FREQUENT CONSUMPTION OF SUGAR- AND ARTIFICIALLY SWEETENED BEVERAGES, AND NATURAL AND BOTTLED FRUIT JUICES IS ASSOCIATED WITH AN INCREASED RISK OF METABOLIC SYNDROME IN A MEDITERRANEAN POPULATION AT HIGH CVD RISK.

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ii. Abbreviations used: CVD, Cardiovascular Disease; ICC, intraclass correlation coefficients; MetS, Metabolic Syndrome; PREDIMED, Prevención con Dieta Mediterránea; SSBs, SugarSweetened Beverages; TGs, Triglycerides; T2DM, Type 2 Diabetes Mellitus.

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v. Trial registered at clinicaltrials.gov Identifier: ISRCTN35739639.

ABSTRACT

Background: The relation between the consumption of sweetened beverages and Metabolic Syndrome (MetS) is controversial.

Objective: This analysis evaluated the associations between intakes of sugar-sweetened beverages (SSBs), artificially sweetened beverages, and natural and bottled fruit juices and the incidence of MetS in elderly individuals at high risk of cardiovascular disease (CVD) and without MetS at baseline.

Methods: We prospectively examined 1868 participants free of MetS at baseline from the PREDIMED (PREvención con DIeta MEDiterránea) study. MetS was defined using the updated harmonized criteria of the International Diabetes Federation and the American Heart Association and National Heart, Lung and Blood Institute. Energy and nutrients were evaluated at baseline and yearly using a validated 137-item food frequency questionnaire. Multivariable-adjusted HRs for MetS and its components were estimated from the mean intake during follow-up. We compared the two highest consumption categories (1-5 servings/week, and $\geq$5 servings/week) with the lowest category (<1 serving/week).

Results: A total of 930 incident cases of MetS were documented during a median follow-up of 3.24 years. When comparing the consumption of >5 servings/week with <1 serving/week, multivariable hazard ratios (95% CI) for MetS incidence were 1.43 (1.00-2.15), 1.74 (1.26-2.41), 1.30 (1.00-1.69) and 1.14 (1.04-1.65) in case of SSBs, artificially sweetened beverages, natural fruit juices, and bottled fruit juices, respectively.

Conclusions: Occasional consumption of SSBs and artificially sweetened beverages (between 1 and 5 servings/week) was not associated with MetS in middle-aged and elderly individuals at high risk of CVD. Consumptions of more than 5 servings/week of all the types of beverages analyzed was associated with an increased risk of MetS and some of its components. However, for SSBs and bottled fruit juices these associations must be interpreted with caution because of the low frequency of consumption in this population.

Trial registered: at clinicaltrials.gov; Identifier: ISRCTN35739639.

Key words: sugar-sweetened beverages, artificially sweetened beverages, fruit juices, Metabolic Syndrome, Metabolic Syndrome components, PREDIMED study

INTRODUCTION

Metabolic Syndrome (MetS) is a cluster of metabolic alterations associated with visceral obesity including atherogenic dyslipidaemia, high fasting plasma glucose, and increased blood pressure (1). The disorder entails an increased risk of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and cause-specific mortality (1–3). Because MetS is increasing in industrialized countries in parallel with the obesity epidemic, this disorder has become a major public-health concern in developed countries (4). Lifestyle modification, such as engaging in more physical activity, adopting a healthy dietary pattern and maintaining normal weight are the first-line measures for both the prevention (5–7) and treatment of MetS (8).

In recent years, the intake of sugar- and artificially sweetened beverages and fruit juices has steadily increased worldwide among children, adolescents and adults (9–12). An increase in the intake of sweetened beverages has also been observed in Mediterranean-diet consumers (13), although it remains lower than in other industrialized countries (14).

In recent decades, the relationship between the consumption of sweetened beverages and the development of MetS has been investigated in epidemiological studies. However, most of these are cross-sectional (5,15–19), so their potential for discerning relationships is limited. To date, only four prospective studies have investigated the association between the consumption of sweetened beverages and MetS incidence, with contradictory results (20–23). Three of them were part of a meta-analysis (24) that concluded that a higher consumption of sugar-sweetened beverages (SSB) was associated with the development of MetS. The fourth, not included in the aforementioned meta-analysis, was conducted in a Mediterranean population (20) and suggested a positive association between changes in the consumption of SSBs and incident MetS in university graduates.

No studies have been performed on the association between the accumulative average consumption of sweetened beverages and incident MetS in a middle-aged to elderly Mediterranean population. Therefore, the aim of the present study was to examine the associations between the average consumption of SSB, artificially sweetened beverages, and natural and bottled fruit juices and the risk of MetS in the PREDIMED (PREvención con DIeta MEDiterránea) cohort of middle-aged and elderly individuals at high risk of CVD.

METHODS

Design and study population

The present study was conducted within the framework of the PREDIMED trial. Full details of the study design and protocol have been published elsewhere (25,26) and are available on the PREDIMED study's website (27). The PREDIMED study is a large, multicentre, randomized, parallel group and controlled field trial conducted in Spain for the primary prevention of cardiovascular disease (CVD) events. The main results of the PREDIMED trial at the primary endpoints (a composite of myocardial infarction, stroke and cardiovascular mortality) have been published (28). Briefly, between October 2003 and June 2009, a total of 7447 participants (men aged 55-80 years and women 60-80 years) were randomized to one of the three intervention groups: a Mediterranean diet supplemented with extra virgin olive oil (approximately 50 mL/day), a Mediterranean diet supplemented with mixed nuts (15 g of walnuts, 7.5 g of hazelnuts and 7.5 g of almonds daily), or advice about a low-fat diet (control group). Participants had no history of CVD at baseline, but were at high cardiovascular risk because of the presence of T2DM or at least three of the following risk factors: current smoking (>1 cigarette/d during the last month), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥ 90 mmHg, or taking antihypertensive medication), high low-density lipoprotein (LDL)-cholesterol (≥160 mg/dL), low high-density lipoprotein (HDL)-cholesterol (<40 mg/dL for men or <50 mg/dL for women), overweight or obesity (body mass index ≥25 kg/m^2), or family history of premature CVD. Participants with severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, and a low predicted likelihood of changing dietary habits according to Prochaska and DiClemente's stages-of-change model (29) were excluded from the study. The institutional review boards of each recruitment centre approved the protocol, and all subjects provided written informed consent. The study follow-up ended in December 2010.

The present data was analysed using an observational prospective design, and participants were selected from all the PREDIMED recruitment centres with biochemical determinations available for a follow-up of ≥2 years (n=5801). The main aim of the present report was to explore the associations between the consumption of SSB, artificially sweetened beverages, natural fruit juices and bottled fruit juices and incidence of MetS. For this reason, participants with MetS at baseline (n=3707) were excluded. Those who did not complete the baseline food frequency questionnaire (FFQ) or who reported implausible total energy intake (≤500 and ≥ 3500 kcal/day in women and ≤800 and ≥ 4000 kcal/day in men) were also excluded. Of a total of 2094 participants fulfilling these characteristics, 226 were excluded because of missing data that prevented MetS from being diagnosed. Of the 5801 participants, 1019, 1766, 1804, 240 and 1269 did not meet the criteria of abdominal obesity, hypertriglyceridemia, low-HDL-cholesterol, high blood pressure, and high fasting glucose concentrations of the MetS at baseline. Finally, 1868 participants were included in the present analysis.

Metabolic Syndrome

MetS was defined in accordance with the updated harmonized criteria of the International Diabetes Federation and the American Heart Association and National Heart, Lung and Blood Institute (1). Participants were considered to have MetS if they had three or more of the following: abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.

Dietary assessment

Dietary intake was assessed by trained dietitians using a 137-item semi-quantitative FFQ validated for the PREDIMED study (30), administered at baseline and yearly during follow-up. The reproducibility and relative validity of the FFQ used in the present study were assessed for several nutrients and food groups (30). The reproducibility and relative validity of the FFQ were also assessed in relation to the consumption of SSBs, artificially sweetened beverages, natural fruit juices (freshly extracted juice, for which the only procedure accepted was the squeezing of the whole piece of fruit), and bottled fruit juices (natural fruit juice that has been chemically changed using authorized methods, packed and commercialized for subsequent consumption). Using the intraclass correlation coefficients (ICC) between the FFQ and dietary records, the following reliabilities were found: 0.67 for SSB, 0.46 for artificially sweetened beverages, 0.81 for natural fruit juices, and 0.88 for bottled fruit juices. In the reproducibility analysis, the correlation coefficients were 0.69 for SSB, 0.63 for artificially sweetened beverages, 0.71 for natural fruit juices, and 0.48 for bottled fruit juices.

The intake of sweetened beverages and fruit juices was assessed yearly using five items (SSBs, artificially sweetened beverages, bottled fruit juices, natural orange juice and natural juices from other fruits) from the FFQ. To assess habitual intake during the previous year, frequencies of consumption were measured in 9 categories (from never/almost never to more than 6 servings per day) for each FFQ item. The responses to individual items were then converted into mean daily consumption (mL per day) during the follow-up by multiplying the typical portion sizes (mL) by the consumption frequency for each food and making the appropriate division for the period assessed to obtain the daily consumption. Each serving of sweetened beverages was considered to be 200 mL. In the present analysis the categories were SSB, artificially sweetened beverages, natural fruit juices (the result of combining natural orange fruit juice and other natural fruit juices) and bottled fruit juices. Energy and nutrient intakes were calculated using Spanish food composition tables (31,32).

Anthropometric, Biochemical and Lifestyle Measurements

At baseline and yearly, participants completed 1) a questionnaire on medical history, medication use and lifestyle variables, 2) a 14-item validated questionnaire designed to assess adherence to the Mediterranean diet (33), and 3) a validated Spanish version of the Minnesota Leisure time Physical Activity Questionnaire (34). Also at baseline and yearly thereafter, trained personnel measured weight and height using calibrated scales and a wall-mounted stadiometer. Participants wore light clothing and no shoes. Waist circumference was measured using an anthropometric tape midway between the lower rib and the superior border of the iliac crest. Blood pressure was measured in triplicate after 5 minutes of rest using a validated semiautomatic sphygmomanometer (HEM-705CP, Omron, Hoofddorp, the Netherlands), and the mean of these measurements was recorded. Blood samples were collected after an overnight fast, coded, shipped to a central laboratory, and stored at -80ºC until analysis. Biochemical analysis was performed in local laboratories. Plasma glucose was analysed by glucose-oxidase methodology, serum cholesterol by esterase-oxidase-peroxidase, serum TGs by glycerol-phosphate oxidase-peroxidase, and serum HDL cholesterol by direct measurement mainly, or precipitation methodology. All local laboratories satisfied external quality control requirements. A concordance study of nine laboratories was conducted. From each study, a mean of 200 samples was analysed for total cholesterol, HDL cholesterol and TGs. The laboratory of the Medical Research Institute of the Del Mar Hospital, which used ABX-Horiba commercial kits in a PENTRA-400 autoanalyzer (ABX-Horiba), was used as a reference. One centre was unable to provide samples for the concordance study. The concordance analysis of lipid measurements showed, respectively, an r^2 and an ICC (95% CI) between 0.85 and 0.97, and 0.85 (0.77, 0.90) and 0.97 (0.95, 0.98) for total cholesterol; between 0.82 and 0.92, and 0.81 (0.78, 0.83) and 0.92 (0.89, 0.95) for HDL cholesterol; between 0.81 and 0.99, and 0.81 (0.73, 0.87) and 0.99 (0.99, 0.99) for triglycerides; and between 0.82 and 0.96, and 0.82 (0.74, 0.88) and 0.99 (0.99, 0.99) for glucose.

Statistical analyses

The intake reported during the baseline interview and yearly during follow-up was averaged. The participants were classified according to the frequency of servings of different beverages. To better represent the long-term consumption of the different types of beverage we used the mean beverage consumption for all analyses based on assessments of items from all FFQs, which were made at baseline and yearly during the follow-up for participants who did not develop MetS. For those who did develop MetS, and because participants could have changed their dietary pattern after developing MetS, we only used data from all the available FFQs until the year before MetS was diagnosed. The baseline characteristics of the participants are expressed as mean ± SD or median [IQR] for continuous variables and number and percentages for categorical variables. Chi-square and 1-factor

ANOVA tests were used to assess differences in the baseline characteristics of the study population. Multivariable time-dependent Cox proportional regression models were fitted to assess the Hazard Ratio (HR) for the incidence of MetS and its components during the follow-up according to servings (200 ml) of SSB, artificially sweetened beverages, natural fruit juices and bottled fruit juices. Both of the highest categories (1-5/week and >5/week) were compared with the lowest category (<1/ week) as a reference. The assumption of proportional hazards was tested with time-dependent covariates. The time variable was defined as the interval between random assignment and the date of the last follow-up or the last recorded clinical event (MetS incidence) of participants who were still alive, whichever occurred first. Participants who were free of MetS or who were lost during follow-up were censored at the date of the last visit. Three different Cox regression models were adjusted for potential confounders. Model 1 was adjusted for intervention group, age in years, sex, leisure time physical activity (METs/day) measured by the Minnesota Leisure time Physical Activity Questionnaire, BMI (kg/m^2), and smoking status (never, current and former), at baseline. Model 2 was additionally adjusted for total energy intake (in kcal/day) and average consumption (g/day) during follow-up of vegetables, legumes, fruits, cereals, meat, fish, bakery products, dairy products, olive oil, nuts, and alcohol (with a quadratic form being added only in the case of alcohol consumption). Model 3 was additionally adjusted for the prevalence of MetS components at baseline, including abdominal obesity (yes/no), hypertriglyceridemia or drug treatment for elevated TGs (yes/no), low HDL cholesterol (yes/no), hypertension or antihypertensive treatment (yes/no), and high fasting plasma glucose or medication for hyperglycemia (yes/no). When the association between the intake of sweetened beverages and the incidence of each component of MetS was assessed, the components were excluded from the analysis, and model 2 was the fully adjusted model. Statistical interactions between categories of sweetened beverage intake and potential effect-modifying variables such as sex, intervention group, diabetes and smoking status were assessed by including product terms in the models; no statistical interactions were found. To assess the linear trend, the median value of each category of each type of sweetened beverage analysed was assigned and used as a continuous variable in the Cox regression models. The level of significance for all statistical tests was set at $P < 0.05$ for bilateral contrast. All analyses were performed with SPSS software, version 22.0.

RESULTS

The present analysis was conducted in 1868 participants, of whom 930 (430 men and 500 women) without MetS at baseline developed new-onset MetS during a median follow-up time of 3.24 years (interquartile range: 1.91, 5.80). The average mean daily intake during follow-up was 14.5 mL, 17.1 mL, 29.3 mL, and 16.6 mL for SSBs, artificially sweetened beverages, natural fruit juices, and bottled fruit juices, respectively.

The baseline characteristics of the population in terms of total consumption of SSBs are shown in **Table 1**. Compared with those in the lowest category, participants in the highest category of SSB consumption were younger and presented higher levels of diastolic blood pressure and TGs. Those consuming more SSBs also showed lower adherence to the Mediterranean diet and consumed less fruit and more baked products, alcohol and total energy than participants consuming less than 3 servings per month. The baseline characteristics of the population in terms of artificially sweetened beverages, natural fruit juices and bottled fruit juices are available in the online supporting material (**supplementary files 1, 2** and **3**, respectively).

Table 2 shows the multivariable-adjusted hazard ratio (95% CI) for MetS incidence for the average servings of various beverages during follow-up. After adjusting for potential confounders, individuals consuming >5 servings/week of total SSBs had a higher risk of MetS [HR: 1.43; 95% CI: 1.00, 2.15; P-trend=0.27] than those consuming fewer than one per week. A positive association was also found between the consumption of artificially sweetened beverages and incidence of MetS [HR: 1.74; 95% CI: 1.26, 2.41; P-trend=0.004 for participants consuming >5 servings/week compared to those consuming <1 per week]. An average consumption of between 1 and 5 servings of natural fruit juices per week during follow-up was associated with a decreased risk of MetS [HR: 0.77; 95% CI: 0.65, 0.93]. However, risk was higher when consumption was >5 servings per week [HR: 1.30; 95% CI: 1.00, 1.69; P-trend=0.39]. An average consumption of between 1 and 5 servings of bottled fruit juices per week was inversely associated with MetS incidence [HR: 0.66; 95% CI: 0.53, 0.81]. However, when intake was equal to or higher than 5 servings/week the association was positive [HR: 1.14; 95% CI: 1.04, 1.65; P-trend= 0.311].

The association between average beverage consumption during follow-up and MetS components is presented in **table 3**. The consumption of >5 servings/week of SSB was associated with a higher risk of low HDL-cholesterol [HR: 1.18; 95% CI: 1.06, 2.11; P-trend=0.71] and high blood pressure [HR: 1.09; 95% CI: 1.04, 2.80; P-trend=0.39] than the consumption of <1 serving/week. Individuals consuming between 1 and 5 servings per week of SSBs also had a higher risk of high blood pressure than those who rarely consumed SSBs [HR: 1.89; 95% CI: 1.14, 3.13]. Consumption of >5 servings/week of artificially sweetened beverages was associated with an increased risk of developing abdominal obesity [HR: 1.82; 95% CI: 1.13, 2.92; P-trend=0.039] and the hypertriglyceridemia component of MetS [HR: 1.52; 95% CI: 1.00, 2.37; P-trend=0.08]. The results for the hypertriglyceridemia component were similar for bottled fruit juices when the consumption during follow-up was >5 servings/week [HR: 1.51; 95% CI: 1.03, 2.46; P-trend=0.23]. A positive association between the intake of >5 servings/week of natural fruit juices and abdominal obesity was also observed [HR: 1.52; 95% CI: 1.02, 2.25; P-trend=0.08].

DISCUSSION

In the present longitudinal analysis conducted in a middle-aged and elderly Mediterranean population at high risk of CVD, we evaluated the consumption of SSBs, artificially-sweetened beverages, natural fruit juices and bottled fruit juices and their association with the risk of MetS. The results showed that participants consuming >5 servings/week of all these types of beverage had an increased risk of MetS.

Those participants consuming >5 servings/week of SSBs during follow-up had a 43% higher risk of developing MetS than those not consuming or rarely consuming SSBs. These results are consistent with Malik et al’s meta-analysis of studies on different races and ethnicities in which individuals in the highest category of SSB intake showed a 20% greater risk of MetS than those in the lowest category (24). In contrast, our results are not in agreement with the findings of the only study not included in Malik’s meta-analysis and conducted in a Mediterranean population (the SUN cohort) in which no association was reported between baseline intake of SSBs and risk of MetS (20). These discrepancies may be due to differences in the age and type of participants. Frequent consumption of SSBs has been related to an increased risk of weight gain and obesity due to the high amount of added sugar, which entails a lack of satiety signals when consumed in liquid form (35–37). Most SSBs contain high amounts of fructose, and various studies suggest that high-fructose corn syrup, the primary sweetener used in SSBs, may have particularly deleterious metabolic effects (38), because it increases the risk of both low HDL-cholesterol levels (39,40) and hypertension (21,23), MetS components that in our study are related to the consumption of SSBs. Furthermore, the consumption of high-fructose corn syrup has also been related to other components of MetS such as insulin resistance (41,42) and hypertriglyceridemia (39,43). However, in the present cohort study these metabolic abnormalities were not significantly related to SSB consumption.

To the best of our knowledge, the present analysis is the first to demonstrate a positive relationship between the consumption of natural and bottled fruit juice analysed separately and the incidence of MetS. In our study a consumption of between 1 and 5 servings/week of fruit juice, regardless of whether they were natural or bottled (containing added sugar or not), was inversely related with incident MetS. However, when the consumption of both types of fruit juice was >5 servings per week, the association was positive and the risk of MetS increased. The lack of a dose response might be due to the high content of antioxidants in fruit juices, which counteracts the possible harmful effects of the sugar content when these beverages are consumed in small amounts (44). However, as observed in the present study, when fruit juices are consumed frequently, this inverse response may disappear, thus increasing the risk of MetS.

The observed association between fruit juice consumption and MetS could be attributed to an associated unhealthy lifestyle. Individuals with a higher intake of sweetened-beverages, including SSB and fruit juices, are known to have a higher intake of fat and sugar-rich products and a lower intake of fibre, and they tend to be less physically active (45,46). However, we adjusted our analyses for such confounding factors and we still observed a significant association between consumption of fruit juices and MetS incidence. In addition, the consumption of fruit in liquid form has been associated with a lower degree of energy compensation than when fruit is consumed in solid form, thus promoting the overconsumption of energy. In other words, energy intake in subsequent meals is not adjusted to previous consumption (47,48). Therefore, fruit juice consumption seems to induce less satiety than solid fruit (20).

Epidemiological studies have suggested that there is an association between the regular intake of sweetened beverages and risk of T2DM (24,49). We found no association between the consumption of any of the beverages analysed and impaired glucose metabolism. Furthermore, levels of baseline fasting glucose tended to be lower in the highest category of consumption. Similar results have also been observed by other authors (16), which may be due to reverse causation, because patients aware of their hyperglycaemia may reduce consumption of beverages containing sugar.

In this longitudinal analysis, individuals consuming >5 servings per week of artificially sweetened beverages presented a 74% higher risk of MetS than those who rarely consumed these beverages. This association can be explained by the fact that, in the present study, hypertriglyceridemia and abdominal obesity, both components of MetS were also observed to be associated with a higher consumption of this type of beverage. These results concur with those recently reported by Crichton and co-workers (5), which show that Americans who consumed 1 serving or more per day of artificially sweetened beverages had a 2.2 times higher risk of MetS than those who rarely consumed this type of beverage. Similar results were found by the same authors in the Luxembourg cohort of healthy individuals consuming two or more servings of artificially sweetened beverages per day (5). Cross-sectional and longitudinal analyses in the Framingham Heart cohort study also reported a positive association between the consumption of one serving/day of artificially sweetened beverages and MetS (23). To date, it has been suggested that three mechanisms may explain these associations: 1) artificial sweeteners can interfere with learned responses that help to control glucose and energy homeostasis (50); 2) artificial sweeteners interact with sweet-taste receptors that are expressed throughout the digestive system and which may play a role in glucose absorption and trigger insulin secretion (21); and 3) artificial sweeteners (such as saccharin, sucralose or aspartame) can interfere with gut microbiota, thus decreasing glucose sensitivity and favouring MetS development (21,50–52).

Our study has several strengths: it uses yearly repeated measurements of diet as exposure, and data are adjusted for a sizable number of potential confounders. However, it also has some limitations. First, the incidence of MetS was not a primary endpoint of the PREDIMED cohort, so our results are only exploratory. Second, our study subjects were elderly individuals at high risk of CVD, making it difficult to generalize the results to other populations. Third, the consumption of the various types of SSB was very low among our participants, so the categories of consumption were heterogeneous with respect to the number of participants, and the attributable risk associated with the consumption of sweetened beverages is also low. In addition, the frequency of SSBs in the highest category of consumption in our population is low, therefore, even if the associations observed are causal, the implications for intervention are limited to a few individuals. Fourth, because of the limited number of individuals in the highest categories of consumption and the adjustment for many variables, it is not clear that all the models of SSBs and bottled fruit juices are robust enough. Fifth, although the types of beverage and food consumption were assessed with a validated FFQ, measurement errors might have occurred. Nevertheless, to minimize the measurement error caused by within-person variations, the average consumption during the follow-up was calculated. Finally, although individual laboratory methods and procedures were subject to quality control, the fact that biochemical measurements were made in different centres means that we cannot discount a certain degree of measurement bias between laboratories, since the measurements were not standardized. Even so, the concordance analysis of lipid and glucose measurements reveal correlation coefficients higher than 0.81.

The present study is the first to make a separate analysis of the association between categories of each type of sweetened beverage and MetS risk. Occasional consumption (between 1 and 5 servings/week) of SSBs and artificially sweetened beverages was not associated with overall MetS. The consumption of more than 5 servings/week of all the types of beverages analyzed was associated with an increased risk of MetS and some of its components in middle-aged and elderly individuals at high risk of CVD. However, these associations (especially in the case of SSBs and bottled fruit juices) should be interpreted with caution because of the low frequency of consumption in our population. Furthermore, a consumption of between 1 and 5 servings per week of natural and bottled fruit juices may reduce the risk of MetS.

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D.C, R.E, E.R, L.S-M, F.A, J.L, E.G-G, M.F, and J.S-S: designed the PREDIMED study; C.F-P, N.B, M.B-R; D.C, R.E, E.R, M.F, L.S-M, F.A, J.L, M.F; E.G-G, X.P, M.R-C and J.S-S: conducted the research; C.F-P and N.B: analyzed data; C.F-P, N.B and J.S.-S: wrote the manuscript; D.C, R.E, E.R, L.S-M, M.F, J.L: were the coordinators of subject recruitment an follow-up at the outpatient clinics; N.B and J.S-S had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the final manuscript.

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Table 1. Baseline characteristics of the study participants according to servings (200mL) of sugar-sweetened beverages[1]

	Servings (200mL) of sugar-sweetened beverages			
	<1/ week (*n*=1601)	1-5/ week (*n*=184)	> 5/ week (*n*=83)	*P*-value[2]
Sugar-sweetened beverage intake (mL/d)	1.6 ± 4.4	51.9 ± 28.1	254 ± 127	
Age, years	67.1 ± 6.1	65.0 ± 5.6	67.0 ± 6.4	<0.001
Women, % (n)	52.8 (846)	51.6 (95)	47.0 (39)	0.56
Waist circumference, cm				
Women	91.7 ± 10.4	96.3 ± 10.8	95.4 ± 10.8	<0.001
Men	97.7 ± 7.6	99.9 ± 7.9	98.5 ± 7.7	0.041
BMI, kg/m^2	28.2 ± 3.5	29.3 ± 3.6	28.8 ± 3.2	<0.001
Leisure time physical activity, METs-min/d	275 ± 252	269 ± 282	269 ± 231	0.93
Smoking habit, % (n)				0.62
Never	58.9 (943)	57.6 (106)	51.8 (43)	
Current	15.2 (244)	17.4 (32)	20.5 (17)	
Former	25.9 (414)	25.0 (46)	27.7 (23)	
Blood pressure, mmHg				
Systolic	146 ± 20.3	144 ± 21.3	148 ± 22.4	0.28
Diastolic	81.8 ± 10.6	82.8 ± 11.2	84.6 ± 12.0	0.040
Biochemical parameters, mg/dL				
Plasma glucose	105 ± 35.0	96.3 ± 21.2	92.8 ± 15.6	<0.001
Serum HDL-Cholesterol	58.6 [51.0-68.0]	56.0 [48.8-65.0]	57.0 [50.9-67.0]	0.047
Serum triglycerides	95.0 [74.0-118]	99.0 [74.2-125]	108 [74.0-130]	0.035
Use of medication, % (n)				
Oral anti-diabetic drugs	15.6 (249)	6.5 (12)	8.4 (7)	0.001
Fibrates	0.1 (1)	0 (0)	0 (0)	0.92
Antihypertensive agents	64.8 (1037)	66.3 (122)	71.1 (59)	0.75
Insulin	5.0 (80)	0.0 (0)	1.2 (1)	0.002
Metabolic Syndrome components, % (n)[3]				
Abdominal obesity	42.4 (674)	55.2 (100)	48.2 (40)	0.003
Hypertriglyceridemia	4.7 (75)	7.6 (14)	9.6 (8)	0.042
Low HDL-cholesterol	2.7 (43)	3.8 (7)	7.2 (6)	0.049
High blood pressure	87.1 (1393)	85.3 (157)	90.4 (75)	0.52
High fasting glucose	33.8 (539)	21.4 (39)	13.3 (11)	<0.001
Intervention group, % (n)				0.16
Mediterranean diet + EVOO	35.1 (562)	34.8 (64)	24.1 (20)	
Mediterranean diet + nuts	33.6 (538)	35.9 (66)	45.8 (38)	
Control group	31.3 (501)	29.3 (54)	30.1 (25)	
Mediterranean diet score (14-point score)	9.0 ± 1.9	8.7 ± 1.9	7.8 ± 2.0	<0.001
Total energy intake (kcal/d)	2295 ± 521	2447 ± 569	2579 ± 551	<0.001
Food consumption (g/d)				
Vegetables	338 ± 142	343 ± 171	322 ± 144	0.56
Fruit	386 ± 209	380 ± 200	312 ± 188	0.007
Legumes	21 ± 14	20 ± 14	20 ± 10	0.52
Dairy products	390 ± 228	379 ± 215	368 ± 263	0.58
Total meat	129 ± 57	132 ± 58	134 ± 66	0.59
Fish	102 ± 47	104 ± 45	102 ± 44	0.88
Cereals	230 ± 103	237 ± 108	223 ± 108	0.51
Bakery	22 ± 28	31 ± 33	34 ± 33	<0.001
Nuts	12 ± 15	11 ± 11	11 ± 15	0.45
Total olive oil	42 ± 17	41 ± 17	40 ± 19	0.48
Alcohol	10 ± 15	11 ± 14	14 ± 19	0.027

Abbreviations: BMI, body mass index; EVOO, Extra Virgin Olive Oil; HDL, high-density lipoprotein.

[1]Continuous variables are expressed as means ± standard deviation or median [IQR, interquartile range] and categorical variables as a percentage and number (n).

[2]*P*-values for differences between categories were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.

[3]Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.

Table 2. HRs (95% CI) for Metabolic Syndrome incidence according to servings of consumption[1] of 200ml of sugar and artificial sweetened beverages and fruit juices in the PREDIMED cohort[2]

	Servings of consumption (200ml)			
	<1/ week	1-5/ week	> 5/ week	*P*-for trend
Sugar-sweetened beverages	(*n*=1610)	(*n*=216)	(*n*=42)	
Metabolic Syndrome incidence, %	48.6	54.9	69.0	0.010
Crude model	1 (ref)	1.06 (0.87, 1.30)	1.81 (1.24, 2.64)	0.004
Adjusted model 1[3]	1 (ref)	0.98 (0.80, 1.19)	1.87 (1.28, 2.73)	0.010
Adjusted model 2[4]	1 (ref)	0.93 (0.76, 1.13)	1.38 (0.93, 2.07)	0.30
Full-Adjusted model[5]	1 (ref)	0.91 (0.74, 1.12)	1.43 (1.00, 2.15)	0.27
Artificial-sweetened beverages	(*n*=1625)	(*n*=183)	(*n*=60)	
Metabolic Syndrome incidence, %	49.0	49.7	71.7	0.003
Crude model	1 (ref)	0.93 (0.75, 1.16)	2.15 (1.57, 2.94)	<0.001
Adjusted model 1[3]	1 (ref)	0.95 (0.76, 1.18)	2.02 (1.47, 2.78)	<0.001
Adjusted model 2[4]	1 (ref)	0.94 (0.76, 1.18)	1.97 (1.43, 2.71)	<0.001
Full-Adjusted model[5]	1 (ref)	0.93 (0.75, 1.17)	1.74 (1.26, 2.41)	0.004
Natural fruit juices	(*n*=1361)	(*n*=381)	(*n*=126)	
Metabolic Syndrome incidence, %	51.4	42.8	53.2	0.009
Crude model	1 (ref)	0.73 (0.62, 0.87)	1.10 (0.86, 1.42)	0.64
Adjusted model 1[3]	1 (ref)	0.71 (0.60, 0.85)	1.13 (0.88, 1.46)	0.69
Adjusted model 2[4]	1 (ref)	0.75 (0.63, 0.89)	1.22 (0.94, 1.59)	0.75
Full-Adjusted model[5]	1 (ref)	0.77 (0.65, 0.93)	1.30 (1.00, 1.69)	0.39
Bottled fruit juices	(*n*=1547)	(*n*=268)	(*n*=53)	
Metabolic Syndrome incidence, %	50.7	40.3	69.8	<0.001
Crude model	1 (ref)	0.71 (0.58, 0.87)	1.80 (1.28, 2.53)	0.24
Adjusted model 1[3]	1 (ref)	0.68 (0.56, 0.84)	1.60 (1.13, 2.27)	0.63
Adjusted model 2[4]	1 (ref)	0.64 (0.52, 0.78)	1.26 (1.08, 1.81)	0.46
Full-Adjusted model[5]	1 (ref)	0.66 (0.53, 0.81)	1.14 (1.04, 1.65)	0.31
Total sweetened beverages	(*n*=841)	(*n*=657)	(*n*=370)	
Metabolic Syndrome incidence, %	53.2	43.2	53.8	<0.001
Crude model	1 (ref)	0.69 (0.59, 1.80)	1.00 (0.84, 1.19)	0.880
Adjusted model 1[3]	1 (ref)	0.66 (0.57, 1.77)	0.97 (0.81, 1.15)	0.575
Adjusted model 2[4]	1 (ref)	0.67 (0.56, 1.79)	0.88 (0.73, 1.06)	0.160
Full-Adjusted model[5]	1 (ref)	0.69 (0.59, 1.81)	0.90 (0.74, 1.09)	0.227

[1]The consumption was averaged during follow-up.

[2]Data expressed as HRs (95% CI).

[3]Model 1: adjusted for intervention group, age in years, sex, leisure-time physical activity (METs/d), BMI (kg/m^2) and smoking status (never, former, and current).

[4]Model 2: additionally adjusted for cumulative average consumption of dietary variables in continuous (vegetables, legumes, fruits, cereals, meat, fish, bakery, dairy products, olive oil, and nuts), cumulative total energy intake, alcohol and alcohol squared in g/d.

[5]Model 3 (Full-adjusted model): additionally adjusted for metabolic syndrome components at baseline (yes/no).

Table 3. HRs (95% CI) for Metabolic Syndrome components incidence according to servings of consumption[1] of 200mL of sugar and artificially-sweetened beverages and fruit juices in the PREDIMED cohort[2]

	Incidence, %	Servings of consumption (200mL)			
		<1/ week	1-5/ week	> 5/ week	*P*-for trend
Abdominal obesity[3]	(*n*=1019)				
Sugar-sweetened beverages	48.6	1 (ref)	1.13 (0.81, 1.57)	1.20 (0.62, 2.30)	0.42
Artificially sweetened beverages	50.0	1 (ref)	0. 91 (0.65, 1.28)	1.82 (1.13, 2.92)	0.039
Natural fruit juices	46.9	1 (ref)	0.97 (0.76, 1.24)	1.52 (1.02, 2.25)	0.08
Bottled fruit juices	41.5	1 (ref)	0.96 (0.72, 1.29)	0.46 (0.21, 1.03)	0.08
Total sweetened beverages	45.8	1 (ref)	0.94 (0.75, 1.17)	1.23 (0.93, 1.62)	0.164
Hypertriglyceridemia[3]	(*n*=1766)				
Sugar-sweetened beverages	35.3	1 (ref)	1.22 (0.94, 1.59)	1.48 (0.87, 2.53)	0.06
Artificially sweetened beverages	31.6	1 (ref)	0.99 (0.73, 1.33)	1.52 (1.00, 2.37)	0.08
Natural fruit juices	27.3	1 (ref)	0.81 (0.63, 1.03)	1.16 (0.80, 1.68)	0.85
Bottled fruit juices	30.8	1 (ref)	0.94 (0.72, 1.22)	1.51 (1.03, 2.46)	0.23
Total sweetened beverages	28.4	1 (ref)	0.75 (0.60,1.03)	1.13 (0.88, 1.45)	0.344
Low-HDL cholesterol[3]	(*n*=1804)				
Sugar-sweetened beverages	28.0	1 (ref)	0.97 (0.72, 1.29)	1.18 (1.06, 2.11)	0.71
Artificially sweetened beverages	26.1	1 (ref)	0.92 (0.66, 1.27)	1.08 (0.66, 1.78)	0.87
Natural fruit juices	22.1	1 (ref)	0.84 (0.65, 1.08)	0.74 (0.47, 1.16)	0.11
Bottled fruit juices	25.2	1 (ref)	0.77 (0.57, 1.04)	1.08 (0.62, 1.85)	0.63
Total sweetened beverages	23.9	1 (ref)	0.76 (0.61, 1.04)	0.66 (0.49, 1.08)	0.003
High blood pressure[3]	(*n*=240)				
Sugar-sweetened beverages	86.2	1 (ref)	1.89 (1.14, 3.13)	1.09 (1.04, 2.80)	0.39
Artificially sweetened beverages	74.4	1 (ref)	0.91 (0.51, 1.62)	1.00 (0.45, 2.20)	0.92
Natural fruit juices	83.6	1 (ref)	1.11 (0.73, 1.68)	1.04 (0.58, 1.86)	0.82
Bottled fruit juices	80.2	1 (ref)	0.94 (0.57, 1.54)	2.18 (0.74, 6.42)	0.31
Total sweetened beverages	81.8	1 (ref)	1.06 (0.71, 1.57)	1.22 (0.79, 1.91)	0.360
High fasting glucose[3]	(*n*=1269)				
Sugar-sweetened beverages	44.7	1 (ref)	1.03 (0.80, 1.33)	1.02 (0.61, 1.70)	0.88
Artificially sweetened beverages	42.5	1 (ref)	0.87 (0.65, 1.17)	1.66 (0.97, 2.85)	0.24
Natural fruit juices	41.1	1 (ref)	0.80 (0.63, 1.00)	1.18 (0.84, 1.65)	0.74
Bottled fruit juices	44.4	1 (ref)	0.69 (0.53, 1.90)	1.15 (0.69, 1.91)	0.45
Total sweetened beverages	41.7	1 (ref)	0.77 (0.63, 1.05)	0.96 (0.74, 1.23)	0.781

[1]The consumption was averaged during the follow-up

[2]Data expressed as HRs (95% CI).

[3]All the data shown was adjusted for intervention group, age in years, sex, leisure-time physical activity (METs/d), BMI (kg/m^2), smoking status (never, former, and current), average consumption during the follow-up of dietary variables as continuous variables (vegetables, legumes, fruits, cereals, meat, fish, baked products, dairy products, olive oil, and nuts), average total energy intake during follow-up, alcohol and alcohol squared in g/d.

ONLINE SUPPORTING MATERIAL

Supplemental Table 1. Baseline characteristics of the study participants according to servings (200mL) of artificially-sweetened beverages[1]

	Servings (200mL) of artificially-sweetened beverages			
	<1/ week (*n*=1648)	1-5/ week (*n*=137)	> 5/ week (*n*=83)	*P*-value[2]
Artificially-sweetened beverage intake (mL/d)	0.7 ± 3.0	58.6 ± 28.6	294 ± 210	
Age, years	67.0 ± 6.2	66.2 ± 5.7	66.2 ± 5.2	0.18
Women, % (n)	52.5 (866)	53.3 (73)	49.4 (41)	0.84
Waist circumference, cm				
Women	92.0 ± 10.5	93.4 ± 10.8	97.1 ± 9.8	0.007
Men	97.9 ± 7.4	99.7 ± 10.1	96.7 ± 6.4	0.10
BMI, kg/m^2	28.3 ± 3.5	28.9 ± 3.7	28.5 ± 3.8	0.16
Leisure time physical activity, METs-min/d	275 ± 253	254 ± 231	287 ± 305	0.58
Smoking habit, % (n)				0.81
Never	58.3 (960)	57.7 (79)	63.9 (53)	
Current	16.0 (263)	14.6 (20)	12.0 (10)	
Former	25.8 (425)	27.7 (38)	24.1 (20)	
Blood pressure, mmHg				
Systolic	146 ± 20.4	147 ± 21.5	146 ± 20.7	0.95
Diastolic	81.9 ± 10.7	83.2 ± 10.1	83.0 ± 12.4	0.26
Biochemical parameters, mg/dL				
Plasma glucose	104 ± 33.0	102 ± 29.6	109 ± 45.1	0.30
Serum HDL-Cholesterol	58.0 [51.0-68.0]	57.0 [50.0-66.4]	58.0 [49.0-66.8]	0.79
Serum triglycerides	96.0 [75.0-119]	91.0 [70.0-123]	95.0 [74.5-119]	0.83
Use of medication, % (n)				
Oral anti-diabetic drugs	13.8 (227)	19.1 (26)	18.1 (15)	0.14
Fibrates	0.1 (1)	0.0 (0)	0.0 (0)	0.93
Antihypertensive agents	66.0 (1088)	60.6 (83)	56.6 (47)	0.18
Insulin	4.4 (72)	2.2 (3)	7.2 (6)	0.21
Metabolic Syndrome components, % (n)[3]				
Abdominal obesity	42.9 (702)	53.7 (73)	47.0 (39)	0.044
Hypertriglyceridemia	5.3 (87)	5.8 (8)	2.4 (2)	0.48
Low HDL-cholesterol	2.7 (45)	4.4 (6)	6.0 (5)	0.14
High blood pressure	87.5 (1441)	85.4 (117)	80.7 (67)	0.16
High plasma glucose	31.5 (516)	32.1 (44)	34.9 (29)	0.80
Intervention group, % (n)				0.15
Mediterranean diet + EVOO	35.3 (581)	29.9 (41)	28.9 (24)	
Mediterranean diet + nuts	33.6 (553)	37.2 (51)	45.8 (38)	
Control group	31.2 (514)	32.8 (45)	25.3 (21)	
Mediterranean diet score (14-point score)	8.9 ± 1.9	8.8 ± 1.9	8.6 ± 2.0	0.33
Total energy intake (kcal/d)	2309 ± 529	2455 ± 539	2370 ± 535	0.006
Food consumption (g/d)				
Vegetables	337 ± 147	340 ± 127	350 ± 139	0.72
Fruit	382 ± 207	359 ± 175	414 ± 266	0.16
Legumes	21 ± 13	21 ± 16	20 ± 11	0.83
Dairy products	391 ± 230	370 ± 204	363 ± 221	0.34
Total meat	128 ± 56	141 ± 65	136 ± 73	0.019
Fish	101 ± 46	107 ± 48	110 ± 53	0.10
Cereals	230 ± 104	240 ± 107	217 ± 97	0.28
Baked products	23 ± 28	25 ± 28	29 ± 45	0.15
Nuts	12 ± 15	13 ± 18	14 ± 17	0.28
Total olive oil	42 ± 17	44 ± 18	41 ± 17	0.36
Alcohol	10 ± 15	11 ± 14	11 ± 13	0.50

Abbreviations: BMI, body mass index; EVOO, Extra Virgin Olive Oil; HDL, high-density lipoprotein.

[1]Continuous variables are expressed as means ± standard deviation or median [IQR, interquartile range] and categorical variables as a percentage and number (n).

[2]*P*-values for differences between categories were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.

[3]Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.

ONLINE SUPPORTING MATERIAL

Supplemental Table 2. Baseline characteristics of the study participants according to servings (200mL) of bottled fruit juices[1]

	Servings (200mL) of bottled fruit juices			
	<1/ week (*n*=1608)	1-5/ week (*n*=168)	> 5/ week (*n*=92)	*P*-value[2]
Bottled fruit-juice intake (mL/d)	0.9 ± 3.4	58.8 ± 28.6	210 ± 79.1	
Age, years	67.0 ± 6.1	66.7 ± 6.1	66.1 ± 6.5	0.34
Women, % (n)	51.6 (829)	56.5 (95)	60.9 (56)	0.12
Waist circumference, cm				
Women	92.0 ± 10.6	94.1 ± 9.7	93.4 ± 11.5	0.16
Men	97.9 ± 7.6	98.7 ± 7.7	98.3 ± 8.9	0.72
BMI, kg/m^2	28.3 ± 3.4	28.8 ± 3.6	29.1 ± 4.3	0.024
Leisure time physical activity, METs-min/d	277 ± 254	238 ± 243	292 ± 259	0.13
Smoking habit, % (n)				0.54
Never	58.1 (934)	63.7 (107)	55.4 (51)	
Current	15.7 (253)	13.1 (22)	19.6 (18)	
Former	26.2 (421)	23.2 (39)	25.0 (23)	
Blood pressure, mmHg				
Systolic	146 ± 20.6	147 ± 20.2	144 ± 19.6	0.41
Diastolic	81.9 ± 10.7	83.9 ± 10.8	81.0 ± 10.9	0.042
Biochemical parameters, mg/dL				
Plasma glucose	105 ± 34.1	99.1 ± 26.9	99.9 ± 31.9	0.06
Serum HDL-Cholesterol	58.0 [50.8-67.6]	57.0 [51.0-66.0]	58.0 [51.0-68.5]	0.98
Serum triglycerides	96.0 [74.0-120]	98.5 [77.2-120]	93.5 [78.5-117]	0.83
Use of medication, % (n)				
Oral anti-diabetic drugs	15.0 (240)	11.3 (19)	9.8 (9)	0.19
Fibrates	0.1 (1)	0 (0)	0 (0)	0.92
Antihypertensive agents	65.0 (1045)	66.7 (112)	66.3 (61)	0.95
Insulin	4.7 (76)	1.8 (3)	2.2 (2)	0.12
Metabolic Syndrome components, % (n)[3]				
Abdominal obesity	42.7 (683)	51.5 (86)	50.0 (45)	0.046
Hypertriglyceridemia	5.2 (84)	6.0 (10)	3.3 (3)	0.64
Low HDL-cholesterol	3.0 (49)	3.0 (5)	2.2 (2)	0.89
High blood pressure	87.2 (1400)	86.9 (146)	85.9 (79)	0.93
High fasting glucose	32.6 (521)	23.8 (40)	30.8 (28)	0.07
Intervention group, % (n)				0.001
Mediterranean diet + EVOO	33.8 (543)	47.6 (80)	25.0 (23)	
Mediterranean diet + nuts	34.7 (558)	26.2 (44)	43.5 (40)	
Control group	31.5 (507)	26.2 (44)	31.5 (29)	
Mediterranean diet score (14-point score)	9.0 ± 1.9	8.8 ± 2.0	8.5 ± 2.0	0.030
Total energy intake (kcal/d)	2307 ± 534	2404 ± 508	2444 ± 507	0.006
Food consumption (g/d)				
Vegetables	339 ± 146	330 ± 126	330 ± 160	0.66
Fruit	383 ± 206	373 ± 196	381 ± 254	0.84
Legumes	21 ± 12	22 ± 17	27 ± 27	<0.001
Dairy products	384 ± 230	397 ± 200	444 ± 232	0.042
Total meat	130 ± 57	130 ± 60	120 ± 57	0.29
Fish	102 ± 46	101 ± 47	98 ± 50	0.68
Cereals	232 ± 10	224 ± 98	206 ± 97	0.051
Baked products	22 ± 28	28 ± 34	29 ± 37	0.008
Nuts	12 ± 15	13 ± 17	12 ± 15	0.60
Total olive oil	42 ± 17	39 ± 17	39 ± 20	0.034
Alcohol	10 ± 15	7 ± 11	9 ± 15	0.006

Abbreviations: BMI, body mass index; EVOO, Extra Virgin Olive Oil; HDL, high-density lipoprotein.

[1]Continuous variables are expressed as means ± standard deviation or median [IQR, interquartile range] and categorical variables as a percentage and number (n).

[2]*P*-values for differences between categories were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.

[3]Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.

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Supplemental Table 3. Baseline characteristics of the study participants according to servings (200mL) of natural fruit juices[1]

	Servings (200mL) of natural fruit juices			
	<1/ week (*n*=1457)	1-5/ week (*n*=228)	> 5/ week (*n*=183)	*P*-value[2]
Natural fruit-juice intake (mL/d)	1.7 ± 4.7	62.5 ± 28.6	210 ± 66.1	
Age, years	67.1 ± 6.1	65.8 ± 5.9	66.9 ± 6.0	0.011
Women, % (n)	51.1 (745)	57.5 (131)	56.8 (104)	0.09
Waist circumference, cm				
Women	92.5 ± 10.6	91.7 ± 10.6	91.8 ± 10.4	0.63
Men	98.0 ± 7.6	97.7 ± 8.1	98.6 ± 7.6	0.74
BMI, kg/m^2	28.4 ± 3.5	28.2 ± 3.6	28.3 ± 3.5	0.89
Leisure time physical activity, METs-min/d	274 ± 253	286 ± 265	262 ± 249	0.62
Smoking habit, % (n)				0.59
Never	58.4 (851)	57.0 (130)	60.7 (111)	
Current	15.8 (230)	18.0 (41)	12.0 (22)	
Former	25.8 (376)	25.0 (57)	27.3 (50)	
Blood pressure, mmHg				
Systolic	147 ± 20.9	144 ± 19.3	145 ± 18.9	0.15
Diastolic	81.9 ± 10.9	82.1 ± 10.8	82.6 ± 9.7	0.72
Biochemical parameters, mg/dL				
Plasma glucose	105 ± 35.0	101 ± 29.7	98.2 ± 23.2	0.011
Serum HDL-Cholesterol	58.0 [50.4-67.0]	59.5 [52.0-68.0]	59.0 [52.0-68.2]	0.19
Serum triglycerides	96.0 [74.9-120]	96.5[77.0-121]	93.0 [72.0-114]	0.37
Use of medication, % (n)				
Oral anti-diabetic drugs	15.6 (227)	12.7 (29)	6.6 (12)	0.003
Fibrates	0 (0)	0.4 (1)	0 (0)	0.027
Antihypertensive agents	64.6 (941)	64.9 (148)	70.5 (129)	0.51
Insulin	4.8 (70)	2.6 (6)	2.7 (5)	0.17
Metabolic Syndrome components, % (n)[3]				
Abdominal obesity	43.0 (623)	46.2 (104)	48.1 (87)	0.32
Hypertriglyceridemia	5.6 (81)	4.4 (10)	3.3 (6)	0.36
Low HDL-cholesterol	2.8 (41)	2.6 (6)	4.9 (9)	0.27
High blood pressure	86.8 (1263)	87.7 (200)	88.5 (162)	0.77
High plasma glucose	33.1 (480)	29.2 (66)	23.6 (43)	0.024
Intervention group, % (n)				0.44
Mediterranean diet + EVOO	34.1 (497)	36.8 (84)	35.5 (65)	
Mediterranean diet + nuts	33.8 (492)	36.8 (84)	36.1 (66)	
Control group	32.1 (468)	26.3 (60)	28.4 (52)	
Mediterranean diet score (14-point score)	8.8 ± 1.9	9.0 ± 2.1	9.5 ± 1.8	<0.001
Total energy intake (kcal/d)	2294 ± 531	2398 ± 511	2461 ± 533	<0.001
Food consumption (g/d)				
Vegetables	330 ± 141	354 ± 143	377 ± 171	<0.001
Fruit	375 ± 208	373 ± 185	450 ± 220	<0.001
Legumes	20 ± 12	23 ± 18	24 ± 16	<0.001
Dairy products	382 ± 226	398 ± 222	422 ± 249	0.07
Total meat	130 ± 57	129 ± 58	119 ± 56	0.05
Fish	100 ± 45	109 ± 48	113 ± 47	<0.001
Cereals	234 ± 106	215 ± 92	217 ± 100	0.008
Baked products	23 ± 30	26 ± 25	23 ± 24	0.27
Nuts	11 ± 15	14 ± 16	15 ± 17	0.002
Total olive oil	42 ± 17	40 ± 18	43 ± 17	0.39
Alcohol	10 ± 15	10 ± 15	9 ± 12	0.61

Abbreviations: BMI, body mass index; EVOO, Extra Virgin Olive Oil; HDL, high-density lipoprotein.

[1]Continuous variables are expressed as means ± standard deviation or median [IQR, interquartile range] and categorical variables as a percentage and number (n).

[2]*P*-values for differences between categories were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.

[3]Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.

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ONLINE SUPPORTING MATERIAL

Supplemental Table 1. Baseline characteristics of the study participants according to servings (200mL) of artificially-sweetened beverages[1]

	Servings (200mL) of artificially-sweetened beverages			
	<1/ week (*n*=1648)	1-5/ week (*n*=137)	> 5/ week (*n*=83)	*P*-value[2]
Artificially-sweetened beverage intake (mL/d)	0.7 ± 3.0	58.6 ± 28.6	294 ± 210	
Age, years	67.0 ± 6.2	66.2 ± 5.7	66.2 ± 5.2	0.18
Women, % (n)	52.5 (866)	53.3 (73)	49.4 (41)	0.84
Waist circumference, cm				
Women	92.0 ± 10.5	93.4 ± 10.8	97.1 ± 9.8	0.007
Men	97.9 ± 7.4	99.7 ± 10.1	96.7 ± 6.4	0.10
BMI, kg/m^2	28.3 ± 3.5	28.9 ± 3.7	28.5 ± 3.8	0.16
Leisure time physical activity, METs-min/d	275 ± 253	254 ± 231	287 ± 305	0.58
Smoking habit, % (n)				0.81
Never	58.3 (960)	57.7 (79)	63.9 (53)	
Current	16.0 (263)	14.6 (20)	12.0 (10)	
Former	25.8 (425)	27.7 (38)	24.1 (20)	
Blood pressure, mmHg				
Systolic	146 ± 20.4	147 ± 21.5	146 ± 20.7	0.95
Diastolic	81.9 ± 10.7	83.2 ± 10.1	83.0 ± 12.4	0.26
Biochemical parameters, mg/dL				
Plasma glucose	104 ± 33.0	102 ± 29.6	109 ± 45.1	0.30
Serum HDL-Cholesterol	58.0 [51.0-68.0]	57.0 [50.0-66.4]	58.0 [49.0-66.8]	0.79
Serum triglycerides	96.0 [75.0-119]	91.0 [70.0-123]	95.0 [74.5-119]	0.83
Use of medication, % (n)				
Oral anti-diabetic drugs	13.8 (227)	19.1 (26)	18.1 (15)	0.14
Fibrates	0.1 (1)	0.0 (0)	0.0 (0)	0.93
Antihypertensive agents	66.0 (1088)	60.6 (83)	56.6 (47)	0.18
Insulin	4.4 (72)	2.2 (3)	7.2 (6)	0.21
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Abdominal obesity	42.9 (702)	53.7 (73)	47.0 (39)	0.044
Hypertriglyceridemia	5.3 (87)	5.8 (8)	2.4 (2)	0.48
Low HDL-cholesterol	2.7 (45)	4.4 (6)	6.0 (5)	0.14
High blood pressure	87.5 (1441)	85.4 (117)	80.7 (67)	0.16
High plasma glucose	31.5 (516)	32.1 (44)	34.9 (29)	0.80
Intervention group, % (n)				0.15
Mediterranean diet + EVOO	35.3 (581)	29.9 (41)	28.9 (24)	
Mediterranean diet + nuts	33.6 (553)	37.2 (51)	45.8 (38)	
Control group	31.2 (514)	32.8 (45)	25.3 (21)	
Mediterranean diet score (14-point score)	8.9 ± 1.9	8.8 ± 1.9	8.6 ± 2.0	0.33
Total energy intake (kcal/d)	2309 ± 529	2455 ± 539	2370 ± 535	0.006
Food consumption (g/d)				
Vegetables	337 ± 147	340 ± 127	350 ± 139	0.72
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Legumes	21 ± 13	21 ± 16	20 ± 11	0.83
Dairy products	391 ± 230	370 ± 204	363 ± 221	0.34
Total meat	128 ± 56	141 ± 65	136 ± 73	0.019
Fish	101 ± 46	107 ± 48	110 ± 53	0.10
Cereals	230 ± 104	240 ± 107	217 ± 97	0.28
Baked products	23 ± 28	25 ± 28	29 ± 45	0.15
Nuts	12 ± 15	13 ± 18	14 ± 17	0.28
Total olive oil	42 ± 17	44 ± 18	41 ± 17	0.36
Alcohol	10 ± 15	11 ± 14	11 ± 13	0.50

Abbreviations: BMI, body mass index; EVOO, Extra Virgin Olive Oil; HDL, high-density lipoprotein.
[1]Continuous variables are expressed as means ± standard deviation or median [IQR, interquartile range] and categorical variables as a percentage and number (n).
[2]*P*-values for differences between categories were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.
[3]Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.

ONLINE SUPPORTING MATERIAL

Supplemental Table 2. Baseline characteristics of the study participants according to servings (200mL) of bottled fruit juices[1]

	Servings (200mL) of bottled fruit juices			
	<1/ week (*n*=1608)	1-5/ week (*n*=168)	> 5/ week (*n*=92)	*P*-value[2]
Bottled fruit-juice intake (mL/d)	0.9 ± 3.4	58.8 ± 28.6	210 ± 79.1	
Age, years	67.0 ± 6.1	66.7 ± 6.1	66.1 ± 6.5	0.34
Women, % (n)	51.6 (829)	56.5 (95)	60.9 (56)	0.12
Waist circumference, cm				
Women	92.0 ± 10.6	94.1 ± 9.7	93.4 ± 11.5	0.16
Men	97.9 ± 7.6	98.7 ± 7.7	98.3 ± 8.9	0.72
BMI, kg/m^2	28.3 ± 3.4	28.8 ± 3.6	29.1 ± 4.3	0.024
Leisure time physical activity, METs-min/d	277 ± 254	238 ± 243	292 ± 259	0.13
Smoking habit, % (n)				0.54
Never	58.1 (934)	63.7 (107)	55.4 (51)	
Current	15.7 (253)	13.1 (22)	19.6 (18)	
Former	26.2 (421)	23.2 (39)	25.0 (23)	
Blood pressure, mmHg				
Systolic	146 ± 20.6	147 ± 20.2	144 ± 19.6	0.41
Diastolic	81.9 ± 10.7	83.9 ± 10.8	81.0 ± 10.9	0.042
Biochemical parameters, mg/dL				
Plasma glucose	105 ± 34.1	99.1 ± 26.9	99.9 ± 31.9	0.06
Serum HDL-Cholesterol	58.0 [50.8-67.6]	57.0 [51.0-66.0]	58.0 [51.0-68.5]	0.98
Serum triglycerides	96.0 [74.0-120]	98.5 [77.2-120]	93.5 [78.5-117]	0.83
Use of medication, % (n)				
Oral anti-diabetic drugs	15.0 (240)	11.3 (19)	9.8 (9)	0.19
Fibrates	0.1 (1)	0 (0)	0 (0)	0.92
Antihypertensive agents	65.0 (1045)	66.7 (112)	66.3 (61)	0.95
Insulin	4.7 (76)	1.8 (3)	2.2 (2)	0.12
Metabolic Syndrome components, % (n)[3]				
Abdominal obesity	42.7 (683)	51.5 (86)	50.0 (45)	0.046
Hypertriglyceridemia	5.2 (84)	6.0 (10)	3.3 (3)	0.64
Low HDL-cholesterol	3.0 (49)	3.0 (5)	2.2 (2)	0.89
High blood pressure	87.2 (1400)	86.9 (146)	85.9 (79)	0.93
High fasting glucose	32.6 (521)	23.8 (40)	30.8 (28)	0.07
Intervention group, % (n)				0.001
Mediterranean diet + EVOO	33.8 (543)	47.6 (80)	25.0 (23)	
Mediterranean diet + nuts	34.7 (558)	26.2 (44)	43.5 (40)	
Control group	31.5 (507)	26.2 (44)	31.5 (29)	
Mediterranean diet score (14-point score)	9.0 ± 1.9	8.8 ± 2.0	8.5 ± 2.0	0.030
Total energy intake (kcal/d)	2307 ± 534	2404 ± 508	2444 ± 507	0.006
Food consumption (g/d)				
Vegetables	339 ± 146	330 ± 126	330 ± 160	0.66
Fruit	383 ± 206	373 ± 196	381 ± 254	0.84
Legumes	21 ± 12	22 ± 17	27 ± 27	<0.001
Dairy products	384 ± 230	397 ± 200	444 ± 232	0.042
Total meat	130 ± 57	130 ± 60	120 ± 57	0.29
Fish	102 ± 46	101 ± 47	98 ± 50	0.68
Cereals	232 ± 10	224 ± 98	206 ± 97	0.051
Baked products	22 ± 28	28 ± 34	29 ± 37	0.008
Nuts	12 ± 15	13 ± 17	12 ± 15	0.60
Total olive oil	42 ± 17	39 ± 17	39 ± 20	0.034
Alcohol	10 ± 15	7 ± 11	9 ± 15	0.006

Abbreviations: BMI, body mass index; EVOO, Extra Virgin Olive Oil; HDL, high-density lipoprotein.

[1]Continuous variables are expressed as means ± standard deviation or median [IQR, interquartile range] and categorical variables as a percentage and number (n).

[2]*P*-values for differences between categories were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.

[3]Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.

ONLINE SUPPORTING MATERIAL

Supplemental Table 3. Baseline characteristics of the study participants according to servings (200mL) of natural fruit juices[1]

	Servings (200mL) of natural fruit juices			
	<1/ week (*n*=1457)	1-5/ week (*n*=228)	> 5/ week (*n*=183)	*P*-value[2]
Natural fruit-juice intake (mL/d)	1.7 ± 4.7	62.5 ± 28.6	210 ± 66.1	
Age, years	67.1 ± 6.1	65.8 ± 5.9	66.9 ± 6.0	0.011
Women, % (n)	51.1 (745)	57.5 (131)	56.8 (104)	0.09
Waist circumference, cm				
Women	92.5 ± 10.6	91.7 ± 10.6	91.8 ± 10.4	0.63
Men	98.0 ± 7.6	97.7 ± 8.1	98.6 ± 7.6	0.74
BMI, kg/m^2	28.4 ± 3.5	28.2 ± 3.6	28.3 ± 3.5	0.89
Leisure time physical activity, METs-min/d	274 ± 253	286 ± 265	262 ± 249	0.62
Smoking habit, % (n)				0.59
Never	58.4 (851)	57.0 (130)	60.7 (111)	
Current	15.8 (230)	18.0 (41)	12.0 (22)	
Former	25.8 (376)	25.0 (57)	27.3 (50)	
Blood pressure, mmHg				
Systolic	147 ± 20.9	144 ± 19.3	145 ± 18.9	0.15
Diastolic	81.9 ± 10.9	82.1 ± 10.8	82.6 ± 9.7	0.72
Biochemical parameters, mg/dL				
Plasma glucose	105 ± 35.0	101 ± 29.7	98.2 ± 23.2	0.011
Serum HDL-Cholesterol	58.0 [50.4-67.0]	59.5 [52.0-68.0]	59.0 [52.0-68.2]	0.19
Serum triglycerides	96.0 [74.9-120]	96.5[77.0-121]	93.0 [72.0-114]	0.37
Use of medication, % (n)				
Oral anti-diabetic drugs	15.6 (227)	12.7 (29)	6.6 (12)	0.003
Fibrates	0 (0)	0.4 (1)	0 (0)	0.027
Antihypertensive agents	64.6 (941)	64.9 (148)	70.5 (129)	0.51
Insulin	4.8 (70)	2.6 (6)	2.7 (5)	0.17
Metabolic Syndrome components, % (n)[3]				
Abdominal obesity	43.0 (623)	46.2 (104)	48.1 (87)	0.32
Hypertriglyceridemia	5.6 (81)	4.4 (10)	3.3 (6)	0.36
Low HDL-cholesterol	2.8 (41)	2.6 (6)	4.9 (9)	0.27
High blood pressure	86.8 (1263)	87.7 (200)	88.5 (162)	0.77
High plasma glucose	33.1 (480)	29.2 (66)	23.6 (43)	0.024
Intervention group, % (n)				0.44
Mediterranean diet + EVOO	34.1 (497)	36.8 (84)	35.5 (65)	
Mediterranean diet + nuts	33.8 (492)	36.8 (84)	36.1 (66)	
Control group	32.1 (468)	26.3 (60)	28.4 (52)	
Mediterranean diet score (14-point score)	8.8 ± 1.9	9.0 ± 2.1	9.5 ± 1.8	<0.001
Total energy intake (kcal/d)	2294 ± 531	2398 ± 511	2461 ± 533	<0.001
Food consumption (g/d)				
Vegetables	330 ± 141	354 ± 143	377 ± 171	<0.001
Fruit	375 ± 208	373 ± 185	450 ± 220	<0.001
Legumes	20 ± 12	23 ± 18	24 ± 16	<0.001
Dairy products	382 ± 226	398 ± 222	422 ± 249	0.07
Total meat	130 ± 57	129 ± 58	119 ± 56	0.05
Fish	100 ± 45	109 ± 48	113 ± 47	<0.001
Cereals	234 ± 106	215 ± 92	217 ± 100	0.008
Baked products	23 ± 30	26 ± 25	23 ± 24	0.27
Nuts	11 ± 15	14 ± 16	15 ± 17	0.002
Total olive oil	42 ± 17	40 ± 18	43 ± 17	0.39
Alcohol	10 ± 15	10 ± 15	9 ± 12	0.61

Abbreviations: BMI, body mass index; EVOO, Extra Virgin Olive Oil; HDL, high-density lipoprotein.

[1]Continuous variables are expressed as means ± standard deviation or median [IQR, interquartile range] and categorical variables as a percentage and number (n).

[2]*P*-values for differences between categories were calculated by chi-square tests for categorical variables and ANOVA tests for continuous variables.

[3]Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥88 cm in women and ≥102cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma triglyceride (TG) concentration, low HDL-cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2DM.