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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 Cardiovascular Disease Risk[1–3]

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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 by using the updated harmonized criteria of the International Diabetes Federation, the American Heart Association, and National Heart, Lung, and Blood Institute. Energy and nutrient intakes were evaluated at baseline and then yearly by using a validated 137-item food-frequency questionnaire. Multivariable-adjusted HRs for MetS and its components were estimated from mean intakes during follow-up. We compared the 2 highest consumption categories (1–5 and >5 servings/wk) with the lowest category (<1 serving/wk).

Results: A total of 930 incident cases of MetS were documented during a median follow-up of 3.24 y. When we compared consumption of >5 servings/wk with consumption of <1 serving/wk, multivariable HRs (95% CIs) 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) for SSBs, artificially sweetened beverages, natural fruit juices, and bottled fruit juices, respectively.

Conclusions: The occasional consumption of SSBs and artificially sweetened beverages (1–5 servings/wk) was not associated with the incidence of MetS in middle-aged and elderly individuals at high risk of CVD. The consumption of >5 servings/wk of all of 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. This trial was registered at clinicaltrials.gov as ISRCTN35739639. *J Nutr* doi: 10.3945/jn.116.230367.

Keywords: sugar-sweetened beverages, artificially sweetened beverages, fruit juices, metabolic syndrome, metabolic syndrome components, PREDIMED study

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Introduction

Metabolic syndrome (MetS)[19] is a cluster of metabolic alterations associated with visceral obesity, including atherogenic dyslipidemia, high fasting plasma glucose, and increased blood pressure (1). The disorder entails an increased risk of type 2 diabetes (T2D), cardiovascular disease (CVD), and cause-specific mortality (1–3). Because the incidence of 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 modifications, such as engaging in more physical activity, adopting a healthy dietary pattern, and maintaining normal weight, are the first-line measures for both 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 consumers of the Mediterranean diet (13), although it remains lower than in other industrialized countries (14).

In recent decades, the relation between the consumption of sweetened beverages and the development of MetS has been investigated in epidemiologic studies. However, most of these were cross-sectional (5, 15–19), so their potential for discerning relations is limited. To date, to our knowledge, only 4 prospective studies have investigated the association between the consumption of sweetened beverages and MetS incidence, with contradictory results (20–23). Three of these were part of a meta-analysis (24) that concluded that a higher consumption of sugar-sweetened beverages (SSBs) 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.

To our knowledge, no studies have been performed on the association between the mean consumption during the follow-up of sweetened beverages and incident MetS in a Mediterranean population of middle-aged to elderly adults. Therefore, the aim of the present study was to examine the associations between the average consumption of SSBs, 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 (clinicaltrials.gov; ISRCTN35739639) 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, multicenter, randomized parallel-group and controlled field trial conducted in Spain for the primary prevention of cardiovascular events (a list of the PREDIMED Investigators can be found in **Supplemental Text**). 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 y and women aged 60–80 y) were randomly assigned to 1 of the 3 intervention groups: a Mediterranean diet supplemented with extra-virgin olive oil (~50 mL/d), a Mediterranean diet supplemented with mixed nuts (15 g walnuts, 7.5 g hazelnuts, and 7.5 g almonds daily), or advice on 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 T2D or ≥3 of the following risk factors: current smoking (>1 cigarette/d during the past month), hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or taking antihypertensive medication), high LDL cholesterol (≥160 mg/dL), low HDL cholesterol (<40 mg/dL for men or <50 mg/dL for women), overweight or obese [BMI (in kg/m^2) ≥25], 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 center approved the protocol, and all of the subjects provided written informed consent. The study follow-up ended in December 2010.

The present data were analyzed by using an observational prospective design, and participants were selected from all of the PREDIMED recruitment centers with biochemical determinations available for a follow-up of ≥2 y (n = 5801). The main aim of the present report was to explore the associations between the consumption of SSBs, artificially sweetened beverages, and natural and bottled fruit juices and the incidence of MetS. For this reason, participants with MetS at baseline (n = 3707) were excluded. Those who did not complete the baseline FFQ or who reported implausible total energy intakes (≤500 and ≥3500 kcal/d in women and ≤800 and ≥4000 kcal/d 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 MetS criteria of abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose concentrations at baseline. Finally, 1868 participants were included in the present analysis.

MetS. MetS was defined in accordance with the updated harmonized criteria of the International Diabetes Federation, the American Heart Association, and National Heart, Lung, and Blood Institute (1). Participants were considered to have MetS if they had ≥3 of the following: abdominal obesity for European individuals (waist circumference ≥88 cm

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[3] Supplemental Tables 1–3 and Supplemental Text are available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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[19] Abbreviations used: CVD, cardiovascular disease; ICC, intraclass correlation coefficient; MetS, metabolic syndrome; PREDIMED, Prevención con Dieta Mediterránea; SSB, sugar-sweetened beverage; T2D, type 2 diabetes.

in women and ≥102 cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma TG concentrations, low HDL cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for T2D.

Dietary assessment. Dietary intake was assessed by trained dietitians with the use of a 137-item semiquantitative FFQ validated for the PREDIMED study (30), which was 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 by using authorized methods and packed and commercialized for subsequent consumption). By using the intraclass correlation coefficients (ICCs) between the FFQ and dietary records, the following reliabilities were found: 0.67 for SSBs, 0.46 for artificially sweetened beverages, 0.81 for natural fruit juices, and 0.88 for bottled fruit juices. In the reproducibility analysis, the ICCs were 0.69 for SSBs, 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 by using 5 items (SSBs, artificially sweetened beverages, bottled fruit juices, natural orange juice, and natural juices from other fruit) from the FFQ. To assess habitual intake during the previous year, frequencies of consumption were measured in 9 categories (from never or almost never to >6 servings/d) for each FFQ item. The responses to individual items were then converted into mean daily consumption (mL/d) 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 SSBs, 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 by using Spanish food-composition tables (31, 32).

Anthropometric, biochemical, and lifestyle measurements. At baseline and yearly, participants completed the following: *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). In addition, at baseline and yearly thereafter, trained personnel measured weight and height with the use of calibrated scales and a wall-mounted stadiometer. Participants wore light clothing and no shoes. Waist circumference was measured by 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 min of rest by using a validated semiautomatic sphygmomanometer (HEM-705CP; Omron), 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 −80°C until analysis. Biochemical analysis was performed in local laboratories. Plasma glucose was analyzed by glucose-oxidase methodology, serum cholesterol by esterase-oxidase-peroxidase, serum TGs by glycerol-phosphate oxidase-peroxidase, and serum HDL cholesterol mainly by direct measurement, or precipitation methodology. All local laboratories satisfied external quality-control requirements. A concordance study of 9 laboratories was conducted. From each study, a mean of 200 samples was analyzed 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 center was unable to provide samples for the concordance study. The concordance analysis of lipid measurements showed the following values: r^2 [ICC (95% CI)] values between 0.85 and 0.97 [0.85 (0.77, 0.90) and 0.97 (0.95, 0.98)] for total cholesterol, between 0.82 and 0.92 [0.81 (0.78, 0.83) and 0.92 (0.89, 0.95)] for HDL cholesterol, between 0.81 and 0.99 [0.81 (0.73, 0.87) and 0.99 (0.99, 0.99)] for TGs, and between 0.82 and 0.96 [0.82 (0.74, 0.88) and 0.99 (0.99, 0.99)] for glucose.

Statistical analyses. Intakes reported during the baseline interview and yearly during follow-up were 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 on the basis of 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 used only data from all of the available FFQs until the year before MetS was diagnosed. The baseline characteristics of the participants are expressed as means ± SDs or as medians (IQRs) 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 HRs for the incidence of MetS and its components during the follow-up according to servings (200 mL) of SSBs, artificially sweetened beverages, natural fruit juices, and bottled fruit juices. Both of the highest categories (1–5 servings/wk and >5 servings/wk) were compared with the lowest category (<1 serving/wk) 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 to follow-up were censored at the date of the last visit.

Three different Cox regression models were adjusted for potential confounders. Model 1 adjusted for intervention group, age in years, sex, leisure-time physical activity (metabolic equivalent tasks/d) measured by the Minnesota Leisure Time Physical Activity Questionnaire, BMI (kg/m^2), and smoking status (never, current, or former) at baseline. Model 2 additionally adjusted for total energy intake (in kcal/d) and average consumption (g/d) during follow-up of vegetables, legumes, fruit, 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 additionally adjusted for the prevalence of MetS components at baseline, including abdominal obesity (yes or no), hypertriglyceridemia or drug treatment for elevated TGs (yes or no), low HDL cholesterol (yes or no), hypertension or antihypertensive treatment (yes or no), and high fasting plasma glucose or medication for hyperglycemia (yes or 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 represented 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 significant interactions were found.

To assess the linear trend, the median value of each category of each type of sweetened beverage analyzed 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 of the 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 y (IQR: 1.91–5.80). The mean daily intakes during follow-up were 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 diastolic blood pressure and TG concentrations. Those who consumed more SSBs also showed lower adherence to the Mediterranean diet and consumed less fruit and more baked products, alcohol, and total energy than did participants who consumed <3 servings/mo. The baseline characteristics of the population in terms of artificially sweetened beverages, natural fruit juices, and bottled fruit juices are shown in **Supplemental Tables 1–3**, respectively.

Table 2 shows the multivariable-adjusted HRs (95% CIs) for MetS incidence for mean servings of various beverages during follow-up. After adjusting for potential confounders, individuals who consumed >5 servings total SSBs/wk had a higher risk of MetS (HR: 1.43; 95% CI: 1.00, 2.15; *P*-trend = 0.27) than those who consumed <1 serving/wk. A positive association was also found between consumption of artificially sweetened beverages and incidence of MetS for participants who consumed >5 servings/wk compared with those who consumed <1 serving/wk (HR: 1.74; 95% CI: 1.26, 2.41; *P*-trend = 0.004). An average consumption of 1–5 servings natural fruit juices/wk during follow-up was associated with a decreased risk of MetS (HR: 0.77; 95% CI: 0.65, 0.93). However, the risk was higher when consumption was >5 servings/wk (HR: 1.30; 95% CI: 1.00, 1.69; *P*-trend = 0.39). An average consumption of 1–5 servings of bottled fruit juices/wk was inversely associated with MetS incidence (HR: 0.66; 95% CI: 0.53, 0.81). However, when intake was >5 servings/wk 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 components of MetS is presented in **Table 3**. Consumption of >5 servings SSBs/wk 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 was consumption of <1 serving/wk. Individuals who consumed 1–5 servings SSBs/wk also had a higher risk of high blood pressure than did those who rarely consumed SSBs (HR: 1.89; 95% CI: 1.14, 3.13). Consumption of >5 servings artificially sweetened beverages/wk 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 consumption during follow-up was >5 servings/wk (HR: 1.51; 95% CI: 1.03, 2.46; *P*-trend = 0.23). A positive association between the intake of >5 servings natural fruit juices/wk 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 who consumed >5 servings/wk of all of these types of beverage had an increased risk of MetS.

Those participants who consumed >5 servings SSBs/wk during follow-up had a 43% higher risk of developing MetS than those who did not consume or rarely consumed SSBs. These results are consistent with the meta-analysis by Malik et al. (24) 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. In contrast, our results are not in agreement with the findings of the only study not included in the meta-analysis by Malik et al. and conducted in a Mediterranean population [the SUN (Seguimiento Universidad de Navarra) 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, when consumed in liquid form, shows a lack of satiety signals (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 concentrations (39, 40) and hypertension (21, 23), MetS components that in our study were related to the consumption of SSBs. Furthermore, 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 show a positive relation between consumption of natural and bottled fruit juice analyzed separately and the incidence of MetS. In our study, consumption of 1–5 servings fruit juice/wk, regardless of whether natural or bottled (containing added sugar or not), was inversely related to incident MetS. However, when consumption of both types of fruit juice was >5 servings/wk, 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 SSBs and fruit juices, are known to have higher intakes of fat and sugar-rich products and lower intakes of fiber, and they tend to be less physically active (45, 46). However, we adjusted our analyses for such confounding factors and still observed a significant association between consumption of fruit juices and MetS incidence. In addition, 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).

Epidemiologic studies have suggested that there is an association between the regular intake of sweetened beverages and risk of T2D (24, 49). We found no association between consumption of any of the beverages analyzed and impaired glucose metabolism. Furthermore, concentrations of baseline fasting glucose tended to be lower in the highest category of consumption. Similar results were also observed by other authors (16), which may be due to reverse causation, because patients aware of their hyperglycemia may reduce their consumption of beverages containing sugar.

TABLE 1 Baseline characteristics of the study participants by servings of sugar-sweetened beverages[1]

	Servings (200 mL)			
	<1/wk (*n* = 1601)	1–5/wk (*n* = 184)	>5/wk (*n* = 83)	*P*[2]
Sugar-sweetened beverage intake, mL/d	1.6 ± 4.4	51.9 ± 28.1	254 ± 127	
Age, y	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, MET-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, mm Hg				
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 variables, 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 TGs	95.0 (74.0–118)	99.0 (74.2–125)	108 (74.0–130)	0.035
Use of medication, % (*n*)				
Oral antidiabetic 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
MetS components,[3] % (*n*)				
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

[1] Continuous variables are expressed as means ± SDs or as medians (IQRs); categorical variables are expressed as percentages (*n*). EVOO, extra-virgin olive oil; MET-min, metabolic equivalent task-minutes; MetS, metabolic syndrome.
[2] *P* values for differences between categories were calculated by using chi-square tests for categorical variables and ANOVA tests for continuous variables.
[3] Definition of MetS components: abdominal obesity for European individuals (waist circumference ≥88 cm in women and ≥102 cm in men), hypertriglyceridemia (≥150 g/dL) or drug treatment for high plasma TG concentration, low HDL cholesterol (<50 mg/dL in women and <40 mg/dL in men), high blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg) or antihypertensive drug treatment, or high fasting glucose (≥100 mg/dL) or drug treatment for type 2 diabetes.

In this longitudinal analysis, individuals who consumed >5 servings artificially sweetened beverages/wk presented a 74% higher risk of MetS than did 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

TABLE 2 HRs (95% CIs) for MetS incidence by servings of sugar- and artificially sweetened beverages and fruit juices in the PREDIMED cohort[1]

	Servings (200 mL)			
	<1/wk	1–5/wk	>5/wk	*P*-trend
Sugar-sweetened beverages[2]				
MetS 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	1 (ref)	0.98 (0.80, 1.19)	1.87 (1.28, 2.73)	0.010
Adjusted model 2	1 (ref)	0.93 (0.76, 1.13)	1.38 (0.93, 2.07)	0.30
Fully adjusted model	1 (ref)	0.91 (0.74, 1.12)	1.43 (1.00, 2.15)	0.27
Artificially sweetened beverages[3]				
MetS 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	1 (ref)	0.95 (0.76, 1.18)	2.02 (1.47, 2.78)	<0.001
Adjusted model 2	1 (ref)	0.94 (0.76, 1.18)	1.97 (1.43, 2.71)	<0.001
Fully adjusted model	1 (ref)	0.93 (0.75, 1.17)	1.74 (1.26, 2.41)	0.004
Natural fruit juices[4]				
MetS 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	1 (ref)	0.71 (0.60, 0.85)	1.13 (0.88, 1.46)	0.69
Adjusted model 2	1 (ref)	0.75 (0.63, 0.89)	1.22 (0.94, 1.59)	0.75
Fully adjusted model	1 (ref)	0.77 (0.65, 0.93)	1.30 (1.00, 1.69)	0.39
Bottled fruit juices[5]				
MetS 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	1 (ref)	0.68 (0.56, 0.84)	1.60 (1.13, 2.27)	0.63
Adjusted model 2	1 (ref)	0.64 (0.52, 0.78)	1.26 (1.08, 1.81)	0.46
Fully adjusted model	1 (ref)	0.66 (0.53, 0.81)	1.14 (1.04, 1.65)	0.31
Total sweetened beverages[6]				
MetS 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	1 (ref)	0.66 (0.57, 1.77)	0.97 (0.81, 1.15)	0.575
Adjusted model 2	1 (ref)	0.67 (0.56, 1.79)	0.88 (0.73, 1.06)	0.160
Fully adjusted model	1 (ref)	0.69 (0.59, 1.81)	0.90 (0.74, 1.09)	0.227

[1] Consumption data are means determined during the follow-up period. Model 1 adjusted for intervention group, age in years, sex, leisure-time physical activity (metabolic equivalent tasks/d), BMI (kg/m^2), and smoking status (never, former, or current). Model 2 additionally adjusted for cumulative average consumption of dietary variables in continuous (vegetables, legumes, fruit, cereals, meat, fish, bakery, dairy products, olive oil, and nuts), cumulative total energy intake, alcohol, and alcohol squared in grams per day. Model 3 (fully adjusted model): additionally adjusted for MetS components at baseline (yes or no). MetS, metabolic syndrome; PREDIMED, Prevención con Dieta Mediterránea; ref, reference.
[2] n = 1610, 216, and 42 for <1 serving/wk, 1–5 servings/wk, and >5 servings/wk, respectively.
[3] n = 1625, 183, and 60 for <1 serving/wk, 1–5 servings/wk, and >5 servings/wk, respectively.
[4] n = 1361, 381, and 126 for <1 serving/wk, 1–5 servings/wk, and >5 servings/wk, respectively.
[5] n = 1547, 268, and 53 for <1 serving/wk, 1–5 servings/wk, and >5 servings/wk, respectively.
[6] n = 841, 657, and 370 for <1 serving/wk, 1–5 servings/wk, and >5 servings/wk, respectively.

with a higher consumption of this type of beverage. These results concur with those recently reported by Crichton et al. (*5*), which showed that Americans who consumed ≥1 serving artificially sweetened beverages/d had 2.2 times the risk of MetS than did those who rarely consumed this type of beverage. Similar results were found by the same authors in the Luxembourg cohort of healthy individuals who consumed ≥2 servings artificially sweetened beverages/d (*5*). Cross-sectional and longitudinal analyses in the Framingham Heart Study cohort also reported a positive association between consumption of 1 serving artificially sweetened beverages/d and MetS (23). To date, it has been suggested that 3 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 that may play a role in glucose absorption and trigger insulin secretion (21), and *3*) artificial sweeteners (e.g., saccharin, sucralose, or aspartame) can interfere with the gut microbiota, thus decreasing glucose sensitivity and favoring 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, consumption of the various types of SSBs 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

TABLE 3 HRs (95% CIs) for incidence of MetS components by servings of sugar- and artificially sweetened beverages and fruit juices in the PREDIMED cohort[1]

		Servings (200 mL)			
	Incidence, %	<1/wk	1–5/wk	>5/wk	*P*-trend
Abdominal obesity (*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 (*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 (*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 (*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 (*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] Consumption data are means determined during the follow-up period. All of the data shown were adjusted for intervention group, age in years, sex, leisure-time physical activity (metabolic equivalent tasks/d), BMI (kg/m^2), smoking status (never, former, or current), average consumption during the follow-up of dietary variables as continuous variables (vegetables, legumes, fruit, cereals, meat, fish, baked products, dairy products, olive oil, and nuts), average total energy intake during follow-up, alcohol, and alcohol squared in grams per day. MetS, metabolic syndrome; PREDIMED, Prevención con Dieta Mediterránea; ref, reference.

population was 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 of 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 centers means that we cannot discount a certain degree of measurement bias between laboratories, because the measurements were not standardized. Even so, the concordance analysis of lipid and glucose measurements revealed correlation coefficients >0.81.

The present study is the first, to our knowledge, to make a separate analysis of the association between categories of each type of sweetened beverage and MetS risk. Occasional consumption (1–5 servings/wk) of SSBs and artificially sweetened beverages was not associated with overall MetS. Consumption of >5 servings/wk of all of 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, consumption of 1–5 servings of natural and bottled fruit juices/wk may reduce the risk of MetS.

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