

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.

1 **ABSTRACT**

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

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

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

16 **Results:** A total of 930 incident cases of MetS were documented during a median follow-up of 3.24
17 years. When comparing the consumption of >5 servings/week with <1 serving/week, multivariable
18 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)
19 and 1.14 (1.04-1.65) in case of SSBs, artificially sweetened beverages, natural fruit juices, and bottled
20 fruit juices, respectively.

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

- 27 **Trial registered:** at clinicaltrials.gov; Identifier: ISRCTN35739639.
- 28 **Key words:** sugar-sweetened beverages, artificially sweetened beverages, fruit juices, Metabolic
- 29 Syndrome, Metabolic Syndrome components, PREDIMED study

30 INTRODUCTION

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

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

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

52 No studies have been performed on the association between the accumulative average consumption of
53 sweetened beverages and incident MetS in a middle-aged to elderly Mediterranean population.

54 Therefore, the aim of the present study was to examine the associations between the average
55 consumption of SSB, artificially sweetened beverages, and natural and bottled fruit juices and the risk

56 of MetS in the PREDIMED (PREvención con DIeta MEDiterránea) cohort of middle-aged and elderly
57 individuals at high risk of CVD.

58 METHODS

59 *Design and study population*

60 The present study was conducted within the framework of the PREDIMED trial. Full details of the
61 study design and protocol have been published elsewhere (25,26) and are available on the
62 PREDIMED study's website (27). The PREDIMED study is a large, multicentre, randomized, parallel
63 group and controlled field trial conducted in Spain for the primary prevention of cardiovascular
64 disease (CVD) events. The main results of the PREDIMED trial at the primary endpoints (a
65 composite of myocardial infarction, stroke and cardiovascular mortality) have been published (28).
66 Briefly, between October 2003 and June 2009, a total of 7447 participants (men aged 55-80 years and
67 women 60-80 years) were randomized to one of the three intervention groups: a Mediterranean diet
68 supplemented with extra virgin olive oil (approximately 50 mL/day), a Mediterranean diet
69 supplemented with mixed nuts (15 g of walnuts, 7.5 g of hazelnuts and 7.5 g of almonds daily), or
70 advice about a low-fat diet (control group). Participants had no history of CVD at baseline, but were
71 at high cardiovascular risk because of the presence of T2DM or at least three of the following risk
72 factors: current smoking (>1 cigarette/d during the last month), hypertension (systolic blood pressure
73 ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or taking antihypertensive medication), high low-
74 density lipoprotein (LDL)-cholesterol (≥ 160 mg/dL), low high-density lipoprotein (HDL)-cholesterol
75 (< 40 mg/dL for men or < 50 mg/dL for women), overweight or obesity (body mass index ≥ 25 kg/m²),
76 or family history of premature CVD. Participants with severe chronic illness, drug or alcohol
77 addiction, history of allergy or intolerance to olive oil or nuts, and a low predicted likelihood of
78 changing dietary habits according to Prochaska and DiClemente's stages-of-change model (29) were
79 excluded from the study. The institutional review boards of each recruitment centre approved the
80 protocol, and all subjects provided written informed consent. The study follow-up ended in December
81 2010.

82 The present data was analysed using an observational prospective design, and participants were
83 selected from all the PREDIMED recruitment centres with biochemical determinations available for a

84 follow-up of ≥ 2 years ($n=5801$). The main aim of the present report was to explore the associations
85 between the consumption of SSB, artificially sweetened beverages, natural fruit juices and bottled
86 fruit juices and incidence of MetS. For this reason, participants with MetS at baseline ($n=3707$) were
87 excluded. Those who did not complete the baseline food frequency questionnaire (FFQ) or who
88 reported implausible total energy intake (≤ 500 and ≥ 3500 kcal/day in women and ≤ 800 and ≥ 4000
89 kcal/day in men) were also excluded. Of a total of 2094 participants fulfilling these characteristics,
90 226 were excluded because of missing data that prevented MetS from being diagnosed. Of the 5801
91 participants, 1019, 1766, 1804, 240 and 1269 did not meet the criteria of abdominal obesity,
92 hypertriglyceridemia, low-HDL-cholesterol, high blood pressure, and high fasting glucose
93 concentrations of the MetS at baseline. Finally, 1868 participants were included in the present
94 analysis.

95 *Metabolic Syndrome*

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

104 *Dietary assessment*

105 Dietary intake was assessed by trained dietitians using a 137-item semi-quantitative FFQ validated for
106 the PREDIMED study (30), administered at baseline and yearly during follow-up. The reproducibility
107 and relative validity of the FFQ used in the present study were assessed for several nutrients and food
108 groups (30). The reproducibility and relative validity of the FFQ were also assessed in relation to the
109 consumption of SSBs, artificially sweetened beverages, natural fruit juices (freshly extracted juice, for

110 which the only procedure accepted was the squeezing of the whole piece of fruit), and bottled fruit
111 juices (natural fruit juice that has been chemically changed using authorized methods, packed and
112 commercialized for subsequent consumption). Using the intraclass correlation coefficients (ICC)
113 between the FFQ and dietary records, the following reliabilities were found: 0.67 for SSB, 0.46 for
114 artificially sweetened beverages, 0.81 for natural fruit juices, and 0.88 for bottled fruit juices. In the
115 reproducibility analysis, the correlation coefficients were 0.69 for SSB, 0.63 for artificially sweetened
116 beverages, 0.71 for natural fruit juices, and 0.48 for bottled fruit juices.

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

128 *Anthropometric, Biochemical and Lifestyle Measurements*

129 At baseline and yearly, participants completed 1) a questionnaire on medical history, medication use
130 and lifestyle variables, 2) a 14-item validated questionnaire designed to assess adherence to the
131 Mediterranean diet (33), and 3) a validated Spanish version of the Minnesota Leisure time Physical
132 Activity Questionnaire (34). Also at baseline and yearly thereafter, trained personnel measured weight
133 and height using calibrated scales and a wall-mounted stadiometer. Participants wore light clothing
134 and no shoes. Waist circumference was measured using an anthropometric tape midway between the
135 lower rib and the superior border of the iliac crest. Blood pressure was measured in triplicate after 5

136 minutes of rest using a validated semiautomatic sphygmomanometer (HEM-705CP, Omron,
137 Hoofddorp, the Netherlands), and the mean of these measurements was recorded. Blood samples were
138 collected after an overnight fast, coded, shipped to a central laboratory, and stored at -80°C until
139 analysis. Biochemical analysis was performed in local laboratories. Plasma glucose was analysed by
140 glucose-oxidase methodology, serum cholesterol by esterase-oxidase-peroxidase, serum TGs by
141 glycerol-phosphate oxidase-peroxidase, and serum HDL cholesterol by direct measurement mainly, or
142 precipitation methodology. All local laboratories satisfied external quality control requirements. A
143 concordance study of nine laboratories was conducted. From each study, a mean of 200 samples was
144 analysed for total cholesterol, HDL cholesterol and TGs. The laboratory of the Medical Research
145 Institute of the Del Mar Hospital, which used ABX-Horiba commercial kits in a PENTRA-400
146 autoanalyzer (ABX-Horiba), was used as a reference. One centre was unable to provide samples for
147 the concordance study. The concordance analysis of lipid measurements showed, respectively, an r^2
148 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
149 cholesterol; between 0.82 and 0.92, and 0.81 (0.78, 0.83) and 0.92 (0.89, 0.95) for HDL cholesterol;
150 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
151 and 0.96, and 0.82 (0.74, 0.88) and 0.99 (0.99, 0.99) for glucose.

152 *Statistical analyses*

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

162 ANOVA tests were used to assess differences in the baseline characteristics of the study population.
163 Multivariable time-dependent Cox proportional regression models were fitted to assess the Hazard
164 Ratio (HR) for the incidence of MetS and its components during the follow-up according to servings
165 (200 ml) of SSB, artificially sweetened beverages, natural fruit juices and bottled fruit juices. Both of
166 the highest categories (1-5/week and >5/week) were compared with the lowest category (<1/ week) as
167 a reference. The assumption of proportional hazards was tested with time-dependent covariates. The
168 time variable was defined as the interval between random assignment and the date of the last follow-
169 up or the last recorded clinical event (MetS incidence) of participants who were still alive, whichever
170 occurred first. Participants who were free of MetS or who were lost during follow-up were censored at
171 the date of the last visit. Three different Cox regression models were adjusted for potential
172 confounders. Model 1 was adjusted for intervention group, age in years, sex, leisure time physical
173 activity (METs/day) measured by the Minnesota Leisure time Physical Activity Questionnaire, BMI
174 (kg/m^2), and smoking status (never, current and former), at baseline. Model 2 was additionally
175 adjusted for total energy intake (in kcal/day) and average consumption (g/day) during follow-up of
176 vegetables, legumes, fruits, cereals, meat, fish, bakery products, dairy products, olive oil, nuts, and
177 alcohol (with a quadratic form being added only in the case of alcohol consumption). Model 3 was
178 additionally adjusted for the prevalence of MetS components at baseline, including abdominal obesity
179 (yes/no), hypertriglyceridemia or drug treatment for elevated TGs (yes/no), low HDL cholesterol (yes/
180 no), hypertension or antihypertensive treatment (yes/no), and high fasting plasma glucose or
181 medication for hyperglycemia (yes/no). When the association between the intake of sweetened
182 beverages and the incidence of each component of MetS was assessed, the components were excluded
183 from the analysis, and model 2 was the fully adjusted model. Statistical interactions between
184 categories of sweetened beverage intake and potential effect-modifying variables such as sex,
185 intervention group, diabetes and smoking status were assessed by including product terms in the
186 models; no statistical interactions were found. To assess the linear trend, the median value of each
187 category of each type of sweetened beverage analysed was assigned and used as a continuous variable

188 in the Cox regression models. The level of significance for all statistical tests was set at $P < 0.05$ for
189 bilateral contrast. All analyses were performed with SPSS software, version 22.0.
190

191 **RESULTS**

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

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

205 **Table 2** shows the multivariable-adjusted hazard ratio (95% CI) for MetS incidence for the average
206 servings of various beverages during follow-up. After adjusting for potential confounders, individuals
207 consuming >5 servings/week of total SSBs had a higher risk of MetS [HR: 1.43; 95% CI: 1.00, 2.15;
208 P-trend=0.27] than those consuming fewer than one per week. A positive association was also found
209 between the consumption of artificially sweetened beverages and incidence of MetS [HR: 1.74; 95%
210 CI: 1.26, 2.41; P-trend=0.004 for participants consuming >5 servings/week compared to those
211 consuming <1 per week]. An average consumption of between 1 and 5 servings of natural fruit juices
212 per week during follow-up was associated with a decreased risk of MetS [HR: 0.77; 95% CI: 0.65,
213 0.93]. However, risk was higher when consumption was >5 servings per week [HR: 1.30; 95% CI:
214 1.00, 1.69; P-trend=0.39]. An average consumption of between 1 and 5 servings of bottled fruit juices
215 per week was inversely associated with MetS incidence [HR: 0.66; 95% CI: 0.53, 0.81]. However,

216 when intake was equal to or higher than 5 servings/week the association was positive [HR: 1.14; 95%
217 CI: 1.04, 1.65; P-trend= 0.311].

218 The association between average beverage consumption during follow-up and MetS components is
219 presented in **table 3**. The consumption of >5 servings/week of SSB was associated with a higher risk
220 of low HDL-cholesterol [HR: 1.18; 95% CI: 1.06, 2.11; P-trend=0.71] and high blood pressure [HR:
221 1.09; 95% CI: 1.04, 2.80; P-trend=0.39] than the consumption of <1 serving/week. Individuals
222 consuming between 1 and 5 servings per week of SSBs also had a higher risk of high blood pressure
223 than those who rarely consumed SSBs [HR: 1.89; 95% CI: 1.14, 3.13]. Consumption of >5
224 servings/week of artificially sweetened beverages was associated with an increased risk of developing
225 abdominal obesity [HR: 1.82; 95% CI: 1.13, 2.92; P-trend=0.039] and the hypertriglyceridemia
226 component of MetS [HR: 1.52; 95% CI: 1.00, 2.37; P-trend=0.08]. The results for the
227 hypertriglyceridemia component were similar for bottled fruit juices when the consumption during
228 follow-up was >5 servings/week [HR: 1.51; 95% CI: 1.03, 2.46; P-trend=0.23]. A positive association
229 between the intake of >5 servings/week of natural fruit juices and abdominal obesity was also
230 observed [HR: 1.52; 95% CI: 1.02, 2.25; P-trend=0.08].

231 DISCUSSION

232 In the present longitudinal analysis conducted in a middle-aged and elderly Mediterranean population
233 at high risk of CVD, we evaluated the consumption of SSBs, artificially-sweetened beverages, natural
234 fruit juices and bottled fruit juices and their association with the risk of MetS. The results showed that
235 participants consuming >5 servings/week of all these types of beverage had an increased risk of MetS.
236 Those participants consuming >5 servings/week of SSBs during follow-up had a 43% higher risk of
237 developing MetS than those not consuming or rarely consuming SSBs. These results are consistent
238 with Malik et al's meta-analysis of studies on different races and ethnicities in which individuals in
239 the highest category of SSB intake showed a 20% greater risk of MetS than those in the lowest
240 category (24). In contrast, our results are not in agreement with the findings of the only study not
241 included in Malik's meta-analysis and conducted in a Mediterranean population (the SUN cohort) in
242 which no association was reported between baseline intake of SSBs and risk of MetS (20). These
243 discrepancies may be due to differences in the age and type of participants. Frequent consumption of
244 SSBs has been related to an increased risk of weight gain and obesity due to the high amount of added
245 sugar, which entails a lack of satiety signals when consumed in liquid form (35–37). Most SSBs
246 contain high amounts of fructose, and various studies suggest that high-fructose corn syrup, the
247 primary sweetener used in SSBs, may have particularly deleterious metabolic effects (38), because it
248 increases the risk of both low HDL-cholesterol levels (39,40) and hypertension (21,23), MetS
249 components that in our study are related to the consumption of SSBs. Furthermore, the consumption
250 of high-fructose corn syrup has also been related to other components of MetS such as insulin
251 resistance (41,42) and hypertriglyceridemia (39,43). However, in the present cohort study these
252 metabolic abnormalities were not significantly related to SSB consumption.

253 To the best of our knowledge, the present analysis is the first to demonstrate a positive relationship
254 between the consumption of natural and bottled fruit juice analysed separately and the incidence of
255 MetS. In our study a consumption of between 1 and 5 servings/week of fruit juice, regardless of
256 whether they were natural or bottled (containing added sugar or not), was inversely related with

257 incident MetS. However, when the consumption of both types of fruit juice was >5 servings per week,
258 the association was positive and the risk of MetS increased. The lack of a dose response might be due
259 to the high content of antioxidants in fruit juices, which counteracts the possible harmful effects of the
260 sugar content when these beverages are consumed in small amounts (44). However, as observed in the
261 present study, when fruit juices are consumed frequently, this inverse response may disappear, thus
262 increasing the risk of MetS.

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

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

279 In this longitudinal analysis, individuals consuming >5 servings per week of artificially sweetened
280 beverages presented a 74% higher risk of MetS than those who rarely consumed these beverages. This
281 association can be explained by the fact that, in the present study, hypertriglyceridemia and abdominal
282 obesity, both components of MetS were also observed to be associated with a higher consumption of

283 this type of beverage. These results concur with those recently reported by Crichton and co-workers
284 (5), which show that Americans who consumed 1 serving or more per day of artificially sweetened
285 beverages had a 2.2 times higher risk of MetS than those who rarely consumed this type of beverage.
286 Similar results were found by the same authors in the Luxembourg cohort of healthy individuals
287 consuming two or more servings of artificially sweetened beverages per day (5). Cross-sectional and
288 longitudinal analyses in the Framingham Heart cohort study also reported a positive association
289 between the consumption of one serving/day of artificially sweetened beverages and MetS (23). To
290 date, it has been suggested that three mechanisms may explain these associations: 1) artificial
291 sweeteners can interfere with learned responses that help to control glucose and energy homeostasis
292 (50); 2) artificial sweeteners interact with sweet-taste receptors that are expressed throughout the
293 digestive system and which may play a role in glucose absorption and trigger insulin secretion (21);
294 and 3) artificial sweeteners (such as saccharin, sucralose or aspartame) can interfere with gut
295 microbiota, thus decreasing glucose sensitivity and favouring MetS development (21,50–52).

296 Our study has several strengths: it uses yearly repeated measurements of diet as exposure, and data are
297 adjusted for a sizable number of potential confounders. However, it also has some limitations. First,
298 the incidence of MetS was not a primary endpoint of the PREDIMED cohort, so our results are only
299 exploratory. Second, our study subjects were elderly individuals at high risk of CVD, making it
300 difficult to generalize the results to other populations. Third, the consumption of the various types of
301 SSB was very low among our participants, so the categories of consumption were heterogeneous with
302 respect to the number of participants, and the attributable risk associated with the consumption of
303 sweetened beverages is also low. In addition, the frequency of SSBs in the highest category of
304 consumption in our population is low, therefore, even if the associations observed are causal, the
305 implications for intervention are limited to a few individuals. Fourth, because of the limited number of
306 individuals in the highest categories of consumption and the adjustment for many variables, it is not
307 clear that all the models of SSBs and bottled fruit juices are robust enough. Fifth, although the types
308 of beverage and food consumption were assessed with a validated FFQ, measurement errors might
309 have occurred. Nevertheless, to minimize the measurement error caused by within-person variations,

310 the average consumption during the follow-up was calculated. Finally, although individual laboratory
311 methods and procedures were subject to quality control, the fact that biochemical measurements were
312 made in different centres means that we cannot discount a certain degree of measurement bias
313 between laboratories, since the measurements were not standardized. Even so, the concordance
314 analysis of lipid and glucose measurements reveal correlation coefficients higher than 0.81.

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

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325 **MANUSCRIPT**

326 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,
327 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
328 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,
329 L.S-M, M.F, J.L: were the coordinators of subject recruitment an follow-up at the outpatient clinics;
330 N.B and J.S-S had full access to all the data in the study and take responsibility for the integrity of the
331 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 beverages¹

	Servings (200mL) of sugar-sweetened beverages			<i>P</i> -value ²
	<1/ week (<i>n</i> =1601)	1-5/ week (<i>n</i> =184)	> 5/ week (<i>n</i> =83)	
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.

¹Continuous 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.

³Definition of MetS components: Abdominal obesity for European individuals (waist circumferences ≥ 88 cm in women and ≥ 102 cm 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 consumption¹ of 200ml of sugar and artificial sweetened beverages and fruit juices in the PREDIMED cohort²

	Servings of consumption (200ml)			P-for trend
	<1/ week (n=1610)	1-5/ week (n=216)	> 5/ week (n=42)	
Sugar-sweetened beverages				
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				
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				
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				
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				
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

¹The consumption was averaged during follow-up.

²Data expressed as HRs (95% CI).

³Model 1: adjusted for intervention group, age in years, sex, leisure-time physical activity (METs/d), BMI (kg/m²) and smoking status (never, former, and current).

⁴Model 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.

⁵Model 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 consumption¹ of 200mL of sugar and artificially-sweetened beverages and fruit juices in the PREDIMED cohort²

	Incidence, %	Servings of consumption (200mL)			P-for trend
		<1/ week	1-5/ week	> 5/ week	
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

¹The consumption was averaged during the follow-up

²Data expressed as HRs (95% CI).

³All the data shown was adjusted for intervention group, age in years, sex, leisure-time physical activity (METs/d), BMI (kg/m²), 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 beverages¹

	Servings (200mL) of artificially-sweetened beverages			P-value ²
	<1/ week (n=1648)	1-5/ week (n=137)	> 5/ week (n=83)	
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.

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

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

³Definition 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 2. Baseline characteristics of the study participants according to servings (200mL) of bottled fruit juices¹

	Servings (200mL) of bottled fruit juices			P-value ²
	<1/ week (n=1608)	1-5/ week (n=168)	> 5/ week (n=92)	
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.

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

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

³Definition 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 juices¹

	Servings (200mL) of natural fruit juices			<i>P</i> -value ²
	<1/ week (<i>n</i> =1457)	1-5/ week (<i>n</i> =228)	> 5/ week (<i>n</i> =183)	
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.

¹Continuous 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.

³Definition 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

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ONLINE SUPPORTING MATERIAL

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ONLINE SUPPORTING MATERIAL

Supplemental Table 1. Baseline characteristics of the study participants according to servings (200mL) of artificially-sweetened beverages¹

	Servings (200mL) of artificially-sweetened beverages			P-value ²
	<1/ week (n=1648)	1-5/ week (n=137)	> 5/ week (n=83)	
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.

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

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

³Definition 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 juices¹

	Servings (200mL) of bottled fruit juices			<i>P</i> -value ²
	<1/ week (<i>n</i> =1608)	1-5/ week (<i>n</i> =168)	> 5/ week (<i>n</i> =92)	
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.

¹Continuous 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.

³Definition 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 juices¹

	Servings (200mL) of natural fruit juices			P-value ²
	<1/ week (n=1457)	1-5/ week (n=228)	> 5/ week (n=183)	
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.

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