Fruit consumption and cardiometabolic risk in the PREDIMED-plus study: a cross-sectional analysis

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Abbreviation list: BP, blood pressure; CVDs, cardiovascular diseases; DBP, diastolic blood pressure; FFQ, food frequency questionnaire; MedDiet, Mediterranean Diet; MetS, metabolic syndrome; PREDIMED, Prevención Dieta MEDiterránea; SBP, systolic blood pressure; WC, waist circumference;

Abstract

Background and aims: Total fruit consumption is important for cardiovascular disease prevention, but also the variety and form in which is consumed. The aim of the present study was to assess the associations between total fruit, subgroups of fruits based on their color and fruit juices consumption with different cardiometabolic parameters.

Methods and results: A total of 6,633 elderly participants (aged 55-75 years) with metabolic syndrome from the PREDIMED-Plus study were included in this ancillary analysis. Fruit and fruit juice consumption was assessed using a food frequency questionnaire. Linear regression models were fitted to evaluate the association between the consumption of total fruit, subgroups based on the color of the edible part, fruit juices and different cardiometabolic risk factors. Individuals in the highest category of total fruit consumption (≥3 servings/d) had lower waist circumference (WC) (β=-1.04 cm; 95%CI:-1.81, -0.26), fasting glucose levels (β=-2.41 mg/dL; 95%CI(-4.19, -0.63) and LDL-cholesterol (β=-4.11 mg/dL; 95%CI:-6.93, -1.36), but, unexpectedly, higher systolic blood pressure (β=1.84 mmHg; 95%CI: 0.37, 3.30) and diastolic blood pressure (β=1.69 mmHg; 95%CI:0.83, 2.56) were significantly higher when compared to those in the lowest category of consumption (<1 servings/d). Participants consuming ≥1 serving/day of total fruit juice had lower WC (β=-0.92 cm; 95%CI:-1.56, -0.27) and glucose levels (β=-1.59mg/dL; 95%CI:-2.95, -0.23) than those consuming <1serving/month. The associations with cardiometabolic risk factors differed according to the color of fruits.

Conclusion: Fruit consumption is associated with several cardiometabolic risk factors in Mediterranean elders with metabolic syndrome. The associations regarding blood pressure levels could be attributed, at least partially, to reverse causality bias inherent to the cross-sectional design of the study.

Introduction

Cardiovascular diseases (CVDs) are among the top causes of mortality worldwide [1]. High body mass index (BMI), abnormal lipid profile and elevated blood pressure (BP) are well recognized CVDs risk factors [2]. Importantly, these modifiable risk factors are susceptible to improve by dietary changes, as demonstrated in nutritional intervention studies [3]. In this context, an increased consumption of fruits, which are rich in fiber, vitamins, minerals and bioactive compounds, has been widely recommended by public health organizations in order to prevent CVDs [4]. These guidelines are supported by a recent meta-analysis of prospective cohort studies where a 16% lower risk of CVDs was observed when comparing highest *versus* lowest categories of fruit consumption [5]. However, evidence from the last years suggests that not only total fruit intake may contribute to reduce the risk of CVDs, but also the variety and the way in which fruit is consumed (whole fruit or fruit juice) are important factors determining the disease risk [6–8]. For instance, whereas it is generally accepted that whole fruit consumption reduces the risk of CVDs, there is no consensus about the role of fruit juices [9]. Moreover, it has been suggested that not all varieties of fruit are associated in the same manner with CVD risk. In a dose-response meta-analysis, consumption of apples, pears and citrus fruits was inversely associated with coronary heart disease, total stroke and CVD risk, whereas bananas, berries, grapes, strawberries and watermelon intakes were not significantly associated [10]. Another study classifying fruit and vegetables according to the color of the edible portion, which reflects the presence of pigmented phytochemicals and other components, showed that different colors of fruit and vegetables subgroups are differently associated with CVD risk factors [6]. Nonetheless, to the best of our knowledge, no previous study has investigated the association between various colors of fruits subgroups, independently of vegetable consumption, and CVDs risk factors. Therefore, we cross-sectionally evaluated the association between total fruit consumption, different forms of fruit consumption (whole and juices) and different varieties of fruit according to color groups with cardiometabolic risk factors (BMI, fasting glucose, lipid profile and blood pressure) in a large cohort of individuals with metabolic syndrome (MetS) participating in the PREDIMED-Plus study.

Methods

Study population

Briefly, PREDIMED-Plus is a 6-year, multicenter, parallel group clinical trial conducted in Spain aiming to evaluate the effect of an intensive intervention focused on weight loss (based on an energy-restricted Mediterranean diet, promotion of physical activity and behavioral support) on CVD events compared to usual care advices in individuals with MetS. A detailed explanation of the trial design has been published elsewhere [11], and the study protocol can be accessed at www.predimedplus.com. The study was registered at ClinicalTrials.gov (ISRCTN89898870). Recently, the results of the pilot study in relation to the effect of changes in body weight on CVD risk factors have been published [12].

From October 2013 to December 2016, we recruited 6,784 community-dwelling men (aged 55-75 years) and women (aged 60-75 years) with overweight/obesity (BMI ≥27kg/m^2 and <40kg/m^2), free from CVD at baseline and harboring the MetS (meeting at least three criteria for the updated harmonized criteria of the International Diabetes Federation and the AHA/National Heart, Lung, and Blood Institute[13]. Therefore, individuals were considered as having MetS if they had three or more of the following components: elevated waist circumference for European individuals (≥ 88 cm in women and ≥102 cm in men), hypertriglyceridemia (>150 mg/dl) or drug treatment for elevated triglycerides, low concentrations of HDL-cholesterol (<50 mg/dl and <40 mg/dL in women and men, respectively) or drug treatment for low HDL-cholesterol, elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥ 85 mmHg) or taking antihypertensive medication; and high fasting plasma glucose (≥100 mg/dl) or drug treatment for hyperglycemia. Institutional review boards of each center approved the final protocol and all participants provided written informed consent. More information about the timeline of the data collection can be found elsewhere [11]

Among the 6,874 participants, we excluded 53 participants who did not complete the food frequency questionnaire (FFQ) at baseline. Furthermore, we also excluded 188 participants with extreme total energy intakes according to predefined limits [14] (<500 or >3,500 kcal/d for women and <800 or >4,000 kcal/d for men). Therefore, the final sample size for the analyses was 6,633 participants. The data were analyzed using the latest available complete PREDIMED-Plus database, dated March 25th 2019.

Dietary assessment

Trained dietitians administered a 143-item semi-quantitative FFQ, based on the validated FFQ used in PREDIMED study [15], in a face-to-face interviews at baseline. The frequency consumption of each item, with nine possible answers (never, one to three servings per month, one serving per week, two to four servings per week, five to six servings per week, one serving per day, two to three servings per day, four to six servings per day or more than six servings per day) during the preceding year, was asked to each participant. Ten items from the FFQ specifically addressed fruit consumption and three items to fruit juice intake. For the present analysis, we considered total fruit consumption as the sum of: 1) oranges, grapefruits or tangerines; 2) bananas; 3) apples or pears; 4) strawberries; 5) cherries or plums; 6) peaches, apricots or nectarines; 7) watermelon; 8) melon; 9) kiwi; and 10) grapes. Furthermore, as it has previously been reported [6,7], we also categorized fruit consumption according to the color of the edible part in orange fruits (oranges, tangerines, grapefruits and peaches); green fruits (kiwis and melons); red/purple fruits (strawberries, cherries, watermelons and grapes); and white fruits (bananas, apples and pears). Total fruit juice consumption was considered as the sum of natural orange juice, natural juice from other fruits and bottled fruit juice. Two Spanish food composition databases were used to calculate total energy and nutrient intake [16,17].

Other covariates assessment

At baseline, trained personnel (dietitians or nurses) collected socio demographic and lifestyle variables including age, sex, marital status, educational level, smoking habit, physical activity and Mediterranean diet (MedDiet) adherence as well as medication use and personal and family history of illness.

A validated version of the Minnesota Leisure Time Physical Activity Questionnaire was used to estimate leisure time physical activity [18,19].

Adherence to an energy-reduced MedDiet was assessed using a 17-item questionnaire adapted from a previous validated one [20]. The score obtained from the questionnaire ranged from 0 to 17 and one item related to fruit consumption. To control the analysis for the overall dietary pattern, we removed this item from the questionnaire, hence, the total score ranged from 0 to 16 points.

Outcomes

The outcomes of the present study were cross-sectional differences in BMI, waist circumference (WC), fasting blood glucose, triglycerides, LDL-cholesterol, HDL-cholesterol, systolic BP (SBP) and diastolic BP (DBP) between categories of fruit and juice consumption. These outcomes were selected because, although several cardiovascular risk factors have been identified, these are the main modifiable ones recorded in PREDIMED-Plus[21].

Following the study protocol, which can be found at www.predimedplus.com, trained staff of the PREDIMED-Plus study collected anthropometric and BP measurements. Weight and height were measured with participants with light clothes and no shoes using calibrated scales and wall-mounted stadiometers, respectively. BMI was calculated dividing the weight in kilograms by the square of height in meters. WC was measured at the midway between the lowest rib and the iliac crest using an anthropometric tape.

SBP and DBP were measured, in triplicate, after 5 minutes of rest with the participant seated using a validated semiautomatic oscillometer (Omron HEM-705CP, Netherlands). The mean of the three measures was recorded.

At baseline, blood samples were collected after an overnight fast, and laboratory technicians, who were blinded to the intervention group, performed biochemical analyses on fasting plasma glucose, triglycerides, and HDL-cholesterol using standard enzymatic procedures. The

Friedewald formula was used to estimate LDL-cholesterol when levels of triglycerides were less than 400 mg/dL.

Statistical analyses

Analyses were performed using Stata software, version 15.0 (StataCorp LP, College Station, TX). Prior to analyses, we used multiple imputation with chained equations (STATA "mi" command) and created 20 imputed datasets to deal with missing data. The proportion of missing data ranged from 0.42% to 2.64%. Binary variables were imputed using the "logit" function, nominal variables using "mlogit", ordinal variables using "ologit" and continuous variables using "regress" function or "pmm" function (when the distribution was slightly skewed). The imputation model included all confounder variables used in the full-adjusted model as well as all exposures and outcomes. Diagnostic for multiple imputation was performed using the STATA command "midiagplots" [22].

Study participants were categorized by the frequency of consumption of servings of total fruit in: < 1 serving per day, 1 serving per day, 2 servings per day and ≥3 servings per day). We used this categorization to ensure that the highest category represented the recommendation of eating at least 3 servings of fruit per day [23]. For total juices and different types of juices (natural and bottled) participants were also classified based on the frequency of servings consumed in less than one serving per month, 1-4 servings per month, 2-6 servings per week and one or more servings per day. We followed this classification because the fruit juice intake was lower compared to fruit consumption. For subgroups according to fruit color, due to the low amount consumed in some groups because their availability is lower as they are seasonal fruits, individuals were categorized in tertiles of servings/week to ensure a homogeneous distribution of participants across categories.

Continuous variables were assessed for normality using the Shapiro Wilk test and the visual inspection of the histograms and scatter plots. To compare baseline characteristics of the study participants according to categories of total fruit consumption and total fruit juice consumption the Chi-square test and the ANOVA or Kruskal-Wallis test were conducted, as appropriate. Multivariable linear regression models or median regression analyses (if data were skewed) were carried out to evaluate the adjusted β-coefficients and 95% confidence interval for different CVD risk factors (BMI, WC, fasting glucose, LDL-cholesterol, HDL-cholesterol, tryglicerides, SBP and DBP) according to categories of total fruit consumption, tertiles of colors of fruit subgroups, and categories of total, natural and bottled fruit juices. All models were adjusted for potential confounders including: age (years), sex, diabetes prevalence (yes/no), hypertension prevalence (yes/no), hypercholesterolemia prevalence (yes/no), recruitment center (in categories by number of participants), leisure time physical activity (METs, min/week), BMI (kg/m^2; except for waist circumference and BMI outcomes), smoking habit (never, current or former smoker), educational level (primary, secondary or university/graduate), alcohol consumption (in grams per day and adding the quadratic term), energy intake (kcal/day) and 16-point screener (excluding the fruit item) of MedDiet adherence. We used the robust variance estimators to account for intra-cluster correlations in linear regression models (considering as clusters the members of the same household). In a sensitivity analysis, we conducted a complete case analysis (including only those individuals who had available data for all the variables) in 6,190 participants. Statistical significance was set at a 2-tailed P-value <0.05.

Results

Baseline characteristics of the study population according to extreme categories of total fruit and total fruit juice consumption are shown in **Table 1**. Regarding total fruit consumption, compared to participants who consumed less than one serving per day, those who consumed three or more servings per day, were more likely to be women, older, and physically more active. They also were less likely to smoke, had lower educational level, and had higher energy intake and MedDiet adherence. When participants were compared according to their fruit juice consumption, those who consumed one or more servings per day were more likely to be men, presented lower BMI values, had lower diabetes prevalence, and were more physically active. They also were more likely to smoke, had higher educational level, higher energy intake and higher adherences to the MedDiet. Significant differences among categories of total fruit and total fruit juice consumption were also observed on the type of fruit according to the color of the edible part.

The mean consumption of total fruit in the study population was 2.43 servings/day. The main type of fruit consumed was oranges, grapefruits or tangerines (24.73%), apples or pears (23.80%) and bananas (10.70%). The other 40% of total fruit consumption came from kiwis (7.89%), watermelon (7.38%), melon (7.07%), peaches (6.65%), cherries or plums (4.59%), strawberries (4.12%), and grapes (3.05%). Regarding fruit juice, the mean consumption of the study population was 0.21 servings/day, being natural fruit juices the most consumed (69.80%). The correlation between total fruit consumption and total fruit juice intake was low (correlation coefficient = 0.089).

Table 2 displays β-coefficients and 95%CI for different cardiovascular risk factors according to categories of total fruit consumption and total juice consumption, after adjusting for multiple potential confounders. Compared to participants who consumed less than one serving per day of total fruit, those who consumed three or more servings per day of total fruit had 1.04 cm, 2.41 mg/dL and 4.11 mg/dL lower values of WC, fasting glucose and LDL-cholesterol, respectively. In contrast, individuals who consumed three or more servings of total fruit had 1.84 mmHg and 1.69mmHg higher values of SBP and DBP, respectively. Similar results for total fruit juice consumption were observed. WC and glucose levels were lower (0.92cm and 1.59mg/dL, respectively) in participants who consumed more than one serving per day compared to those who consumed less than one serving of fruit juice per month. However, LDL-cholesterol levels and SBP and DBP, did not differ across categories of total fruit juice consumption.

Results for multivariable linear regression analyses according to tertiles of colors of fruit consumption are shown in **Table 3**. In relation to orange fruit consumption, participants located in the highest tertile of consumption had 1.90 mg/dL lower levels of triglycerides. Contrary, same participants exhibited 2.32 mmHg and 1.65 mmHg higher values of SBP and DBP, respectively. Regarding to green fruit consumption, participants in the highest tertile had 1.07 mg/dL lower glucose levels and 0.84 mg/dL higher HDL-cholesterol levels. Individuals located in the highest tertile of red purple fruit consumption had 2.10 mg/dL lower levels of fasting glucose compared to those individuals in the lowest tertile. Finally, those participants in the highest tertile of white fruit consumption had 0.40 kg/m^2 lower BMI and 1.13 cm lower WC than those in the bottom tertile.

In addition, we evaluated whether the type of fruit juice consumed (natural or bottled) was associated with different cardiovascular risk factors. **Figure 1** shows multivariate-adjusted β-coefficients and 95% CI for various cardiovascular risk factors according to frequency of natural fruit juice consumption. The consumption of one or more servings of natural fruit juice was only associated with lower values of WC (0.93 cm) and glucose levels (1.26 mg/dL).

Bottled fruit juice consumption was not associated with any of the cardiovascular risk factors considered (**Figure 2**).

Sensitivity analyses were conducted with data from completers only and results remained essentially unchanged (**Supplemental Table 1, Supplemental Table 2, Supplemental Figure 1 and Supplemental Figure 2**). However, the association between tertiles of orange fruit consumption and triglycerides levels and HDL-cholesterol became non-significant and significant, respectively (**Supplemental Table 2**).

Discussion

As far as we know, this is the first study that depicts the association between not only the amount of fruit consumed, but also the variety and the way in which it is consumed with different cardiometabolic risk factors in individuals with metabolic syndrome. The results showed that the higher fruit consumption, the lower WC, plasma glucose and LDL-cholesterol levels, but unexpectedly, the higher SBP and DBP. Subgroup analyses according to the color of fruits showed different associations with cardiometabolic risk factors, suggesting that not all varieties of fruits are associated in the same way with CVD risk. Moreover, total fruit juice and natural juice intake was inversely associated with WC and fasting glucose levels, while bottled juice consumption was not associated with cardiometabolic risk factors.

Our results regarding total fruit consumption and WC are in line with a meta-analysis of prospective cohort studies [24] where fruit intake was associated with a decreased WC over time (β-coefficient: -0.04 cm/year; 95%CI: -0.05 to -0.02). Since WC is a well-known risk factor for CVD, fruit intake could help to prevent its development. The findings in relation to glucose levels also concur with prior research. In an additional meta-analysis of prospective cohort studies, a non-linear dose-response association was observed between fruit consumption and type 2 diabetes risk, with a 10% decreased risk in intakes up to 200 to 300 g/day, although, no more apparent benefits above this value were reported [25]. However, it should be noted that in another recent meta-analysis of randomized clinical trials, fruit intake had no effect on fasting glucose levels in the substitution (replacement of foods rich in refined starches for equal amounts of calories from fruits) or addition studies (excess energy from sugars added to diets), but a beneficial effect on glycated hemoglobin in substitution studies was detected [26]. Of note, our results are consistent with previous studies despite the fact that they come from a cross-sectional analysis and that fruit and juice intake were assessed using an FFQ, while in other studies different dietary assessment methods could have been used.

Previous cross-sectional studies evaluating fruit and vegetable consumption in relation to LDL-cholesterol levels reported inverse correlations [27,28], results that are consistent with our findings.

Contrary to previous epidemiological studies [29,30], our results surprisingly revealed a positive association between fruit consumption and SBP and DBP. However, in the INTERMAP study [31], despite non-statistically significant results, a trend toward higher levels of SBP and DBP was observed per >50 g/1000 kcal of fruit consumption. When analysis were stratified by regions, fruit consumption was associated with high DBP (0.37 mmHg; 95%CI: 0.02, 0.71) in participants from East Asian countries, whereas no association was observed in those from Western countries. Of note, fruits are a fructose-rich food, and high consumption of fructose has been related to adverse effects on blood pressure. Although the exact mechanisms are not well understood, it could be related to the impact of fructose on uric acid [32,33] and its interaction with salt absorption in the gut [34]. However, due to the cross-sectional design of both the aforementioned and the present study, as well as the paucity of evidence and the contradictory results in this field, it is premature to make inference about causality. Future studies, with a prospective design, evaluating the effect of fructose derived solely from fruits on BP could help to clarify these associations and to elucidate the exact mechanisms implicated.

To the best of our knowledge, this is the first study examining the association between groups of fruits (and not vegetables) based on the color of the edible part and different cardiometabolic risk factors. The present results suggest that certain colors of fruit, may be more relevant than others for cardiovascular disease prevention. Whereas For instance, only white fruits were associated with WC and BMI (anthropometrical features), only orange fruits associated with BP, only green fruits were associated with HDL-cholesterol and only green and red/purple fruits were associated with glucose levels. Limited previous research has focused on evaluating the association between fruit and vegetable consumption according to its color and cardiometabolic risk factors, stroke and coronary heart disease. Our results support those obtained from the Tehran lipid and glucose study [6], where different color of fruits and vegetables were differently associated with cardiometabolic risk factors. Besides, in a Dutch cohort of men and women aged 20–65 years, only white fruit and vegetable consumption was inversely associated with the incidence of stroke [7], and deep orange fruit and vegetables with lower risk of coronary heart disease [35]. Nevertheless, due to the limited evidence in this field, the extent to which fruit color groups contribute to cardiometabolic risk factors is uncertain.

In the present study we also evaluated the association between fruit juices consumption (total, natural and bottled) and different cardiometabolic risk factors, since there is still debate about their role on cardiovascular disease prevention due to the amount of naturally occurring sugar they contain and the presence of most of the nutrients found in whole fruit. Our results showed a significant inverse association between total and natural fruit juice intake with WC and fasting glucose levels. Similarly, previous cross-sectional studies also reported an inverse association between fruit juice consumption and BMI [36], and between 100% fruit juice intake and BMI, WC, and homeostasis model assessment (HOMA) insulin resistance [37]. Of note, bottled fruit juice usually contains a significant amount of sugar, which could counteract the beneficial effects of other nutrients. This fact could explain the lack of association between bottled fruit juices and cardiometabolic risk factors in the present study. However, there is still some controversy about the potential health impact of fruit juice consumption. Therefore, further longitudinal and clinical trials are needed to clarify this issue.

The mechanisms by which fruit consumption may protect against cardiometabolic risk are unlikely to be related to a single constituent [38]. Besides the high fiber content, fruit contains other nutrient and non-nutrient components, such as beta-carotenes, vitamins C and E, potassium and polyphenols that could act synergistically through the reduction of oxidative stress, inflammation, platelet aggregation, cholesterol levels and the improvement of the endothelial function [39,40]. Moreover, the high fiber content could increase satiation and modulate gut microbiota in a positive way [41]. Finally, fruit consumption may displace other unhealthy foods rich in saturated fatty acids, sugar and sodium that are detrimental for cardiovascular health. It is important to highlight, that color pigments of food correspond to specific phytonutrients. For instance, orange to beta-carotenes, purple to flavonoids and green to chlorophyll. These molecules seems to have different health effects, which could explain the diverse associations reported in the present analysis. Accordingly to a recent review, orange pigments are mainly antioxidant for fat-soluble tissues; red pigments have anti-inflammatory properties and are implicated in general antioxidant activity; green pigments are frequently antioxidants and are involved in blood vessel support; and red/purple pigments have antioxidant capacities [42].

Regarding fruit juices, although their fiber content is low, other healthy components such as polyphenols and vitamins and minerals are still present, which could explain the beneficial associations reported in the current analysis [43].

Our study has several limitations that deserve to be discussed. First, the results cannot be extrapolated to other populations since participants included in the analysis were elderly Mediterranean individuals with metabolic syndrome. Therefore, as they were already at risk of cardiovascular disease the results of the present study could be influenced by this condition. Second, the cross-sectional study design does not allow to draw inference about causation, and, importantly, reverse causality is a well-known concern in this type of studies, which could explain the unexpected results observed regarding SBP and DBP. Finally, the assessment of food intake through a FFQ is prone to possible measurements errors. Moreover, fruit and juice intake could be underestimated since our FFQ has a food-based design that does not take into account other ways of eating fruits or juices as do the dish-based FFQs. However, despite this limitation, food-based FFQs have been widely used as a tool in epidemiological studies since the 1990s [44].

The present study also has some strengths that need to be highlighted such as the control for several potential confounding factors, the use of multiple imputation to deal with missing data, and the analysis of different fruit groups based on the color of their edible part.

In conclusion, the present findings showed that higher total fruit consumption is associated with lower WC, plasma glucose and LDL-cholesterol levels, and higher SBP and DBP in elderly individuals with metabolic syndrome. However, varieties of fruits, based on their color, are differently associated with each cardiometabolic risk factor. In addition, despite the low fiber content, total and natural fruit juice consumption was associated with lower WC and glucose levels. The present study adds new insights into the potential association between different fruits based on their colors and cardiometabolic risk. So far science has been mainly focused on fruit quantity, but in the last years, it has been demonstrated that variety could be even more important for human health. Therefore, the results of the present study open a new line of research for better understanding the potential benefits of consuming different types of fruit (variety) using observational prospective design studies and randomized clinical trials. The obtained results will help to update evidence-based clinical practice guidelines for the prevention of cardiovascular diseases emphasizing the consumption of a variety of colorful fruits. This strategy could serve not only to increase the consumption of thousands of phytochemicals but also to increase the quantity of fruit intake which continues to be less than what is recommended.

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Contribution statement

Study concept and design: N.B and J.S-S. Statistical analyses: N.B-T and J.S-S. Drafting the manuscript: N.B-T, I.P-G and J.S-S. All authors reviewed the manuscript for important intellectual content and approved the final version to be published. N.B-T and J.S-S had full access to all the data for the present study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data statement

Data described in the article, code book, and analytic code will be made available upon request pending.

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Conflict of interest

The authors declare that they have no conflict of interest related to this article

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Table 1. Baseline characteristics of the study population according to categories of total fruit and total fruit juice consumption[1]

	Total fruit consumption			Total fruit juice consumption		
	<1 serving/day (n= 785)	≥ 3 servings/day (n= 1,857)	P-value	<1 serving/month (n= 2,876)	≥ 1servings/day (n= 957)	P-value
Age, years	63 ± 5	66 ± 5	<0.01	65 ± 5	65 ± 5	<0.01
Women, % (n)	37.58 (295)	53.85 (1,000)	<0.01	46.94 (1,350)	46.50 (445)	0.01
BMI, kg/m^2	32.74 ± 3.48	32.42 ± 3.42	0.09	32.58 ± 3.40	32.25 ± 3.33	0.04
Leisure time physical activity, METs.min/week	2,061 ± 2056	2,617 ± 2,421	<0.01	2,403 ± 2,259	2,638 ± 2,348	0.01
Smoking habit, % (n)			<0.01			<0.01
Never	31.75 (248)	49.27 (912)		42.32 (1,210)	43.65 (416)	
Former	46.09 (360)	40.95 (758)		45.23 (1,293)	42.81 (408)	
Current	22.15 (173)	9.78 (181)		12.45 (356)	13.54 (129)	
Education, % (n)			<0.01			<0.01
Primary or less	38.67 (302)	52.42 (965)		50.82 (1,448)	43.86 (418)	
Secondary	34.19 (267)	26.89 (495)		29.06 (828)	28.86 (275)	
University/graduate	27.14 (212)	20.70 (381)		20.11 (573)	27.28 (260)	
Hypertension, % (n)	82.20 (642)	84.79 (1,561)	0.22	84.99 (2,429)	82.72 (785)	0.20
Diabetes, % (n)	30.70 (241)	30.86 (573)	0.99	34.77 (1,000)	25.29 (242)	<0.01
Hypercholesterolemia, % (n)	68.98 (536)	70.09 (1,289)	0.68	68.76 (1,963)	70.83 (675)	0.05
Total energy intake, Kcal/day	2209 ± 593	2532 ± 531	<0.01	2291 ± 541	2531 ± 571	<0.01
Orange fruits, servings/day	0.13 [0.14]	1.07 [0.57]	<0.01	0.57 [0.86]	0.86 [0.86]	<0.01
Green fruits, servings/day	0.07 [0.13]	0.57 [0.79]	<0.01	0.14 [0.43]	0.21 [0.43]	<0.01
Red/purple fruits, servings/day	0.14 [0.20]	0.63 [0.86]	<0.01	0.28 [0.37]	0.34 [0.37]	<0.01
White fruits, servings/day	0.14 [0.23]	1.14 [0.93]	<0.01	0.85 [0.64]	0.86 [0.71]	<0.01
Natural fruit juices, servings/day	0 [0.13]	0.07 [0.43]	<0.01	0 [0]	1.00 [0.21]	<0.01
Bottled fruit juices, servings/day	0 [0]	0 [0]	0.15	0 [0]	0 [1.00]	<0.01

MedDiet score (16-points)	7.34 ± 2.45	8.41 ± 2.59	<0.01	8.03 ± 2.54	8.22 ± 2.67	0.03

Data expressed as percentage (number) and mean ± standard deviation or median [interquartile range] for categorical and continuous variables, respectively.

[1]All categories were included in the analyses. P-value for comparisons between categories of total fruit consumption and total fruit juice consumption was calculated by Pearson's chi-square test for categorical variables or one-factor ANOVA and Kruskal-Wallis tests for continuous variables.

In the analyses, there were missing data for smoking habit in 28 participants (0.42%), education in 54 participants (0.81%), hypertension in 42 participants (0.63%) and hypercholesterolemia in 48 participants (0.72%).

Table 2. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of total fruit consumption and total juice consumption

	Total Fruit consumption				
	<1 serving/day (n= 785)	**≥1 to <2 servings/day (n= 2,019)**	**≥2 to <3 servings/day (n= 1,972)**	**≥ 3 servings/day (n= 1,857)**	***P*-trend**
BMI, kg/m²	0 Ref.	-0.20 (-0.48, 0.08)	-0.04 (-0.33, 0.25)	-0.24 (-0.55, 0.06)	0.14
Waist circumference, cm	0 Ref.	-0.67 (-1.41, 0.06)	-0.82 (-1.56, -0.08)	-1.02 (-1.80, -0.24)	0.01
Glucose, mg/dL¥	0 Ref.	-1.08 (-2.81, 0.65)	-1.45 (-3.18, 0.28)	-2.30 (-4.14, -0.45)	0.01
Triglycerides, mg/dL¥	0 Ref.	-5.56 (-11.29, 0.17)	-3.72 (-9.50, 2.05)	-5.40 (-11.29, 0.50)	0.42
LDL-cholesterol, mg/dL	0 Ref.	-2.15 (-4.80, 0.49)	-3.67 (-6.36, -1.00)	-4.08 (-6.87, -1.30)	<0.01
HDL-cholesterol, mg/dL	0 Ref.	-0.25 (-1.14, 0.65)	-0.44 (-1.36, 0.48)	0.33 (-0.64, 1.29)	0.19
SBP, mmHg	0 Ref.	1.58 (0.21, 2.96)	1.25 (-0.15, 2.66)	1.81 (0.35, 3.28)	0.06
DBP, mmHg	0 Ref.	1.01 (0.20, 1.82)	1.37 (0.55, 2.20)	1.67 (0.81, 2.53)	<0.01
	Total Fruit Juice consumption				
	<1 serving/month (n= 2,876)	**1-4 servings/month (n= 1,481)**	**2-6 servings/week (n= 1,319)**	**≥ 1 servings/day (n= 957)**	***P*-trend**
BMI, kg/m²	0 Ref.	0.04 (-0.18, 0.25)	0.04 (-0.18, 0.26)	-0.22 (-0.47, 0.03)	0.15
Waist circumference, cm	0 Ref.	0.04 (-0.52, 0.61)	-0.23 (-0.81, 0.35)	-0.90 (-1.55, -0.26)	<0.01
Glucose, mg/dL¥	0 Ref.	-0.93 (-2.03, 0.16)	-1.93 (-3.21, -0.65)	-1.72 (-3.06, -0.38)	<0.01
Triglycerides, mg/dL¥	0 Ref.	-2.31 (-6.68, 2.05)	2.04 (-2.48, 6.56)	-1.95 (-7.02, 3.12)	0.45
LDL-cholesterol, mg/dL	0 Ref.	0.37 (-1.59, 2.33)	0.39 (-1.69, 2.46)	-0.80 (-3.22, 1.61)	0.39
HDL-cholesterol, mg/dL	0 Ref.	0.03 (-0.64, 0.70)	0.14 (-0.57, 0.85)	-0.17 (-0.99, 0.65)	0.72
SBP, mmHg	0 Ref.	-0.92 (-1.96, 0.12)	-1.28 (-2.39, -0.17)	-0.58 (-1.80, 0.64)	0.23
DBP, mmHg	0 Ref.	-0.77 (-1.38, -0.16)	-0.22 (-0.85, 0.39)	-0.25 (-0.97, 0.46)	0.93

Abbreviations: BMI, body mass index; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. Linear regression models and median regression analyses: were adjusted for sex, age (in years), smoking habit (never, former or current smoker), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no), leisure time physical activity (METs.min/week), recruitment center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous) and BMI (except for BMI and waist circumference). Total fruit consumption and total fruit juice consumption were mutually adjusted. ¥Data are median (95%CI).

Table 3. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to tertiles of colors of fruit consumption in servings/week

	Tertiles of fruit consumption			
	T1 (Lowest)	**T2**	**T3 (Highest)**	*P*-trend
Orange fruits, median (P25-P75)	1.47 (0.93-3.00)	5.97 (4.00-6.00)	8.00 (7.47-10.00)	
BMI, kg/m^2	0 Ref.	0.11 (-0.11, 0.33)	0.06 (-0.14, 0.26)	0.59
Waist circumference, cm	0 Ref.	0.44 (-0.13, 1.02)	0.32 (-0.20, 0.84)	0.97
Glucose, mg/dL[¥]	0 Ref.	0.23 (-0.86, 1.33)	0.53 (-0.61, 1.66)	0.61
Triglycerides, mg/dL[¥]	0 Ref.	-3.63 (-7.99, 0.73)	-1.77 (-5.54, -2.00)	0.53
LDL-cholesterol, mg/dL	0 Ref.	-0.72 (-2.77, 1.33)	-1.38 (-3.29, 0.53)	0.05
HDL-cholesterol, mg/dL	0 Ref.	-0.07 (-0.77, 0.63)	-0.63 (-1.26, 0.01)	0.44
SBP, mmHg	0 Ref.	0.54 (-0.52, 1.61)	2.27 (1.26, 3.29)	<0.01
DBP, mmHg	0 Ref.	0.41 (-0.20, 1.03)	1.64 (1.06, 2.22)	<0.01
Green fruits, median (P25-P75)	0.47 (0-0.47)	1.47 (1.00-2.00)	5.97 (4.00-7.47)	
BMI, kg/m^2	0 Ref.	0.15 (-0.06, 0.36)	0.17 (-0.07, 0.39)	0.22
Waist circumference, cm	0 Ref.	0.01 (-0.46, 0.64)	0.01 (-0.59, 0.60)	0.48
Glucose, mg/dL[¥]	0 Ref.	-0.10 (-1.32, 1.11)	-1.04 (-2.25, 0.16)	0.01
Triglycerides, mg/dL[¥]	0 Ref.	6.58 (2.42, 10.74)	-0.11 (-4.44, 4.22)	0.46
LDL-cholesterol, mg/dL	0 Ref.	-1.28 (-3.27, 0.70)	-1.99 (-4.12, 0.14)	0.08
HDL-cholesterol, mg/dL	0 Ref.	-0.15 (-0.82, 0.53)	0.83 (0.11, 1.56)	0.01
SBP, mmHg	0 Ref.	-1.01 (-2.07, 0.05)	-0.97 (-2.09, 0.16)	0.10
DBP, mmHg	0 Ref.	0.26 (-0.35, 0.87)	-0.25 (-0.89, 0.39)	0.93
Red/purple fruits, median (P25-P75)	0.93 (0.47-1.40)	2.40 (1.87-2.47)	5.47 (4.00-8.00)	
BMI, kg/m^2	0 Ref.	-0.10 (-0.31, 0.11)	0.01 (-0.22, 0.24)	0.32
Waist circumference, cm	0 Ref.	-0.07 (-0.62, 0.49)	0.16 (-0.45, 0.77)	0.13
Glucose, mg/dL[¥]	0 Ref.	-1.66 (-2.80, -0.53)	-2.20 (-3.50, -0.91)	0.01
Triglycerides, mg/dL[¥]	0 Ref.	4.48 (0.30, 8.67)	3. 62 (-0.93, 8.18)	0.92
LDL-cholesterol, mg/dL	0 Ref.	0.52 (-1.45, 2.50)	-0.59 (-2.83, 1.65)	0.11
HDL-cholesterol, mg/dL	0 Ref.	0.23 (-0.45. 0.91)	0.39 (-0.36, 1.14)	0.60
SBP, mmHg	0 Ref.	-0.32 (-1.36, 0.73)	-0.83 (-2.00, 0.35)	0.36
DBP, mmHg	0 Ref.	0.38 (-0.23, 0.99)	0.06 (-0.61, 0.74)	0.57

White fruits, median (P25-P75)	2.00 (0.93-3.00)	6.00 (4.00-6.50)	10.00 (8.00-14.00)	
BMI, kg/m^2	0 Ref.	-0.06 (-0.26, 0.13)	-0.40 (-0.61, -0.19)	<0.01
Waist circumference, cm	0 Ref.	-0.09 (-0.61, 0.42)	-1.14 (-1.67, -0.60)	<0.01
Glucose, mg/dL¥	0 Ref.	0.21 (-0.93, 1.34)	-0.42 (-1.52, 0.69)	0.89
Triglycerides, mg/dL¥	0 Ref.	0.82 (-3.34, 4.97)	-0.19 (-3.95, 3.56)	0.72
LDL-cholesterol, mg/dL	0 Ref.	-1.98 (-3.83, -0.14)	-0.42 (-2.38, 1.55)	0.67
HDL-cholesterol, mg/dL	0 Ref.	-0.17 (-0.79, 0.46)	0.43 (-0.25, 1.10)	0.78
SBP, mmHg	0 Ref.	0.15 (-0.81, 1.11)	-0.11 (-1.15, 0.94)	0.50
DBP, mmHg	0 Ref.	0.12 (-0.43, 0.68)	0.08 (-0.51, 0.66)	0.30

Abbreviations: BMI, body mass index; LDL. Low-density lipoprotein; HDL, High-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. Linear regression models and median regression analyses were adjusted for: sex, age (in years), smoking habit (never, former or current), educational level (primary or less, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), fruit juice intake (<1 serving/month, 1-4 servings/month, 2-6 servings/week or ≥1serving/day) and BMI (except for BMI and waist circumference). Individual fruit consumption was mutually adjusted.

¥Data are median (95%CI).

Figure legends

Figure 1. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of natural fruit juice consumption. Linear regression models and median regression analyses were adjusted for sex, age (in years), smoking habit (never, former or current smoker), educational level (primary, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), recruitment center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), total fruit consumption (<1 serving/day, ≥1 to <2 servings/day, ≥ 2 to <3 servings/day or ≥3 servings/day) and BMI (except for BMI and waist circumference). *Data are median (95%CI).

Figure 2. Multivariate-adjusted β-coefficients and 95%CI for different cardiovascular risk factors according to categories of bottled fruit juice consumption. Linear regression models and median regression analyses were adjusted for: sex, age (in years), smoking habit (never, former or current), educational level (primary, secondary or university/graduate), diabetes prevalence (yes/no), hypertension prevalence or antihypertensive use (yes/no), hypercholesterolemia prevalence (yes/no) leisure time physical activity (METs.min/week), center (in quartiles by number of participants), energy intake (Kcal/day), alcohol intake (g/d and adding the quadratic term), 16-point screener (excluding fruit item) of Mediterranean diet adherence (continuous), total fruit consumption (<1 serving/day, ≥1 to <2 servings/day, ≥ 2 to <3 servings/day or ≥3 servings/day)and BMI (except for BMI and waist circumference). *Data are median (95%CI).