Title page

Title: Carbohydrate quality, weight change and incident obesity in a Mediterranean cohort: the SUN Project

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ABSTRACT

Background/ Objectives: To evaluate the association between the carbohydrate quality (CQI) and weight change or incident overweight/obesity (BMI≥25 kg/m^2) in the "Seguimiento Universidad de Navarra (SUN)" cohort.

Subjects/ Methods: 8 741 participants initially free of overweight/obesity were followed-up for a median of 7.9 years. We evaluated at baseline the CQI following 4 criteria: dietary fibre intake, glycemic index (GI), whole grains/total grains ratio and solid carbohydrates/total carbohydrates ratio. Subjects were classified into quintiles according to CQI. Weight was recorded at baseline and updated every 2 years during follow-up.

Results: Increasing CQI of diet was not significantly associated with lower weight gain, although participants in the highest quintile had the lowest average crude weight gain (+211 g/year). We observed 1 862 incident cases of overweight/obesity during follow-up. CQI was significantly associated (p for trend 0.006) with lower risk of overweight/obesity: adjusted OR for the 4rd and 5th quintiles: 0.81 (95% CI 0.66 to 0.99), and 0.74 (95% CI 0.60 to 0.92), respectively.

Conclusions: In this Mediterranean cohort, CQI showed a significant inverse association with the incidence of overweight/obesity, which highlights that carbohydrate intake guidelines related to obesity prevention should be focused in improving the CQI of the diet.

KEW WORDS: Obesity; Carbohydrate quality; Glycemic index, Fibre, whole grain; liquid carbohydrates

INTRODUCTION

Overweight and obesity present major public health problems in both developed and transition countries and if trends continue, by 2030 up to 57.8% of the world's adult population could be either overweight or obese.[1]

Obesity is a strong risk factor for major chronic disease, such as diabetes and cardiovascular disease. Thus, although weight gain involves genetic components, lifestyle and dietary behaviours are the more important modifiable risk factors.[2] However, there is relatively little evidence to recommend any specific intervention (including dietary strategies) to help adults in the general population to achieve the goal of long-term maintenance of a healthy weight. Thus, an emerging challenge in obesity research is to identify the role of specific foods and macronutrient distribution.[3]

Different proportions and sources of carbohydrates, [4,5] proteins [6] and fats [7,8] have been proposed for obesity prevention or treatment. But there is ample controversy on this issue. In spite of previous evidence on the role of dietary macronutrients and food consumption as determinants of weight change[9], there is an ongoing scientific interest to assess whether the *"quality"* of fat, carbohydrates or protein might be more important than its *"quantity"* to prevent obesity.

With respect to carbohydrates, in 2003, the World Health Organization (WHO), advised that a high intake of sugar-sweetened soft drinks and fruit juices increased the risk of weight gain or obesity, whereas non-starch polysaccharides and dietary fibre were protective.[10]

Specifically, the evidence on the association between carbohydrate quality and primary prevention of obesity is scarce[11,12] and needs further clarification.[13] However is far from been completely consistent.

Previous epidemiological studies have suggested different measures to evaluate the carbohydrate *quality.* The main criteria are related to whole grains consumption, dietary fibre intake, the solid or liquid form of carbohydrates and the GI.[14,15]

To the best of our knowledge, no previous studies have examined in a multidimensional way, (i.e., taking into account at the same time several concepts including the glycemic index (GI), fibre content, solid or liquid form and the degree of processing), the effect of the nutritional quality of carbohydrates on weight gain or obesity in an adult population. Thus, the purpose of the present study was to examine the association between the overall dietary quality of carbohydrates and the average yearly weight change or the risk of becoming overweight/obese in a large prospective Mediterranean cohort.

METHODS AND PROCEDURES

Study population

The SUN (Seguimiento Universidad de Navarra) project is an ongoing, multipurpose, prospective and dynamic Spanish cohort of University graduates designed to establish associations between diet and the occurrence of several disease and chronic conditions, including obesity.[16] Information is collected through self-administered questionnaires sent by mail or e-mail every 2 years. A detailed description of the study methods are available elsewhere.[17] The study protocol was approved by the

Institutional Review Board of the University of Navarra. Voluntary completion of the first questionnaire was considered to imply informed consent according the Helsinki declaration guidelines.

For this longitudinal analysis, we included participants who had already been followed up for at least 2 years and who completed a baseline assessment (Q_0) before September 2010 (n=20 490). Among them, we excluded participants with overweight or obesity at baseline (n= 6 145), participants who were outside of predefined limits for total energy intake[18] <3 349 kJ/d (800 kcal/d) for men or <2 093 kJ/d (500 kcal/d) for women, >16 747 kJ/d (4 000 kcal/d) for men or >14 654 kJ/d (3 500 kcal/d) for women (n=1 482), women who were pregnant at baseline or during follow-up (n=2 421), participants who were following a special diet at baseline (n= 731), participants who did not answer any of the follow-up questionnaires (n= 925), and finally, participants with missing values in the variables of interest (n= 45). Therefore, the final sample comprised 8 741 participants.

Dietary assessment and calculation of CQI

Dietary exposures at baseline were assessed using a semi-quantitative food frequency questionnaire (FFQ) with 136 items repeatedly validated in Spain.[19, 20] The validation study for this FFQ showed a reasonably good validity for assessing carbohydrate intake.[21] Frequencies of consumption were measured in 9 categories. Energy and nutrient intake were derived by trained dieticians using data from Spanish food composition.[22]

We used baseline dietary intake data to identify a carbohydrate quality index. [23] The carbohydrate quality index (CQI) was defined summing up the following four criteria:

ratio of solid carbohydrates to total carbohydrates, dietary fibre intake (g/d), GI, and finally ratio of whole grains to total grains (whole grains, refined grains and its products). For each of these 4 dietary items, subjects were categorized into quintiles and received a value (ranging from 1 to 5) according to each quintile (for GI those in the fifth quintile received 1 point and those in the first quintile received 5 points). Finally, we constructed the new index summing up all values of the CQI (ranging from 4 to 20) and it was also categorized roughly into quintiles.

We estimated whole grain consumption according to the item "whole bread consumption" (serving size 60g, 9 categories in the validated FFQ). Refined grain consumption corresponded to 13 items related to the consumption of white rice, refined bread, refined pasta and different biscuit and pastries products made with refined grains.

On the other hand, liquid carbohydrates were calculated summing up sugar-sweetened beverages and fruit juices consumption (4 items), while solid carbohydrates corresponded to the CHO content of the rest of foods with any CHO content.

Assessment of the outcome

Information on weight was collected at baseline and every 2 y during follow-up. The reliability and validity of self-reported weight was evaluated in a subsample of the cohort. The correlation coefficient between measured and self-reported weight was 0.99 (95% CI 0.98-0.99). The mean relative error in self-reported weight was 1.45%.[24]

The median follow-up time for this analysis was 7.9 y. The outcomes after follow-up were: 1) average change per year in body weight during follow-up as a continuous variable calculated as the difference between the last answered questionnaire and the baseline questionnaire divided by the years of follow-up and 2) incident overweight or obesity (participants with a BMI <25 kg/m^2 at baseline and with a BMI ≥25 kg/m^2 at follow-up).

We repeated the analyses after excluding those participants who had prevalent chronic diseases at baseline (cardiovascular disease, diabetes or cancer).

Assessment of other variables

The baseline questionnaire also gathered information on socio-demographic, anthropometric variables, lifestyle and health-related habits, medical history of major diseases and family history of obesity. Information regarding physical activity during leisure-time was gathered at baseline with a specific questionnaire previously validated in Spain.[25]

Statistical analysis

Multiple linear regressions models were used to assess the association between CQI and average yearly weight change (in g) during the follow-up period. We fit four models: a crude (univariate) model and three multivariate- adjusted models: a) controlling for age (continuous) and sex, b) additionally adjusted for baseline BMI (continuous), smoking status (never, former, and current smokers), leisure-time physical activity (metabolic equivalent-h/wk, continuous) and sitting (h/week, continuous), and c) additionally adjusted for total energy intake (continuous), alcohol intake (continuous), snacking between meals (yes/no), years of university education (some college, completed college, university degree, master degree or doctorate), weight gain in the past 5 y previous to entering the cohort (>= 3 kg /<3 kg) and family history of obesity (yes/no).

Non-conditional logistic regression models were fit to assess the relationship between CQI (in quintiles) and the risk of becoming overweight/obese. Tests of linear trend across successive quintiles were fit assigning the median value to each quintile and treating the variable as continuous.

We performed one sensitivity analysis to assess the robustness of our findings, excluding participants with cardiovascular, diabetes or cancer disease at baseline.

We always considered the lowest quintile of baseline CQI as the reference category. Analyses were performed with STATA version 12 (STATA Corp., TX, USA). All P values are two-tailed and statistical significance was set at the conventional cut-off of $P < 0.05$.

RESULTS

Baseline characteristics of subjects according to quintiles of baseline CQI are shown in **Table 1**. The mean age at baseline was 37.6 y.

Participants with the highest CQI tended to be older, more physically active, former smokers and had a higher prevalence of cancer or diabetes at baseline. On the other hand, subjects with lower CQI were more likely to be men and current smokers. Baseline CQI was positively associated with total energy, carbohydrate and protein, n-3 fatty acid and fibre intake and with a higher consumption of fruits, vegetables, legumes, fish, whole grains and olive oil. In contrast, CQI was inversely associated with fat, PUFA, SFA, n-6 fatty acid and alcohol intake, and with dairy products, meats, refined grains and fast-food consumption.

The results of the linear regression models fitted to evaluate the association between baseline CQI and average yearly change in body weight (in g) are presented in **Table 2**. On average, participants increased their weight during follow-up, although those with the highest CQI experienced a lower weight gain (+211 g/y), whereas those with the lowest CQI showed the highest weight change (+302 g/y). We found a significant inverse association between the CQI at baseline and weight change in multivariable model adjusted for age and sex (*ß* = -55.4, 95 % CI:-102.7 to -8.1). However, this association disappeared (p>0.135) when we additionally adjusted for baseline BMI (continuous), smoking status (never, former, and current smokers), leisure-time physical activity (metabolic equivalent-h/week, continuous), sitting (h/week, continuous), total energy intake (continuous), alcohol consumption (continuous), snacking between meals (yes/no), years of university education (four categories), weight gain in the past 5 y (>= 3 kg /<3 kg) and family history of obesity (yes/no) (*ß* = -38.0, 95 % CI:-86.3 to 10.4).

We also assessed the risk of becoming overweight or obese according to quintiles of CQI at baseline (**Table 3).** We observed 1 862 incident cases of overweight/obesity during follow-up. Subjects in the 2 upper quintiles of CQI exhibited a significant lower (p for trend 0.006) risk compared to those in the first quintile (the worst CQI): adjusted OR for the 4^{rd} and 5^{th} quintiles: 0.81 (95% CI 0.66 to 0.99), and 0.74 (95% CI 0.60 to 0.92), respectively.

Finally, our main results did not change when we additionally excluded those participants with chronic diseases at baseline such as cardiovascular disease, diabetes or cancer (data not shown).

DISCUSSION

To our knowledge this is the first prospective cohort study to investigate the longitudinal association between a new score based on the quality of carbohydrates measured in a multidimensional way and the average yearly weight change or the risk of becoming overweight/obese in a cohort. The CQI was defined taking into account at the same time the GI, the solid or liquid form of carbohydrates, the intake of dietary fibre, and the degree of processing of carbohydrate-rich foods (whole or refined grains). Thus, we consistently observed that normal weight adults with worse quality of dietary carbohydrate had a significantly higher risk of becoming overweight or obese.

In our study, the overall dietary food pattern was apparently healthier among subjects with better CQI (quintile 5 of the score) compared with those who had the worst CQI (quintile 1). On the other hand, as expected, although participants increased their average weight during follow-up (243 g/y), crude increments were higher among those with the worst quality of carbohydrates according to the score.

From the point of view of quantity of carbohydrates, in our sample, participants with best CQI had a higher energy intake, but a very similar percentage of total energy from carbohydrates across quintiles of CQI, ranging from 43.2 to 44.6%. In general, carbohydrate intake was closely associated with energy intake and most of the variation between individuals regarding carbohydrate intake was therefore due to differences in total energy intake.[26] These results suggest that quality but not quantity of carbohydrates is what could mainly contribute to the development of overweight/obesity in this cohort. In this direction, the available studies conducted on adults indicate that total carbohydrate intake or dietary carbohydrate proportion is not associated with the risk of obesity.[27, 28] Besides, a recent review suggests that the proportion of macronutrients in the diet is not important in predicting changes in weight or in preventing obesity. The focus should rather be in the attention types of food containing carbohydrates such as grains, dairy products and sugar-rich foods and drinks.[9,29] On the other hand, the National Health and Examination Surveys, have observed that total energy intake and the percentage of it from carbohydrate increased substantially over four decades whereas fat and protein intake declined. However, intakes of energy and macronutrients among people of different BMI categories trended similarly over time, so trends in fat or carbohydrate intake do not clearly explain the rise in obesity prevalence. In fact, it has been proposed that a reduction in fat intake was compensated with an increased intake of refined starches and sugars.[30] In Spain, according to National Food Consumption Surveys from 1964 to 2012, energy intake declined and there are differences in energy profile trends, in particular in case of percentage of energy from carbohydrates, which steadily decreased since 1964.[31] However the prevalence of overweight in Spain in 1987 and 2012 was 39.4 and 53.7, respectively.[32] These results suggest that there is no apparent association between the quantity of this macronutrient and the risk of obesity.

In addition, to the total quantity of carbohydrate intake or the proportion of energy that carbohydrates account for, the quality of carbohydrates and the dietary sources of carbohydrates constitute an emerging concern for obesity prevention. However, there is no agreement on which is the best measure of the quality of carbohydrates, although GI and glycemic load (GL) have been widely used.[15.] However, recent controversies about GI suggest that fibre and whole grain could also be good markers of carbohydrate quality and they can even superior to GI of GL.[33]

In the last decades, the role of GI in promoting chronic diseases related to dietary variables has received considerable attention although it is still an issue of debate. A recent systematic review provided evidence for beneficial effects of long-term interventions with low GI or GL on fasting insulin and pro-inflammatory markers, which could be helpful in the primary prevention of obesity associated-diseases.[34] Further studies are needed to clarify the association between GI and the primary prevention of obesity and obesity-related complications.

The physical form (solid vs. liquid) of carbohydrates is an important component, because liquid carbohydrates promote a positive energy balance and may affect the satiety process and energy intake, and may consequently lead to weight gain.[11] In fact, it is a resolved question that there is a direct dose–response relationship between sugar-sweetened beverages consumption and long-term weight gain and also obesity-related diseases.[29,35] In this direction, prospective investigations in several cohorts have confirmed that changes in the consumption of liquid carbohydrates were positively associated with weight gain, whereas the consumption of unprocessed foods such as whole grains, fruits, nuts, and vegetables were inversely associated with weight gain.[9, 36,37.]

In relation to the intake of dietary fibre, epidemiologic studies indicate that there is an inverse association between dietary fibre intake and subsequent weight change [26]. Dietary fibre contributes to weight management by modulating food ingestion, digestion, absorption and metabolism. There is moderate evidence that consumption of foods rich in cereal fibre or mixtures of whole grains and bran are associated with a reduced risk of obesity, type 2 diabetes and cardiovascular disease according to the American Society for Nutrition position, recently published [38].

The potential mechanisms that could explain the relation to the whole-grains consumption and prevention to overweight and obesity are their effect on satiety and the capacity to slow down starch digestion and absorption, which may lead to lower glucose and insulin responses.[38] Besides, foods made with whole grain, compared with refined-grain foods, contain more micronutrients and phytochemicals and fewer starches and calories, which could be associated to health benefits[39] . However, data from whole grains alone are limited probably because of the controversies and disparities on the definition of whole-grain food used in previous epidemiological studies.

In this context, eating less refined grains and more whole grain foods remain an important healthy dietary recommendation in order to protect against chronic diseases[40]. Thus, the last US Dietary Guidelines published in 2010, advices to limit the consumption of foods rich in refined grains, and to consume at least half of all grains as whole grains.

At this present there are no studies that have examined at the same time, the relationship between the overall dietary CQI and weight change or the risk of becoming overweight/obese. For this reason, we created a new dietary index to assess the quality of carbohydrates in a multidimensional way, taking into account GI, fibre content, solid or liquid form and degree of processing.

The strengths of the present study include a prospective design, a large sample of participants, a high retention rate and control for a wide number of potential confounders. Moreover, the high educational level of this cohort allows a higher accuracy in their self-reported data and a better retention in the cohort. Another relevant strength is the use of validated methods. Furthermore, the robustness of findings in additional sensitivity analyses is other strength. Finally, although the CQI has been previously used to assess micronutrient intake adequacy,[23] to our knowledge it has not been used before in assessing weight change and obesity which could be helpful in dietary advice related to weight management in young adults.

We acknowledge that our study has potential limitations. First, the use of self-reported FFQ for dietary assessment potentially resulted in the underreporting of unhealthy carbohydrates, particularly in the overweight/obese subjects. However, our study excluded subjects with prevalent overweight or obesity at baseline, which minimizes such social desirability bias. Second, we assessed obesity through weight change, because other measures of adiposity were not available. Third, weight change was self-reported. Participants may tend to underestimate their weight while overestimate their height, which may affect the results. However, the validity of self-reported weight and height in this cohort has been previously demonstrated. [24] Fourth, residual confounding may have affected our results. However, we attempted to adjust for the known overweight/obesity risk factors. Fifth, dietary assessment was conducted only at baseline, and as dietary habits may change over time, future studies with a repeated assessment of the FFQ during follow-up are needed to confirm our results. And finally, the homogeneity of participants in the SUN cohort (all were university graduates), can limit the generalizability of our findings to the general population.

In conclusion, in this Mediterranean prospective cohort, the CQI, defined in a multidimensional way, showed a significant inverse association with the incidence of overweight or obesity during follow-up. This results contribute to highlight the importance that carbohydrate intake guidelines related to obesity prevention, should be focused on improving quality (increasing the dietary fibre intake, consumption of whole grains, preferring solid carbohydrates and choosing low GI food), rather than limiting quantity or percentage of total energy.

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TABLE LEGENDS

Table 1. Baseline main characteristics of the 8741 participants without overweight/obesity at baseline of the SUN project according to quintiles of carbohydrates quality [mean (standard deviations) or percentages]

Table 2. Yearly weight change (g) in participants without overweight/ obesity at baseline according to quintiles of CQI. Beta regression coefficients and 95 % confidence interval (CI).

Table 3. Incident Overweight or Obesity (BMI ≥25 kg/m2) in participants without overweight/ obesity at baseline based on quintiles of CHI. Odds Ratios (ORs) and 95 % confidence intervals (CI).