat (g)	23.73	25.36	27.89	<0.01	22.62	24.69	26.46	<0.01
Trans fat (g)	0.79	0.83	0.85	<0.01	0.83	0.85	0.86	0.03
Cholesterol (mg)	258.00	258.63	243.84	0.14	246.89	258.28	245.84	0.27
MUFA (g)	22.42	23.74	25.72	<0.01	21.44	23.06	24.60	<0.01
PUFA (g)	12.34	12.21	11.54	<0.01	11.93	11.81	11.34	0.02
Omega 3 (g)	1.56	1.55	1.52	0.358	1.50	1.49	1.45	0.12
Omega 6 (g)	10.32	10.32	9.77	0.01	10.04	10.05	9.72	0.17
Fibers (g)	24.58	20.88	17.00	<0.01	26.94	22.08	17.90	<0.01
Thiamine (mg)	1.51	1.40	1.36	<0.01	1.57	1.47	1.38	<0.01
Riboflavin (mg)	1.71	1.58	1.54	<0.01	1.74	1.62	1.56	<0.01
Niacin (mg)	16.83	16.57	15.78	0.01	16.95	16.36	15.13	<0.01
Pyridoxine (mg)	1.55	1.33	1.19	<0.01	1.61	1.37	1.25	<0.01
Folic acid (µg)	423.93	373.35	343.31	<0.01	434.94	377.15	342.19	<0.01
Vitamin B12 (µg)	3.24	3.23	3.19	0.86	3.24	3.15	3.10	0.41
Vitamin A (µg)	417.36	350.23	305.45	<0.01	482.36	412.79	357.51	<0.01
Vitamin C (mg)	162.93	98.16	72.33	<0.01	199.90	130.70	93.63	<0.01
Vitamin D (µg)	2.82	2.66	2.49	0.03	2.97	2.66	2.57	0.01
Vitamin E (mg)	5.55	4.75	4.03	<0.01	6.03	5.05	4.27	<0.01
Iron (mg)	12.20	12.23	11.19	<0.01	12.06	11.71	10.66	<0.01
Zinc (mg)	11.36	11.40	10.96	0.01	11.26	11.08	10.70	0.01

Selenium (μg)	106.05	100.65	92.04	<0.01	97.68	96.82	87.03	<0.01
Magnesium (mg)	275.60	251.67	213.18	<0.01	287.51	251.90	210.95	<0.01
Flavonoids (mg)	41.28	39.36	29.59	<0.01	40.15	32.57	25.22	<0.01
Flavones (mg)	0.97	0.62	0.49	<0.01	1.21	0.83	0.55	<0.01
Flavonones (mg)	23.57	13.19	8.84	<0.01	26.61	17.34	13.27	<0.01
Flavanols (mg)	16.75	8.99	6.51	<0.01	16.86	14.80	10.78	<0.01
Anthocyanidins (mg)	32.97	19.96	14.73	<0.01	39.87	30.31	18.06	<0.01
Caffeine (g)	52.48	48.84	46.05	0.25	44.68	47.62	42.07	0.36
Alcohol (g)	9.40	7.57	7.14	0.01	5.81	4.81	4.04	0.03
Black tea (g)	107.06	55.97	39.29	0.01	90.05	77.87	56.39	0.09

DII, Dietary Inflammatory Index; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Table 3. Crude and adjusted analysis of the association between insulin resistance or metabolic syndrome with the dietary inflammatory index, Ribeirão Preto, 2002-2004.

	MEN			WOMEN		
	Crude PR	**CI 95%**	**p-value**	**Crude PR**	**CI 95%**	**p-value**
Insulin resistance						
DII (unit)	0.97	0.88-1.07	0.55	0.95	0.86-1.05	0.29
	Adjusted PR[a]	**CI 95%**	**p-value**	**Adjusted[a] PR**	**CI 95%**	**p-value**
Insulin resistance						
DII (unit)	0.98	0.89-1.08	0.76	0.96	0.87-1.07	0.48
	Crude PR	**CI 95%**	**p-value**	**Crude PR**	**CI 95%**	**p-value**
Metabolic syndrome						
DII (unit)	0.98	0.91-1.07	0.68	1.04	0.91-1.20	0.57
	Adjusted PR[a]	**CI 95%**	**p-value**	**Adjusted[a] PR**	**CI 95%**	**p-value**
Metabolic syndrome						
DII (unit)	0.98	0.91-1.07	0.67	1.05	0.91-1.20	0.53

DII, Dietary Inflammatory Index; PR, Prevalence Ratio; CI, Confidence Interval.
[a] adjusted by age, family income in multiples of the month minimum wage and schooling.