ABSTRACT:

Objective: To assess the association between the consumption of sugar sweetened carbonated beverages (SSCB) and obesity in children and adolescents from Navarra (Spain).

Design: We used a matched case-control study design. The exposure, SSCB consumption (1 serving: 200 ml), was measured with a previously validated food frequency questionnaire. Anthropometrical measures were taken using standardized protocols. The outcome, obesity, was defined as body mass index above age- and sex-specific 97th percentile according to the Spanish reference charts. In the analysis we used a conditional logistic regression. Potential confounders were controlled using a multivariable model.

Setting: Subjects were recruited in the Pediatric departments of the Universidad de Navarra Clinic and the Navarra Hospital Complex, and in three Primary Health Centers of Navarra. Controls were recruited when attending for a routine medical examination or vaccination.

Subjects: 174 obese children and 174 individually sex- and age-matched controls, 52.87% boys, with a mean age 11.6 year old. Exclusion criteria were dietary interventions, exposure to hormone treatment, development of secondary obesity due to endocrinopathy or serious intercurrent illness.

Results: Independently of other factors, high consumption of SSCB (>4 servings/week) was significantly associated with obesity (OR 3.46; 95% CI: 1.24-9.62). Besides, each additional daily serving of SSCB was associated with a 69% relative increase in the risk of obesity (OR 1.69; 95% CI: 1.04-2.73).

Conclusions: We found a strong and significant association between SSCB consumption and obesity risk. Our results suggest a monotonic dose-response linear shape for this association in children and adolescents (p for trend=0.02).

INTRODUCTION

Obesity is a chronic disease that results from an imbalance of energy homeostasis. The mechanisms underlying this metabolic disorder reflect complex interactions of genetic, environmental and behavioral factors. Many studies suggest that obesity increases the risk of many other chronic diseases as type 2 diabetes, metabolic syndrome or some type of cancers, and that becoming obese earlier in life clearly amplifies that risk. The increasing prevalence of obesity among children and adolescents has become an important public health problem and a priority issue for authorities.^(1,2)

The worldwide study conducted in 2004 by the International Association for the Study of the Obesity (IASO)⁽¹⁾ found a 10% of overweight and a 2-3% of obesity among children aged 5 to 17 years, according to the International Obesity Task Force criteria. In Europe the prevalence of overweight or obesity is over 20% with many differences among countries. According to the IASO, Spain shows one of the highest prevalence of obesity in Europe, with 29.5% of girls and 32.3% of boys being overweight or obese. These numbers are similar to those of the Aladino study, developed in Spain between October 2010 and May 2011 including more than 7,600 children aged 6 to 9 years.⁽³⁾ This cross-sectional study found a prevalence of 26.2% for overweight and a prevalence of 18.3% for obesity among Spanish children.

The consumption of soft drinks has globally increased in parallel to the obesity epidemic. According to the Beverage Marketing Corporation, the U.S. liquid refreshment beverage market grew by 1.0% in 2012 with the production of 29.8 billion gallons, and carbonated soft drinks remain by far the biggest liquid refreshment beverage category.⁽⁴⁾ Something similar happened in Spain. According to the latest data published by the Refreshment Beverages Association (ANFABRA), the refreshment production increased by 1.4% in 2007 with the production of 4,400 million liters only in Spain.⁽⁵⁾ Although the sugar-free beverage production has increased, nowadays it represents only 25% of the total production. The consumption of soft drinks in Spain increased by 41.5% from 1991 to 2001 and it is still on the rise.⁽⁶⁾ According to the Dietary Intake National Survey developed in 2008 in Madrid among children aged from 5 to 12 year old, the mean consumption of sugar-sweetened beverages was 55.7 ml/d (1.92 fl oz). The consumption tends to increase with age, being twice among preadolescents comparing to children aged 5 year old (92.6 vs. 45.2 ml/d) (3.13 vs 1.52 fl oz).⁽⁷⁾

Many studies suggest that the obesity epidemic is strongly related to an increase of soft drink consumption.⁽⁸⁻¹⁰⁾ The term soft drink includes sodas and other sugar-sweetened beverages such as fruit-flavored juices, lemonade and iced tea. The term soda refers specifically to sugarsweetened carbonated beverages (SSCB). Depending on the flavor and the brand, one soda provides 176 to 218 kJ (42 to 52 kcal) and 10.6 to 12.9 gr of added sugar per 100 ml (3.38 fl oz), which means 2.2 to 2.7 teaspoons of sugar per 100 ml (7.2 to 9 teaspoons of sugar in a regular can of 330 ml). This added sugar appears in the form of high-fructose corn syrup (HFCS) (45% glucose and 55% fructose) in the United States and in the form of sucrose (50% glucose, 50% fructose) in Europe. It has been suggested that the change in body fatness might be mediated principally by higher actual energy intake due to the amount of rapidly absorbable sugars and to the lower satiety associated with liquid carbohydrates compared to carbohydrates consumed in solid form.⁽¹¹⁻¹³⁾ In addition, according to some authors, fructose, which is digested, absorbed and metabolized differently than glucose, is much more likely than glucose to be the culprit of the deleterious effects of added sugars in inducing weight gain and other metabolic traits. Fructose acutely increases thermogenesis, triglycerides levels and lipogenesis as well as blood pressure, and raises uric acid, which has been defined as an important and independent predictor of obesity and metabolic syndrome. However, fructose does not enhance insulin secretion or leptin production, both important factors in food intake and body weight regulation.⁽¹⁴⁻¹⁸⁾

The aim of this study was to assess the association between SSCB consumption and obesity in a matched case-control study conducted in Navarra (Spain).

EXPERIMENTAL METHODS

Subjects:

The study population was 348 children and adolescents (174 cases and 174 matched controls) aged 5.5-18-8 years (mean and median age: 11.6 years) enrolled in the GENOI (Grupo Navarro de Estudio de la Obesidad Infantil) case-control study, started in 2001.⁽¹⁹⁾ Subjects were recruited from the Pediatric Departments at the Navarra Hospital Complex and the University of Navarra Clinic and from three primary health centers of Navarra (Spain). Cases (n=174) were subjects with body mass index (BMI) above the age- and sex-specific 97th percentile according to the Spanish BMI reference charts.⁽²⁰⁾ Exclusion criteria were dietary intervention, exposure to hormone treatment, development of secondary obesity due to endocrinopathy or serious intercurrent illness. Controls (n=174) were healthy subjects with BMI below the 97th percentile of the same

reference charts, recruited when they attended to the primary care centers for a routine medical examination or vaccination. Controls were individually matched to cases by sex and age (± 6 month).

Anthropometric measures were collected in a medical environment by trained personal using standard procedures. Height was measured to the nearest centimeter and weight to the nearest 100 g with a digital balance (TBF-300A Body Composition Analyzer/Scale, TANITA, Tokyo, Japan). Body fat percentage was determined by bioelectrical impedance (TBF-300A Body Composition Analyzer/Scale, TANITA).

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the correspondent ethics committee. Written informed consent was obtained from participants older than 12 year old and the parents of younger participants.

Exposure assessment:

A trained researcher conducted individual interviews to each participant and their parents according to standardized protocols. Information about SSCB consumption was obtained from a previously validated semi-quantitative food-frequency questionnaire (FFQ).^(21, 22) For each item in the questionnaire an average portion size was defined and each participant and their parents were asked how often they had consumed them throughout the previous year. One serving of SSCB was estimated as 200 ml (6.76 fl oz). The FFQ offered nine possible response categories ranging from "never or almost never" to "six or more times a day". From this information, four different categories were defined for SSCB consumption: never or almost never, less than 1 serving per week, from 1 to 4 serving per week and more than 4 serving per week. The total consumption per day was calculated for each participant from the information in the FFQ.

Statistical analysis:

Student-t and Chi-squared tests were used when comparing means and proportions. A value for $p \le 0.05$ was set as the statistically significance level for all statistical analyses.

Conditional multivariable logistic regression models were used to assess the association between SSCB consumption and obesity among children and adolescents. Cases and controls were matched by sex and age. We calculated the conditional (matched) odds ratios (ORs) and their 95% confidence intervals (95% CI) for obesity associated to each category of SSCB consumption.

Additionally, the consumption of SSCB was introduced in the model as a continuous variable and we calculated the OR and the 95% CI for obesity associated to each additional daily serving of SSCB (200 ml, 6.76 fl oz). Potential confounders were taken into account in the multivariable model.

The association between SSCB consumption and continuous variables, such as BMI or body fat percentage, was assessed by a multivariable-adjusted linear regression model. We used the first category (never or almost never consumption) as the reference category for all the analyses.

Besides the information about SSCB consumption, the FFQ included other 118 food items, grouped in the following categories: dairy products, eggs, meat and fish, vegetables, fruits, legumes and cereals, fats an oils, bakery, beverages and other foods not included in the previously categories. The beverage section of the FFQ included, not only SSCB, but also other soft drinks as fruit juices, fruit-flavored juices, non-caloric or diet beverages and water. Total energy intake was estimated from the data in the FFQ.

Many different foods and dietary patterns have been suggested to be associated with obesity. We calculated the adherence to the Mediterranean dietary pattern (MDP) according to the index described by Trichopoulou et al. In our study, the score ranged from 0 to 8 because alcohol intake was excluded from the index.⁽²³⁾ Nowadays, the Mediterranean dietary pattern is being displaced by a westernized pattern, characterized by a higher fast-food consumption. The indicator of fast-food consumption in our study was estimated as the sum of three items of the FFQ: pizza, hamburgers and sausages.⁽¹⁰⁾ In order to adjust by potential confounders, we introduced this indicator and other sugar sweetened beverages, such as fruit-flavored juices, in the multivariable model.

The interviews also included a previously validated physical activity questionnaire containing 17 activities and ten possible response categories for frequency, ranging from "never" to "eleven hours or more per week".⁽²⁴⁾ Based on the published studies, a multiple of resting metabolic rate was assigned to each activity (METs-hour). We defined an activity metabolic equivalent index and calculated the physical activity developed by each participant (METs-hour per week). Sedentary behavior was estimated as the sum of hours spent watching television and in front of the computer. Physical activity and sedentary behavior were introduced separately and as continuous variables in the multivariable model to control for their potential confounding effect.

We used the residual method (linear regression model) to calculate the age-adjusted BMI. An ANCOVA was used to calculate the sex- and age-adjusted means and 95% CI of BMI across categories of SSCB consumption.

RESULTS

Table 1 shows the main baseline characteristics of both case and control groups. As expected, cases and controls were very different in anthropometric indexes. Cases showed a significantly higher z-BMI score and fat mass percentage than controls. We found an unexpected significantly higher total energy intake in controls than in cases, which might be related to higher energy expenditure in controls and higher prevalence of sedentary lifestyles in cases. In fact, we found a significantly higher physical activity in controls. The sedentary behavior was included separately in the multivariable analysis. Cases referred more hours per week watching television or using a computer but this difference was not statistically significant.

As it is also shown in Table 1, the estimated daily serving of SSCB, calculated from the FFQ, was significantly higher in cases than in controls, on the contrary, cases referred lower consumption of fruit-flavored juices but this difference was not statistically significant.

We found a similar and low adherence to the MDP in either group. Cases exhibited a higher consumption of fast-food but lower consumption of commercial bakery items than controls, although these differences were not statistically significant.

Figure 1 shows the mean of sex- and age-adjusted BMI across categories of SSCB consumption. Higher categories of SSCB consumption were not statistically different from the lowest category regarding average BMI, but we did find a significant p for trend supporting a direct association between higher SSCB consumption and higher sex- and age-adjusted BMI.

We calculated the ORs and their 95%CI for obesity associated with each category of SSCB consumption. As it is shown in Table 2, independently to other factors, the point estimate of the OR was above the null value for all the categories of SSCB consumption, but it was not significant for the intermediate categories (<1 or 1-4 servings/week). Nevertheless, we found a direct, strong and significant association for the highest category of SSCB consumption (>4 servings/week) and obesity (OR 2.41; 95%CI 1.12-5.19), which became stronger when confounders were controlled for in the multivariable model (OR 3.46; 95%CI 1.24-9.62).

Figure 2 shows the linear trend for obesity and SSCB consumption. We represented the previously defined four categories of consumption and used the same reference category. We used a continuous scale and each category is represented according to the median value of SSCB consumption within that category. We drew a fitting line that showed a significant linear trend (p for trend=0.02) suggesting a monotonic dose-response effect of SSCB consumption on obesity among children and adolescents.

When we assessed SSCB consumption as a continuous exposure (Table 2), we found a significant association for obesity (OR 1.56; 95%CI 1.09-2.25) and each additional daily serving of SSCB, which remained significant in the multivariable model (OR 1.69; 95%CI 1.04-2.73) after adjusting for age, sex, total energy intake, physical activity, sedentary behavior, fast-food and fruit-flavored juices consumption.

In an ancillary analysis, we assessed the age-adjusted BMI as dependent variable (data not shown). We used a logarithmic transformation in order to achieve a normal distribution of the data. The adjusted multivariable linear regression showed a significant association between age-adjusted BMI and each daily serving of SSCB consumption (β coefficient +0.03 kg/m²; 95% CI: +0.001 to +0.06). When we studied the different categories of SSCB consumption, the adjusted multivariable linear regression model showed a significant association for age-adjusted BMI and the consumption of more than four servings of SSCB per week versus the category of reference (β coefficient +0.07 kg/m²; 95% CI: +0.003 to +0.15).

The assessment of the association between SSCB consumption and body fat mass percentage is shown in Table 3. We found a direct but non-significant association for the intermediate versus the lowest category of SSCB consumption and body fat mass percentage (β coefficient +2.82 in the crude model and +2.15 in the adjusted model). Nevertheless, our results showed a direct and significant association between body fat mass percentage and the highest versus the lowest category of SSCB consumption (β coefficient: +5.14; 95% CI: +0.98 to +9.30) that remained significant in the multivariable adjusted model (β coefficient: +4.80; 95% CI: +1.04 to +8.56). We also found a significant and direct association between each daily extra serving of SSCB and body fat percentage in both the crude (β coefficient: +1.83; 95% CI: +0.32 to +3.35) and in the adjusted model (β coefficient: +1.47; 95% CI: +0.11 to +2.82).

DISCUSSION.

This case-control study suggests a monotonic linear dose-response direct association between SSCB consumption and obesity among children and adolescents (p for trend=0.02). We found that, independently to other factors, each daily serving of SSCB was significantly associated with a higher risk of obesity (p=0.03). We also found a strong and significant association for obesity and the highest category of SSBC consumption (>4 servings/week) versus the category of reference (never or almost never) (p=0.01).

The inclusion of BMI as the dependent variable in the multivariable analysis may provide useful information, especially for clinicians. Our results showed, independently of other factors, a direct, monotonic and significant association between each extra daily serving of SSCB and age-adjusted BMI (p=0.038), as well as a significant difference in age-adjusted BMI between the highest versus the lowest category of SSCB consumption. (p=0.042).

According to our results, the consumption of more than four servings per week of SSCB was significantly associated with a 4.80% increment in body fat mass percentage (p=0.012), independently of other factors. Our results also suggest that, independently of other factors, each extra daily serving of SSCB was significantly associated with a 1.47% increment in body fat mass percentage (p=0.03). These results agree with the published literature, which considers that the association between SSCB and obesity may be explained by increments in body fat percentage.⁽¹¹⁻¹³⁾

The association between soft drinks and obesity is controversial. The interpretation of published studies finding no association is difficult because of small sample sizes, short duration of follow up, some method-related issues and possible uncontrolled confounding.⁽²⁵⁻²⁷⁾ Two systematic reviews published in 2006 and 2007 found evidence enough to recommend population to reduce soft drink consumption.^(28,29) A recent systematic review published in 2013 found 21 cohort studies in children which assessed the effect of sugar intake on body fatness.⁽³⁰⁾ In most of these cohorts sugar-sweetened beverages were the major source of sugar intake. This systematic review found 15 studies that showed a positive association and 4 that showed null associations; 2 of these studies reported fruit juice as the main sugar exposure. The quantitative meta-analysis of these cohorts showed a significantly increased risk of being overweight associated with higher consumptions of sugar-sweetened beverages. That study also found 5 intervention trials in children that assessed the effect of advising to reduce dietary sugars on children's body mass index. The meta-analysis of these trials found no association, but the authors suggested significant heterogeneity and poor compliance with the intervention trial as possible explanations for the inconsistent results.

Two recently published intervention trials in children found that the replacement of sugarsweetened beverages by non-caloric beverages reduced weight gain.^(31,32) One of these studies was developed among overweight and obese children. The experimental group received a 1-year intervention designed to reduce the consumption of sugar-sweetened beverages. The increase in BMI was smaller in the intervention group after 1-year intervention, but not after 2-year follow-up. In any case, the role of non-caloric beverages in weight change is still debated. High glycemic index foods seem to stimulate the consumption of other such foods. It has been suggested that sugar-sweetened beverages promote weight gain by increasing energy intake because of both, the amount of added sugar and the low satiety associated to liquid carbohydrates. Nevertheless, noncaloric beverages have been associated with weight gain and the underlying mechanism remains still unclear.⁽³³⁻³⁵⁾ Soft drink consumption, even of non-caloric soft drinks, is considered an unhealthy habit and it has been suggested that unhealthy habits tend to cluster.^(36,37) It is also believed that subjects who consume non-caloric soft drinks seem to eat more because they have the sensation of having reduced their total energy intake. Linked to these two theories, some studies suggest that the palatability of both, sugar-sweetened and non-caloric soft drinks, increases the subjective feeling of hunger and consequently the energy intake and weight gain.^(11,12)

Despite the direct association suggested by the point estimates, we could not find a significant association between obesity and intermediate categories of SSCB consumption. In our opinion, this might be because of small sample size, but also because of the inherent limitations of a semi quantitative FFQ. Overall, our results agree with the published literature and current knowledge about SSCB consumption and obesity.

Many studies support that physical activity has a protective role against obesity in children by increasing energy expenditure.⁽¹⁹⁾ In our study, we found a significant negative association between physical activity and obesity in agreement with those studies (p<0.01 in the multivariable model).

The Mediterranean dietary pattern has been suggested as protective factor for obesity and cardiovascular disease among adults but also among adolescents.⁽³⁸⁻⁴⁰⁾ In our study, both cases and controls showed similar and low adherence to the Mediterranean dietary pattern (p=0.77). Thus, this result does not allow us to affirm that the Mediterranean dietary pattern had a protective role against obesity among children. In the same way, both fast-food and commercial bakery items have been suggested as risk factors for obesity and cardiovascular disease.^(10,41) We did not find any statistically significant difference nor in commercial bakery items neither in fast-food consumption

between cases and controls. Although the difference between groups in fast-food consumption was close to the significance level when comparing means, it became much lower in the multivariable model (p=0.2).

TV watching has been defined as a proxy for sedentary behavior in children. It has been suggested that TV watching could even modify the association between some single nucleotide polymorphisms and obesity risk.⁽⁴²⁾ The HELENA study (Healthy Lifestyle in Europe by Nutrition in Adolescence) found that excessive TV watching was associated with higher consumption of energy-dense food and drinks, enhancing the idea that unhealthy habits tend to cluster.⁽³⁷⁾ Although obese children referred more hours per week watching TV or in front of a computer screen, we did not find any significant difference in sedentary behaviors between cases and controls (p=0.74 in the multivariable model).

We found an unexpected inverse association between obesity and total energy intake. In our sample, cases referred significant lower energy intake than controls. However, controls reported a significant higher physical activity and consequently a higher total energy expenditure that may explain this difference. The change in body fatness associated with higher sugar-sweetened beverages consumption seems to be mediated by higher energy intakes. According to this hypothesis, some authors defend that including total energy intake in the multivariable model reduces the actual strength of the association.⁽²⁸⁾ In our study, the introduction of total energy intake in the multivariable model did not affect the association between SSCB consumption and obesity found in the crude model. Although this may be due to the high energy intake referred by non obese children, it may also suggest more complex mechanisms underlying the association between SSBC consumption and obesity.

Nevertheless, our study is not exempt of limitations. The main limitation of a case-control study is the misreporting of food habits, which usually becomes into a differential information bias that reduces, or even inverts, the measures of association. Some studies defend that underreporting is directly associated with children's BMI or with parents' appreciation of the child status and that it is more common when referring to non-desirable exposures. This social desirability bias may be an explanation for the difference in energy intake reported by cases and controls in our study. However, a differential information bias in our study would result in a reduction of the real strength of the measures of association.⁽⁴³⁾

As explained in the methods section, when assessing the exposure, we used a FFQ in order to obtain information about food and beverages consumption during the previous year. Nevertheless, we cannot completely avoid a potential reverse causality bias, because the assessed dietary variables might be causes as well as consequences of the outcome. Attending to our data, this potential bias may also be an explanation for the results obtained in some dietary variables with unexpected results (total energy intake, adherence to the MDP or commercial bakery items consumption) and for the relatively high BMI found among occasionally consumers of SSCB (<1 serving/week). However, in our opinion, this potential bias would not affect the main results of our study, because the potential effect of this bias would be in the opposite direction to our findings.

In addition, we cannot deny the existence of potential residual confounding due to other factors, already suggested as potential confounders, but not included in our model because of a lack of information, such as parental educational level.

The association between SSCB consumption and obesity is supported by many welldesigned studies. The high intake of energy in form of added sugars, particularly the high quantity of sucrose (or HFSC in US), seems to explain, at least partially, this association. However, the association between obesity and non-caloric beverages reported by some studies reflects that the underlying mechanisms may be more complex and multifactorial. In addition, the association between obesity and other sugar-sweetened beverages such as fruit flavored juices remains still unclear. The published literature about this issue is not conclusive. In our opinion, due the extended consumption of this kind of beverages among children and adolescents, deeper studies are needed to clarify this possible association of other sugared beverages, different from SSCB, with obesity risk.

CONCLUSION

In conclusion, our study suggests that SSCB consumption might be associated with an increment in BMI and body fat percentage. According to our results, a high consumption of SSCB, more than four servings per week, was strongly associated with obesity in childhood and adolescence (OR 3.46; p=0.01). In addition, each additional daily serving of SSCB (200 ml, 6.76 fl oz) was associated with a 69% relatively increased risk of obesity among children and adolescents (p=0.03).

According to current knowledge, children and adolescents should be encouraged to reduce sugar-sweetened beverages consumption, particularly SSCB, and to increase the consumption of water as main sources of liquid⁽⁴⁴⁾. It seems reasonable to conclude that the strategies designed to

reduce the high prevalence of overweight and obesity should include education in beverage consumption in order to modify unhealthy habits of beverages consumption among children and adolescents.

REFERENCES

(1) International Association for the Study of Obesity (IASO). Available at: <u>http://www.iaso.org/resources/world-map-obesity/?map=children</u>. Accessed April/16.

(2) Daniels SR. (2006) The consequences of childhood overweight and obesity. *Future of Children* **16**, 47-67.

(3) Estudio Aladino. Available at:

http://www.naos.aesan.msssi.gob.es/naos/ficheros/investigacion/ALADINO.pdf. Accessed April/16.

(4) Beverage Marketing Corporation. Available at: <u>http://www.beveragemarketing.com/news.asp</u>. Accessed April/16.

(5) Asociación de Bebidas Refrescantes (ANFABRA). Available at: www.refrescantes.es/page_view.php?PageID=ESP_Sector&ContentID=228. Accessed April/16.

(6) Comité de Nutrición de la Asociación Española de Pediatría. (2003) Consumption of fruit juices and beverages by Spanish children and teenagers: health implications of their poor use and abuse. *An Pediatr (Barc)* **58**, 584-593.

(7) Agencia Española de Seguridad Alimentaria y Nutrición. Available at: <u>http://www.aesan.msc.es/AESAN/web/evaluacion_riesgos/subseccion/otras_encuestas.shtml</u>. Accessed April/16.

(8) Mozaffarian D, Hao T, Rimm EB et al. (2011) Changes in Diet and Lifestyle and Long-Term Weight Gain in Women and Men. *N Engl J Med* **364**, 2392-2404.

(9) Pan A, Malik VS, Hao T et al. (2013) Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies. *Int J Obes*. (Epublication ahead of print version).

(10) Bes-Rastrollo M, Sanchez-Villegas A, Gomez-Gracia E et al. (2006) Predictors of weight gain in a Mediterranean cohort: the Seguimiento Universidad de Navarra Study. *Am J Clin Nutr* 83, 362-370.

(11) DiMeglio DP, Mattes RD. (2000) Liquid versus solid carbohydrate: effects on food intake and body weight. *Int J Obes* **24**, 794-800.

(12) Schulze MB, Manson JE, Ludwig DS et al. (2004) Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA* **292**, 927-934.

(13) Ludwig DDS. (2002) The glycemic index - Physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* **287**, 2414-2423.

(14) Sievenpiper JL, de Souza RJ, Mirrahimi A et al. Effect of Fructose on Body Weight in Controlled Feeding Trials A Systematic Review and Meta-analysis. (2012) *Ann Intern Med* **156**, 291-304.

(15) Livesey G, Taylor R. (2008) Fructose consumption and consequences for glycation, plasma triacylglycerol, and body weight: meta-analyses and meta-regression models of intervention studies. *Am J Clin Nutr* **88**, 1419-1437.

(16) Johnson RJ, Perez-Pozo SE, Sautin YY et al. (2009) Hypothesis: Could Excessive Fructose Intake and Uric Acid Cause Type 2 Diabetes? *Endocr Rev* **30**, 96-116.

(17) Silbernagel G, Machann J, Unmuth S, et al. (2011) Effects of 4-week very-high-fructose/glucose diets on insulin sensitivity, visceral fat and intrahepatic lipids: an exploratory trial. *Br J Nutr* **106**, 79-86.

(18) Bray GA. Soft drink consumption and obesity: it is all about fructose. (2010) *Curr Opin Lipidol* **21**, 51-57.

(19) Ochoa MC, Moreno-Aliaga MJ, Martinez-Gonzalez MA, et al. (2007) Predictor factors for childhood obesity in a Spanish case-control study. *Nutr* **23**, 379-384.

(20) Sobradillo B. Curvas y tablas de crecimiento (estudios longitudinal y transversal). Bilbao:Fundación Faustino Orbegozo Eizaguirre 2004.

(21) Martin-Moreno JM, Boyle P, Gorgojo L et al. (1993) Development and validation of a food frequency questionnaire in Spain. *Int J Epidemiol* **22**, 512-519.

(22) de la Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, et al. (2010) Reproducibility of a FFQ

validated in Spain. Public Health Nutr 13, 1364-1372.

(23) Trichopoulou A, Costacou T, Bamia C et al. (2003) Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* **348**, 2599-2608.

(24) Ainsworth BE, Haskell WL, Leon AS, et al. (1993) Compendium of Physical Activities - Classification of Energy Costs of Human *Physical Activities*. *Med Sci Sports Exerc* **25**, 71-80.

(25) Ruxton CHS, Gardner EJ, McNnulty HM. (2010) Is Sugar Consumption Detrimental to Health? A Review of the Evidence 1995-2006. *Crit Rev Food Sci Nutr* **50**, 1-19.

(26) Van Baak MA, Astrup A. (2009) Consumption of sugars and body weight. Obes Rev 10, 9-23.

(27) Mattes RD, Shikany JM, Kaiser KA et al. (2011) Nutritively sweetened beverage consumption an body weight: a systematic review and meta-analysis of randomized experiments. *Obes Rev* **12**, 346-365.

(28) Vartanian LR, Schwartz MB, Brownell KD. (2007) Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *Am J Public Health* **97**, 667-675.

(29) Malik VS, Schulze MB, Hu FB. (2006) Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr* **84**, 274-288.

(30) Te Morenga L, Mallard S, Mann J. (2013) Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* **346**, 7492-7492.

(31) de Ruyter JC, Olthof MR, Seidell JC et al. (2012) A Trial of Sugar-free or Sugar-Sweetened Beverages and Body Weight in Children. *N Engl J Med* **367**, 1397-1406.

(32) Ebbeling CB, Feldman HA, Chomitz VR et al. (2012) A Randomized Trial of Sugar-Sweetened Beverages and Adolescent Body Weight. *N Engl J Med* **367**,1407-1416.

(33) Forshee RA, Storey ML. (2003) Total beverage consumption and beverage choices among children and adolescents. *Int J Food Sci Nutr* **54**, 297-307.

(34) Black RM, Tanaka P, Leiter LA et al. (1991) Soft Drinks with Aspartame - Effect on Subjective Hunger, Food Selection, and Food-Intake of Young-Adult Males. *Physiol Behav* **49**, 803-810.

(35) Black RM, Leiter LA, Anderson GH. (1993) Consuming Aspartame with and without Taste. Differential-Effects on Appetite and Food-Intake of Young-Adult Males. *Physiol Behav* **53**, 459-466.

(36) Schuit AJ, van Loon AJ, Tijhuis M et al. (2002) Clustering of lifestyle risk factors in a general adult population. *Prev Med* **35**, 219-224.

(37) Rey-Lopez JP, Vicente-Rodriguez G, Repasy J et al. (2011) Food and drink intake during television viewing in adolescents: the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study. *Public Health Nutr* **14**, 1563-1569.

(38) Estruch R, Ros E, Salas-Salvado J et al. (2013) Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* **368**, 1279-90.

(39) Bibiloni M, Martinez E, Llull R et al. (2011) Metabolic syndrome in adolescents in the Balearic Islands, a Mediterranean region. *Nutr Metab Cardiovasc Dis* **21**, 446-454.

(40) Beunza JJ, Toledo E, Hu FB et al. (2010) Adherence to the Mediterranean diet, long-term weight change, and incident overweight or obesity the Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr* **92**, 1484-1493.

(41) Sayon-Orea C, Bes-Rastrollo M, Basterra-Gortari FJ et al. (2013) Consumption of fried foods and weight gain in a Mediterranean cohort: The SUN project. *Nutr Metab Cardiovasc Dis* **23**, 144-150.

(42) Ochoa MC, Moreno-Aliaga MJ, Martinez-Gonzalez MA et al. (2006) TV watching modifies obesity risk linked to the 27Glu polymorphism of the ADRB2 gene in girls. *Int J Pediatr Obes* **1**, 83-88.

(43) Boernhorst C, Huybrechts I, Hebestreit A et al. (2013) Diet-obesity associations in children: approaches to counteract attenuation caused by misreporting. *Public Health Nutr* **16**, 256-266.

(44) Muckelbauer R, Libuda L, Clausen K, et al. (2009) Promotion and provision of drinking water in schools for overweight prevention: randomized, controlled cluster trial. *Pediatrics* 123, e661-667.

Table 1. Baseline main characteristic of	CONTROLS	CASES	p
	(N=174)	(N=174)	
Sex (male)	92 (52.87)	92 (52.87)	1
Age (years)	11.60 (2.71)	11.50 (2.62)	0.73
BMI (kg/m²)	19.03 (2.80)	27.78 (4.67)	< 0.01
Z-BMI	0.20 (0.89)	3.82 (1.65)	< 0.01
Fat mass (%)	18.19 (8.09)	35.39 (7.25)	< 0.01
SSCB (serving/d) ¹	0.23 (0.46)	0.45 (1.01)	< 0.01
Never or almost never	68 (39.08)	56 (32.18)	
<1 serving/week	35 (20.11)	28 (16.09)	
1-4 servings/week	57 (32.76)	64 (36.78)	
>4 servings/week	14 (8.05)	26 (14.94)	
Fruit flavored juice (servings/d) ¹	0.82 (1.64)	0.73 (1.70)	0.56
Energy intake (kJ/d)	13,414 (2880)	11,911 (381)	< 0.01
Physical activity (METs-h/week)	36 (21)	20 (12)	< 0.01
TV or PC use (hours/week)	16.21 (10.79)	18.00 (10.64)	0.12
Adherence to the MDP ² (0-8 points)	3.09 (1.52)	3.14 (1.54)	0.77
Fast food ³ (servings/d)	0.26 (0.22)	0.31 (0.27)	0.06
Commercial Bakery (servings/d)	1.81 (1.30)	1.72 (1.37)	0.51

Table 1. Baseline main characteristic of the participants. Mean (SD) or N (%).

¹ 1 SSCB serving = 200 ml

² MDP: Mediterranean Dietary Pattern. Adaptation of the index described by Trichopoulou et al⁽²²⁾. The consumption of alcohol was excluded in this modified index.

³ Fast-food consumption indicator was calculated as the sum of hamburgers, pizza and sausages consumption.

Table 2. Odds Ratios (OR) and 95% Confidence Intervals (95% CI) for obesity according to SSCB consumption. "Never or almost never consumption" was considered as the reference category. (1 serving: 200 mL or 6,76 us fl oz).

	OR	95% CI	р
Model 1			
For each +1 daily serving consumption	1.56	1.09-2.25	0.01
Consumption categories			
Never or almost never	1		
<1 serving/week	0.94	0.51-1.73	0.85
1-4 servings/week	1.40	0.86-2.29	0.17
>4 servings/week	2.25	1.12-5.19	0.02
Model 2			
For each +1 daily serving consumption	1.69	1.04 -2.73	0.03
Consumption categories			
Never or almost never	1		
<1serving/week	1.11	0.46-2.69	0.80
1-4 servings/week	1.52	0.75 -3.08	0.24
>4 servings/week	3.46	1.24 -9.62	0.01

Model 1: adjusted for sex and age (matching variables).

Model 2: adjusted for sex, age, total energy intake, physical activity, sedentary behavior (time spent watching TV or using a computer), fast-food consumption (pizza, hamburgers and sausages) and other sugar sweetened beverages (fruit-flavored juices).

Table 3. Beta coefficients and 95% Confidence Intervals (95% CI) for the percentage of body fat mass according to categories of SSCB consumption. "Never or almost never consumption" was considered as the reference category. (1 serving: 200 mL or 6,76 fl oz).

	Beta	95% CI	р
Model 1 For each +1 daily serving consumption	+1.83	+0.32 to +3.35	0.02
For each +1 daily serving consumption	+1.05	+0.32 t0 +3.33	0.02
Consumption categories			
Never or almost never	0		
<1 serving/week	-0.06	-3.46 to +3.34	0.97
1-4 servings/week	+2.82	-0.07 to +5.72	0.06
>4 servings/week	+5.14	+0.98 to +9.30	0.01
Model 2	_		
For each +1 daily serving consumption	+1.47	+0.11 to +2.82	0.03
Consumption categories			
Never or almost never	0		
<1serving/week	-0.06	-3.23 to +3.11	0.97
1-4 servings/week	+2.15	-0.56 to +4.87	0.12
>4 servings/week	+4.80	+1.04 to +8.56	0.01

Model 1: adjusted for sex and age (matching variables).

Model 2: adjusted for sex, age, total energy intake, physical activity, sedentary behavior (time spent watching TV or using a computer), fast-food consumption (pizza, hamburgers and sausages) and other sugar sweetened beverages (fruit-flavored juices).

FIGURE LEGENDS:

Figure 1. Mean and 95% confidence intervals of age and sex-adjusted BMI in each category of SSCB consumption (p for trend).

Figure 2. OR and 95% CI for obesity in each category of SSCB consumption (servings/week). The linear trend is represented using the median consumption (servings/d) for each category in the x-axis.