Prunes preserve hip bone mineral density in a 12-month randomized controlled trial in postmenopausal women: the Prune Study

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ABSTRACT

Background: Dietary consumption of prunes has favorable impacts on bone health, but more research is necessary to improve upon study designs and refine our understandings.

Objectives: We evaluated the effects of prunes (50 g or 100 g/d) on bone mineral density (BMD) in postmenopausal women during a 12-mo dietary intervention. Secondary outcomes include effects on bone biomarkers.

Methods: The single-center, parallel-arm 12-mo randomized controlled trial tested the effects of 50 g and 100 g prunes compared with a control group on BMD (every 6 mo) and bone biomarkers in postmenopausal women.

Results: In total, 235 women (age 62.1 ± 5.0 y) were randomly allocated into control ($n = 78$), 50-g prune ($n = 79$), or 100-g prune ($n = 78$) groups. Compliance was 90.2 ± 1.8% and 87.1 ± 2.1% in the 50-g and 100-g prune groups. Dropout was 22%; however, the dropout rate was 41% for the 100-g prune group (compared with other groups: 10%, control; 15%, 50 g prune; $P < 0.001$). A group × time interaction for total hip BMD was observed in control compared with 50-g prune groups ($P < 0.05$) but not in control compared with 100-g prune groups ($P > 0.05$). Total hip BMD decreased –1.1 ± 0.2% in the control group at 12 mo, whereas the 50-g prune group preserved BMD (–0.3 ± 0.2%) at 12 mo ($P < 0.05$). Although hip fracture risk (FRAX) worsened in the control group at 6 mo compared with baseline (10.3 ± 0.5% compared with 9.8 ± 0.5%, $P < 0.05$), FRAX score was maintained in the pooled (50 g + 100 g) prune groups.

Conclusions: A 50-g daily dose of prunes can prevent loss of total hip BMD in postmenopausal women after 6 mo, which persisted for 12 mo. Given that there was high compliance and retention at the 50-g dosage over 12 mo, we propose that the 50-g dose represents a valuable nonpharmacologic treatment strategy that can be used to preserve hip BMD in postmenopausal women and possibly reduce hip fracture risk. This trial was registered at clinicaltrials.gov as NCT02822378. *Am J Clin Nutr* 2022;00:1–14.

Keywords: prune, dried plum, osteoporosis, osteopenia, menopause, bone

Introduction

Osteoporosis is a disease characterized by reduced bone mineral density (BMD), deterioration in the microarchitecture, and reduced bone strength, which increases bone fragility and the risk for fracture (1) with a prevalence rate projected to reach 57.8 million by 2030 (2). Despite new drug discoveries to treat low BMD, compliance to pharmacologic therapy remains remarkedly low among postmenopausal women (3), posing a major challenge to treatment success (4, 5). Alternative nonpharmacologic whole-food interventions for both the prevention and treatment of postmenopausal bone loss have shown promise (i.e., phenolic-rich foods in both animal models and human preclinical and clinical studies) (6–10).

Prunes (i.e., dried plums) represent an attractive strategy because the phenolic compounds in prunes may mitigate postmenopausal bone loss (10–12) mechanistically by exerting favorable effects on bone metabolism (6, 7, 9) and by targeting inflammatory signaling pathways that may modulate bone loss (10, 13, 14). Dietary supplementation with prunes has been

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

Supplemental Figure 1 and Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BMD, bone mineral density; CTx, C-terminal telopeptide; IGF-1, insulin-like growth factor 1; ISCD, International Society for Clinical Densitometry; IRB, institutional review board; ITT, intent to treat; P1NP, procollagen type I N-terminal propeptide; PSU, Pennsylvania State University; RCT, randomized controlled trial; TBS, trabecular bone score; $25(OH)D_3$, 25-hydroxyvitamin D.

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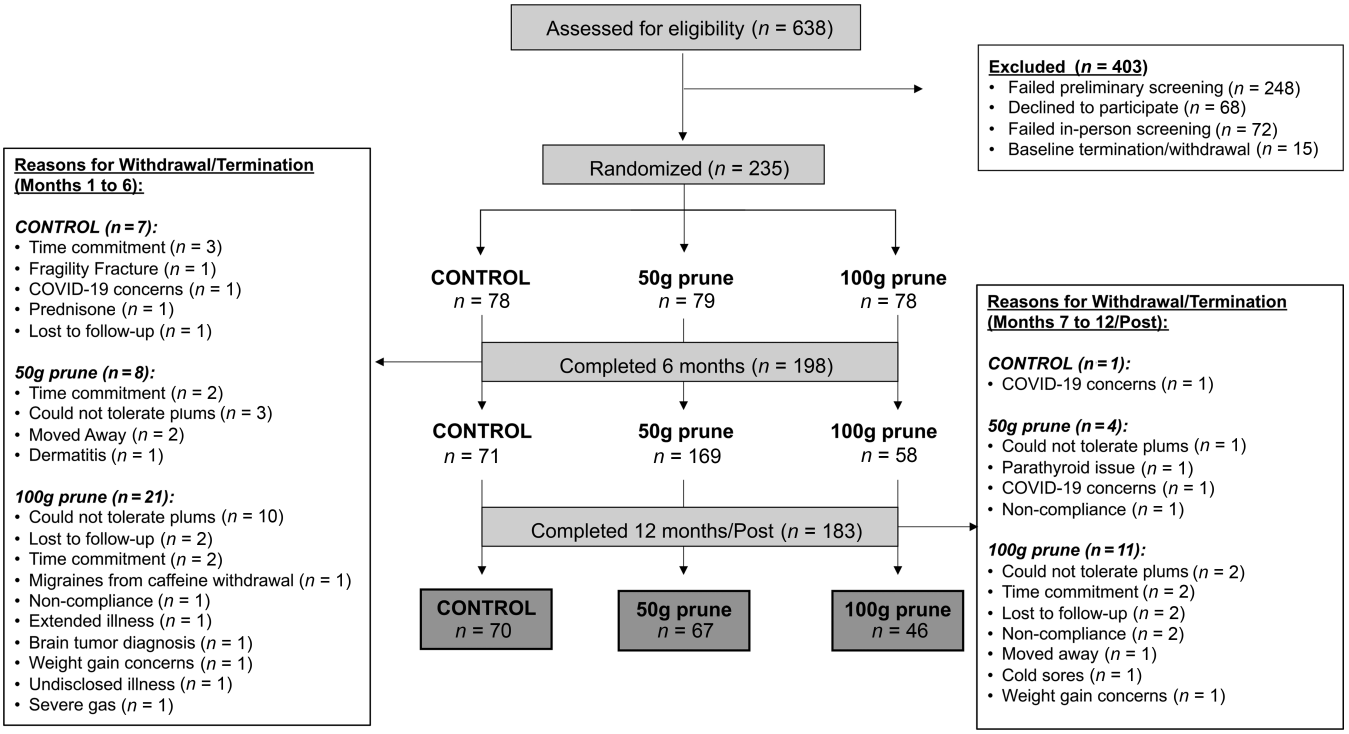

FIGURE 1 Consolidated Standards of Reporting Trials diagram depicting number of participants enrolled at each study phase and the reasons for dropout. Of the 235 participants randomly allocated, a total of 52 women dropped out of the study early. Dropout rate was highest (53.8%; 28/52) within the first 3 mo of the intervention (control group, $n = 4$; 50-g prune group, $n = 6$; 100-g prune group, $n = 18$). Between 3 and 6 mo, the dropout rate was 15.4% (8/52; control group, $n = 3$; 50-g prune group, $n = 2$; 100-g prune group, $n = 3$). Between 6 and 9 mo, the dropout rate was 23% (12/52; control group, $n = 0$; 50-g prune group, $n = 2$; 100-g prune group, $n = 10$). Between 9 mo and the postintervention time point, the dropout rate was 7.7% (4/52). These 4 dropouts included 2 participants who dropped out due to concerns of COVID-19 (control group, $n = 1$; 50-g prune group, $n = 1$) and 2 who dropped out due to noncompliance (control group, $n = 0$; 50-g prune group, $n = 1$; 100-g prune group, $n = 1$).

shown to decrease bone resorption and prevent or preserve bone (6, 9, 15, 16). In animal models with established bone loss, prune supplementation increased BMD (17), whereas moderate and high doses of prunes prevented decreases in BMD (16).

To date, the only available data on 50- or 100-g/d prune dosage studies in postmenopausal women are from 3-, 6-, and 12-mo randomized controlled trials (RCTs) (18–20), and investigation to determine dose response (control compared with 50 g/d compared with 100 g/d) is limited to a single 6-mo RCT (21). The short 3-mo duration investigations of 100 g prune/d improved bone formation markers (20), whereas longer 12-mo 100-g/d prune consumption was associated with increased ulnar and lumbar spine BMD and decreased bone formation and resorption, compared with 75 g/d of dried apples (18). At 6 mo, both 50-g and 100-g/d prune dosages were effective at preventing a loss in total body BMD compared to controls, but no effect was observed on other BMD sites (21).

As a next step, we have completed a 12-mo RCT that employs an experimental design to address limitations of prior work in humans (18, 19, 21) while also addressing endocrine mechanisms, and uses added phenolic markers to document compliance to therapy. The primary objectives of the current study were to evaluate the effects of 2 dosages of prunes (50 g and 100 g) on areal BMD sites in postmenopausal women during a 12-mo dietary intervention. Secondary outcomes studied include the effects on markers of bone formation and resorption, as well as hormones to further elucidate potential mechanisms driving BMD outcomes. Both 50-g and 100-g dosages of prunes are hypothesized to effectively prevent BMD loss in postmenopausal women.

Methods

Study design

The Prune Study (registered at clinicaltrials.gov as NCT02822378) is a single-center, parallel-arm 12-mo RCT to compare dietary supplementation with 50 g (i.e., 4–6 prunes) and 100 g of prunes (i.e., 10–12 prunes) compared with a no-prune control group (control) in postmenopausal women aged 55–75 y with a BMD T-score of <0.0 and >-3.0 at any site and determine effects on areal BMD at the total body, lumbar spine, total hip, or femoral neck (22). The study duration was increased for 23 participants (control: 10; 50 g: 10; 100 g: 3) during the COVID-19 university closure (**Figure 1** and **Figure 2**). Detailed study procedures are outlined in **Supplemental Figure 1**. Body weight and review of symptoms occurred monthly for 12 mo. Bone health and body composition were assessed every 6 mo, and every 3 mo, total phenolic content and phenolic metabolites were assessed in 48-h pooled urine collections. At baseline and post intervention, fasted blood samples were taken to assess biomarkers.

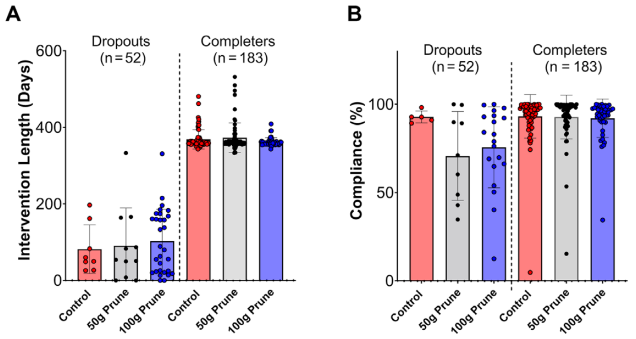

FIGURE 2 Duration of intervention (A) and compliance (B) for the Prune Study. Due to the high dropout rate in the 100-g prune group, the average length of time in the intervention group for all participants (completers and those who dropped out) was significantly shorter compared with control and 50-g prune groups ($P < 0.001$). Duration of intervention extended for some participants due to COVID-19 disruption of the clinic. However, in those who completed the full 12-mo intervention, the average length of time in the intervention was comparable ($P = 0.410$).

Recruitment.

Procedures were performed at Penn State University (PSU) from June 2016 to February 2021. Recruitment occurred through fliers, e-mail announcements, information sessions, and advertisements.

Ethics.

The study was approved by the PSU Institutional Review Board (IRB), and participants signed an approved informed consent.

Screening and eligibility.

Preliminary screening was completed via phone. If eligibility criteria were met, a physical exam and evaluation of medical health history, BMD, and results from the fasted blood draw were reviewed to determine eligibility. Eligibility criteria are as follows (22): *1*) postmenopausal women aged 55–75 y; *2*) not severely obese [BMI (in kg/m^2) <40]; *3*) healthy (determined by a screening questionnaire, complete metabolic panel); *4*) willing to include prunes in their daily diet; *5*) not taking any natural dietary supplement containing phenolics or <1 cup/d of blueberries or apples for at least 2 mo prior to study entry; *6*) nonsmoking; *7*) ambulatory; and *8*) had eligible BMD as measured by DXA. Eligible BMD values (T-scores) for DXA measures of the lumbar spine, total hip, and/or femoral neck corresponded to T-scores between 0.0 and –3.0. Participants were not on any hormonal, osteoporosis, or other medications within a year of study participation that would interfere with bone health during the study. Specifically, participants could not have taken intravenous bisphosphonates at any time, fluoride within 24 mo, denosumab at any time, oral bisphosphonates within 12 mo, selective estrogen receptor modulators within 12 mo, hormone therapy within 3 mo, or glucocorticosteroids within 3 mo of enrollment.

Randomization.

Randomized allocation was achieved using a computer-generated list of random numbers with a 1:1:1 group allocation using fixed random block sizes of 3. It was not possible to blind participants and study staff to the allocated treatment arm; however, outcome assessors and data analysts were kept blinded to the allocation. A total of 235 participants were randomized into 1 of 3 groups: *1*) control ($n = 78$; no prunes), *2*) 50 g prune ($n = 79$; 4–6 prunes daily), or *3*) 100 g prune ($n = 78$; 10–12 prunes daily). Participants were supplemented as necessary to meet the required intake of 1200 mg calcium carbonate and 800 IU vitamin D_3 daily from diet plus supplements (Nature Made Pharmavite LLC). Participants randomly allocated to a prune group consumed California prunes of the "Improved French" variety, which are a type of La Petite D'Agen native to southwest France (**Supplemental Table 1**). The prunes were provided by the California Prune Board. Participants underwent a "run-in" period to slowly increase prune consumption, as follows (22): the 50-g prune run-in plan included 2 prunes/d for 3 d (1 prune after breakfast and 1 prune after dinner), followed by 4 prunes/d for 4 d (1 prune after breakfast, 1 prune after lunch, and 2 prunes after dinner), followed by 5 prunes/d for 4 d (2 prunes after breakfast, 1 prune after lunch, and 2 prunes after dinner), followed by the desired dose of 6 prunes/d (2 prunes after breakfast, 2 prunes after lunch, and 2 prunes after dinner) for the remainder of the 12-mo study duration. The 100-g prune run-in plan included 2 prunes/d for 3 d (1 prune after breakfast and 1 prune after dinner), followed by 4 prunes/d for 4 d (1 prune after breakfast, 1 prune after lunch, and 2 prunes after dinner), followed by 6 prunes/d for 4 d (2 prunes after breakfast, 2 prunes after lunch, and 2 prunes after dinner), followed by 9 prunes/d for 4 d (3 prunes after breakfast, 3 prunes after lunch, and 3 prunes after dinner), and, last, an increase to the desired dose of 12 prunes/d for the remainder of the 12-mo study duration (4 prunes after breakfast, 4 prunes after lunch, and 4 prunes after dinner). After the "run-in" period, participants were instructed to eat the assigned daily number of prunes and record time and number of prunes consumed each day.

Anthropometric assessment.

Height was measured in centimeters using a stadiometer. Total body weight was measured to the nearest 0.5 kg on a physician's scale (Model 770; Seca). BMI was calculated as the body mass divided by height squared.

Medical and health history assessment.

Participants completed questionnaires to detail medical histories, exercise, and dietary practices.

Exercise assessment.

Every 6 mo, exercise assessments were performed using a 7-d record of daily purposeful exercise duration and mode. Exercise type was also classified by bone loading type according to Nikander et al. (23, 24).

Dietary assessment.

At baseline and 12 mo, diet assessments were performed. Participants completed a 3-d diet diary (1 weekend day and 2 weekdays) to assess energy intake and macronutrient dietary composition. Participants were instructed to measure (using standard measuring cups/tools) and record all food and beverages consumed in detail. The nutrient data from the 3-d diet logs were coded and analyzed for total kilocalories and macronutrients using Nutritionist Pro software (Axxya Systems). Daily kilocalories consumed over the 3-d recording period were averaged. A brief validated calcium assessment tool (25) was used to determine the dietary intake of calcium during 1 laboratory visit every 3 mo. Participants were provided calcium carbonate and vitamin D_3 supplements in order to meet the RDA of 1200 mg calcium carbonate and 800 IU vitamin D_3 daily from diet plus supplements.

Blood serum assessment.

At baseline and month 12/post intervention time points, fasted blood samples were collected for serum measurements of procollagen type I N-terminal propeptide (P1NP), C-terminal telopeptide (CTx), insulin-like growth factor 1 (IGF-1), and 25-hydroxyvitamin D [25(OH)D_3]. PINP was measured using an radioimmunoassay (Orion Diagnostica) (intra-assay and interassay CVs of 10% each). CTx, IGF-1, and 25(OH)D_3 were measured using an automated chemiluminescent immunoassay (iSYS; Immunodiagnostic Systems) [intra-assay and interassay CVs of 3% and 10%, respectively, for CTx; 1.9% and 3.9%, respectively, for IGF-1; and 5% and 7.4%, respectively, for 25(OH)D_3].

Body composition assessment and DXA assessment.

Every 6 mo, a DXA scan was performed to assess body composition and BMD. Participants were scanned on a Hologic QDR4500 system by an International Society for Clinical Densitometry (ISCD)–certified technologist. Laboratory precision was $\leq$1.1% CV for body composition and <0.8% CV at all BMD sites (total body, spine, and hip). Fracture risk assessment was determined using the trabecular bone score (TBS)–adjusted FRAX tool (www.shef.ac.uk/FRAX) (26, 27). Participants were classified as osteopenic if T-scores were <–1.0 but >–2.5 at any site or osteoporotic if T-scores were <–2.5 at any site.

Compliance assessment.

To monitor compliance, prune and/or calcium + vitamin D_3 consumption logs were completed daily and adverse symptoms recorded (bloating, cramping, gas, diarrhea, etc. to be reported in a separate manuscript). Compliance was calculated as the reported prunes consumed divided by the prescribed number of prunes to be consumed each month (%). The self-report compliance measure was supported by urinary assessments of total phenolics and phenolic metabolites (4-hydroxybenzoic acid, hippuric acid, 3-hydroxyhippuric acid) in 48-h pooled urinary samples every 3 mo on which quantitative measurement was performed to determine total phenolics (Folin–Ciocalteu assay), normalized by creatinine (colorimetric assay kit 500,701; Cayman Chemical) and phenolic metabolites by LC-MS/MS as described previously (22).

Statistics.

Data normality was assessed using the Shapiro–Wilk test. For normally distributed variables, independent *t*-tests were performed to compare baseline demographic variables between groups; for non-normally distributed variables, the Mann–Whitney *U* tests were performed.

Main intent-to-treat analysis. All analyses were based on the intent-to-treat (ITT) principle, in that the analysis set included all study participants who were randomly allocated. To compare the effects of the intervention on the primary and secondary outcomes, we used a general linear mixed-effects model fit to the longitudinal observations at 3 time points (baseline, 6 mo, 12 mo/post) during the study with random subject-level intercept and fixed effects of time, study group, and study group × time interaction. Baseline body weight, time since menopause, compliance, and minutes of high-magnitude loading exercise were used as covariates, based on previous investigations demonstrating relevance to bone-related outcomes in postmenopausal women (28–30) and changes over the course of the study. For variables with a significant group × time interaction, simple contrasts using sequential Bonferroni correction were performed. These models were run comparing control compared with 50-g prune groups only and control compared with 100-g prune groups only. As a sensitivity analysis, for those who completed the intervention (i.e., completers only), percent changes from baseline were also calculated and independent *t*-tests/Mann–Whitney *U* tests were used to determine group differences. Due to a higher than expected dropout rate in the 100-g prune group, a parallel ITT analysis was run comparing the control compared with pooled (50 g + 100 g) prune groups to maximize statistical power.

Missing data. Little's missing completely at random (MCAR) test was performed on main variables of body composition and BMD to assess if data were missing completely at random. When Little's MCAR test was significant (indicating data were not missing completely at random), *t*-tests were used to determine if there were baseline differences between those with and without missing data for the dependent variables in the study. Nonsignificant *t* tests indicated that those with and without missing data were similar at baseline, and their attrition is unlikely to bias the results. No data were imputed.

Subanalysis. Due to an unequal distribution of low BMD T-score categories among the groups, attributed to random chance, a subanalysis was completed in a subset of participants characterized as having "low BMD," defined as having a T-score <–1.0 at total body, lumbar spine, total hip, or femoral neck site, which represented the majority of the study sample. General linear mixed-effects models were repeated in this subset (see main analysis) for changes in body composition, BMD, and bone biomarkers among the study groups to determine the effect of the intervention in only osteopenic and osteoporotic participants.

To demonstrate a statistically significant difference between groups for the primary outcomes of percent change of total hip (effect size: 0.57) and lumbar spine (effect size: 0.54) BMD, sample sizes of 50 and 55 women per group, respectively, provide

80% power at a significance level of 5%, as described previously (22). IBM SPSS Statistics for Windows (version 27.0) was used for analyses. Baseline descriptive characteristics were reported as mean ± SD and counts and proportion (%), and longitudinal outcomes were reported as estimated marginal means ± SEMs. All tests were 2-sided, and a difference with a $P < 0.05$ was considered significant.

Results

Demographics

Descriptive characteristics were balanced among the 3 randomly allocated groups, as shown in **Table 1**. The average age of the participants was 62.1 ± 5.0 y (range: 55–75 y), and age of menopause was 50.2 ± 4.8 y (range: 30–61 y), with a majority of participants (65.5%; range: 1–33 y) characterized as "late" menopause [STRAW + 10 classification >8 y postmenopause (31)]. Participants were primarily Caucasian (227/235, 97%), with few participants reporting their race as black ($n = 1$), Asian ($n = 2$), Hispanic/Latina ($n = 1$), other ($n = 2$), or biracial ($n = 1$). Based on BMI, 51.4% of participants were overweight or had obesity. Regarding BMD classification, 14.5% had normal BMD, 67.7% had osteopenia, and 17.9% had osteoporosis, with T-scores listed in Table 1. Most participants reported no previous hormone therapy (75%) or previous osteoporosis medication use (83%).

After initially screening 638 women by phone, 322 women were screened in-person, and 250 entered baseline. In total, 235 women were randomly allocated into 1 of 3 groups: *1*) control ($n = 78$), *2*) 50 g prune ($n = 79$), or *3*) 100 g prune ($n = 78$) (Figure 1). In total, 160 women completed 12 mo (control: 60; 50 g: 57; 100 g: 43). Due to COVID-19 university closure, 23 women (control: 10; 50 g: 10; 100 g: 3) completed an IRB-approved postvisit beyond the 12-mo intended study duration upon university reopening; in these participants, there was a mean measurement timing of 14.3 mo (429 d; range: 383–532 d). A total of 183 women completed 12-mo/poststudy visits (70 in the control group, 67 in the 50-g prune group, and 46 in the 100-g prune group).

Dropout/early termination

Overall dropout/early termination rate was 22% (Figure 1); however, the rates varied among the groups. In the control group, the dropout rate was 10% and the primary reason for dropout was time commitment. In the 50-g prune group, the dropout rate was 15% with the primary reasons for dropout being poor tolerance to prunes and time commitment. In the 100-g prune group, the dropout rate was 41% and significantly greater than the control and 50-g prune groups ($P < 0.001$), with the primary reasons for dropout being poor tolerance consuming the prunes, time commitment, or lost to follow-up. Due to the high dropout rate in the 100-g prune group, the average length of time in the intervention for all participants (completers and those who dropped out) was significantly shorter (260 ± 16 d in the 100-g prune group, compared with 335 ± 11 d in the control and 333 ± 13 d in the 50-g prune groups; $P < 0.001$) (Figure 2). However, in those who completed the full 12-mo intervention, the average length of time in the intervention was comparable (control group: 364 ± 4 d, 50-g prune group: 372 ± 5 d, 100-g prune group: 362 ± 2 d; $P = 0.410$) (Figure 2).

Compliance

Compliance, characterized by self-reported daily prune consumption, was 90.2 ± 1.8% in the 50-g prune group and 87.1 ± 2.1% in the 100-g prune group. Compliance for calcium + vitamin D_3 consumption was 93.2 ± 1.4% in the control group. Compliance was different based on randomization group ($P = 0.036$), with compliance being significantly lower in the 100-g prune group compared with the control group ($P = 0.045$). However, among those who completed the full 12-mo intervention, average compliance was comparable among the 3 groups ($P = 0.379$), with compliance at 93.2 ± 1.4% in the control group, 92.8 ± 1.5% in the 50-g prune group, and 92.1 ± 1.6% in the 100-g prune group.

Urinary analysis of total phenolics did not indicate group differences throughout the intervention (all time points $P > 0.05$). However, LC-MS/MS analysis permitted more refined detection of individual phenolic metabolites. Concentrations of hippuric acid, a key marker of phenolic intake, did not differ between groups at 6 mo ($P = 0.180$), but there was a group difference at the post intervention time point ($P < 0.001$), with 50-g (222.7 ± 27 μM; $P = 0.070$) and 100-g (316.6 ± 51 μM; $P < 0.001$) groups having greater concentrations compared with the control group (125.3 ± 24 μM). At the post intervention time point, 3-hydroxyhippuric acid also tended to be significantly different between groups ($P = 0.056$). However, other individual metabolites quantified, such as 4-hydroxybenzoic acid ($P = 0.137$), did not differ among groups.

Body composition outcomes: main ITT analysis.

50-g prune compared with control groups. Body fat percentage increased during the intervention in both the 50-g and control groups (main effect of time, $P = 0.030$; **Table 2**).

100-g prune compared with control groups. Fat mass and body fat percentage (both main effect of time, $P = 0.003$; **Table 3**) increased during the intervention in both the 100-g and control groups.

Pooled prune compared with control groups. Fat mass (main effect of time, $P = 0.013$; **Table 4**) and body fat percentage (main effect of time, $P = 0.002$; Table 4) increased in both pooled prune and control groups over time.

Subanalysis by low BMD by T-score. Fat mass (main effect of time, $P = 0.013$; **Supplemental Table 2**) and percent body fat (main effect of time, $P = 0.022$; Supplemental Table 2) increased during the intervention in both the control compared with the 50-g prune groups with low BMD. Fat mass (main effect of time, $P = 0.038$; **Supplemental Table 3**) and percent body fat (main effect of time, $P = 0.012$; Supplemental Table 3) increased during the intervention in both control compared with the 100-g prune groups with low BMD. Fat mass (main effect of time, $P = 0.013$; **Supplemental Table 4**) and percent body fat (main effect of time, $P = 0.002$; Supplemental Table 4) increased during the intervention in both control and pooled prune groups with low BMD.

TABLE 1 Baseline characteristics for prune study groups[1]

Characteristic	Control ($n = 78$)	Prune ($n = 157$)	50 g Prune ($n = 79$)	100 g Prune ($n = 78$)
Demographics				
Age, y	62.0 ± 4.8	62.2 ± 5.1	62.0 ± 4.7	62.3 ± 5.4
Age at menopause, y	50.1 ± 4.9	50.3 ± 4.8	50.6 ± 4.8	49.9 ± 4.8
Time since menopause, y	11.9 ± 6.9	11.7 ± 7.0	11.2 ± 6.7	12.2 ± 7.4
Height, cm	164.0 ± 5.8	162.0 ± 6.0	162.0 ± 5.8	162.5 ± 6.2
Body mass, kg	67.2 ± 11.1	68.8 ± 10.9	69.1 ± 11.4	68.4 ± 10.4
BMI, kg/m^2	25.1 ± 4.0	26.1 ± 4.2	26.3 ± 4.5	25.9 ± 3.8
BMI category, %				
Normal[2]	53.8	45.8	46.8	44.8
Overweight	30.7	37.6	35.4	39.7
Obese	15.5	16.6	17.7	15.4
Body composition				
Fat mass, kg	26.9 ± 8.4	28.3 ± 7.2	28.6 ± 7.7	28.0 ± 6.7
Lean body mass, kg	36.9 ± 4.0	37.2 ± 4.4	37.3 ± 4.6	37.1 ± 4.3
Body fat, %	40.0 ± 6.7	41.4 ± 5.0	41.5 ± 5.4	41.3 ± 4.6
Bone mineral density				
BMD category, %				
Normal	6.4	18.5	17.7	19.2
Osteopenia	73.1	65.0	60.8	69.2
Osteoporosis	20.5	16.5	21.5	11.5
Total body, g/cm^2	1.054 ± 0.077	1.059 ± 0.087	1.051 ± 0.082	1.100 ± 0.091
Total body T-score	–0.7 ± 1.0	–0.6 ± 1.1	–0.7 ± 1.0	–0.5 ± 1.2
Lumbar spine, g/cm^2	0.880 ± 0.090	0.910 ± 0.110	0.893 ± 0.105	0.927 ± 0.113
Lumbar spine T-score	–1.5 ± 0.8	–1.2 ± 1.0	–1.4 ± 1.0	–1.1 ± 1.0
Total hip, g/cm^2	0.803 ± 0.076	0.812 ± 0.089	0.807 ± 0.100	0.800 ± 0.078
Total hip T-score	–1.1 ± 0.6	–1.1 ± 0.7	–1.1 ± 0.8	–1.0 ± 0.6
Femoral neck, g/cm^2	0.675 ± 0.078	0.679 ± 0.083	0.672 ± 0.087	0.700 ± 0.077
Femoral neck T-score	–1.6 ± 0.7	–1.5 ± 0.7	–1.6 ± 0.8	–1.5 ± 0.7
Trabecular bone score	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1
FRAX major osteoporotic fracture, %	9.9 ± 4.0	9.5 ± 4.2	9.9 ± 4.1	9.1 ± 4.2
FRAX hip fracture, %	1.3 ± 1.7	1.2 ± 1.4	1.2 ± 1.2	1.2 ± 1.6
Bone biomarkers				
CTx, ng/mL	0.48 ± 0.20	0.42 ± 0.22	0.41 ± 0.20	0.43 ± 0.23
P1NP, ng/mL	76.2 ± 22.8	66.1 ± 23.7	65.5 ± 22.6	66.6 ± 25.0
IGF-1, ng/mL	126.4 ± 40.0	122.8 ± 39.8	123.0 ± 42.9	123.0 ± 36.7
25(OH)D_3, ng/mL	37.1 ± 14.7	35.3 ± 11.5	35.7 ± 12.0	35.0 ± 11.0
Exercise				
Weekly exercise, min	321.2 ± 268.5	278.0 ± 221.8	276.6 ± 222.6	279.4 ± 222.3
High-impact loading, min	1.2 ± 10.5	0.1 ± 0.8	0.0 ± 0.0	0.1 ± 1.1
Odd-impact loading, min	6.8 ± 30.6	12.7 ± 42.8	7.9 ± 33.1	17.6 ± 50.7
High-magnitude loading, min	43.5 ± 7	16.8 ± 41.7	15.0 ± 38.6	18.8 ± 44.9
Repetitive low-impact loading, min	164.0 ± 178.1	173.0 ± 142.0	184.0 ± 152.3	161.0 ± 130.3
Nonimpact loading, min	84.9 ± 203.1	46.1 ± 97.8	50.8 ± 120.1	41.2 ± 67.8
Diet				
Kilocalories	1837.6 ± 429	1737.4 ± 490.3	1767.0 ± 546.9	1696.6 ± 401.9
Protein, g	78.3 ± 19.7	71.1 ± 19.6	71.8 ± 18.6	70.2 ± 21.1
Carbohydrate, g	206.4 ± 69.9	194.4 ± 56.6	193.5 ± 56.7	195.5 ± 57.2
Fat, g	75.5 ± 23.5	73.0 ± 30.4	76.0 ± 36.1	68.8 ± 20.0
Health history, %				
Previous hysterectomy				
No	89.7	84.7	83.5	85.9
Yes	10.3	15.3	16.5	14.1
Previous oophorectomy				
No	92.3	86.0	84.8	87.2
Yes	7.7	14.0	15.2	12.8
Previous hormone therapy use				
No	78.2	74.4	73.4	75.3
Yes	21.8	25.6	26.6	24.7
Previous osteoporosis medication use				
No	82.1	83.4	81.0	85.9
Yes	17.9	16.6	19.0	14.1

(*Continued*)

TABLE 1 (*Continued*)

Characteristic	Control ($n = 78$)	Prune ($n = 157$)	50 g Prune ($n = 79$)	100 g Prune ($n = 78$)
Previous smoker				
No	76.6	79.6	78.5	80.8
Yes	23.4	20.4	21.5	19.2
Menopause STRAW + 10 classification[3]				
Early	37.2	33.1	35.4	30.8
Late	62.8	66.9	64.6	69.2

[1]Values are presented as mean ± SD unless otherwise indicated. BMI classification was scored as follows: normal, 18.5 < BMI < 24.9; overweight, 25 < BMI < 29.9; obese, BMI >30. BMD classification was scored as follows: normal, T-score <–1.5; osteopenia, –1.5 < T-score <–2.5; osteoporosis, T-score <–2.5. BMD, bone mineral density; CTx, C-terminal telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type I procollagen; IGF-1, insulin-like growth factor 1; $25(OH)D_3$, serum 25-hydroxyvitamin D.

[2]One participant was classified as underweight (BMI <18.5) for BMI in the 100-g prune group.

[3]STRAW + 10 classification is based on Harlow et al. (31), where "early" menopause is characterized as being less than 8 y from menopause and "late" menopause if characterized as >8 y from menopause.

BMD outcomes: main ITT analysis.

50-g prune compared with control groups. A group × time interaction for total hip BMD was observed when comparing control with the 50-g prune group ($P = 0.017$; Table 2), where the control group experienced a decreased total hip BMD at both the 6- and 12-mo/post intervention time points compared with baseline (both $P < 0.05$), while the 50-g prune group preserved BMD at both the 6- and 12-mo/post intervention time points. In the completers of the full 12-mo intervention, there was a significant difference in percent change in total hip BMD when comparing the control with the 50-g prune groups [–1.1 ± 0.2% compared with –0.27 ± 0.2%, $P = 0.011$; effect size: –0.442 (–0.780, –0.101)] (**Figure 3**G). Although femoral neck BMD decreased with time in both groups, other BMD outcomes remained unchanged (all $P > 0.05$) during the intervention in the control compared with the 50-g prune groups (Table 2).

100-g prune compared with control groups. A group × time interaction for FRAX major osteoporotic fracture risk was observed when comparing control compared with the 100-g prune groups ($P = 0.030$; Table 3, **Figure 4**C), where the control group experienced an increased risk at the 6-mo time point. There was no group × time interaction for total hip BMD when comparing the control with the 100-g prune groups ($P = 0.287$; Table 3). In the participants who completed the full 12-mo intervention, there was no difference in percent change in total hip BMD for the control compared with the 100-g prune groups [–1.1 ± 0.2% compared with –0.23 ± 0.4%, $P = 0.131$; effect size: –0.391 (–0.768, –0.012)] (Figure 3C). Other BMD outcomes remained unchanged (all $P > 0.05$) during the intervention in the control compared with the 100-g prune groups (Table 3).

Pooled prune compared with control groups. When comparing the control compared with pooled (50 g + 100 g) prune groups, a group × time interaction for FRAX hip fracture risk ($P = 0.038$; Table 4) indicated that the control group demonstrated an increase in the risk of hip fracture at 6 mo compared with baseline ($P < 0.05$), whereas the pooled prune groups maintained FRAX hip fracture risk throughout the 12-mo intervention. Additionally, a group × time interaction for FRAX major osteoporotic fracture risk ($P = 0.027$; Table 4) indicated that the control group demonstrated an increase in the risk of major osteoporotic fracture at 6 and 12 mo compared with baseline (both $P < 0.05$), whereas the pooled prune groups maintained fracture risk throughout the 12-mo intervention. A group × time interaction tended to be significant for total hip BMD ($P = 0.051$; Table 4). To account for baseline group BMD categorization differences, models were run with T-score BMD group as a covariate, which did not change the current findings. In the participants who completed the full 12-mo intervention, the control group lost 1.1 ± 0.2% BMD at the total hip compared with the pooled prune group, who lost 0.25 ± 0.2% [$P = 0.007$; effect size: –0.415 (–0.716, –0.112)]. Total body and lumbar L1–L4 spine BMD remained unchanged (all $P > 0.05$) during the intervention in the control compared with pooled prune groups analyses. Similarly, percent changes in T-scores for total body, lumbar L1–L4 spine, total hip, and femoral neck were not significantly different for the control compared with pooled prune groups analyses (all $P > 0.05$).

Subanalysis of participants with low BMD by T-score. There was a group × time interaction for total hip BMD ($P = 0.035$; Supplemental Table 2) when comparing control with 50-g prune groups with low BMD, such that control participants with low BMD decreased hip BMD at 6- and 12-mo time points (both $P < 0.05$). There was a group × time interaction for FRAX major osteoporotic fracture risk when comparing control with 100-g prune groups ($P = 0.030$; Supplemental Table 3), indicating that the control group experienced an increase risk at the 6-mo time point compared with baseline ($P < 0.05$), whereas the 100-g prune group did not. There were group × time interactions for total hip BMD ($P = 0.017$; Supplemental Table 4) and FRAX major osteoporotic fracture risk ($P = 0.040$; Supplemental Table 4) when comparing control with pooled prune groups with low BMD, such that control participants with low BMD worsened at 6- and 12-mo time points (all $P < 0.05$).

Bone biomarkers and hormone outcomes: main ITT analysis.

50-g prune compared with control groups. The 50-g prune and control groups had increases in IGF-1 and serum $25(OH)D_3$ concentrations (main effect of time, all $P < 0.05$; Table 2). A decrease in P1NP concentration was observed in both the 50-g and control groups (main effect of time, $P = 0.036$), and the 50-g group had lower P1NP concentrations compared with the

TABLE 2 Analysis for control compared with 50-g prune groups: estimated marginal means for body composition, bone mineral density, bone biomarkers, and hormones[1]

	Control			50 g Prune			*P* values		
Characteristic	Baseline ($n = 78$)	6 mo ($n = 71$)	Post ($n = 70$)	Baseline ($n = 79$)	6 mo ($n = 69$)	Post ($n = 67$)	Group	Time	Group * time
Body composition									
Body mass, kg	67.7 ± 0.2	68.0 ± 0.2	67.9 ± 0.2	67.9 ± 0.2	67.9 ± 0.2	67.9 ± 0.2	0.776	0.676	0.916
Fat mass, kg	27.3 ± 0.4	27.6 ± 0.4	27.6 ± 0.4	27.8 ± 0.4	28.1 ± 0.4	28.0 ± 0.4	0.345	0.164	0.949
Body fat, %	40.2 ± 0.5	40.4 ± 0.5	40.7 ± 0.5	41.1 ± 0.5	41.5 ± 0.5	41.5 ± 0.5	0.182	0.030	0.757
Bone mineral density									
Total body BMD, g/cm^2	1.054 ± 0.009	1.051 ± 0.009	1.053 ± 0.009	1.046 ± 0.009	1.048 ± 0.009	1.045 ± 0.009	0.623	0.880	0.295
Lumbar L1–L4 BMD, g/cm^2	0.879 ± 0.011	0.873 ± 0.011	0.874 ± 0.011	0.885 ± 0.011	0.886 ± 0.011	0.882 ± 0.011	0.557	0.201	0.332
Total hip BMD, g/cm^2	0.807 ± 0.009	0.801 ± 0.009[2]	0.798 ± 0.009[2]	0.804 ± 0.009	0.803 ± 0.009	0.801 ± 0.009	0.961	<0.001	0.017
Femoral neck BMD, g/cm^2	0.678 ± 0.008	0.671 ± 0.008	0.672 ± 0.008	0.670 ± 0.009	0.668 ± 0.009	0.666 ± 0.009	0.627	0.005	0.206
Trabecular bone score	1.325 ± 0.011	1.314 ± 0.011	1.318 ± 0.011	1.322 ± 0.008	1.324 ± 0.008	1.319 ± 0.008	0.853	0.316	0.268
FRAX–major osteoporotic fracture risk, %	9.8 ± 0.5	10.3 ± 0.5	10.0 ± 0.5	9.9 ± 0.5	10.0 ± 0.5	10.2 ± 0.5	0.983	0.004	0.109
FRAX–hip fracture risk, %	1.2 ± 0.2	1.4 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.691	0.057	0.179
Bone biomarkers and hormones									
CTx, ng/mL	0.5 ± 0.0	—	0.5 ± 0.0	0.4 ± 0.0	—	0.4 ± 0.0	0.051	0.362	0.903
P1NP, ng/mL	76.2 ± 2.8	—	73.8 ± 2.8	65.5 ± 2.8	—	62.2 ± 2.9	0.004	0.036	0.752
IGF-1, ng/mL	128.3 ± 4.5	—	136.9 ± 4.5	122.2 ± 4.5	—	125.2 ± 4.6	0.145	0.005	0.178
25(OH)D_3, ng/mL	36.0 ± 1.7	—	45.7 ± 1.7	37.0 ± 1.7	—	43.7 ± 1.8	0.709	<0.001	0.291
Exercise									
Exercise, min/wk	295.3 ± 23.9	254.1 ± 25.5	248.7 ± 24.9	253.2 ± 24.7	260 ± 26.2	279.4 ± 26.3	0.948	0.639	0.126
High-impact loading, min/wk	1.2 ± 0.5	0.0 ± 0.6	0.0 ± 0.6	0.0 ± 0.5	0.0 ± 0.6	0.0 ± 0.6	0.427	0.431	0.445
Odd-impact loading, min/wk	6.8 ± 5.0	17.9 ± 5.3	14.4 ± 5.1	8.6 ± 5	4.9 ± 5.4	5.4 ± 5.4	0.282	0.570	0.088
High-magnitude loading, min/wk	42.1 ± 6.2	30.3 ± 6.5[2]	20.8 ± 6.3	16.5 ± 6.2	12.4 ± 6.7	14.8 ± 6.6	0.037	0.009	0.036
Repetitive loading, min/wk	155.9 ± 19.2	149.1 ± 20.6	175.8 ± 20	183.8 ± 19.4	199.6 ± 21.3	213.1 ± 20.9	0.090	0.219	0.759
Nonimpact loading, min/wk	86.7 ± 15.1	54.0 ± 16.2	67.1 ± 15.7	42.8 ± 15.3	39.6 ± 16.7	48.2 ± 16.4	0.155	0.313	0.386
Diet									
Calories, kcal	1840.5 ± 60.4	—	1830.7 ± 61.6	1794.2 ± 64	—	1791.8 ± 64.3	0.592	0.877	0.925
Protein, g	78.1 ± 2.4	—	77.3 ± 2.5	72.9 ± 2.6	—	70.8 ± 2.6	0.059	0.404	0.707
Carbohydrate, g	206.6 ± 7.9	—	211.3 ± 8.1	193.8 ± 8.4	—	212.8 ± 8.5	0.580	0.039	0.210
Fat, g	75.7 ± 3.5	—	74.1 ± 3.6	77.9 ± 3.7	—	71.8 ± 3.8	0.990	0.109	0.341

[1]General linear mixed-effects models were run and values are estimated marginal mean ± SEM. BMD, bone minderal density; CTx, C-terminal telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type I procollagen; IGF-1, insulin-like growth factor-1; 25(OH)D_3, 25-hydroxyvitamin D.

[2]Significantly different than baseline ($P < 0.05$).

TABLE 3 Analysis for control compared with 100-g prune groups: estimated marginal means for body composition, bone mineral density, bone biomarkers, and hormones[1]

	Control			100 g Prune			*P* values		
Characteristic	Baseline ($n = 78$)	6 mo ($n = 71$)	Post ($n = 70$)	Baseline ($n = 78$)	6 mo ($n = 58$)	Post ($n = 46$)	Group	Time	Group * time
Body composition									
Body mass, kg	67.3 ± 0.2	67.5 ± 0.2	67.4 ± 0.2	67.3 ± 0.2	68.1 ± 0.3	67.2 ± 0.3	0.446	0.029	0.190
Fat mass, kg	27.0 ± 0.3	27.3 ± 0.3	27.3 ± 0.3	27.2 ± 0.4	28 ± 0.4	27.3 ± 0.4	0.519	0.003	0.081
Body fat, %	40.0 ± 0.5	40.3 ± 0.5	40.6 ± 0.5	40.7 ± 0.5	41.4 ± 0.5	41.0 ± 0.5	0.282	0.003	0.144
Bone mineral density									
Total body BMD, g/cm^2	1.053 ± 0.01	1.049 ± 0.01	1.052 ± 0.01	1.069 ± 0.011	1.067 ± 0.011	1.067 ± 0.011	0.265	0.375	0.839
Lumbar L1–L4 BMD, g/cm^2	0.875 ± 0.012	0.870 ± 0.012	0.871 ± 0.012	0.923 ± 0.013	0.923 ± 0.013	0.921 ± 0.013	0.003	0.379	0.556
Total Hip BMD, g/cm^2	0.805 ± 0.008	0.799 ± 0.008	0.796 ± 0.008	0.814 ± 0.009	0.809 ± 0.009	0.810 ± 0.009	0.360	<0.001	0.287
Femoral neck BMD, g/cm^2	0.675 ± 0.008	0.668 ± 0.008	0.669 ± 0.008	0.687 ± 0.009	0.686 ± 0.009	0.685 ± 0.009	0.191	0.024	0.278
Trabecular bone score	1.327 ± 0.010	1.314 ± 0.011	1.318 ± 0.011	1.339 ± 0.008	1.336 ± 0.008	1.341 ± 0.008	0.189	0.211	0.428
FRAX–major osteoporotic fracture risk, %	9.8 ± 0.5	10.3 ± 0.5[2]	10.1 ± 0.5	9.2 ± 0.5	9.1 ± 0.5	9.0 ± 0.5	0.152	0.137	0.030
FRAX–hip fracture risk, %	1.3 ± 0.2	1.4 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.2	0.539	0.279	0.061
Bone biomarkers and hormones									
CTx, ng/mL	0.5 ± 0.0	—	0.5 ± 0.0	0.4 ± 0.0	—	0.4 ± 0.0	0.150	0.451	0.847
P1NP, ng/mL	76.2 ± 2.8	—	73.8 ± 2.9	68.9 ± 3.2	—	62.9 ± 3.4	0.025	0.012	0.268
IGF-1, ng/mL	128.3 ± 4.5	—	136.9 ± 4.6	122.6 ± 4.9	—	125 ± 5.2	0.172	0.019	0.181
25(OH)D_3, ng/mL	36.6 ± 1.6	—	45.9 ± 1.7	35.9 ± 1.8	—	43.3 ± 1.9	0.233	<0.001	0.387
Exercise									
Exercise, min/wk	295.3 ± 23.3	256 ± 25.1	249.1 ± 24.5	243.3 ± 25.7	227.8 ± 28.2	272.7 ± 29.1	0.500	0.402	0.183
High-impact loading, min/wk	1.2 ± 0.6	0.0 ± 0.6	0.0 ± 0.6	0.2 ± 0.6	0.0 ± 0.7	0.0 ± 0.7	0.562	0.415	0.611
Odd-impact loading, min/wk	6.6 ± 6.5	17.7 ± 6.9	14.2 ± 6.7	20.8 ± 7.1	12.6 ± 7.6	18.1 ± 7.9	0.617	0.859	0.106
High-magnitude loading, min/wk	42.3 ± 7.1	30.7 ± 7.5	21.3 ± 7.3[2]	22.0 ± 7.7	29.5 ± 8.3	25.7 ± 8.6	0.533	0.231	0.041
Repetitive loading, min/wk	153.7 ± 18.6	147.7 ± 20.1	173.7 ± 19.4	163.6 ± 20.3	140.9 ± 22.5	191.8 ± 23.5	0.748	0.090	0.771
Nonimpact loading, min/wk	87.7 ± 15.0	55.1 ± 16.1	68.1 ± 15.6	38.6 ± 16.4	53.5 ± 18	33.5 ± 18.7	0.132	0.577	0.146
Diet									
Calories, kcal	1842.7 ± 51.7	—	1836.8 ± 53	1686 ± 63.8	—	1773.2 ± 64.3	0.592	0.877	0.925
Protein, g	78.3 ± 2.4	—	77.5 ± 2.5	69.6 ± 3.0	—	68.6 ± 3.0	0.007	0.670	0.966
Carbohydrate, g	206.9 ± 8.7	—	212.1 ± 8.9	195.2 ± 10.7	—	231.9 ± 10.8[2]	0.729	0.007	0.041
Fat, g	75.8 ± 2.7	—	74.4 ± 2.7	68.1 ± 3.3	—	65.1 ± 3.3	0.022	0.306	0.715

[1]General linear mixed-effects models were run and values are estimated marginal mean ± SEM. BMD, bone minderal density; CTx, C-terminal telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type I procollagen; IGF-1, insulin-like growth factor-1; 25(OH)D_3, 25-hydroxyvitamin D.

[2]Significantly different than baseline ($P < 0.05$).

TABLE 4 Estimated marginal means for body composition, bone mineral density, bone biomarkers, and hormones for control compared with pooled prune study groups[1]

	Control			Pooled 50 g + 100 g prune			*P* values		
Characteristic	Baseline ($n = 78$)	6 mo ($n = 71$)	Post ($n = 70$)	Baseline ($n = 157$)	6 mo ($n = 127$)	Post ($n = 113$)	Group	Time	Group * time
Body composition									
Body mass, kg	67.8 ± 0.2	68.0 ± 0.2	67.9 ± 0.2	67.9 ± 0.2	68.3 ± 0.2	67.9 ± 0.2	0.578	0.154	0.662
Fat mass, kg	27.3 ± 0.3	27.6 ± 0.4	27.7 ± 0.3	27.7 ± 0.3	28.3 ± 0.3	27.9 ± 0.3	0.287	0.013	0.388
Body fat, %	40.2 ± 0.5	40.4 ± 0.5	40.7 ± 0.5	41.1 ± 0.4	41.6 ± 0.4	41.4 ± 0.4	0.117	0.002	0.310
Bone mineral density									
Total body BMD, g/cm^2	1.054 ± 0.009	1.051 ± 0.009	1.053 ± 0.009	1.055 ± 0.007	1.055 ± 0.007	1.054 ± 0.007	0.859	0.549	0.429
Lumbar L1–L4 BMD, g/cm^2	0.878 ± 0.012	0.873 ± 0.012	0.874 ± 0.012	0.903 ± 0.009	0.903 ± 0.009	0.900 ± 0.009	0.063	0.201	0.329
Total hip BMD, g/cm^2	0.807 ± 0.008	0.801 ± 0.009	0.798 ± 0.008	0.810 ± 0.006	0.807 ± 0.006	0.806 ± 0.006	0.612	<0.001	0.051
Femoral neck BMD, g/cm^2	0.678 ± 0.008	0.670 ± 0.008	0.671 ± 0.008	0.679 ± 0.006	0.677 ± 0.006	0.675 ± 0.006	0.702	0.003	0.173
Trabecular bone score	1.325 ± 0.011	1.313 ± 0.011	1.317 ± 0.011	1.329 ± 0.008	1.328 ± 0.008	1.327 ± 0.008	0.462	0.153	0.270
FRAX–major osteoporotic fracture risk, %	9.8 ± 0.5	10.3 ± 0.5[2]	10.1 ± 0.5	9.6 ± 0.4	9.6 ± 0.4	9.7 ± 0.4	0.483	0.006	0.027
FRAX–hip fracture risk, %	1.2 ± 0.2	1.4 ± 0.2[2]	1.3 ± 0.2	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.559	0.045	0.038
Bone biomarkers and hormones									
CTx, ng/mL	0.5 ± 0.0	—	0.5 ± 0.0	0.4 ± 0.0	—	0.4 ± 0.0	0.046	0.358	0.841
P1NP, ng/mL	76.1 ± 2.8	—	73.7 ± 2.8	67.2 ± 2.1	—	62.7 ± 2.2	0.003	0.006	0.388
IGF-1, ng/mL	127.8 ± 4.3	—	137.1 ± 4.4	122.7 ± 3.2	—	125.4 ± 3.3	0.103	<0.001	0.073
25(OH)D_3, ng/mL	36.2 ± 1.6	—	45.6 ± 1.6	36.2 ± 1.2	—	43.3 ± 1.2	0.329	<0.001	0.262
Exercise									
Exercise, min/wk	295.8 ± 23.2	255.2 ± 24.8	249.3 ± 24.2	246.8 ± 17.4	244.2 ± 18.8	275.2 ± 19.1	0.632	0.413	0.068
High-impact loading, min/wk	1.2 ± 0.5	0.0 ± 0.5	0.0 ± 0.5	0.1 ± 0.3	0.0 ± 0.4	0.0 ± 0.4	0.312	0.183	0.275
Odd-impact loading, min/wk	6.8 ± 5.6	17.8 ± 5.9	14.3 ± 5.8	14.1 ± 4.2	8.5 ± 4.5	11.1 ± 4.5	0.781	0.653	0.031
High-magnitude loading, min/wk	42.2 ± 6.2	30.6 ± 6.6	21.1 ± 6.4[2]	18.2 ± 4.6	19.7 ± 5.0	19.2 ± 5.0	0.071	0.026	0.012
Repetitive loading, min/wk	155.2 ± 19.4	148.6 ± 21.0	175.1 ± 20.2	173.1 ± 14.4	170.8 ± 15.9	202.4 ± 16.0	0.255	0.088	0.942
Nonimpact loading, min/wk	87.1 ± 13.5	54.5 ± 14.5	67.5 ± 14.1	41.3 ± 10.0	46.3 ± 11.0	42.4 ± 11.1	0.061	0.310	0.127
Diet									
Calories, kcal	1841.4 ± 58.7	—	1832.2 ± 60	1749.3 ± 47.2	—	1784.8 ± 47.5	0.295	0.721	0.544
Protein, g	78.3 ± 2.4	—	77.5 ± 2.5	71.5 ± 1.9	—	69.9 ± 2	0.009	0.444	0.793
Carbohydrate, g	206.6 ± 8.5	—	211.5 ± 8.7	194.5 ± 6.8	—	220.9 ± 6.9	0.888	0.008	0.065
Fat, g	75.7 ± 3.3	—	74.2 ± 3.4	73.9 ± 2.6	—	69.1 ± 2.7	0.356	0.117	0.418

[1]General linear mixed-effects models were run and values are estimated marginal mean ± SEM. BMD, bone minderal density; CTx, C-terminal telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type I procollagen; IGF-1, insulin-like growth factor-1; 25(OH)D_3, 25-hydroxyvitamin D.

[2]Significantly different than baseline ($P < 0.05$).

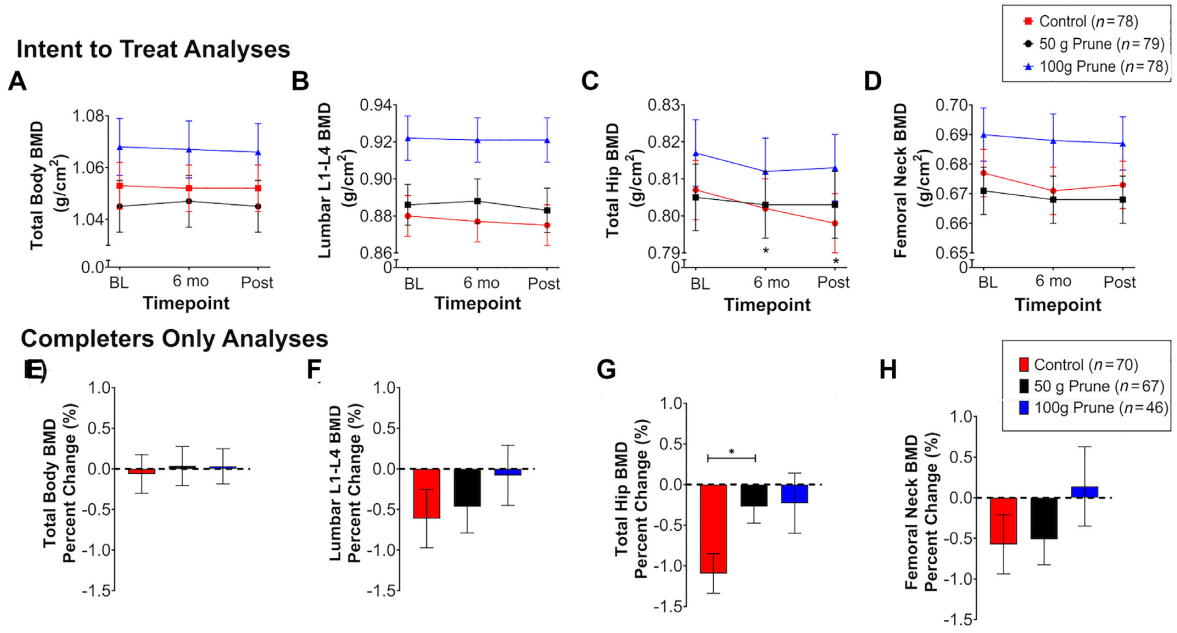

FIGURE 3 Estimated marginal means for intent-to-treat analyses (A–D) and percent changes for completers-only analyses (E–H) for bone mineral density (BMD) outcomes for baseline (BL), 6 mo (6 mo), and post intervention time points. Control compared with 50-g prune analysis indicated a significant (∗) group × time interaction for total hip BMD, where the control group was different from baseline ($P < 0.05$). Control compared with 100-g prune analysis did not indicate group × time interactions for BMD outcomes. Control compared with 50-g prune analysis indicated a significant difference (∗$P = 0.01$) in percent change of total hip BMD. Control compared with 100-g prune analysis did not indicate group differences in percent change of BMD outcomes. Samples sizes for each group and time point are as follows: at baseline: control, $n = 78$; 50 g prune, $n = 79$; 100 g prune, $n = 78$. At 6 mo: control, $n = 71$; 50 g prune, $n = 69$; 100 g prune, $n = 58$. At postintervention: control, $n = 70$; 50 g prune, $n = 67$; 100 g prune, $n = 46$. For those who completed the entire intervention, the sample size is as follows: control, $n = 70$; 50 g prune, $n = 67$; 100 g prune, $n = 46$.

control group throughout the intervention (main effect of group, $P = 0.004$).

100-g prune compared with control groups. The 100-g prune and control groups had increases in IGF-1 and serum 25(OH)D_3 concentrations (main effect of time, all $P < 0.05$; Table 3). A decrease in P1NP concentration was observed in both 100-g and control groups (main effect of time, $P = 0.012$), and the 100-g group had lower P1NP concentrations compared with the control group throughout the intervention (main effect of group, $P = 0.025$).

Pooled prune compared with control groups. When comparing the control with pooled prune groups, concentrations of IGF-1 and serum 25(OH)D_3 increased in both the pooled prune and control groups (main effect of time, $P < 0.001$; Table 4).

Subanalysis of participants with low BMD by T-score. P1NP concentrations were higher in the control group compared with the 50-g prune groups ($P < 0.05$, Supplemental Table 2) and pooled prune groups ($P < 0.05$, Supplemental Table 4). IGF-1 and serum 25(OH)D_3 concentrations increased over time (all $P < 0.01$), regardless of group comparison (Supplemental Tables 2–4), in participants with low BMD.

Diet and exercise outcomes: main ITT analysis.

50-g prune compared with control groups. There was a group × time interaction for minutes of high-magnitude loading exercise ($P = 0.036$, Table 2) when comparing control with 50-g prune groups, where the control group decreased at 6- and 12-mo time points compared with baseline (both $P < 0.05$). All other exercise and diet characteristics remained unchanged (group × time effects all $P > 0.05$) during the intervention in the control compared with the 50-g prune groups analyses.

100-g prune compared with control groups. There was a group × time interaction for minutes of high-magnitude loading exercise ($P = 0.041$, Table 3) when comparing control with 100-g prune groups, where the control group decreased at 12-mo time points compared with baseline ($P < 0.05$). There was a group × time interaction for carbohydrate intake ($P = 0.041$, Table 3) when comparing control with 100-g prune groups, where the 100-g prune group increased at the 12-mo time point compared with baseline ($P < 0.05$). All other exercise and diet characteristics remained unchanged (group × time effects all $P > 0.05$) during the intervention in the control compared with the 100-g prune groups analyses.

Pooled prune compared with control groups. There was a group × time interaction for minutes of high-magnitude loading exercise ($P = 0.012$, Table 4) when comparing control with pooled prune groups, where the control group decreased at the 12-mo time point compared with baseline ($P < 0.05$). There was a group × time interaction for odd impact loading ($P = 0.031$, Table 4) when comparing control with pooled prune groups, but there was no post hoc significance ($P > 0.05$). All other exercise and diet characteristics remained unchanged (group × time effects all $P > 0.05$) during the intervention in the control compared with pooled groups analyses.

Subanalysis of participants with low BMD by T-score. There were group × time interactions for minutes of high-magnitude loading exercise when comparing control with the 50-g prune

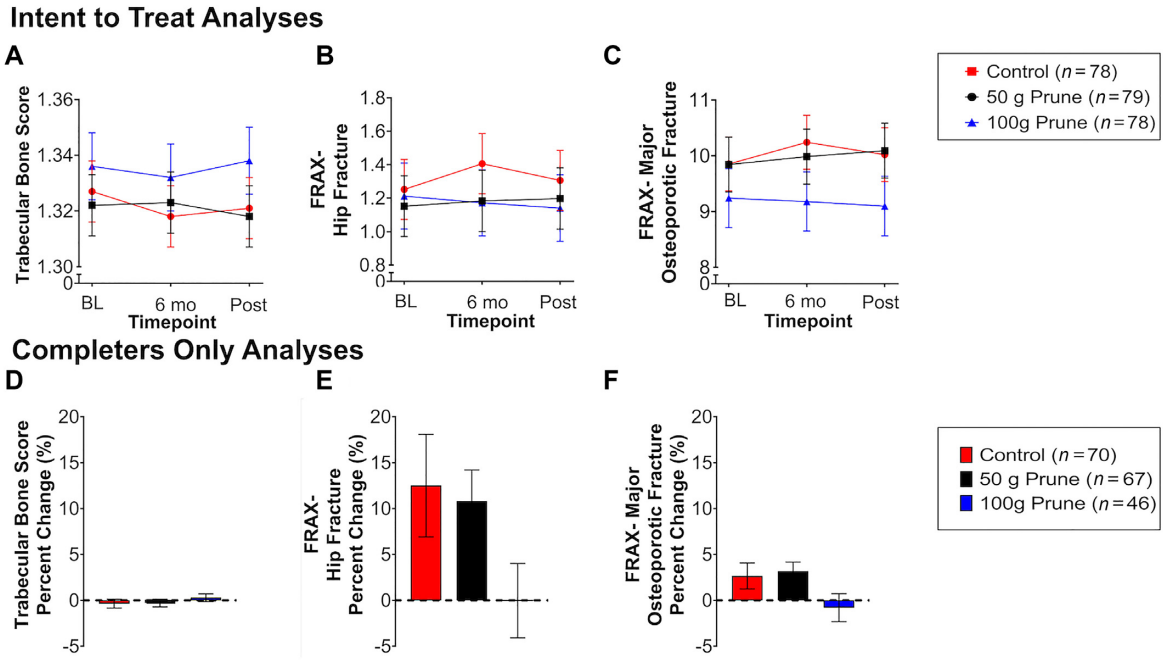

FIGURE 4 Estimated marginal means for intent-to-treat analyses (A–C) and percent changes for completers-only analyses (D–F) for trabecular bone score and FRAX outcomes. Control compared with 100-g prune analysis indicated a significant (∗) group × time interaction for FRAX major osteoporotic fracture risk, where the control group was different from baseline ($P < 0.05$). Samples sizes for each group and time point are as follows: At baseline: control, $n = 78$; 50 g prune, $n = 79$; 100 g prune, $n = 78$. At 6 mo: control, $n = 71$; 50 g prune, $n = 69$; 100 g prune, $n = 58$. At post intervention: control, $n = 70$; 50 g prune, $n = 67$; 100 g prune, $n = 46$. For those who completed the entire intervention, the sample size is as follows: control, $n = 70$; 50 g prune, $n = 67$; 100 g prune, $n = 46$.

groups ($P = 0.039$, Supplemental Table 2), control compared with the 100-g prune groups ($P = 0.041$, Supplemental Table 3), and control compared with pooled prune groups ($P = 0.010$, Supplemental Table 4), where control participants decreased this type of exercise over time. There were group × time interactions for carbohydrate intake when comparing control with 100-g prune groups ($P = 0.017$, Supplemental Table 3) and control compared with pooled prune groups ($P = 0.031$, Supplemental Table 4), where the prune groups increased carbohydrate intake over time.

Discussion

To our knowledge, this is the first RCT to test the effects of 2 doses (50 g and 100 g) of prune consumption for 12 mo in postmenopausal women. Herein, we demonstrate that a 50-g dose of daily prune consumption can prevent loss of BMD at the total hip region in postmenopausal women with T-scores between 0.0 and –3.0 after just 6 mo of daily consumption. These positive effects at 6 mo persisted throughout the 12-mo study. Due to a higher than expected dropout rate in the 100-g prune group, investigation of the 100-g dose of prunes had reduced power to detect differences in total hip compared with the control group. However, even if the 100-g prune dosage was as effective as the lower 50-g dosage, the compliance to this 100-g dosage was poor and associated with a significantly higher dropout rate, suggesting limited feasibility of this dose. Notably, compliance to the 50-g dose of prune consumption was >90% in our sample of postmenopausal women and the dropout rate was comparable to that observed in women taking calcium and vitamin D_3 in the control group in our study, and it exceeded that observed in the Women's Health Initiative (WHI) calcium and vitamin D trial (32). Supportive of our compliance data, urinary analysis showed that phenolic metabolite hippuric acid concentrations were greater in the prune groups compared with the control group, findings that provide further evidence of successful incorporation of prunes into participant diets. As such, we underscore that although a 100-g daily dose of prune consumption for 12 mo was not tolerable for the 12-mo study duration, a 50-g dose was met with preservation of bone at the total hip and very good compliance. Specifically, BMD declined by 1.1% in the control group, whereas in the 50-g prune group, there was no change from baseline values. In fact, calculations of TBS-adjusted FRAX scores indicate that although hip fracture risk worsened in the control group at 6 mo, the FRAX score was maintained in the pooled (50 g + 100 g) prune groups, indicating that prunes prevented the 6-mo increase in the risk of fracture. Because the primary aim of treatments for osteoporosis and low BMD is to reduce fragility fracture risk (33), and the use of TBS-adjusted FRAX scores has been supported by the ISCD in postmenopausal women (34, 35), these findings provide an informative metric for a population of individuals at increased fracture risk.

The 2021 position stand from the North American Menopause Society clearly states that postmenopausal bone loss is a key strategy to combat osteoporosis and its complications from fractures (36). The pharmacologic industry has been met with a long history of poor compliance to pharmacologic therapies to mitigate bone loss (37, 38). For example, in a large multicenter

study of >18,000 women on various drugs for postmenopausal osteoporosis, ~75% of the women were nonadherent within 12 mo and almost 50% had discontinued therapy within 21 mo (37). In contrast, we had high retention of participants (85%) consuming 50 g of prunes daily, and compliance in this group exceeded 90%. This is consistent with a 6-mo investigation, which indicated 100% retention and 95% compliance for 50 g prunes/d (21), but other studies that attempted a 100-g daily prune dosage reported reduced compliance (~82%) and high dropout rates (18, 20), which is consistent to the high dropout rate of 41% observed in our 100-g group. Indeed, the dropout rate for 100 g prunes daily was 31% in a 3-mo study (20) and 37.5% in a 12-mo study (18). As such, our findings suggest that 50 g of daily prune consumption, in conjunction with calcium + vitamin D_3 supplementation, may be a well-tolerated nonpharmacologic strategy that preserves bone at a site important for fracture prevention, the total hip. In fact, it may be prudent to recommend prune therapy for women on pharmacologic therapy who require a drug-free holiday (39) and who can benefit from preservation of bone at the hip with daily consumption of 50 g prunes, as there are no adverse effects to low-dose prune consumption. However, the magnitude of the effect of prune treatment on bone density is not comparable to osteoporosis medication.

Our data extend the findings of smaller RCTs (18–20) and specifically addresses how different dosages may affect BMD in postmenopausal women. Our data suggest that the main site of benefit is the total hip, particularly for women consuming 50 g daily. This finding is in contrast to a similar but smaller ($n = 16$) 6-mo study that demonstrated preservation of total body BMD but not other areal BMD sites (21). In another smaller ($n = 45$) 12-mo RCT of 100 g prunes compared with dried apples (75 g/d, $n = 55$), prune consumption was associated with a significant increase in ulnar and lumbar spine BMD, but not total body or hip (18). However, it is difficult to interpret this study because traditional data of the BMD results expressed as g/cm^2 were not presented and the use of a control group consuming dried apples was not ideal because it is established that phenolics in apple, like prunes, also have bone bioactive phenolics like chlorogenic acid (40).

The last year of study data collection occurred during the COVID-19 pandemic and subsequent university shutdown, which required us to shut down out laboratory. As such, we investigated whether prolonged study duration for the participants ($n = 23$) affected by the shutdown affected the primary BMD outcomes. A sensitivity analysis was performed by removing these subjects (data not shown), which demonstrated that total hip BMD and TBS-adjusted FRAX findings remained significant and therefore do not appear to be influencing the increased study duration. Additionally, fat mass and body fat percentage increased over the course of the study, regardless of treatment group, indicating that prune treatment did not negatively contribute to body composition changes over the 12-mo study, despite a significant increase in carbohydrates intake in the 100-g prune group. Although this study cannot confirm the cause of this increase, it is plausible to suggest that aging could contribute to this increase in body fat. Regarding exercise characteristics, although overall weekly exercise minutes did not change during the study, the control group did decrease the minutes of weekly high-magnitude loading exercise. Even when accounting for this change in exercise habit, BMD changes at the hip and TBS-adjusted FRAX scores remained significant.

The 2 bone markers recommended by the ISCD to monitor osteoporosis therapy are P1NP for bone formation and CTx for bone resorption, although we did not observe any significant changes in either of these bone biomarkers. We did observe increased IGF-1; however, the increase was observed in all participants and may be secondary to the administration of vitamin D_3 in our intervention, although IGF-1 has been previously observed to increase following prune consumption (12, 20). The 25(OH)D_3 concentrations also increased in all participants after 12 mo in our study, a finding likely secondary to the calcium + vitamin D_3 supplementation prescribed.

Strengths of this investigation include the largest cohort studied to date to explore effects of 2 dosages of prunes and the incorporation of novel compliance measurements, to include total and specific phenolic metabolite assessments not reported in previous prune studies. Although phenolic metabolite hippuric acid concentrations did differ among the prune groups, total phenolic concentrations did not, which may be attributed to background differences in free-living dietary patterns or differential levels of phenolic metabolism by both host and microbial communities. Additional study limitations include the largely Caucasian participant distribution given our location in central Pennsylvania, thereby limiting generalizability. Our study may also have been limited by the 12-mo study duration, which may have limited effect sizes specific to BMD outcomes. Additionally, it may be likely that changes in bone biomarkers could have occurred earlier in the intervention (i.e., at 3 or 6 mo), which was not captured in the current analyses due to funding limitations.

In conclusion, results from this 12-mo RCT to test the effects of 2 doses of prune consumption on bone health in postmenopausal women demonstrated the effectiveness of a 50-g dose to preserve BMD at the total hip region during a time in life where the loss of bone averages ~1% per year (41). Although FRAX hip fracture risk worsened in the control group, the FRAX score was maintained in the pooled (50 g + 100 g) prune groups, indicating that prunes prevented an increase in the risk of fracture after 12 mo of treatment. The results of this investigation provide compelling evidence of the long-term efficacy of daily prune consumption. Given the high compliance and retention at the 50-g dosage over 12 mo, a moderate dosage of daily prune consumption represents a valuable nonpharmacologic treatment strategy that can be used to preserve bone mass at the hip in postmenopausal women and possibly reduce the risk of hip fracture, which is the primary goal for treatment of low BMD. This RCT represents the largest trial demonstrating the positive impact of a dietary phenolic-rich food that can be used to improve bone health in postmenopausal women.

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