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Dried fruit consumption and cardiometabolic health: a randomized crossover trial

Valerie K. Sullivan[1], **Kristina S. Petersen**[1], **Penny M. Kris-Etherton**[1]

[1]Department of Nutritional Sciences, 110 Chandlee Laboratory, The Pennsylvania State University, University Park, PA 16802

Abstract

Fruit intake is associated with lower risk of cardiometabolic diseases. However, effects of dried fruits on cardiometabolic health are not well researched. We investigated the effect of daily dried fruit consumption compared to a carbohydrate-rich snack on cardiometabolic disease risk factors in adults with increased cardiometabolic risk. A two-period randomized crossover trial was conducted in adults (n=55) with elevated BMI and at least one additional risk factor for cardiometabolic disease to compare the effects of consuming 3/4 cup/d mixed dried fruits (plums, figs, dates, and raisins) or a calorie- and carbohydrate-matched control snack for 4 weeks. The primary outcome was low-density lipoprotein cholesterol (LDL-C); secondary outcomes included other lipids and lipoproteins, glucose and insulin, C-reactive protein, blood pressure, and vascular stiffness. Linear mixed models were used for data analysis. Lipid and lipoprotein concentrations did not differ between conditions, however dried fruit increased LDL-C (0.10 mmol/L, 95% CI: 0.01, 0.20) compared to baseline. Compared to the control, dried fruit increased mean fasting glucose (0.08 mmol/L, 95% CI: 0.005, 0.16; P=0.038). Vascular outcomes, fasting insulin, and C-reactive protein did not differ between conditions. Mean weight changes did not differ (P=0.55) but tended to increase after both conditions (dried fruit: 0.3 kg, 95% CI: −0.09, 0.65; control: 0.4 kg, 95% CI: 0.01, 0.75). Thus, short-term daily consumption of a large portion of mixed dried plums, figs, dates, and raisins, without structured dietary guidance, did not improve cardiometabolic risk factors, compared to carbohydrate-rich snacks, in adults with increased baseline cardiometabolic risk.

Keywords

dried fruit; cardiometabolic; fasting glucose; cholesterol; vascular; sugar; phenolic

Corresponding Author Contact Information: Phone: 814-863-8056, Fax: 814-865-3602, vks5014@psu.edu.

Authorship

The authors' responsibilities were as follows: PMKE designed the research; VKS conducted research; VKS and KSP analyzed data; VKS and KSP authored the manuscript; and PMKE had primary responsibility for final content. All authors have read and approved the final manuscript.

Conflicts of Interest

None

Introduction

Suboptimal fruit intake is a leading dietary contributor to cardiometabolic diseases worldwide[1]. Substantial observational evidence shows that greater fruit consumption is associated with lower risk of cardiovascular diseases[2,3], type 2 diabetes[4,5], and metabolic syndrome[6], and increasing fruit and vegetable intake improves risk factors such as blood pressure and lipids/lipoproteins[7,8]. Strategies to increase fruit intake are needed to reduce the burden of cardiometabolic diseases.

Optimal fruit intakes, associated with the lowest risk of mortality, range from 200–300 grams per day for most diseases[1]. This range is consistent with dietary guidelines in many countries[9–11], which encourage selection of various whole, non-juice forms of fruit including fresh as well as frozen, cooked, canned, and dried fruits. Dried fruits are shelf-stable forms of fruit that are widely available and can be eaten without preparation as a snack or included in a meal, thereby overcoming some common barriers to adequate fruit intake[12,13]. Traditional dried fruits are dried by sun or thermal processing, without addition of sugar or juice[14], and largely retain the nutrients and bioactives in their fresh counterparts, excluding heat- and light-sensitive vitamin C[15]. Most dried fruits are good sources of dietary fiber and potassium[16], which have been associated with lipid-lowering and vascular benefits, respectively[17,18]. Although dried fruits are concentrated sources of simple sugars, the sugars in traditional dried fruits are intrinsic to the fruits and are excluded from recommended limits for added sugar consumption[19]. Compared to fresh fruits, carotenoid contents of dried fruits are generally reduced, while the effect of drying on phenolic contents varies, with increases in some types and decreases in others reported[15]. Authoritative dietary guidelines recognize dried fruits as acceptable alternatives to fresh fruits[9–11]. Though dried fruit consumption is low in Western countries[14,20–22], encouraging consumption could be a strategy to improve fruit intake and, thereby, benefit cardiometabolic health.

Few randomized trials have assessed the cardiometabolic effects of consuming dried fruits[23–28]. Single fruit interventions were used in previous studies, which limits the generalizability of findings and contrasts with the recommendation to consume a variety of fruits[9]. Furthermore, most trials have utilized a parallel design with small sample sizes, making it difficult to distinguish within-person from between-person variation [25,26,28,29]. Therefore, we conducted a randomized crossover trial to determine the effect of daily consumption of mixed dried fruits, compared to calorie- and carbohydrate-matched snacks, on cardiometabolic risk factors in adults with elevated baseline risk. The primary endpoint was low-density lipoprotein cholesterol (LDL-C), an established causal factor in the development of cardiovascular disease[30]. We hypothesized that inclusion of 3/4 cup of mixed dried fruits as part of habitual dietary intake would decrease LDL-C due to the fiber content, compared to the processed low-fiber snacks. We further hypothesized that dried fruits would lower brachial and central blood pressure, and improve arterial stiffness compared to the control group, due to the phenolic compounds[31] and potassium[18] provided by dried fruits. Markers of glycemic control, C-reactive protein, and other lipids/lipoproteins were also assessed.

Methods

Study Design

A two-period randomized crossover trial was conducted to determine the effect of daily dried fruit consumption on cardiometabolic risk factors, compared to a calorie- and carbohydrate-matched control. A computer-generated randomization scheme (www.randomization.com) was used to assign the condition order for enrolled participants; each condition was followed for 4 weeks. After a 2- to 4-week compliance break, subjects crossed over to the alternate condition. The Metabolic Diet Study Center manager kept the randomization code and personnel responsible for endpoint measurement and analysis were blinded to condition allocation until study completion. Participants were not blinded to the condition allocation.

The primary outcome was LDL-C. Secondary outcomes included concentration, size, and particle number of major lipid and lipoprotein classes, fasting glucose, fasting insulin, high-sensitivity C-reactive protein (hsCRP), brachial systolic and diastolic blood pressure (systolic, bSBP; diastolic, bDBP), central systolic and diastolic blood pressure (cSBP, cDBP), central augmentation pressure (AP), augmentation index (AIx), carotid-femoral pulse wave velocity (cfPWV), and blood pressures assessed by 24-hour continuous blood pressure monitoring. Serum PCSK9 concentration was an exploratory outcome. This study was conducted according to the Declaration of Helsinki Ethical Principles for Medical Research and all procedures involving human subjects were approved by the Institutional Review Board of the Pennsylvania State University, STUDY00004871 (University Park, PA). Written informed consent was obtained from all subjects. All data were collected at the Pennsylvania State University Clinical Research Center (CRC). This trial is registered at ClinicalTrials.gov, identifier NCT03020758.

Participants

Adults (age 25–60 years) with a BMI 25–36 kg/m^2 and at least one additional cardiometabolic risk factor were recruited in State College, PA from January 2017 through November 2018. Subjects were recruited using posted flyers, mailed and online advertisements, and direct communication with previous study participants who consented to be contacted. An initial telephone screening was conducted to ascertain eligibility based on key inclusion and exclusion criteria. Individuals who were eligible based on the telephone screening attended a screening visit at the CRC. Participants were instructed to fast for 12 hours (no food or beverage consumption other than water); refrain from strenuous activity for 24 hours; and avoid taking anti-inflammatory medications for 48 hours prior to the screening visit. Weight was assessed to the nearest 0.1 kg using a digital scale, with participants dressed in light clothing with shoes removed. Height was assessed to the nearest 0.5 cm using a mechanical stadiometer. Blood pressure was measured in triplicate using a manual sphygmanometer following a 5-minute rest period; the average of the last two measurements was used. Waist circumference was measured by two nurses to the nearest 0.1 cm using a tape measure positioned in a horizontal plane around the abdomen at the level of the iliac crest; two measurements within 0.5 cm were taken and averaged. Blood samples drawn by venipuncture were processed to separate serum and plasma and then immediately

refrigerated. Blood was analyzed for lipids, lipoproteins, glucose, blood chemistry and complete blood count (Quest Diagnostics, Pittsburgh, PA). Qualifying risk factors included elevated blood pressure (systolic 120–159 mmHg, diastolic 80–99 mmHg); increased waist circumference (men ≥94 cm, women ≥80 cm); fasting glucose ≥100 mg/dL (5.55 mmol/L) and <126 mg/dL (6.99 mmol/L); fasting triglycerides >150 mg/dL (1.69 mmol/L) and <350 mg/dL (3.95 mmol/L); low HDL-C [men <40 mg/dL (1.03 mmol/L), women <50 mg/dL (1.29 mmol/L)]; and LDL-C >116 mg/dL (3.00 mmol/L; mean LDL-C in US adults[32]). Exclusion criteria included the following: allergy to study foods, tobacco use, alcohol consumption >14 drinks/week, use of lipid-, glucose-, or blood pressure-lowering medications or supplements, lactation or pregnancy, diagnosed inflammatory disease, diabetes, cardiovascular disease, kidney disease, untreated thyroid disease, and reported weight loss ≥10% body weight in the past 6 months.

Composition and nutrient profile of study foods

In the dried fruit condition, participants were given individually prepackaged portions of equal parts dried plums (California Dried Plum Board), Black Mission figs (California Fig Advisory Board), Deglet Noor dates (California Date Commission), and raisins (California Raisin Marketing Board) for each day of the study period. These types were selected because they are commonly consumed unsweetened dried fruits in the US and globally[33]. The daily portion provided was 3/4 cup total (112 g), comprised of 28 g of each fruit. Animal crackers (43 g; Stauffer's, York, PA) and fruit snack gummies (51 g; Welch's, The Promotion In Motion Companies, Inc., Allendale, NJ) were selected as control snacks based on their low fiber and potassium contents and were portioned to match the calorie and carbohydrate content of the fruits. Average daily portions of dried fruits deviated slightly from planned due to variation in the fruit weights. The nutrient profiles of study foods are presented in Table 1. All study foods were stored at room temperature, which is consistent with consumers' usual storage practices.

Sugar, carotenoid, and phenolic contents of study foods were chemically analyzed according to previously published methods to verify the study foods had levels comparable to published values. Method details and modifications are described further in Supplementary materials. Sucrose, fructose, and glucose were determined by liquid chromatography (LC) with refractive index detection as described by Fall et al.[34]. Carotenoids were determined by LC with photodiode array detection, according to methods described by Kean et al.[35] with minor modification. Detailed phenolic profiles and quantitation of individual phenolic species was accomplished by ultraperformance liquid chromatography (UPLC) coupled to tandem mass spectrometry using methods adapted from Li et al.[36] and Shahnazari et al.[37]. Total phenolic content was also assessed by the modified Folin-Ciocalteu assay as described by Waterhouse[38] and results expressed as gallic acid equivalents. Carotenoids and phenolic content totals for the dried fruits and control snacks are presented in Table 1. Subtypes are detailed in Supplementary Tables 1 and 2.

Participants were informed of the caloric value of study foods and were instructed to incorporate the foods into their usual diets, substituting them for other foods they were already consuming. No specific or personalized guidance was provided for which foods to

substitute. Participants could consume the study foods whenever and however they preferred as long as the entire portion was consumed daily. In addition, participants were instructed to consume one serving of fresh fruit daily during both conditions; avoid other dried fruits throughout the trial; and otherwise maintain their usual diets and physical activity to support weight maintenance. Compliance with assigned study food consumption was self-reported in weekly written logs. Compliance was quantified as the percentage of days that participants consumed the entire portion of study foods.

Outcome assessment

All data were collected at the CRC on two consecutive days at baseline and at the end of each study period. Participants were instructed to fast for 12 hours and avoid alcohol and anti-inflammatory medications for 48 hours prior to clinic visits. Pre-menopausal women were tested within a week of starting their menstrual period to minimize variability due to hormone fluctuations.

Blood sample collection

Whole blood samples were drawn into serum separator, EDTA-coated, and heparin-coated tubes. Serum separator tubes were allowed to clot at room temperature for 30–60 minutes prior to centrifugation. EDTA- and heparin-coated tubes were immediately centrifuged. Tubes were centrifuged for 15 minutes and aliquots of serum and plasma were stored at −80°C until analysis.

Lipids, lipoproteins, and PCSK9.—Serum lipid and lipoprotein concentrations were measured on two consecutive days at each timepoint and an average used for data analysis (Quest Diagnostics, Pittsburgh, PA). Total and HDL-cholesterol and triglycerides were measured by spectrophotometry. LDL-C was calculated using the Friedewald equation (in mg/dL: LDL-C=TC-HDL-C-triglycerides/5)[39]. Concentration, size and particle number of major plasma lipoprotein classes and subclasses were measured on one day at each time point by NMR spectroscopy (LabCorp, Morrisville, NC). Serum PCSK9 was assessed in a subset of participants (n=45) by solid phase sandwich ELISA (Penn State Biomarker Core Lab, University Park, PA).

Glucose, insulin, and C-reactive protein.—Blood samples collected on one day at baseline and after each condition were used for analysis of glucose, insulin, and hsCRP. Fasting glucose was assessed from heparinized plasma by spectrophotometry (Quest Diagnostics, Pittsburgh, PA). Serum insulin was assessed by immunoassay (Quest Diagnostics). Insulin resistance was estimated by HOMA-IR, calculated using the following formula: fasting plasma glucose (mg/dL) × fasting serum insulin (mU/L) / 405[40]. Serum hsCRP was measured by immunoturbidimetry (Quest Diagnostics). Values exceeding 10 mg/L were assumed to be acute elevations unrelated to study conditions and were excluded from analysis.

Blood pressure and arterial stiffness assessment—Brachial blood pressure was assessed by a nurse using a manual sphygmomanometer after a 5-minute seated rest. Subsequently, a cuff was placed on the upper left arm for central arterial waveform analysis

using the SphygmoCor XCEL (AtCor, Sydney, Australia). Participants then rested in a supine position for assessment of cfPWV using the SphygmoCor XCEL. An automated cuff placed on the upper right thigh inflated to record femoral pulse while the right carotid pulse was concurrently recorded by applanation tonometry. For all blood pressure and vascular assessments, three measurements were taken. The 2nd and 3rd measurements were averaged for analysis.

24-hour blood pressure.—Participants wore an ambulatory blood pressure monitor on the non-dominant arm for a 24-hour period at baseline and after each condition (Mortara Instrument Inc., Milwaukee, WI). The monitor was programmed to automatically capture a reading every 20 minutes during the day and every 30 minutes overnight. Averages of SBP and DBP readings were computed for the entire period worn as well as separately for readings taken while awake versus during sleep.

Weight

Weight was measured at every clinic visit using a digital scale with participants dressed in light clothing and shoes removed. Weights were averaged over the two clinic visits at each time point for analysis.

Statistical Analysis

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). For all variables, normality of the residuals was assessed using univariate analysis to quantitatively evaluate skewness and to visually inspect the distribution and normal probability (Q-Q) plots. Variables with skewed residuals were transformed for analysis. The linear mixed model procedure (PROC MIXED) was used to test the effect of the conditions on end-of-condition means and changes from baseline for all outcomes. Condition was included in the model as a fixed effect and subject was a repeated effect. Interactions between condition and sex or condition sequence were tested for all outcomes. There was no indication for different responses by sex or condition sequence, and there was no deviation from results of the primary analysis. Therefore, these were removed from the model. Significance level for all statistical tests was set at P=0.05. A per protocol analysis was conducted to evaluate whether condition response differed in participants who reported ≥90% compliance with assigned conditions; the between-condition results were unchanged. Therefore, results presented are from the intent-to-treat analysis. A sensitivity analysis was conducted to determine whether weight change explained the observed effects. For endpoints where a significant between-condition difference was detected, analyses were repeated after excluding data from participants who lost or gained 2.0 kg or more of body weight in a study period.

A power calculation estimated that 50 subjects were required to detect a 12 mg/dL (0.31 mmol/L) difference in between-condition LDL-C, assuming a standard deviation of 30 mg/dL (0.78 mmol/L) at a 5% significance level with 80% power [(28)]. Anticipating a 10% dropout rate, we enrolled 55 participants.

Results

Participants

Fifty-five participants were enrolled and randomized, and 52 completed the trial (Figure 1). One withdrew at the first baseline appointment and two withdrew during the first condition due to schedule conflicts. Most participants (87%) had elevated waist circumferences (Table 2). Mean BMI was 28.5 kg/m^2 and mean LDL-C was above optimal (2.94±0.94 mmol/L) at baseline. Baseline characteristics did not differ by randomization sequence (data not presented). Self-reported compliance in participants who returned completed compliance forms for all study days was 98.9% for dried fruit (n=37) and 98.4% (n=39) for the control. Participants gained weight during both conditions (control: 0.4 kg, 95% CI: 0.01, 0.75, P=0.043; dried fruit: 0.3 kg, 95% CI: −0.09, 0.65, P=0.14) with no between-condition difference in weight change detected (P=0.55).

Lipids, lipoproteins, and PCSK9

There were no significant between-condition differences in endpoint-to-endpoint comparison of means or change from baseline for lipid, lipoprotein, or PCSK9 concentrations (Table 3). Following the dried fruit condition, LDL-C (0.10 mmol/L, 95% CI: 0.01, 0.20) and non-HDL-C (0.12 mmol/L, 95% CI: 0.01, 0.23) increased from baseline while HDL-C decreased (−0.05 mmol/L, 95% CI: −0.09, −0.01) (all P<0.05); no changes in these outcomes were detected following the control condition. The total cholesterol (TC):HDL-C ratio increased significantly following both conditions (control: 0.13, 95% CI: 0.01, 0.26, P=0.037; dried fruit: 0.20, 95% CI: 0.08, 0.33, P=0.002). LDL particle number increased from baseline after dried fruit (51 nmol/L, 95% CI: 1, 101; P=0.045); a similar increase after control was not statistically significant (50 nmol/L, 95% CI: 0, 100). Specifically, small LDL particles increased significantly following the control condition (63 nmol/L, 95% CI: 11, 115; P=0.018) whereas the increase in total particles with dried fruit was comprised of both large and small particles. Large HDL particles decreased from baseline following the dried fruit consumption (−0.38 μmol/L, 95% CI: −0.74, −0.01; P=0.045). After exclusion of participants with substantial weight changes (±2.0 kg within condition, vs. baseline), all within-condition changes from baseline were attenuated to non-significance with the exception of HDL-C (Supplementary Table 3).

Glucose, insulin, and C-reactive protein

Mean fasting glucose was significantly greater following the dried fruit condition versus the control condition (mean difference 0.08 mmol/L, 95% CI: 0.005, 0.16; P=0.038) (Figure 2). This difference persisted after exclusion of participants with substantial (±2.0 kg) within-condition weight changes vs. baseline. Changes from baseline were not statistically significant for either condition in the intent-to-treat analysis (Table 3). However, the increase in glucose after the dried fruit condition versus baseline was significant in the per protocol analysis (0.15 mmol/L, 95% CI: 0.01, 0.29; P=0.038; Supplementary Table 4) and after exclusions for substantial weight changes (0.12 mmol/L, 95% CI: 0.004, 0.23; P=0.04; Supplementary Table 3). The between-condition difference in HOMA-IR approached significance (0.1, 95% CI: −0.3, 0.9; P=0.054) but was not changed from baseline for either condition. There were no condition effects or changes from baseline for insulin or hsCRP.

Blood pressure and arterial stiffness

No between-condition differences in endpoint-to-endpoint analysis of means or changes from baseline were detected for blood pressure or measures of central arterial stiffness (Table 4). Brachial diastolic pressure and derived central diastolic pressure assessed by the SphygmoCor increased from baseline on the control condition only (bDBP 2.1 mmHg, 95% CI: 0.5, 3.7 mmHg; cDBP 2.0 mmHg, 95% CI: 0.4, 3.6; both P=0.01). Excluding participants with weight changes of 2.0 kg or greater (n for analysis dried fruit=45, control=44) attenuated the cDBP change-from-baseline to non-significance but bDBP remained significantly elevated after the control compared to baseline (2.1 mmHg, 95% CI: 0.5, 3.7; P=0.01). There were no significant changes in clinician-assessed blood pressures, bSBP, cSBP, or any central arterial stiffness measures compared to baseline.

24-hour blood pressure

An average of 50 blood pressure readings (37 during waking hours and 13 while asleep) were recorded per participant. Mean blood pressure combined across sleeping and wake periods did not differ between conditions (Table 4). When sleeping versus awake periods were analyzed separately, end-of-condition mean diastolic pressure during waking hours was significantly higher after dried fruit versus control condition (mean difference 0.6 mmHg, 95% CI: 0.02, 1.17; P=0.04). Changes from baseline for total, waking, and sleeping SBP and DBP were not significant for either condition and did not significantly differ between conditions.

Discussion

This study aimed to assess the effect of consuming mixed dried fruits, within a self-selected diet, on risk factors for cardiometabolic diseases. Contrary to our hypothesis, consuming a 3/4-cup portion of mixed dried plums, figs, dates, and raisins daily for 4 weeks did not improve LDL-C, blood pressure, or vascular stiffness in overweight/obese subjects at increased risk of cardiometabolic diseases, compared to a carbohydrate-rich control.

Our findings agree with those of Peterson et al., who reported no difference in LDL-C after adults with above optimal or high LDL-C (n=88; mean baseline LDL-C 3.49–3.52 mmol/L) consumed 120 g/day of dried Mission figs versus their usual diet for 5 weeks[24]. In contrast, two previous trials reported lowering of LDL-C with dried plum consumption. Tinker et al. reported significantly lower LDL-C after hypercholesterolemic men (n=41; mean baseline LDL-C 3.89 mmol/L) consumed 12 dried plums (~100 g) daily for 4 weeks compared to an equicaloric daily portion of grape juice (mean difference 0.17 mmol/L, P=0.02)[23]. A numerically small increase from baseline (0.03 mmol/L) was observed with plum consumption but, considering the confidence interval of the estimate, was not statistically significant. Likewise, Clayton et al. reported 0.63 mmol/L lower LDL-C after normocholesterolemic overweight and obese adults (mean baseline LDL-C 2.03–2.04 mmol/L) consumed two 100-kcal servings (84 g) of dried plums daily for 8 weeks (n=26) versus the control group that consumed calorie-matched low-fat muffins (n=23), though changes from baseline were not significant[29].

The conflicting results in these studies versus ours and that of Peterson et al.[24] are not easily explained. Our trial was comparable in duration and fruit dose to Tinker et al.[23], and while elevated LDL-C was not an essential criterion for enrollment in our study, participants' mean baseline LDL-C was classifiable as "above optimal" (≥2.6 mmol/L)[41] and exceeded that of participants in Clayton et al.[29] Thus, differences in duration or baseline health of participants', do not fully explain why LDL-C was not reduced by dried fruits in our study. It is possible that cholesterol-lowering was effected by higher soluble fiber content in the dried plum interventions compared to ours, as dried plums contain nearly twice as much soluble fiber as raisins and dates[17]. Yet, dried figs are higher in soluble fiber than plums and did not lower cholesterol in Peterson et al.[24] Specific bioactives may be responsible for the cholesterol-lowering effect of dried plums that, as part of a dried fruit mixture, may have been consumed in too small a dose or antagonized by other fruits' bioactives[42].

An important distinction between the trials that report LDL-C-lowering with dried fruit consumption[23,29] versus our trial and that of Peterson et al.[24] is maintenance of energy balance. In the study by Peterson et al., mean energy intake increased by about 200 kcal/day while consuming figs, compared to participants' usual diets[24]. Similarly, we observed modest weight gain (0.3 to 0.4 kg) after both conditions suggesting daily overconsumption of approximately 75–105 kcal/day (~25–30% of the study foods' daily caloric values), though without dietary records, total energy intakes cannot be estimated. Therefore our results may be explained by increased sugar intake in the setting of excessive energy intake[43]. Short-term overfeeding with simple carbohydrates increases de novo lipogenesis[44], and fructose-containing sugars may be particularly lipogenic as hepatic fructose uptake is not enzymatically regulated[45]. Within a hypercaloric diet, perhaps even sugars from dried fruits can increase lipogenesis in individuals with elevated cardiometabolic risk. Accordingly, the within-condition increase in LDL-C following dried fruit consumption was attenuated by omission of data from participants with substantial weight changes, though this post hoc analysis should be interpreted with caution due to the loss of statistical power with a reduced sample size (n for analysis dried fruit=45, control=44). Future investigation into the lipidemic effects of dried fruit under eucaloric and hypercaloric conditions is required to understand these findings. In addition, comparison with a low-fructose control would further clarify whether energy excess, fructose content, or a combination of the two explain the finding.

The potassium and phenolic compounds in dried fruits were predicted to improve vascular health. However, a 4-week intervention was likely too short to effect structural changes that alter vascular stiffness. Though numerically lower mean DBP was observed after dried fruit consumption, detection of such a small blood pressure-lowering effect would have required hundreds of subjects. Substantial reductions in blood pressure were reported by Anderson et al. after daily consumption of raisins (85 g) for 12 weeks[25]. Within-condition changes in SBP at 4, 8, and 12 weeks ranged from −5.4 to −8.3 mmHg, all significantly reduced from baseline ($P<0.05$). The raisin group had lower DBP at all timepoints versus the control group consuming processed carbohydrate-rich snacks, with a significant reduction from baseline (−5.5 mmHg) reported at week 12. However, a qualifying enrollment criterion for this

previous study was elevated blood pressure. In contrast, more than half of our participants had a normal blood pressure at baseline.

Although this study was not specifically designed to investigate the effects of dried fruit on glycemic control, the increase in fasting plasma glucose observed after dried fruit consumption, compared to the control snack, is intriguing. This increase persisted in both the sensitivity and per protocol analyses. Dried fruits have a low to moderate glycemic index, and the acute glycemic response to carbohydrate-rich meals is attenuated by replacement of refined starches with dried fruits [46–50]. The lower postprandial glycemic response is likely due to partial glucose replacement by fructose, which does not contribute substantially to blood glucose and may even stimulate hepatic glucose uptake[51]. However, the longer-term glycemic effects of dried fruits have been less investigated. Previous studies did not detect changes in fasting glucose in overweight/obese adults consuming raisins (one cup/day) or dried plums (84 g/d) for 6 weeks and 8 weeks, respectively[28,29]. In a randomized parallel study of overweight/obese adults (n=31), a similar dose of dried fruits to what we provided (85 g raisins) for 12 weeks resulted in a non-significant 0.13 ± 0.11 mmol/L (P=0.36) increase in fasting glucose from baseline, which did not statistically differ from the mean change observed in the control arm (n=15) consuming processed snacks (0.03 ± 0.03 mmol/L)[25]. However, this difference is directionally and numerically similar to that observed in our crossover study. Thus, it is possible that differences in study design may explain the inconsistent findings. However, this finding requires further investigation, as glycemic measures were not the primary focus of our trial.

Many of the hypothesized benefits of dried fruits are attributed to the phytochemicals they contain[52,53]. We assessed the phenolic and carotenoid contents of the provided study foods for comparison with published values. The measured carotenoid contents of our fruits were greater than reference values[16]. Analyzed total phenolic contents were greater for dried plums and raisins and lower for dates than previously reported[54], while reported total phenolics in figs were variably higher[54] or lower[55] than ours. Differences in fruit varieties, growing conditions, maturity, drying conditions, and analytical methods might contribute to differences in our observed values compared to previous reports. Concentrations of these bioactives were not substantially lower compared to other reports, so it is unlikely that the results of our study are explained by lower bioactive content of the studied dried fruits. However, we did not control how the fruits were consumed (i.e., together versus individually) and, thus, possible antagonism of particular bioactive components by coingestion with the other fruits cannot be excluded[42]. Furthermore, reported contents represent amounts present in the foods, as consumed, but most phenolic compounds are metabolized by gut bacteria prior to absorption, thereby altering their biological activity[56]. Thus, physiological responses to these compounds may depend on composition of the gut microbiome. Substantial interindividual variability in plasma concentrations of individual phenolic compound metabolites has been shown[57,58]. Characterization of participants' gut microbial populations may help to explain variation in physiological responses to diet.

To our knowledge, this study is the first to assess a wide range of cardiometabolic disease risk factors in free-living subjects consuming mixed dried fruits with minimal guidance as to

how or when to consume the fruits. This pragmatic design allowed participants to incorporate study foods into their diets however they preferred, and therefore these results are informative about the cardiometabolic consequences of recommending increased dried fruit consumption as a strategy to improve fruit intakes. In addition to the 3/4-cup/day portion of dried fruit provided, equivalent to 1.5 cup-equivalents of fruit according to the 2015–2020 Dietary Guidelines for Americans, subjects were instructed to consume one additional fruit serving per day. Thus, total fruit consumption during the dried fruit condition was consistent with recommended fruit intake, and during the control period fruit intake aligned with average US adult intakes[9,59]. While dietary incorporation of dried fruits did assist with meeting recommended fruit intake, the dried fruits were not effectively substituted for other foods in the diet and thereby contributed to weight gain, which may have obscured the expected cardiometabolic benefits. Fully controlling the diet through provision of all foods and beverages could limit the confounding effects of weight changes and other dietary factors and, thereby, determine the efficacy of dried fruits to effect cardiometabolic improvements. However, the health effects observed under these tightly regulated conditions may not readily translate to free-living individuals who incorporate dried fruits into their diets. At minimum, provision of more detailed guidance may be necessary to support maintenance of energy balance in a supplemental dietary trial and may not be unique to dried fruit supplementation[60].

A major strength of our study was its crossover design, which allows separation of between-person from within-person variability. We utilized functional assessments of cardiometabolic health including lipoprotein subclass analysis, pulse wave analysis, cfPWV measurement, and 24-hour blood pressure monitoring, in addition to established measurements of cardiovascular disease risk including lipid profile and brachial blood pressure. We also analyzed the phenolic contents of our study foods to more accurately quantify the actual doses provided to participants. However, our inferences regarding the effects of dried fruits are limited by the absence of dietary assessment before or during the intervention, as we were unable to confirm that an isocaloric substitution occurred in both periods. We made the assumption that participants altered their usual diets similarly to incorporate dried fruits versus the control snacks. Without dietary records, we cannot confirm that the background dietary intake was consistent in both periods and cannot determine if, or how, calories from participants' usual diets were compensated when study foods were consumed. Unmeasured changes in intake of other foods and nutrients, accompanying either the control or dried fruit conditions, may explain the lack of observed cardiometabolic benefits with dried fruit consumption compared to the control. However, with the current diet assessment methods available, we would likely lack the sensitivity to completely understand dietary alterations that occurred in response to the daily consumption of dried fruits. In addition, due to natural variations in the consumer-grade dried fruits, we provided less fruit than planned (approximately 101 g, vs. 112 g), which may have resulted in underestimation of the effects we observed. We did not adjust *P* values for multiple comparisons, thus the inflation of type I error rate could be responsible for our significant findings. However, we suggest that the observed changes are consistent with metabolic responses to overconsumption of sugars. Finally, given the broad eligibility criteria, participants varied substantially in baseline health status and mean values for most risk factors were within acceptable limits. Individuals with

normal baseline values had little room for improvement, and the absence of changes in these healthier participants may have attenuated improvements in higher-risk participants.

In summary, short-term consumption of 3/4 cup/day of mixed dried plums, figs, dates, and raisins within a self-selected diet did not improve risk factors for cardiometabolic disease compared to non-fruit, carbohydrate-rich snacks in adults with increased risk for cardiometabolic diseases. Further research is needed to determine what, if any, dietary guidance regarding portion or pattern of consumption (e.g. with meals) is warranted to support healthful dried fruit consumption. Maintenance of energy balance should be ensured in future studies investigating the efficacy of routine dried fruit consumption to improve health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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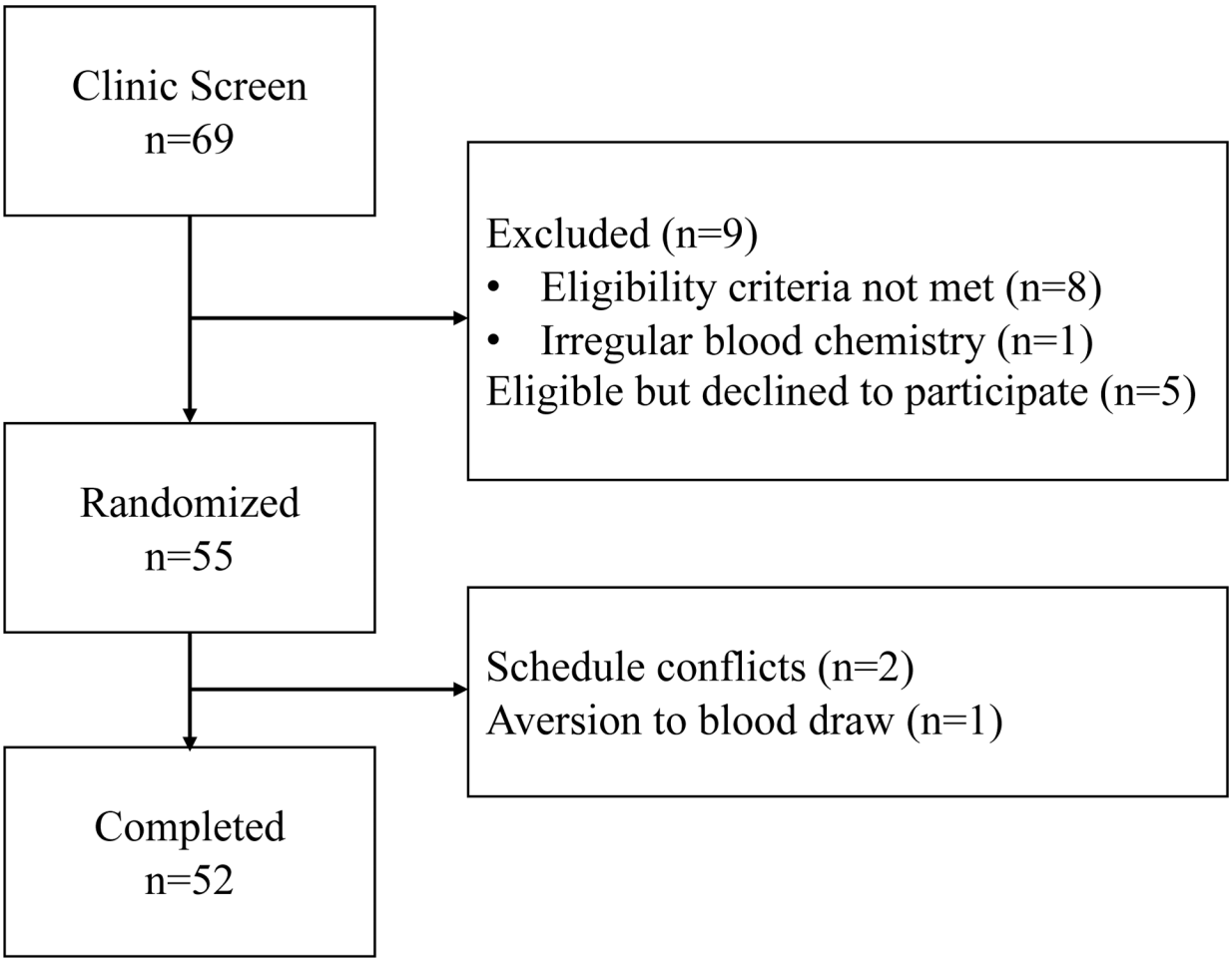

Figure 1.
Consolidated Standards of Reporting Trials 2010 flow diagram.

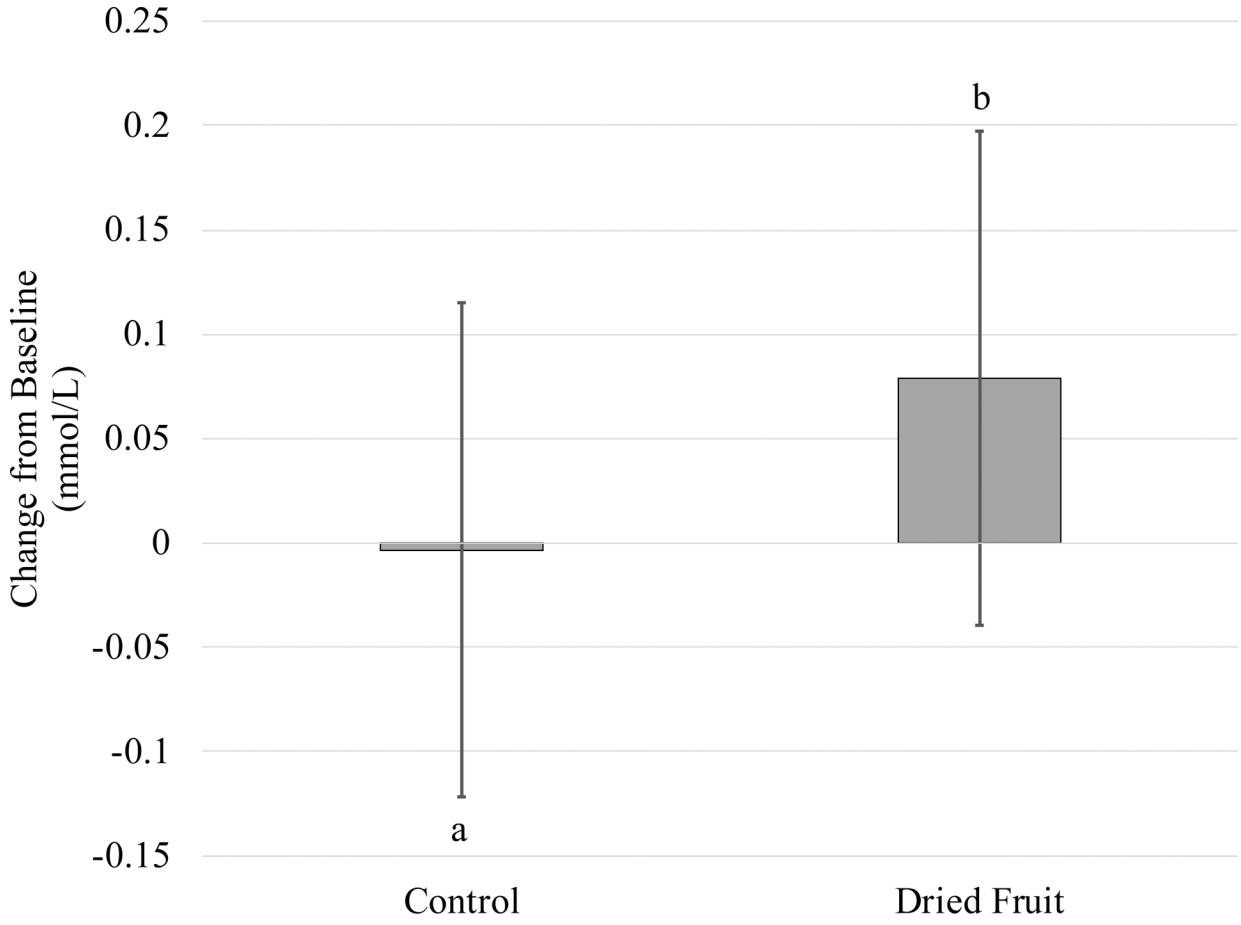

Figure 2. Mean changes from baseline for fasting plasma glucose following 4 weeks of consuming dried fruits or the control snacks (n=55).

Data are presented as unadjusted mean ± 95% CI from linear mixed model comparing changes from baseline. Statistically significant between-treatment effect denoted by different superscripts.

Table 1

Nutrient profiles and bioactive contents for daily portions of Dried Fruits and Control Snacks *

	Control	Dried Fruit (Planned)	Dried Fruit (Actual)
	43 g animal crackers	28 g dried plums	30.7 g dried plums
	51 g fruit gummies	28 g dried figs	18.6 g dried figs
		28 g dried dates	22.9 g dried dates
		28 g raisins	28.7 g raisins
Energy, kcal †	332	300	270
Total Fat, g	2.5	0.5	0.5
Saturated fat, g	0	0	0
Cholesterol, mg	0	0	0
Sodium, mg	170	11	10
Potassium, mg	42	787	715
Total Carbohydrate, g	76	79	71
Dietary Fiber, g	1.4	8.2	7.1
Sugars, g	35‡	60	55‡
Sucrose, g	26‡	7	7‡
Glucose, g	5‡	28	22‡
Fructose, g	3‡	25	21‡
Sorbitol, g	-	-	5‡
Protein, g	3	3	3
Total Phenolics by UPLC, mg	4.9‡		40.9‡
Total Carotenoids, μg	40.6‡		414.7‡

UPLC, ultra-performance liquid chromatography.

*Nutrient information obtained from FoodData Central(16) and manufacturers of control snacks. Planned nutrient profile for dried fruit calculated based on equal portions of dried fruits (28 g each) totaling 3/4 cup. Actual nutrient profile calculated as 7-day weighted average of pre-packaged fruit portions used in study.

†1 kcal = 4.184 kJ.

‡Sugar, carotenoid, and phenolic profiles of study foods measured by chemical analysis.

Table 2

Baseline characteristics of enrolled participants (n=55).

	Mean	SD	Optimal	Participants with Suboptimal Values, n (%)
Female, n	26			
Age, years	40.5	10.7		
BMI, kg/m^2	28.5	2.7	<25	55 (100)
Waist circumference, cm	98.2	8.2	<94 men, <80 women	48 (87)
SBP, mmHg	111	9	<120	8 (15)
DBP, mmHg	77	8	<80	23 (42)
Glucose, mmol/L	5.43	0.43	<5.55	23 (42)
LDL-C, mmol/L	2.94	0.94	<2.60	34 (62)
HDL-C, mmol/L	1.27	0.45	≥1.03 men, ≥1.29 women	26 (47)
Triglycerides, mmol/L	1.30	0.61	<1.69	10 (18)

Table 3

Mean lipid (n=55), lipoprotein (n=52), and PCSK9 (n=45) concentrations for participants at baseline and after dried fruit and control conditions.

	Baseline		Control				Dried Fruit				*P*
	Mean	SEM	Mean	SEM	Change from Baseline	SEM	Mean	SEM	Change from Baseline	SEM	
Weight, kg	85.3	1.8	85.8	1.9	0.4*	0.2	85.7	1.9	0.3	0.2	0.55
TC, mmol/L	4.81	0.14	4.89	0.15	0.05	0.06	4.91	0.15	0.07	0.06	0.84
LDL-C, mmol/L	2.94	0.13	3.01	0.13	0.05	0.05	3.06	0.13	0.10*	0.05	0.36
Non-HDL-C, mmol/L	3.55	0.14	3.64	0.15	0.07	0.06	3.70	0.15	0.12*	0.06	0.39
HDL-C, mmol/L	1.27	0.06	1.26	0.06	−0.03	0.02	1.24	0.06	−0.05*	0.02	0.19†
TC:HDL-C	4.1	0.2	4.2	0.2	0.1*	0.1	4.3	0.2	0.2*	0.1	0.18†
Triglycerides, mmol/L	1.30	0.08	1.37	0.10	0.07	0.07	1.32	0.10	0.01	0.07	0.97†
VLDL & Chylomicron Particles (total), nmol/L	55.3	3.4	54.4	3.7	−0.9	2.6	54.0	3.7	−1.3	2.6	0.94†
Large VLDL & Chylomicron Particles, nmol/L	4.1	0.5	4.8	0.6	0.6	0.6	4.4	0.6	0.3	0.6	0.43†
Medium VLDL Particles, nmol/L	21.6	2.4	20.6	2.2	−1.0	1.9	19.7	2.2	−1.8	1.9	0.83†
Small VLDL Particles, nmol/L	29.6	1.7	29.1	2.2	−0.5	2.2	29.9	2.2	0.3	2.2	0.82†
LDL Particles (total), nmol/L	1102	51	1152	53	50	25	1153	53	51*	25	0.96
IDL Particles, nmol/L	180	14	165	16	−15	17	180	16	−1	17	0.24†
Large LDL Particles, nmol/L	286	27	288	28	2	20	303	28	16	20	0.48
Small LDL Particles, nmol/L	635	30	699	46	63*	26	671	46	36	26	0.23
HDL Particles (total), µmol/L	31.2	0.8	31.3	0.8	0.1	0.4	31.0	0.8	−0.2	0.4	0.48
Large HDL Particles, µmol/L	6.9	0.5	6.8	0.5	−0.2	0.2	6.6	0.5	−0.4*	0.2	0.38†
Medium HDL Particles, µmol/L	8.5	0.7	8.6	0.7	0.1	0.6	9.2	0.7	0.7	0.6	0.07†
Small HDL Particles, µmol/L	15.8	0.8	16.0	0.8	0.2	0.7	15.3	0.8	−0.5	0.7	0.27
VLDL Size, nm	48.5	0.8	49.0	0.9	0.5	1.0	49.1	0.9	0.6	1.0	0.76†
LDL Size, nm	20.6	0.1	20.6	0.1	0	0.1	20.6	0.1	0	0.1	0.32
HDL Size, nm	9.3	0.1	9.3	0.1	−0.1	0	9.3	0.1	−0.1	0	0.85

	Baseline		Control				Dried Fruit				*P*
	Mean	**SEM**	**Mean**	**SEM**	**Change from Baseline**	**SEM**	**Mean**	**SEM**	**Change from Baseline**	**SEM**	
Calculated triglyceride (total), mmol/L	1.33	0.10	1.41	0.11	0.08	0.09	1.36	0.11	0.03	0.09	0.85†
Calculated VLDL & Chylomicron TG, mmol/L	0.95	0.07	0.99	0.08	0.04	0.06	0.94	0.08	0	0.06	0.92†
Calculated HDL Cholesterol, mmol/L	1.29	0.06	1.27	0.06	−0.02	0.02	1.26	0.06	−0.04	0.02	0.45†
Lipoprotein Insulin Resistance Score	46	2	48	3	2	2	50	3	4	2	0.31
HOMA-IR	1.5	0.1	1.5	0.1	0	0.1	1.6	0.1	0.1	0.1	0.05†
Insulin, pmol/L	41.4	2.6	41.0	3.0	−0.6	3.1	44.0	3.0	2.4	3.1	0.09†
hsCRP, mg/L	1.8	0.2	2.0	0.3	0.2	0.2	1.9	0.3	0	0.2	0.44†
PCSK9, ng/mL	168	11	168	12	−1	12	177	12	8	12	0.37†

Baseline values presented as unadjusted means ± SEM. Least squared means ± SEM for end-of condition means and changes from baseline for control and dried fruit. *P* value for linear mixed model comparing end-of-condition means.

*Significant change from baseline ($P<0.05$).

†Transformed means used in linear mixed model for variables with non-normally distributed residuals.

Table 4

Vascular outcome means at baseline and after each condition (n=55).

	Baseline		Control				Dried Fruit				*P*
	Mean	**SEM**	**Mean**	**SEM**	**Change from Baseline**	**SEM**	**Mean**	**SEM**	**Change from Baseline**	**SEM**	
Clinician- assessed brachial SBP, mmHg	111.1	1.3	112.9	1.4	1.8	1.0	112.8	1.4	1.7	1.0	0.99
Clinician- assessed brachial DBP, mmHg	76.9	1.1	76.7	1.1	−0.5	0.8	76.6	1.1	−0.6	0.8	0.87
Brachial SBP, mmHg	119.5	1.3	119.7	1.5	0	1.1	120.7	1.5	0.9	1.1	0.31
Brachial DBP, mmHg	75.9	1.1	78.2	1.2	2.1*	0.8	76.9	1.2	0.8	0.8	0.09
Central SBP, mmHg	109.0	1.3	109.8	1.3	0.5	1.0	110.1	1.3	0.8	1.0	0.70
Central DBP, mmHg	76.8	1.2	78.9	1.2	2.0*	0.8	77.6	1.2	0.7	0.8	0.07
Augmentation Pressure, mmHg	7.0	0.6	6.9	0.6	−0.3	0.5	7.6	0.6	0.3	0.5	0.21
Augmentation Index, %	17.5	1.9	18.7	1.8	0.8	1.2	19.7	1.8	1.8	1.2	0.35
Pulse Wave Velocity, m/s	6.5	0.1	6.6	0.1	0.1	0.1	6.6	0.1	0.1	0.1	0.90
Combined 24- hr SBP	114.4	1.2	115.9	1.4	1.5	1.2	115.2	1.4	0.3	1.2	0.09
Combined 24- hr DBP	74.8	0.7	74.8	0.8	0	0.6	75.0	0.8	−0.1	0.6	0.44
Awake SBP	119.7	1.3	120.8	1.4	1.1	1.3	120.7	1.4	0.4	1.3	0.82
Awake DBP	77.6	0.8	77.6	0.8	−0.1	0.7	78.2	0.8	0	0.7	0.04
Asleep SBP	99.4	1.3	100.8	1.4	1.1	1.5	100.5	1.4	1.2	1.5	0.66
Asleep DBP	66.5	0.8	66.1	0.8	−0.6	0.7	66.6	0.8	0.2	0.7	0.19

Baseline values presented as unadjusted means ± SEM. Least squared means ± SEM for end-of condition-means and changes from baseline for control and dried fruit. *P* value for linear mixed model comparing end-of-condition means.

*Significant change from baseline ($P<0.05$).