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Influence of daily fresh pear consumption on biomarkers of cardiometabolic health in middle-aged/older adults with metabolic syndrome: a randomized controlled trial

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Previous research suggests potential for fresh pears as a functional food for promoting cardiometabolic health. The purpose of this randomized, open-label, placebo-controlled, crossover clinical trial was to evaluate the influence of daily fresh pear consumption on blood pressure (primary outcome) and other biomarkers of cardiometabolic health in middle-aged/older adults with metabolic syndrome (MetS). Forty men and women aged 45–65 years with MetS were included and randomly assigned to receive either two medium-sized fresh pears (Pear) or a calorie-matched control drink (Control) per day for each 12-week treatment period, each separated by a 4-week washout period. After 12 weeks of daily fresh pear consumption, systolic blood pressure tended to be reduced (130 ± 2 mmHg *vs.* 134 ± 2 mmHg at baseline, $P = 0.07$) and pulse pressure was significantly reduced (51 ± 1 *vs.* 54 ± 1 at baseline, $P < 0.05$). At 12 weeks, leptin concentrations were lower in the Pear group than Control (52.5 [7.6, 120.5] ng dL^{-1} *vs.* 53.4 [5.0, 120.5] ng dL^{-1}, respectively, $P < 0.05$), and there was a significant group by time interaction ($P < 0.05$). Leptin concentrations were significantly reduced at 12 weeks compared to baseline in the Pear group (52.5 [7.6, 120.5] ng dL^{-1} *vs.* 54.8 [6.4, 120.5] ng dL^{-1} at baseline, $P < 0.05$) but not in the Control group. Waist circumference was significantly reduced at 12 weeks in the Pear group (107.7 ± 2.0 cm *vs.* 108.4 ± 2 cm at baseline, $P < 0.05$) with a trend for a group by time interaction ($P < 0.1$), and significantly lower in the Pear group than Control (108.1 ± 2.0 cm *vs.* 108.8 ± 2 cm, $P < 0.05$) at 6 weeks with a significant group by time interaction ($P < 0.05$). Conversely, values were significantly increased at 6 weeks (108.8 ± 2 cm *vs.* 108.3 ± 2.0 cm at baseline, $P < 0.05$) in the Control group and sustained at 12 weeks. Waist-to-hip ratio was significantly reduced (0.92 ± 0.01 *vs.* 0.93 ± 0.01 at baseline, $P < 0.05$) at 12 weeks in the Pear group, and significantly lower than Control at 6 weeks (0.93 ± 0.01 *vs.* 0.93 ± 0.01, respectively, $P < 0.05$) and 12 weeks (0.92 ± 0.01 *vs.* 0.93 ± 0.01, $P < 0.05$). These findings suggest that daily fresh pear consumption may promote modest improvements in cardiometabolic health in middle-aged/older adults with MetS. This trial was registered at clinicaltrials.gov as NCT02228837.

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1. Introduction

Metabolic syndrome (MetS) is a cluster of cardiometabolic abnormalities including abdominal obesity, atherogenic dyslipidemia, elevated blood pressure and blood glucose levels, and a pro-inflammatory and pro-thrombotic state.[1] Individuals with MetS have an accelerated risk for developing age-related chronic diseases, namely atherosclerotic cardiovascular disease (CVD), type 2 diabetes (T2DM), and non-alcoholic fatty liver disease, as well as all-cause mortality.[2–4] The prevalence of MetS increases with age.[5,6] In fact, data from the National Health and Nutrition Examination Survey (NHANES) 2003–2012 revealed that 35% of all adults and 50% of adults

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aged 60 years and older in the United States (U.S.) have MetS.[6] As the demographic shifts to a more aged population in the U.S. and worldwide, the prevalence of MetS will likely increase. Aside from increasing the risk of chronic disease and mortality, the medical treatments for MetS and its comorbidities are associated with a significant economic burden for affected individuals and the U.S. healthcare system.[7] For these reasons, the identification, examination, establishment, and dissemination of efficacious, safe, cost-effective, and feasible interventions for the prevention and treatment of MetS in aging individuals are needed.

The etiology of MetS is complex and is thought to be multifactorial; however, the predominant risk factors include abdominal obesity and insulin resistance.[1,8] Abdominal obesity is characterized by an accumulation of subcutaneous and visceral adipose tissue. Current knowledge indicates that visceral adipose tissue is the primary driver of the cardiometabolic abnormalities associated with MetS, including insulin resistance.[8] Other contributing factors include physical inactivity, aging, and menopause.[1] Although a poor diet is not considered to be a risk factor for MetS *per se*, it is highly associated with an increased risk for MetS.[1]

Lifestyle interventions including weight loss, a healthy dietary pattern, and regular physical activity are recommended as initial therapies for the treatment of MetS.[1,4] With respect to diet, several evidence-based healthy dietary patterns exist including the Healthy U.S.-Style Eating Pattern, the Dietary Approaches to Stop Hypertension diet, and the Mediterranean dietary pattern. A central theme of these diets is that they are high in plant foods including fruits and vegetables. Research indicates that most U.S. adults do not meet the federal dietary guidelines for most nutrient-rich food groups, including fruits.[9,10] The Dietary Guidelines for Americans 2015–2020 states that "healthy eating patterns include fruits, especially whole fruits" as they are rich in nutrients including dietary fiber, potassium, and vitamin C, and that most individuals would benefit from increasing their intake of fruits.[9] In addition to their consumption in the context of a healthy dietary pattern, many fruits have been demonstrated to be functional foods and may have a place in the prevention and treatment of MetS, *e.g.* as medical nutrition therapies.[11,12]

Several foods rich in bioactive compounds have been shown to attenuate cardiometabolic abnormalities that contribute to and characterize MetS, though heterogeneity in responses to these interventions have been reported.[4,13,14] Among these, fresh pears (*Pyrus communis*) are relatively low in calories and are an excellent source of dietary fiber including insoluble and soluble fiber, a good source of vitamin C, and contain potassium, vitamin K, and polyphenols including flavonoids and phenolic acids.[15,16] Previous research suggests that fresh pear consumption may attenuate MetS. For instance, preclinical findings suggest that pears may modulate lipid and glucose metabolism, and inhibit the production of the vasoconstrictor molecule angiotensin II.[17–20] Epidemiological evidence indicates that increased pear/apple consumption is associated with a reduced risk of hypertension, T2DM, and CVD.[21–23] Additionally, data from NHANES 2001–2010 indicate that when compared with non-consumers, fresh pear consumers had improved nutrient intake, diet quality, and weight parameters, and were less likely to be obese.[16] Few clinical studies with pears, fresh or otherwise, have been conducted to date. Two clinical trials conducted by de Oliveira *et al.* in Brazil showed modest but beneficial effects of daily pear consumption for 10 and 12 weeks on energy intake, body weight, and blood glucose levels in young healthy women.[24,25] Another clinical trial conducted by Alvarez-Parrilla *et al.* in Mexico examined daily consumption of apple, pear, and orange juice for 26 days found that healthy non-smokers had increased total antioxidant capacity but increased total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) whereas healthy smokers had reduced TC and LDL-C.[26]

Previous research on the health effects of pears is limited but available data suggest that fresh pear consumption may promote cardiometabolic health and attenuate MetS. Although the inclusion of fresh pears into the diet can be viewed as beneficial, their functional properties in humans are largely unknown. The purpose of this study was to investigate the effects of daily fresh pear consumption on biomarkers of cardiometabolic health in middle-aged/older adults with MetS. We hypothesized that daily fresh pear consumption would improve biomarkers of cardiometabolic health.

2. Materials and methods

2.1 Participants

Middle-aged/older men and women with MetS were recruited from Tallahassee, FL and surrounding areas through campus and community advertisements. Participants were included if they were between the ages 45 and 65 years and had three of the MetS diagnostic criteria according to the American Heart Association/National Heart, Lung, and Blood Institute: elevated waist circumference [≥102 cm (40 in) in men and 88 cm (35 in) in women], elevated triglycerides (TG; ≥150 mg dL^{-1}), reduced HDL-C (≤40 mg dL^{-1} in men and 50 mg dL^{-1} in women), elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg), and elevated fasting blood glucose (≥100 mg dL^{-1}).[1] Individuals taking medication to lower blood pressure, blood glucose, and/or blood lipids were included in the study but were required to have been taking their medication for at least three months consistently to ensure that the medication would not have an effect on outcome measures. Additionally, study participants refrained from taking their medications for the 24 hours prior to each study visit. Study participants who previously took such medications were required to have been off of their medications for at least three months prior to enrolment. Exclusion criteria included diagnosed CVD, uncontrolled hypertension (>160/100 mmHg), hormone replacement therapy or insulin use, active cancer, asthma, glaucoma, thyroid, kidney, liver and pancreatic disease, heavy smoking

(>20 cigarettes per day), and heavy drinking (>7 alcoholic drinks/week for women and >14 alcoholic drinks/week for men). After an initial prescreening over the telephone, qualified individuals were invited to the study site for a screening visit during which they provided written informed consent, and inclusion and exclusion criteria were confirmed. Anthropometric measurements (height, weight, and waist and hip circumferences) were performed. Measurements of brachial blood pressure were taken in duplicate 5 minutes apart after 10 minutes of seated rest using an automatic device (Omron Healthcare, Inc., Bannockburn, IL). A finger stick blood draw was performed to assess blood glucose and lipid profiles (Alere Cholestech LDX® Analyzer). Recruitment began in August 2014 and continued until May 2016 when the last participant finished the study. The Florida State University Institutional Review Board approved the study protocol and all participants provided written informed consent. All experiments were performed in accordance with the Declaration of Helsinki. This trial was registered at clinicaltrials.gov as NCT02228837.

2.2 Study design and treatments

This was a 12-week, randomized, open-label, placebo-controlled, crossover clinical trial. Using a statistician generated randomization list, qualified participants were randomly assigned to one of two treatment groups: (1) Pear: two medium-sized (~166 g) fresh pears (green Bartlett or D′ Anjou depending on the season) per day, or (2) Control: 50 g of calorie-matched control drink powder reconstituted in 480 mL water per day. Each treatment period was 12 weeks in duration and separated by a 4-week washout period.

Fresh pears were purchased from a local grocery store in coordination with the Pear Bureau Northwest. The placebo powder consisted of maltodextrin, artificial and natural flavoring, artificial color, citric acid, and silica dioxide and was provided by Green Source Organics (Boynton Beach, FL). The purpose of the Control drink was to match for caloric content of the Pear treatment (200 kcal). Treatment distribution occurred weekly for the Pear group and every three weeks for the Control group. Participants in the Pear group were educated on proper storage of fresh pears, how to check for ripeness, and how to incorporate fresh pears into their diets. They were asked to consume pears fresh and with the peel. They were also asked to consume half of their treatment regimen in the morning and the other half in the afternoon or evening at least five hours apart. Participants in the Control group were provided with shaker bottles and instructed to consume half of their treatment regimen in the morning and the other half in the afternoon or evening (each 25 g dose reconstituted in 240 mL water) and at least 5 hours apart. To monitor treatment compliance, participants were given daily treatment logs and were asked to record the days and times of treatment consumption, as well as to document any missed treatments. Additionally, they were asked to return any unused treatments. Non-compliance was defined as missing ≥2 doses per week. Participants were asked to maintain their normal diet and physical activity patterns throughout the duration of the study.

2.3 Blood pressure

Blood pressure was measured at baseline, 6- and 12-week visits. Measurements were performed in the seated position in a quiet room after an overnight fast and avoidance of alcohol, caffeine, and medication use for at least 24 hours. Seated brachial blood pressure measurements were taken in duplicate after ten minutes of seated rest using an automatic device (Omron Healthcare, Inc., Bannockburn, IL). Pulse pressure was calculated as the difference between systolic blood pressure and diastolic blood pressure. Mean arterial pressure was calculated as diastolic blood pressure + 1/3 (systolic blood pressure – diastolic blood pressure).

2.4 Blood collection and analysis

At baseline, 6- and 12-week visits, 20 mL fasting venous blood samples were collected in appropriate vacutainers. Serum and plasma were separated through centrifugation using an IEC CL31R multispeed centrifuge (Thermo Electron Corporation, Waltham, MA), aliquoted, and stored at −80 °C until analysis. Plasma samples were analyzed for TC, HDL-C, LDL-C, TG, and glucose, and serum samples were analyzed for apolipoprotein-B100 (Apo-B), high-sensitivity-C-reactive protein (hs-CRP), and total antioxidant status (TAS) using a AU480 Automated Chemistry Analyzer (Beckman Coulter, Brea, CA) at the University of Colorado-Denver (UC-Denver) Colorado Clinical and Translational Sciences Institute (CCTSI, Denver, CO). Plasma insulin levels were measured using radioimmunoassay (Millipore) at the UC-Denver CCTSI (Denver, CO). Serum apolipoprotein A-1 (ApoA-1; R&D Systems), leptin, adiponectin (Mercodia), and urine 8-hydroxy-2′deoxyguanosine (8-OHdG, Abcam) were measured using commercially available enzyme-linked immunosorbent assay kits according to the manufacturers' instructions. The Homeostatic Model Assessment (HOMA) of insulin resistance (HOMA-IR) and pancreatic β-cell function (HOMA-%β) were calculated using the HOMA2 Calculator v2.2.3 based on fasting insulin and glucose measurements.[27]

2.5 Anthropometric measurements

Height without shoes was measured using a wall-mounted stadiometer to the nearest 0.5 cm and weight was assessed using a digital scale (Seca Corporation, Hanover, MD) to the nearest 0.1 kg. Body mass index (BMI) was calculated as kg m^{-2}. Midabdominal waist and hip circumferences were measured using a Gulick fiber glass measuring tape with a tension handle (Creative Health Products, Inc., Ann Arbor, MI). With the exception of height which was only measured at baseline, body weight and waist and hip circumferences were measured at baseline, 6- and 12-week visits. Waist-to-hip ratio was calculated as waist circumference divided by hip circumference. Body composition including fat mass, android fat, gynoid fat, and android/gynoid ratio were assessed at baseline, 6- and

12-week visits using dual energy X-ray absorptiometry (DXA, GE Healthcare Lunar, Madison, WI).

2.6 Physical activity energy expenditure and dietary intake assessments

Physical activity was assessed using the Five-City Project Physical Activity Recall[28] and a 3-day food record (two weekdays and one weekend day) was assessed at baseline, 6-week, and 12-week visits to detect significant changes in dietary intake or physical activity energy expenditure over the duration of the study. Collected food records were analyzed using Food Processor SQL Nutrition and Fitness Program (ESHA Research, Salem, OR, USA). Trained project personnel collected the physical activity data; physical activity data were analyzed to determine usual activity level, consistency over time and deviations from baseline.

2.7 Statistical analysis

SAS v9.4 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. PROC GENMOD with linear regression function was used to evaluate the difference between the groups as well as the difference between time points. The 'Group' was a fixed factor, and 'Subject ID' and 'Phase' were random effects in the models. The effect of phase order was evaluated. However, all analyses performed to evaluate the treatment (between group) and time (within group) effects were adjusted for the phase effect as well as subject to control for such effects, if any. All the continuous outcome data were evaluated for normality assumption using Shapiro–Wilk statistics and Q–Q plots. If the outcome data were not normally distributed, log conversion was performed. Carryover effects were evaluated using linear regression. Data were reported as mean ± standard error of the mean for normally distributed data, and median with ranges in parentheses for non-normally distributed data. Effects were considered statistically significant at $P < 0.05$ and tended to be statistically significant at $P < 0.1$. Power analysis indicated that 40 subjects in our study provided a statistical power of >80% to detect a significant change (5 mmHg) from baseline for systolic blood pressure and other parameters assessed with α set at 0.05.

3. Results

3.1 Screening characteristics, attrition, and compliance

A flowchart of study enrollment is presented in Fig. 1. Of the 43 subjects who completed the study, a total of 40 men and women were included in the data analyses. Three subjects were excluded from analysis due to not meeting the diagnostic criteria for MetS. The overall attrition rate for the study was 14% with 7 participants dropping from the study. Common causes for dropping from the study included personal reasons such as lack of time or moving, not wanting to take the placebo powder, and not wanting to give blood (Fig. 1). Tolerance to daily pear consumption was reported as good. Challenges to intake of the treatment regimens included taste fatigue towards the end of the 12-week pear interventions as well as difficulty with maintaining a consistent supply of ripe pears. The participants who completed the study and were included in the analysis were compliant with their treatments as indicated in their daily dosing diaries. Screening characteristics for participants who completed the study are presented in Table 1. Statistical analysis of the data revealed no evidence for carryover effects.

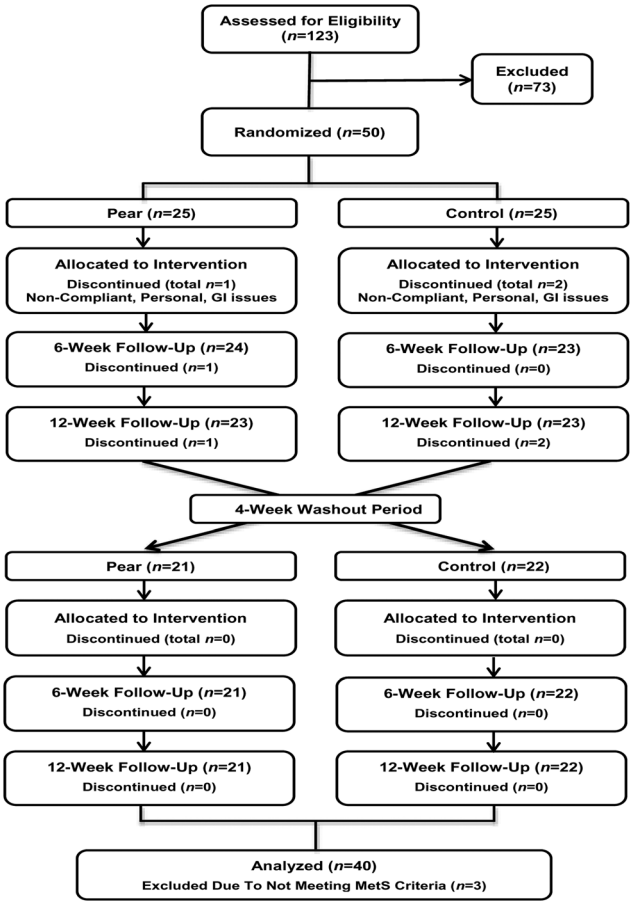

Fig. 1 Flowchart of enrollment. Abbreviation: GI, gastrointestinal.

3.2 Blood pressure

Blood pressure parameters are presented in Table 2. Systolic blood pressure tended to be lower (131 ± 2 mmHg at 6 weeks *vs.* 134 ± 2 mmHg at baseline, $P = 0.07$) at 6 weeks and was significantly lower (131 ± 2 mmHg at 12 weeks *vs.* 133 ± 2 mmHg at 6 weeks, $P < 0.05$) at 12 weeks than 6 weeks in the Pear group. Pulse pressure was significantly lower (51 ± 1 at 12 weeks *vs.* 54 ± 1 at baseline and 53 ± 1 at 6 weeks, $P < 0.05$) than baseline at 6 and 12 weeks in the Pear group. No significant changes were observed over time in the Control group, and no significant differences were observed between groups at any time point.

3.3 Blood and urine biomarkers

Blood and urine biomarkers are presented in Table 3. TC levels were significantly lower at baseline in the Pear group

Table 1 Screening characteristics of study participants

Measures	Mean ± SD	Range
Male/female (*n*/*n*)	10/30	—
Postmenopausal (*n*)	25	—
Age (years)	59 ± 5	46–65
BMI (kg m^{-2})	33.2 ± 4.9	24.2–44.3
Waist circumference (cm)	108 ± 13	87–137
Waist-to-hip ratio	0.93 ± 0.07	0.76–1.12
TC (mg dL^{-1})	197 ± 35	118–314
HDL-C (mg dL^{-1})	43 ± 12	18–90
Triglycerides (mg dL^{-1})	182 ± 79	52–388
Glucose (mg dL^{-1})	98 ± 12	63–137
SBP (mmHg)	136 ± 11	111–160
DBP (mmHg)	82 ± 6	69–96
Taking medications (*n*)	Blood pressure (20) Blood glucose (9) Blood lipids (11)	

Values are mean ± SD. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

than Control (194 ± 6 in Pear *vs.* 201 ± 6 in Control, $P < 0.05$). TC levels were significantly increased in both Pear (198 ± 7 at 6 weeks *vs.* 198 ± 6 at baseline, $P < 0.05$) and Control (206 ± 7 at 6 weeks *vs.* 201 ± 6 at baseline, $P < 0.05$) groups at 6 weeks, but not 12 weeks, compared to baseline. LDL-C levels were significantly increased at 6 and 12 weeks in both Pear (97 ± 6 at 6 weeks and 100 ± 5 at 12 weeks *vs.* 93 ± 5 at baseline, $P < 0.05$) and Control (102 ± 5 at 6 weeks and 103 ± 5 at 12 weeks *vs.* 95 ± 5 at baseline, $P < 0.05$) groups. Apo-B levels were significantly decreased at 12 weeks in the Control (101 ± 4 at 12 weeks *vs.* 106 ± 4 at 6 weeks, $P < 0.05$) groups. No differences between groups were noted for TC, LDL-C, or Apo-B levels at any time point with the exception of TC at baseline. At 12 weeks, leptin concentrations were lower in the Pear group than Control (52.5 [7.6, 120.5] ng dL^{-1} *vs.* 53.4 [5.0, 120.5] ng dL^{-1}, respectively, $P < 0.05$), and there was a significant group by time interaction ($P < 0.05$). Values were significantly reduced at 12 weeks com-

Table 2 Blood pressure parameters at baseline, 6 and 12 weeks in middle-aged/older men and women who completed a randomized controlled trial assessing the effects of daily fresh pear consumption for 12 weeks on cardiometabolic health

	Pear (*n* = 40)			Control (*n* = 40)		
Measures	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
SBP (mmHg)	134 ± 2	133 ± 2	131 ± 2$^{\dagger ¥}$	133 ± 2	135 ± 2	132 ± 2
DBP (mmHg)	80 ± 1	80 ± 1	80 ± 1	81 ± 1	81 ± 1	80 ± 1
PP	54 ± 1	53 ± 1	51 ± 1$^{*¥}$	53 ± 2	54 ± 2	51 ± 2
MAP (mmHg)	98 ± 1	98 ± 2	97 ± 1	98 ± 1	99 ± 2	98 ± 1

Values are mean ± SEM. *Significantly ($P < 0.05$) different compared to baseline. †Tends to be significantly ($P < 0.1$) different compared to baseline. $^{¥}$Significantly ($P < 0.05$) different compared to 6 weeks. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure.

Table 3 Blood and urine biomarkers of lipid and glucose metabolism, inflammation, and oxidative stress at baseline, 6 and 12 weeks in middle-aged/older men and women who completed a randomized controlled trial assessing the effects of daily fresh pear consumption for 12 weeks on cardiometabolic health

	Pear (*n* = 40)			Control (*n* = 40)		
Measures	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
TC (mg dL^{-1})	194 ± 6^{t}	198 ± 7^{*t}	198 ± 6	201 ± 6	206 ± 7*	203 ± 6
LDL-C (mg dL^{-1})	93 ± 5	98 ± 6*	100 ± 5*	95 ± 5	102 ± 5*	103 ± 5*
HDL-C (mg dL^{-1})	48 (35, 69)	47 (31, 66)	47 (28, 178)	49 (38, 74)	50 (31, 68)	50 (32, 64)
TG (mg dL^{-1})	141 ± 11	156 ± 12	138 ± 12	144 ± 10	147 ± 11	149 ± 11
Apo-B (mg dL^{-1})	102 ± 4	103 ± 4	100 ± 4	104 ± 4	106 ± 4	101 ± 4$^{¥}$
Apo-A (ng mL^{-1})	2.26 ± 0.09	2.34 ± 0.10	2.39 ± 0.10	2.33 ± 0.12	2.31 ± 0.07	2.43 ± 0.10
Glucose (mg dL^{-1})	108 ± 2	110 ± 3	111 ± 3	108 ± 2	109 ± 3	108 ± 2
Insulin (pmol L^{-1})	135 (35, 667)	139 (56, 535)	132 (49, 500)	125 (56, 514)	125 (56, 743)	125 (49, 945)
HOMA-IR	2.85 ± 0.28	2.86 ± 0.24	2.86 ± 0.24	2.86 ± 0.27	3.07 ± 0.34	3.10 ± 0.37
HOMA-%β	132.1 ± 7.6	131.4 ± 7.6	130.5 ± 7.8	136.1 ± 7.0	137.2 ± 8.9	141.8 ± 10.4
Leptin (ng mL^{-1})	54.8 (6.4, 120.5)	47.4 (11.5, 790.3)	52.5 (7.6, 120.5)$^{¥\#t}$	54.2 (4.5, 104.1)	53.2 (9.0, 120.5)	53.4 (5.0, 120.5)
Adiponectin (ng mL^{-1})	6.49 ± 0.29	6.35 ± 0.30	6.19 ± 0.26	6.24 ± 0.28	6.26 ± 0.38	6.12 ± 0.32
hs-CRP (mg L^{-1})	5.28 ± 0.75	4.92 ± 0.62	4.57 ± 0.52	5.13 ± 0.67	5.35 ± 0.71	4.81 ± 0.59
8-OHdG (ng mL^{-1})	1.51 ± 0.06	1.55 ± 0.05	1.51 ± 0.07	1.53 ± 0.05	1.58 ± 0.06	1.48 ± 0.05
TAS (mg dL^{-1})	1.38 (1.14, 2.00)	1.40 (1.11, 1.88)	1.37 (1.17, 1.80)	1.38 (1.17, 1.95)	1.42 (1.12, 2.14)	1.38 (1.15, 1.87)

Values reported as mean ± SEM or median with ranges in parentheses for non-normally distributed data (all such values). *Significantly ($P < 0.05$) different compared to baseline. ^{t}Significantly ($P < 0.05$) different compared to Control. $^{\#}$Significant group by time interaction. $^{¥}$Significantly ($P < 0.05$) different compared to 6 weeks. Abbreviations: Apo-A, apolipoprotein-A; Apo-B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; HOMA-%β, homeostasis model assessment of beta-cell function; HOMA-IR, Homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

pared to baseline in the Pear group (52.5 [7.6, 120.5] ng dL^{-1} *vs.* 54.8 [6.4, 120.5] ng dL^{-1} at baseline, $P < 0.05$) but not in the Control group. No significant within group or between group differences were observed for the remaining biomarkers.

3.4 Anthropometrics and body composition

Anthropometric and body composition parameters are presented in Table 4. BMI was significantly increased at 6 weeks in the Control (33.4 ± 0.8 at 6 weeks *vs.* 33.1 ± 0.8 at baseline, $P < 0.05$) group and sustained at 12 weeks. Waist circumference was significantly reduced at 12 weeks in the Pear group (107.7 ± 2.0 cm *vs.* 108.1 ± 2 cm at baseline, $P < 0.05$) with a trend for a group by time interaction ($P < 0.1$), and significantly lower in the Pear group than Control (108.1 ± 2.0 cm *vs.* 108.8 ± 2 cm, $P < 0.05$) at 6 weeks with a significant group by time interaction ($P < 0.05$). Conversely, values were significantly increased at 6 weeks (108.8 ± 2 cm *vs.* 108.3 ± 2.0 cm at baseline, $P < 0.05$) in the Control group and sustained at 12 weeks. Waist-to-hip ratio was significantly reduced (0.92 ± 0.01 *vs.* 0.93 ± 0.01 at baseline, $P < 0.05$) at 12 weeks in the Pear group, and significantly lower than Control at 6 weeks (0.92 ± 0.01 *vs.* 0.93 ± 0.01, respectively, $P < 0.05$) and 12 weeks (0.92 ± 0.01 *vs.* 0.93 ± 0.01, $P < 0.05$). Android-to-gynoid ratio was significantly higher ($P < 0.05$) in the Control group at 6 weeks (1.21 ± 0.03 at 6 weeks *vs.* 1.19 ± 0.03 at baseline) and 12 weeks (1.21 ± 0.03 at 12 weeks *vs.* 1.19 ± 0.03 at baseline) compared to baseline, and a significant group by time interaction was observed at 12 weeks. Percent android fat was significantly increased ($P < 0.05$) at 6 weeks (50.9 ± 1.0 at 6 weeks *vs.* 50.3 ± 1.0 at baseline) and 12 weeks (50.9 ± 0.98 at 12 weeks *vs.* 50.3 ± 1.0 at baseline) compared to baseline in the Control group while no changes were observed in the Pear group. No between group differences were observed. No significant within group or between group differences were observed for the remaining parameters.

3.5 Physical activity energy expenditure and dietary intake

Physical activity energy expenditure, energy intake, and macronutrient intake are presented in Table 5. At 6 weeks, physical

Table 4 Anthropometric and body composition measurements at baseline, 6 weeks, and 12 weeks in middle-aged/older men and women who completed a randomized controlled trial assessing the effects of daily fresh pear consumption for 12 weeks on cardiometabolic health

	Pear ($n = 40$)			Control ($n = 40$)		
Measures	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Weight (kg)	92.3 ± 2.6	92.3 ± 2.6	91.7 ± 2.8	92.1 ± 2.6	92.5 ± 2.6	92.4 ± 2.6
BMI (kg m^{-2})	33.2 ± 0.75	33.2 ± 0.78	33.0 ± 0.83	33.1 ± 0.80	33.4 ± 0.77*	33.7 ± 1.2
WC (cm)	108.4 ± 2.0	108.1 ± 2.0$^{t\#}$	107.7 ± 2.0*†	108.3 ± 2.1	108.8 ± 2.0*	108.5 ± 2.1
HC (cm)	116.8 ± 1.6	116.9 ± 1.7	116.7 ± 1.7	115.8 ± 1.6	116.6 ± 1.7	116.8 ± 1.8
Waist/hip ratio	0.93 ± 0.01	0.92 ± 0.01^{t}	0.92 ± 0.01^{t}	0.93 ± 0.01	0.93 ± 0.01	0.93 ± 0.01
Fat mass (%)	43.8 ± 1.0	43.6 ± 1.0	43.7 ± 1.0	43.6 ± 1.0	43.9 ± 1.0	43.8 ± 1.0
Fat free mass (g)	52 415 ± 1521	52 215 ± 1546	52 353 ± 1581	52 011 ± 1495	52 154 ± 1503	51 365 ± 1959
Android fat (g)	7108 ± 446	7108 ± 446	7092 ± 454	7211 ± 409	7200 ± 459	7090 ± 459
Gynoid fat (g)	12 394 ± 729	12 184 ± 744	12 030 ± 750	12 810 ± 676	121 697 ± 734	11 989 ± 756
Android fat (%)	51.0 ± 1.0	50.8 ± 1.0	50.7 ± 1.0	50.3 ± 1.0	50.9 ± 1.0*	50.9 ± 1.0*
Gynoid fat (%)	43.0 ± 1.27	42.8 ± 1.26	43.2 ± 1.32	43.1 ± 1.28	43.2 ± 1.37	43.2 ± 1.37
A/G ratio	1.18 (0.81, 1.60)	1.20 (0.82, 1.71)	1.19 (0.84, 1.69)$^{\#}$	1.16 (0.86, 1.61)	1.16 (0.84, 1.66)†	1.19 (0.87, 1.61)*

Values reported as mean ± SEM. *Significantly ($P < 0.05$) different compared to baseline. ^{t}Significantly ($P < 0.05$) different compared to control. $^{\#}$Significant group by time interaction. †Tends to be significantly ($P < 0.1$) group by time interaction. Abbreviations: A/G ratio, android/gynoid ratio; BMI, body mass index; FFM, fat-free mass; FM, fat mass; HC, hip circumference; WC, waist circumference.

Table 5 Physical activity energy expenditure, and energy and macronutrient intake at baseline, 6 weeks, and 12 weeks in middle-aged/older men and women who completed a randomized controlled trial assessing the effects of daily fresh pear consumption for 12 weeks on cardiometabolic health

	Pear ($n = 40$)			Control ($n = 40$)		
Measures	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
Physical activity (kcal)	3259 ± 94	3345 ± 113	3439 ± 150	3223 ± 100	3394 ± 124*	3356 ± 135
Energy intake (kcal)	1777 ± 128	1984 ± 113	2012 ± 146	2033 ± 124	1960 ± 165	2167 ± 164
Total fat (g)	74 ± 7	79 ± 7	83 ± 8	84 ± 6	83 ± 8	93 ± 9
Cholesterol (mg)	289 ± 25	289 ± 24	315 ± 34	315 ± 26	270 ± 24	335 ± 34$^{¥}$
Total carbohydrates (g)	209 ± 18	244 ± 16†	241 ± 19	230 ± 19	243 ± 25	257 ± 23
Fiber (g)	15 ± 1	18 ± 2*	17 ± 1†	18 ± 1^{t}	19 ± 2	20 ± 2
Protein (g)	70 ± 6	77 ± 4	78 ± 6	73 ± 5	72 ± 6	84 ± 6$^{\#}$

Values reported as mean ± SEM. *Significantly ($P < 0.05$) different compared to baseline. †Tends to be significantly ($P < 0.1$) different compared to baseline. $^{¥}$Significantly ($P < 0.05$) different compared to 6 weeks. $^{\#}$Tends to be significantly ($P < 0.1$) different compared to 6 weeks. ^{t}Significantly ($P < 0.05$) different compared to Control.

activity energy expenditure was significantly greater than baseline in the Control group (3394 ± 124 kcal at 6 weeks *vs.* 3223 ± 100 kcal at baseline, $P < 0.05$). At 12 weeks, cholesterol intake tended to be higher than 6 weeks in the Control group (335 ± 34 mg at 12 weeks *vs.* 270 ± 24 mg at 6 weeks, $P < 0.1$). At 6 weeks, total carbohydrate intake tended to be significantly higher than baseline in the Pear group (244 ± 16 g at 6 weeks *vs.* 209 ± 18 mg at baseline, $P < 0.1$). At baseline there was a significant difference between groups for fiber intake (15 ± 1 g in Pear *vs.* 18 ± 1 g in Control, $P < 0.05$). At 6 weeks, fiber intake was significantly greater than baseline (18 ± 2 g at 6 weeks *vs.* 15 ± 1 g at baseline, $P < 0.1$), and tended to be significantly greater at 12 weeks than at baseline (17 ± 1 g at 12 weeks *vs.* 15 ± 1 g at baseline, $P < 0.1$) in the Pear group.

4. Discussion

To our knowledge, this is the first randomized controlled trial to utilize fresh pears as an intervention in the U.S., and the first study to investigate the effects of daily fresh pear consumption on cardiometabolic health in middle-aged/older adults with MetS. We found that daily consumption of two fresh pears per day for 12 weeks resulted in lower blood leptin concentrations, waist circumference, waist-to-hip ratio, and android-to-gynoid ratio compared to Control. Other biomarkers improved over the course of 12 weeks in the Pear group but not in the Control group, namely systolic blood pressure and pulse pressure. However, the changes observed were within groups, not between groups, and therefore the effect cannot be solely attributed to fresh pear consumption. Interestingly, adverse changes in BMI, waist circumference, percent android fat, and android-to-gynoid ratio were observed over the course of the 12-week period in the Control group but not in the Pear group. These changes were only observed within group and not between groups. Although a treatment effect cannot be confirmed for several of the studied outcome parameters, it does not preclude that daily fresh pear consumption could promote modest improvements in those parameters of cardiometabolic health in middle-aged/older adults with MetS. Although TC increased over time, these changes were observed in both groups and therefore cannot be attributed to either treatment.

Surprisingly, results indicate that systolic blood pressure and pulse pressure were reduced at 12 weeks compared to baseline in the Pear group, but not in the Control group, and that there were no significant differences between groups. Therefore, a treatment effect cannot be confirmed at this time, *i.e.* the reduction in systolic blood pressure and pulse pressure cannot be attributed solely to pear consumption. One of the features of MetS is elevated blood pressure. Age-related increases in blood pressure and hypertension are characterized by increased systolic blood pressure with no change or decreased diastolic blood pressure resulting in elevated pulse pressure. This is primarily caused by age-related vascular dysfunction, including vascular endothelial dysfunction and arterial stiffness[29,30] which is accelerated by MetS.[29,31,32] Pears are rich in bioactive compounds known to influence vascular function and blood pressure including potassium, dietary fiber, and polyphenols[15,33] and we therefore anticipated the fresh pear consumption would reduce systolic blood pressure. Nonetheless, it is important to note that while the physiological effects of foods and their bioactive components are often small, these seemingly small changes may be clinically relevant with implications at the population level.[34] For instance, a reduction in systolic blood pressure by 3 mmHg has been shown to be associated with an 8% and 5% lower risk of mortality due to stroke and coronary heart disease, respectively.[35] Our findings are consistent with that observed in a prospective cohort study conducted in China which found that individuals who ate fresh fruit daily had a lower systolic blood pressure by 4 mmHg than those who never or rarely consumed fresh fruit.[36] They also found that when compared with non-consumption, daily fresh fruit consumption was associated with a reduced risk for major CVDs and death with a linear dose–response relationship between CVD incidence and the amount of fruit consumed. Although data was not collected on the types of fruits consumed in that study, the authors noted that the most commonly consumed fruit in China are apples, citrus fruit, and pears. Results from other prospective cohort studies conducted in the U.S. indicate that pear consumption is associated with a reduced incidence of hypertension in adult men and women[21] and a reduced risk of CVD-related mortality in postmenopausal women.[37]

Contrary to our hypothesis, we did not observe statistically significant improvements in lipid profiles. In fact, TC and LDL-C increased over time; however, these increases occurred in both groups and therefore cannot be attributed to either treatment and rather may be an effect of time. Atherogenic dyslipidemia is a feature of MetS, and previous research has demonstrated that viscous fiber dietary interventions can improve lipid profiles through fecal excretion of bile acids[38] and through increased short chain fatty acid production which may inhibit lipid and cholesterol synthesis.[39] Results from a recent *meta*-analysis indicate that dietary fiber intake, especially from cereals and fruits, is inversely associated with coronary heart disease risk.[40] Unfortunately, most Americans do not consume adequate dietary fiber.[41] Due to the high fiber content in fresh pears we postulated that daily fresh pear consumption for 12 weeks would improve lipid profiles. Previous clinical trials with apples, another fruit rich in insoluble and soluble fiber, have yielded inconsistent findings with respect to lipid profiles. For instance, we previously demonstrated that apple consumption improves certain blood lipids in postmenopausal women[42] and others have shown that it improves certain blood lipids in healthy and hyperlipidemic adults.[43] However, other investigators have observed no improvement in lipid profiles in hyperlipidemic adults[44] and lipid profiles in overweight hypercholesterolemic adults.[45] The reasons for these discrepancies are unknown. However, differences in study populations, intervention duration, fruit type and form, medication use, among other reasons, may be contributing

factors. With respect to the present study, it is possible that the heterogeneous population, *e.g.* the inclusion of participants meeting different MetS diagnostic criteria, men and women, and medication use may have contributed to our findings.

Contrary to our hypothesis, we did not observe changes in glucose or insulin concentrations or indices of insulin resistance. We were surprised by these findings, and cannot determine the reasons responsible for this observation at this time. However, it is possible that a longer-term measure of glycemic control would have provided a more accurate assessment, since measurement of fasting blood glucose levels only provide a snapshot of blood levels at a specific time and date. Additionally, we did not specify when the treatments were to be consumed, *e.g.* with or without meals. Hyperglycemia resulting from insulin resistance is a feature of MetS, and individuals with MetS are at an increased risk for developing T2DM which further increases the risk of CVD. Previous research suggests that fresh pear consumption may attenuate hyperglycemia thus reducing T2DM risk. Our findings are contrary to previous work which found that consumption of three pears per day for 12 weeks led to significant decreases in serum glucose levels (~5.2 mg dL^{-1}) compared to those consuming oat cookies (~0.75 mg dL^{-1}).[24] Results from a prospective cohort study conducted in the U.S. found that when compared with those consuming less than one serving per month of apples/pears, consumption of ≥5 servings per week of apples/pears was associated with a lower risk of T2DM.[46] Preclinical research suggest that pear phenolics may inhibit alpha-glucosidase activity, an enzyme located in the small intestine involved in the digestion of carbohydrates.[20] In addition, soluble fiber has been reported to decrease glucose concentrations due to its gel-forming properties which slows down carbohydrate degradation and therefore the absorption of glucose in the gut.[38] It is possible that consuming fresh pears with a meal would lead to reductions in postprandial hyperglycemia and hyperinsulinemia which could potentially lead to improved glycemic control in the long-term. However, this needs confirmation.

No changes in measures of inflammation, oxidative stress, or antioxidants (hs-CRP, 8-OHdG, TAS) were observed over time in either group, or between groups. However, only one biomarker was assessed in each category and it is possible that analysis of other biomarkers may have shown different results. Additionally, research suggests that static biomarkers, such as those measured in this study, do not always respond to dietary interventions. For instance, functional biomarkers such as *ex vivo* pro-inflammatory cytokine production in peripheral blood mononuclear cells have been shown to respond to dietary interventions in the absence of a response in static biomarkers.[47,48] For this reason, we believe that it is premature to conclude that fresh pear consumption does not modulate inflammation, oxidative stress, or antioxidant defense in this population, and more research is needed to elucidate their effects.

MetS is typically characterized by excess body weight, and particularly abdominal obesity. Previously published research by de Oliveira *et al.* demonstrated that overweight women who consumed fresh pears daily in Brazil for 10 and 12 weeks had modest reductions in body weight (~2 lbs.).[24,25] They did not report other anthropometric or body composition assessments. With the exception of BMI increasing at 6 weeks in the Control group, we did not observe changes in body weight or BMI over time, or differences between groups in the current study. We did observe significant reductions in waist circumference in the Pear group, while waist circumference increased over time in the Control group. Additionally, waist-to-hip ratio was significantly lower in Pear at 6 and 12 weeks compared to Control. Results also showed an increase in android fat, and android-to-gynoid ratio as determined by DXA in the Control group, with a significant group by time interaction at 12 weeks. These data suggest that daily fresh pear consumption may promote modest reductions in abdominal fat, whereas consumption of a high glycemic index beverage may promote deleterious effects on abdominal fat.

Leptin and adiponectin are two protein hormones secreted by adipose tissue (adipokines), each with differing roles on human health including the regulation of food intake, body weight, immune function, and metabolic processes.[49,50] In the current study, we did not observe any changes in adiponectin concentrations over time, or differences between groups. Interestingly, we did observe reductions in leptin concentrations in the Pear group compared to Control at 12 weeks with a significant group by time interaction. Blood leptin concentrations are associated with body fat such that levels increase with increasing body fat. This is thought to be due to leptin resistance, meaning that leptin has a reduced ability to exert its effects. In addition to its role in regulating satiety, energy intake, and body weight, it also plays a role in the regulation of cardiometabolic processes such as blood pressure. Although leptin exerts vasodilatory effects, high levels of leptin lead to increased peripheral resistance and sympathetic nerve activity, thereby increasing blood pressure.[49] Indeed, a concept known as selective leptin resistance posits that certain actions of leptin persist even when other leptin actions are blocked from leptin resistance.[51] We did not observe reductions in energy intake or body weight in the current study, but did observe modest reductions in blood pressure, waist circumference, and waist-to-hip ratio over time in the Pear group. Additionally, leptin is a pro-inflammatory adipokine,[52] suggesting that fresh pear consumption may reduce inflammation; however, no changes were observed in hs-CRP levels. It is possible that reductions in leptin were not paralleled by improvements in leptin resistance. It is also possible that any improvements in leptin signaling were not strong enough in magnitude to have a substantial impact on downstream targets of leptin such as blood pressure and body weight.

The strengths of this study include the study design employed, *i.e.* a randomized, placebo-controlled, crossover clinical trial as randomized controlled trials are the gold-standard clinical study design, and participants serve as their own controls in a crossover design thereby minimizing the influence of confounding covariates. Additionally, our intervention

utilized fresh pears instead of a juice, dried fruit, powder, or other processed pears. Although this can also be viewed as a limitation, it is a strength in that it is generalizable to a real-world setting in which people typically consume pears in the fresh form. Another strength of our study is the high level of participant retention and compliance. Lastly, our study population is likely representative of the general population of middle-aged/older adults with MetS, in part, due to enrollment of both men and women, inclusion of individuals taking medications for blood pressure and blood glucose and lipids, and minimal control of background diets.

The limitations of this study include a heterogeneous study population, *i.e.* the inclusion of participants meeting different MetS diagnostic criteria, men and women, 1 : 3 ratio of men to women, women with different hormonal states, and varying medication use. It is possible that these factors influenced the outcomes of the study. However, our crossover design minimized variability in that participants served as their own controls. Additionally, this population is likely representative of the general population of middle-aged/older adults with MetS. Another limitation is the lack of blinding of subjects and investigators (*i.e.* open-label); however, this was not possible due to the nature of the intervention. With respect to the intervention, fresh pears, possible limitations include: (1) the use of green pears rather than red pears which contain higher levels of polyphenols, (2) the use of a combination of green D′ Anjou and green Bartlett due to seasonal changes in pear production, and (3) issues related to proper storage and ripening of the pears. The use of a liquid control drink could be viewed as a limitation given there is data demonstrating that carbohydrates from liquid *versus* solid foods are sensed differently with respect to satiety and energy intake.[53] Additionally, foods higher in soluble fibers, such as pears, are known to have lower glycemic index values than those without (*e.g.* the liquid calorie control drink used in this study) which may impact chronic disease risk in overweight and obese populations.[54] Lastly, minor differential changes were observed in energy expenditure and certain macronutrients throughout the duration of the study in both groups. It is possible that these changes may have impact observed results. While these can be viewed as limitations, they are also strengths in that they represent real-world challenges faced by fresh pear consumers.

5. Conclusions

In summary, the findings of the present study suggest that daily fresh pear consumption may promote modest improvements in certain aspects of cardiometabolic health in middle-aged/older adults with MetS. Additionally, the high retention of participants and good compliance observed throughout the study suggests that daily fresh pear consumption is feasible in this population. It is possible that their inclusion into an evidence-based healthy dietary pattern such as the Healthy U.S.-Style Eating Pattern, the Dietary Approaches to Stop Hypertension diet, or the Mediterranean dietary pattern would provide additional health benefits through additive and/or synergistic effects with other foods and bioactive components. Additional research is needed to evaluate the role of fresh pear consumption as a functional food, in combination with other foods and/or meals, and in the context of a healthy dietary pattern, in this population and others.

Author contributions

BHA and SAJ conceived and designed the study. NN and SAJ coordinated the study. NN, SP, NSA, EMF, KSG, MLE, and SAJ collected the data. NN, SP, NSA, NSL, EMF, KSG, SCH, and SAJ performed biochemical analysis and calculations. NN, SP, NSA, NSL, EMF, and KSG performed data entry. SR performed statistical analysis. NN, SR, BHA, and SAJ interpreted the data. NN and SAJ wrote the initial manuscript. All authors reviewed and commented on subsequent drafts of the manuscript and read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1 S. M. Grundy, J. I. Cleeman, S. R. Daniels, K. A. Donato, R. H. Eckel, B. A. Franklin, D. J. Gordon, R. M. Krauss, P. J. Savage, S. C. Smith Jr. and J. A. Spertus, Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement, *Circulation*, 2005, **112**(17), 2735–2752.

2 E. S. Ford, Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence, *Diabetes Care*, 2005, **28**, 1769–1778.
3 S. Malik, N. D. Wong, S. S. Franklin, T. V. Kamath, G. J. L'Italien, J. R. Pio and G. R. Williams, Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults, *Circulation*, 2004, **110**, 1245–1250.
4 P. Perez-Martinez, D. P. Mikhailidis, V. G. Athyros, M. Bullo, P. Couture, M. I. Covas, L. de Koning, J. Delgado-Lista, A. Diaz-Lopez, C. A. Drevon, R. Estruch, K. Esposito, M. Fito, M. Garaulet, D. Giugliano, A. Garcia-Rios, N. Katsiki, G. Kolovou, B. Lamarche, M. I. Maiorino, G. Mena-Sanchez, A. Munoz-Garach, D. Nikolic, J. M. Ordovas, F. Perez-Jimenez, M. Rizzo, J. Salas-Salvado, H. Schroder, F. J. Tinahones, R. de la Torre, B. van Ommen, S. Wopereis, E. Ros and J. Lopez-Miranda, Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation, *Nutr. Rev.*, 2017, **75**, 307–326.
5 A. Mozumdar and G. Liguori, Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006, *Diabetes Care*, 2011, **34**, 216–219.
6 M. Aguilar, T. Bhuket, S. Torres, B. Liu and R. J. Wong, Prevalence of the metabolic syndrome in the United States, 2003–2012, *J. Am. Med. Assoc.*, 2015, **313**, 1973–1974.
7 D. M. Boudreau, D. C. Malone, M. A. Raebel, P. A. Fishman, G. A. Nichols, A. C. Feldstein, A. N. Boscoe, R. H. Ben-Joseph, D. J. Magid and L. J. Okamoto, Health care utilization and costs by metabolic syndrome risk factors, *Metab. Syndr. Relat. Disord.*, 2009, **7**, 305–314.
8 J. P. Despres, I. Lemieux, J. Bergeron, P. Pibarot, P. Mathieu, E. Larose, J. Rodes-Cabau, O. F. Bertrand and P. Poirier, Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk, *Arterioscler., Thromb., Vasc. Biol.*, 2008, **28**, 1039–1049.
9 2015–2020 Dietary Guidelines for Americans, http://health.gov/dietaryguidelines/2015/guidelines/.
10 S. M. Krebs-Smith, P. M. Guenther, A. F. Subar, S. I. Kirkpatrick and K. W. Dodd, Americans do not meet federal dietary recommendations, *J. Nutr.*, 2010, **140**, 1832–1838.
11 K. M. Crowe and C. Francis, Position of the academy of nutrition and dietetics: functional foods, *J. Acad. Nutr. Diet.*, 2013, **113**(8), 1096–1103.
12 L. Brown, H. Poudyal and S. K. Panchal, Functional foods as potential therapeutic options for metabolic syndrome, *Obes. Rev.*, 2015, **16**, 914–941.
13 D. Milenkovic, C. Morand, A. Cassidy, A. Konic-Ristic, F. Tomas-Barberan, J. M. Ordovas, P. Kroon, R. De Caterina and A. Rodriguez-Mateos, Interindividual Variability in Biomarkers of Cardiometabolic Health after Consumption of Major Plant-Food Bioactive Compounds and the Determinants Involved, *Adv. Nutr.*, 2017, **8**, 558–570.
14 C. J. Andersen and M. L. Fernandez, Dietary strategies to reduce metabolic syndrome, *Rev. Endocr. Metab. Disord.*, 2013, **14**, 241–254.
15 H. Reiland and J. Slavin, Systematic Review of Pears and Health, *Nutr. Today*, 2015, **50**, 301–305.
16 C. O'Neill, T. A. Nicklas and V. L. Fulgoni 3rd, Fresh pear consumption is associated with better nutrient intake, diet quality, and weight parameters in adults: national health and nutrition examination survey 2001–2010, *J. Nutr. Food Sci.*, 2015, **5**, DOI: 10.4172/2155-9600.1000377.
17 H. Leontowicz, S. Gorinstein, A. Lojek, M. Leontowicz, M. Číž, R. Soliva-Fortuny, Y. S. Park, S. T. Jung, S. Trakhtenberg and O. Martin-Belloso, Comparative content of some bioactive compounds in apples, peaches and pears and their influence on lipids and antioxidant capacity in rats, *J. Nutr. Biochem.*, 2002, **13**(10), 603–610.
18 C. Ankolekar, M. Pinto, D. Green and K. Shetty, *In vitro* bioassay based screening of antihyperglycemia and antihypertensive activities of *Lactobacillus acidophilus* fermented pear juice, *Innovative Food Sci. Emerging Technol.*, 2012, **13**, 221–230.
19 A. C. L. Barbosa, D. Sarkar, M. D. Pinto, C. Ankolekar, D. Greene and K. Shetty, Type 2 diabetes relevant bioactive potential of freshly harvested and long-term stored pears using *in vitro* assay models, *J. Food Biochem.*, 2013, **37**, 677–686.
20 D. Sarkar, C. Ankolekar, M. Pinto and K. Shetty, Dietary functional benefits of Bartlett and Starkrimson pears for potential management of hyperglycemia, hypertension and ulcer bacteria *Helicobacter pylori* while supporting beneficial probiotic bacterial response, *Food Res. Int.*, 2015, **69**, 80–90.
21 L. Borgi, I. Muraki, A. Satija, W. C. Willett, E. B. Rimm and J. P. Forman, Fruit and Vegetable Consumption and the Incidence of Hypertension in Three Prospective Cohort Studies, *Hypertension*, 2016, **67**, 288–293.
22 D. Aune, E. Giovannucci, P. Boffetta, L. T. Fadnes, N. Keum, T. Norat, D. C. Greenwood, E. Riboli, L. J. Vatten and S. Tonstad, Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies, *Int. J. Epidemiol.*, 2017, **46**, 1029–1056.
23 X. F. Guo, B. Yang, J. Tang, J. J. Jiang and D. Li, Apple and pear consumption and type 2 diabetes mellitus risk: a meta-analysis of prospective cohort studies, *Food Funct.*, 2017, **8**, 927–934.
24 M. Conceicao de Oliveira, R. Sichieri and A. Sanchez Moura, Weight loss associated with a daily intake of three apples or three pears among overweight women, *Nutrition*, 2003, **19**, 253–256.
25 M. C. de Oliveira, R. Sichieri and R. Venturim Mozzer, A low-energy-dense diet adding fruit reduces weight and energy intake in women, *Appetite*, 2008, **51**, 291–295.
26 E. Alvarez-Parrilla, L. A. De La Rosa, P. Legarreta, L. Saenz, J. Rodrigo-Garcia and G. A. Gonzalez-Aguilar, Daily consumption of apple, pear and orange juice differently affects plasma lipids and antioxidant capacity of smoking and non-smoking adults, *Int. J. Food Sci. Nutr.*, 2010, **61**, 369–380.

27 T. M. Wallace, J. C. Levy and D. R. Matthews, Use and abuse of HOMA modeling, *Diabetes Care*, 2004, **27**, 1487–1495.
28 J. F. Sallis, W. L. Haskell, P. D. Wood, S. P. Fortmann, T. Rogers, S. N. Blair and R. S. Paffenbarger Jr., Physical activity assessment methodology in the Five-City Project, *Am. J. Epidemiol.*, 1985, **121**, 91–106.
29 Z. Sun, Aging, arterial stiffness, and hypertension, *Hypertension*, 2015, **65**, 252–256.
30 S. M. Wallace, Yasmin, C. M. McEniery, K. M. Mäki-Petäjä, A. D. Booth, J. R. Cockcroft and I. B. Wilkinson, Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction, *Hypertension*, 2007, **50**(1), 228–233.
31 C. D. Stehouwer, R. M. Henry and I. Ferreira, Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease, *Diabetologia*, 2008, **51**, 527–539.
32 A. Scuteri, S. S. Najjar, D. C. Muller, R. Andres, H. Hougaku, E. J. Metter and E. G. Lakatta, Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness, *J. Am. Coll. Cardiol.*, 2004, **43**, 1388–1395.
33 D. Mozaffarian, Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review, *Circulation*, 2016, **133**, 187–225.
34 C. M. Weaver, Bioactive foods and ingredients for health, *Adv. Nutr.*, 2014, **5**, 306S–311S.
35 R. Stamler, Implications of the INTERSALT study, *Hypertension*, 1991, **17**, I16–I20.
36 H. Du, L. Li, D. Bennett, Y. Guo, T. J. Key, Z. Bian, P. Sherliker, H. Gao, Y. Chen, L. Yang and J. Chen, Fresh fruit consumption and major cardiovascular disease in China, *N. Engl. J. Med.*, 2016, **374**(14), 1332–1343.
37 P. J. Mink, C. G. Scrafford, L. M. Barraj, L. Harnack, C. P. Hong, J. A. Nettleton and D. R. Jacobs Jr., Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women, *Am. J. Clin. Nutr.*, 2007, **85**, 895–909.
38 J. W. McRorie Jr. and N. M. McKeown, Understanding the Physics of Functional Fibers in the Gastrointestinal Tract: An Evidence-Based Approach to Resolving Enduring Misconceptions about Insoluble and Soluble Fiber, *J. Acad. Nutr. Diet.*, 2017, **117**, 251–264.
39 G. den Besten, K. van Eunen, A. K. Groen, K. Venema, D. J. Reijngoud and B. M. Bakker, The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism, *J. Lipid Res.*, 2013, **54**, 2325–2340.
40 Y. Wu, Y. Qian, Y. Pan, P. Li, J. Yang, X. Ye and G. Xu, Association between dietary fiber intake and risk of coronary heart disease: A meta-analysis, *Clin. Nutr.*, 2015, **34**, 603–611.
41 D. E. King, A. G. Mainous 3rd and C. A. Lambourne, Trends in dietary fiber intake in the United States, 1999–2008, *J. Acad. Nutr. Diet.*, 2012, **112**, 642–648.
42 S. C. Chai, S. Hooshmand, R. L. Saadat, M. E. Payton, K. Brummel-Smith and B. H. Arjmandi, Daily apple versus dried plum: impact on cardiovascular disease risk factors in postmenopausal women, *J. Acad. Nutr. Diet.*, 2012, **112**, 1158–1168.
43 G. C. Tenore, D. Caruso, G. Buonomo, E. D'Urso, M. D'Avino, P. Campiglia, L. Marinelli and E. Novellino, Annurca (Malus pumila Miller cv. Annurca) apple as a functional food for the contribution to a healthy balance of plasma cholesterol levels: results of a randomized clinical trial, *J. Sci. Food Agric.*, 2017, **97**, 2107–2115.
44 S. Auclair, G. Chironi, D. Milenkovic, P. C. Hollman, C. M. Renard, J. L. Megnien, J. Gariepy, J. L. Paul, A. Simon and A. Scalbert, The regular consumption of a polyphenol-rich apple does not influence endothelial function: a randomised double-blind trial in hypercholesterolemic adults, *Eur. J. Clin. Nutr.*, 2010, **64**, 1158–1165.
45 M. R. Vafa, E. Haghighatjoo, F. Shidfar, S. Afshari, M. R. Gohari and A. Ziaee, Effects of apple consumption on lipid profile of hyperlipidemic and overweight men, *Int. J. Prev. Med.*, 2011, **2**, 94–100.
46 N. M. Wedick, A. Pan, A. Cassidy, E. B. Rimm, L. Sampson, B. Rosner, W. Willett, F. B. Hu, Q. Sun and R. M. van Dam, Dietary flavonoid intakes and risk of type 2 diabetes in US men and women, *Am. J. Clin. Nutr.*, 2012, **95**, 925–933.
47 S. J. Zunino, M. A. Parelman, T. L. Freytag, C. B. Stephensen, D. S. Kelley, B. E. Mackey, L. R. Woodhouse and E. L. Bonnel, Effects of dietary strawberry powder on blood lipids and inflammatory markers in obese human subjects, *Br. J. Nutr.*, 2012, **108**, 900–909.
48 S. J. Zunino, D. H. Storms, T. L. Freytag, B. E. Mackey, L. Zhao, J. S. Gouffon and D. H. Hwang, Dietary strawberries increase the proliferative response of CD3/CD28-activated CD8(+) T cells and the production of TNF-alpha in lipopolysaccharide-stimulated monocytes from obese human subjects, *Br. J. Nutr.*, 2013, **110**, 2011–2019.
49 J. Kaur, A comprehensive review on metabolic syndrome, *Cardiol. Res. Pract.*, 2014, **2014**, 943162.
50 C. S. Mantzoros, F. Magkos, M. Brinkoetter, E. Sienkiewicz, T. A. Dardeno, S. Y. Kim, O. P. Hamnvik and A. Koniaris, Leptin in human physiology and pathophysiology, *Am. J. Physiol. Endocrinol. Metab.*, 2011, **301**, E567–E584.
51 S. S. Martin, A. Qasim and M. P. Reilly, Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease, *J. Am. Coll. Cardiol.*, 2008, **52**, 1201–1210.
52 N. Iikuni, Q. L. Lam, L. Lu, G. Matarese and A. La Cava, Leptin and Inflammation, *Curr. Immunol. Rev.*, 2008, **4**, 70–79.
53 A. Pan and F. B. Hu, Effects of carbohydrates on satiety: differences between liquid and solid food, *Curr. Opin. Clin. Nutr. Metab. Care*, 2011, **14**, 385–390.
54 N. C. Øverby, E. Sonestedt, D. E. Laaksonen and B. E. Birgisdottir, Dietary fiber and the glycemic index: a background paper for the Nordic Nutrition Recommendations 2012, *Food Nutr. Res.*, 2013, **57**(1), 20709.