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# Effect of high potassium diet on endothelial function

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**KEYWORDS**
Potassium;
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**Abstract** *Background and aims:* Increased potassium intake is related to reduced blood pressure (BP) and reduced stroke rate. The effect of increased dietary potassium on endothelial function remains unknown. The aim was to determine the effect of increased dietary potassium from fruit and vegetables on endothelial function.
*Methods and results:* Thirty five healthy men and women (age 32 ± 12 y) successfully completed a randomised cross-over study of 2 × 6 day diets either high or low in potassium. Flow mediated dilatation (FMD), BP, pulse wave velocity (PWV), augmentation index (AI) and a fasting blood sample for analysis of Intercellular Adhesion Molecule-1 (ICAM-1), E-selectin, asymmetric dimethylarginine (ADMA) and endothelin-1 were taken on completion of each intervention. Dietary change was achieved by including bananas and potatoes in the high potassium and apples and rice/pasta in the low potassium diet. Dietary adherence was assessed using 6 day weighed food diaries and a 24 h urine sample. The difference in potassium excretion between the two diets was 48 ± 32 mmol/d ($P = 0.000$). Fasting FMD was significantly improved by 0.6% ± 1.5% following the high compared to the low potassium diet ($P = 0.03$). There were no significant differences in BP, PWV, AI, ICAM-1, ADMA or endothelin-1 between the interventions. There was a significant reduction in E-selectin following the high (Median = 5.96 ng/ml) vs the low potassium diet (Median = 6.24 ng/ml), $z = -2.49$, $P = 0.013$.
*Conclusion:* Increased dietary potassium from fruit and vegetables improves FMD within 1 week in healthy men and women but the mechanisms for this effect remain unclear.
*Clinical trial registry:* ACTRN12612000822886.


## Introduction

Endothelial dysfunction precedes the development of atherosclerosis [1], correlates with classical risk factors for and severity of coronary disease [2] and predicts cardiovascular events in those with pre-existing vascular disease [2]. Improvement in endothelial function has been associated with reduced cardiovascular disease (CVD) morbidity and mortality [3] in people with and without pre-existing vascular disease. High potassium intakes have been associated with reduced CVD risk [4]. The effects of potassium on other measures of endothelial function assessed by flow mediated dilatation (FMD) are unclear. He et al. [5] demonstrated that potassium supplementation for 4 weeks improved fasting FMD. Whereas Berry et al. [6] found no effect on FMD by increasing dietary potassium for 6 weeks. He et al. [5] reported a higher mean urinary potassium excretion (125 mmol/d) following the potassium intervention compared to the Berry study (87 mmol/d) suggesting there may be a threshold increase required.

In an acute study we have shown that a 36 mmol potassium meal attenuated the postprandial reduction in FMD [7].

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Arterial stiffness predicts CV risk in the general population [8]. Pulse wave velocity (PWV) is considered as the gold standard method for assessing aortic stiffness, and is a strong predictor of future CV events and all-cause mortality [9]. Augmentation index (AI) is also an index of arterial stiffness [10] and an independent predictor of CV events [11].

This study aimed to determine the effect of increasing dietary potassium on endothelial function after a 6 day feeding period. Our secondary aim was to investigate the effects of dietary potassium on blood pressure, measures of arterial stiffness and to elucidate potential mechanisms for any response. Our hypothesis was that increased potassium intake would improve endothelial function and measures of vascular compliance.

## Methods

### *Study population*

Forty men and women 18–70 y were recruited through personal contact and public advertisement. Inclusion criteria were body mass index (BMI) $\geq$18 and $\leq$30 kg/m$^2$, systolic BP (SBP) $<$ 130 mmHg, diastolic BP (DBP) $<$ 90 mmHg, weight stability in the preceding 6 months, and no use of antihypertensive, cholesterol lowering, systemic steroids, non-steroidal anti-inflammatory medications or folate supplementation. Participants were included if taking other vitamin supplements, provided the dose was kept constant for the duration of the study. Exclusion criteria were known metabolic disease such as liver or kidney disease, treated hypertension, known high cholesterol, clinical CV disease and inability to comprehend study protocol. Of the 48 screened participants, one was excluded due to high BMI, one due to medications, four due to potential difficulties with the diet, two failed to attend first appointments. Forty were enrolled to commence the study (Fig. 1).

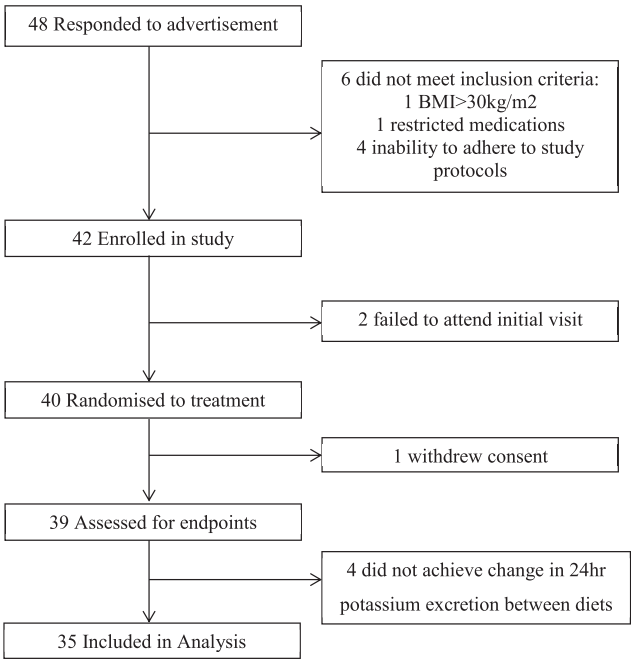


**Figure 1** Diagram of participant recruitment and withdrawal. BMI, body mass index.

## Ethics

This study was approved by University of South Australia's Human Research Ethics Committee (HREC). All participants gave written informed consent.

Ethics approval number: 0000029701.

ANZCTR number: ACTRN12612000822886.

### *Study methods*

Participants completed a randomised single-blinded cross-over design study, over a two week period with a 24 h washout period between the 2 $\times$ 6 day diets. Participants met with a dietitian to ensure eligibility and to assess participants' ability to comply with the dietary protocol. Participants were assigned a diet order by an online generated balanced random number allocation sequence (randomization.com) by a person independent of the study. They received dietary advice from a dietitian for the first diet and then crossed over to the other diet for the second week of the study. Participants completed an online dietary survey (Dietary Questionnaire for Epidemiological Studies, Cancer Council Victoria) prior to commencing the interventions. At the end of each intervention, participants returned fasting for outcome measurements by a person blinded to the interventions.

### *Study diets*

The diets were high potassium (5690 mg/150 mmol/d) and usual potassium (3110 mg/80 mmol/d), achieved by including 300 g banana and 300 g potato (unpeeled) per day in the high potassium diet and rice/pasta (equal portions to replace potatoes) and apples in the low potassium diet. Both diets were designed to ensure weight stability and were $\sim$7000 kJ for women and $\sim$8000 kJ for men. No other diet changes were made. Participants were asked to keep alcohol intake and physical activity consistent, and to refrain from eating out during the study. Participants were given personalised advice by a dietitian on how to achieve diet targets and complete weighed food records for the 2 $\times$ 6 days of the trial. They were given written dietary advice, scales, weighed food diary and key diet foods (e.g. bananas, potatoes or rice/pasta and apples), to aid compliance. Participants prepared all meals at home after the advice was provided. On completion of each intervention the food records were reviewed by the dietitian while the participants were present to ensure accuracy. The food records were analysed using a computerised database of Australian foods (version 7, 2012, Foodworks Professional Edition; Xyris Software, Highgate Hill, Australia).

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### *Weight and height*

Participants had body height (first visit only) measured to the nearest 0.1 cm with a stadiometer (SECA, Germany) while barefoot. Body weight was measured to the nearest 0.05 kg with calibrated electronic digital scales (SECA, Germany) while participants were barefoot wearing light clothing.

### *Flow mediated dilatation*

Endothelium-dependent FMD of the right brachial artery was measured in the longitudinal plane above the antecubital fossa, with an 8.8 MHz linear array transducer (GE Logiq 5 and Samsung Medison MySono U6) as described elsewhere [7]. Measurements were taken under standardised conditions according to published guidelines [12]. Brachial artery diameter was measured before and after forearm ischaemia caused by inflation of a sphygmomanometer cuff applied to the right forearm 2 cm below the olecranon process to 200 mmHg for 5 min. Arterial diameter was measured using ultrasonic callipers at end diastole, incident with the R wave on the electrocardiogram (ECG). Images were recorded before compression, 30 s before cuff release, then every 15 s after cuff release for 3 min [13] and were stored for offline analysis by a single trained observer who was unaware of the diet treatments at the time of measurement (CV for intra observer error is 12%; $n = 32$ calculated in healthy subjects who were scanned on 2 separate occasions after an overnight fast). The FMD response was calculated as the percentage change from the baseline diameter of the artery. Oestrogen grouping was defined as stable (men, postmenopausal women, premenopausal women taking a monophasic oral contraceptive pill) and varied (premenopausal women not taking a monophasic oral contraceptive pill).

### *Pulse wave velocity*

Carotid–femoral (aortic) PWV was measured using a SphygmoCor (AtCor Medical, Sydney, Australia) device, in the supine position by single operator (CV = 6% $n = 7$).

### *Augmentation index*

Augmentation index (AI) was measured using a SphygmoCor (AtCor Medical, Sydney, Australia) device, in the seated position by a single operator (CV = 11%, $n = 5$).

### *Blood pressure*

Brachial blood pressure was measured using a SphygmoCor (AtCor Medical, Sydney, Australia) device, in the seated position by a trained laboratory technician after participants were seated for 2 min. A series of measurements 1 min apart were taken, until four consistent measurements were obtained i.e. systolic within range of 10 mmHg and diastolic within range of 5 mmHg. The first reading was discarded, and three consistent measurements were averaged [14].

### *Laboratory analysis*

Fasting blood samples were collected from a brachial vein into tubes with no additive for measurement of intercellular adhesion molecule-1 (ICAM-1), E-selectin, asymmetric dimethylarginine (ADMA) and endothelin-1. Serum was isolated by centrifugation at 2500 rpm for 10 min and samples were stored at −80 °C until analysed.

Biochemical assays were performed in a single assay on completion of the study. ICAM-1 (eBioscience Human sICAM-1 Platinum ELISA, Jomar Bioscience), E-selectin (eBioscience Humans E-selectin Platinum ELISA, Jomar Bioscience), ADMA (Immunodiagnostik ADMA ELSIA kit, Sapphire Bioscience) and endothelin-1 (Quantikine Human Endothelin-1 ELISA, R&D Systems) were measured in serum by ELISA using a commercially available kits according to manufacturer's instructions.

### *Urinalysis*

A 24 h urine sample was collected following completion of each dietary intervention for measurement of sodium and potassium excretion to assess dietary compliance. Urinary creatinine excretion was used to assess completeness of the sample. Analysis was performed at the Institute of Medical and Veterinary Sciences (IMVS), Adelaide, South Australia.

## Statistical analysis

Power calculations from our previous study [7], with 80% power, $P < 0.05$ to detect a minimum change in FMD of 1.3% absolute, revealed 35 people were required in a cross-over study. The study aimed to recruit 40 participants to allow for drop outs.

All analysis was performed with SPSS 21 for Windows (SPSS Inc., Chicago, IL). Significance was set at $P < 0.05$. Kolmogorov–Smirnov test, Q–Q plots and histograms were used to test for normality of distribution and to ensure that residuals have approximately constant SD. Analyses of variance with repeated measures (with diet as the within-subject factor) was used, with and without covariates including diet order, BP, Age, BMI, oestrogen grouping and habitual potassium intake. Preliminary analyses were performed to ensure no violation of assumptions of linearity. Pearson correlation analyses were conducted to assess the association of change between variables. Data is expressed as mean ± SD or median (interquartile range) as appropriate.

## Results

### *Subjects*

Thirty-five participants completed the study. Baseline characteristics are shown in Table 1. Weight remained stable across diet interventions (High potassium: 61.4 ± 12.9 kg; Low potassium 61.3 ± 12.9 kg; $P = 0.23$).

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### Dietary compliance

Dietary compliance was confirmed by 24 h urinalysis (Table 3). Mean 24 h potassium excretion was higher following the high potassium diet compared to the low potassium diet ($P = 0.001$). Mean change in potassium excretion was 48 ± 32 mmol/day. Sodium excretion was unchanged between treatments (−11 ± 53 mmol/day).

Potassium intake from the weighed food records was different between periods ($P = 0.001$). Potassium intake and excretion were positively correlated following the high and low potassium dietary interventions ($r = 0.57$, $P = 0.001$; and $r = 0.55$, $P = 0.001$ respectively). There was no difference in energy, protein, total fat, saturated fat, sodium, calcium, phosphorus or zinc between the diets. Carbohydrate (28.0 ± 50.4 g/d), sugar (26.9 ± 22.8 g/d), fibre (7.7 ± 5.4 g/d), folate (56 ± 112 μg/d), magnesium (91 ± 76 mg/d), and iron (1.4 ± 3.2 mg/d) intake was higher (all $P < 0.05$) following the high potassium diet compared to the low potassium diet (Table 2).

### Vascular function and blood pressure

FMD was significantly improved following the high potassium diet compared to the low potassium diet (0.6 ± 1.5%, $P = 0.03$).

There were no significant changes in PWV, AI or BP between the diets (Table 3). There was no significant effect of age, BMI, gender, oestrogen group (stable: $n = 16$; variable: $n = 19$) or diet order when used as covariates on FMD, PWV, AI or BP. Baseline BP, age, BMI, oestrogen grouping and habitual potassium intake were not correlated with change in FMD. Baseline SBP was negatively correlated with absolute FMD following the low potassium diet ($r = -0.395$, $P = 0.02$). Following the high potassium diet, DBP and MAP were negatively correlated with FMD (DBP: $r = -0.400$, $P = 0.02$; MAP: $r = -0.370$, $P = 0.03$).

### Biochemical analysis

E-selectin was significantly reduced following the high potassium diet when compared to the low potassium diet (−0.73 ng/ml). There was no significant difference in ICAM-1, ADMA or endothelin-1 between the diets (Table 3). There were no significant correlations between absolute values of FMD and biochemical markers or change in FMD and biochemical markers.

**Table 1** Baseline characteristics of the participants.

| | Mean ± SD |
|---|---|
| Age | 31 ± 11 |
| Baseline weight (kg) | 61.8 ± 12.8 |
| BMI (kg/m$^2$) | 21.7 ± 3.0 |
| Baseline HR (bpm) | 72 ± 12 |
| Baseline SBP (mmHg) | 111 ± 9 |
| Baseline DBP (mmHg) | 66 ± 6 |
| Baseline MAP (mmHg) | 76 ± 6 |
| Potassium intake (mg/day) | 2510 ± 750 |
| (mmol/day) | 64 ± 19 |
| Sodium intake (mg/day) | 2224 ± 818 |
| (mmol/day) | 97 ± 36 |

$n = 35$ (26 women and 9 men); BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure.

**Table 2** Dietary analysis of 6 day weighed food records ($n = 35$).

| | High K | Low K | P |
|---|---|---|---|
| Energy (kJ) | 8441 ± 2309 | 8168 ± 2726 | 0.32 |
| Protein (g) | 83.4 ± 32.2 | 83.3 ± 30.9 | 0.98 |
| Total fat (g) | 69.7 ± 30.4 | 67.9 ± 26.6 | 0.55 |
| Saturated (g) | 25.2 ± 12.1 | 26.1 ± 12.2 | 0.53 |
| Carbohydrate (g) | 245.8 ± 49.7 | 217.8 ± 72.6 | 0.001 |
| Sugars (g) | 116.7 ± 28.9 | 89.8 ± 33.7 | 0.001 |
| Fibre (g) | 29.4 ± 6.6 | 21.8 ± 7.6 | 0.001 |
| Sodium (mg) | 2793 ± 4153 | 2421 ± 1216 | 0.60 |
| (mmol) | 117 ± 172 | 103 ± 51 | |
| Potassium (mg) | 4900 ± 763 | 2462 ± 815 | 0.001 |
| (mmol) | 130 ± 30 | 67 ± 27 | |
| Folate (μg) | 381.0 ± 123.3 | 325.4 ± 128.6 | 0.001 |
| Magnesium (mg) | 390.0 ± 110.5 | 299.3 ± 110.5 | 0.001 |
| Calcium (mg) | 638.0 ± 239.2 | 685.6 ± 300.6 | 0.44 |
| Phosphorus (mg) | 1382 ± 458 | 1347 ± 477 | 0.50 |
| Iron (mg) | 12.6 ± 4.3 | 11.3 ± 4.2 | 0.02 |
| Zinc (mg) | 10.3 ± 4.5 | 10.3 ± 4.2 | 0.92 |

## Discussion

The main outcome of this study was that healthy adults who increased dietary potassium from potatoes and bananas for one week had improved endothelial function as assessed by FMD. The mean change in potassium excretion of 48 mmol/day was approximately 31% less than the planned 70 mmol/day increase. It has previously been demonstrated that improvements in FMD can occur after 2 days of salt reduction [15], and within one week of weight loss [16].

Studies investigating effects of increased potassium on FMD have used varied amounts, source e.g. diet or

**Table 3** Measures of vascular function and blood pressure at the end of each intervention for compliers to the protocol ($n = 35$).[a]

| | High potassium | Low potassium | P |
|---|---|---|---|
| Brachial artery diameter (mm) | 3.67 ± 0.46 | 3.67 ± 0.51 | 1.00 |
| FMD (%) | 7.1 ± 1.8 | 6.5 ± 1.7 | 0.03 |
| PWV (m/s) | 6.1 ± 0.9 | 6.0 ± 0.9 | 0.67 |
| AI (%) | 12.4 ± 6.5 | 13.2 ± 7.7 | 0.31 |
| SBP (mmHg) | 108 ± 9 | 108 ± 9 | 0.85 |
| DBP (mmHg) | 67 ± 8 | 66 ± 7 | 0.09 |
| MAP (mmHg) | 76 ± 7 | 76 ± 6.6 | 0.16 |
| ICAM-1 (ng/mL) | 3.1 ± 0.6 | 3.1 ± 0.7 | 0.73 |
| ADMA (μmol/L) | 0.30 ± 0.8 | 0.30 ± 0.6 | 0.64 |
| Endothelin-1 (pg/ml) | 1.4 ± 0.9 | 1.4 ± 0.8 | 0.68 |
| E-selectin (ng/ml)[b] | 6.0 (3.6–9.3) | 6.2 (3.9–11.7) | 0.013 |
| Potassium excretion (mmol/day) | 94 ± 33 | 46 ± 21 | 0.001 |
| Sodium excretion (mmol/day) | 92 ± 40 | 103 ± 52 | 0.23 |

[a] Mean ± SD (Paired Student's $t$ test).
[b] Median; interquartile range in parentheses (Wilcoxon's signed-rank test).

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supplements and time and reported inconsistent results. Berry et al. [6] found no change in FMD after six weeks of increased potassium intake through fruit and vegetables and potassium citrate. The study reported a maximum increase in mean 24 h potassium excretion of 27 mmol/d in the potassium supplemented treatment. Another study [5] reported an improvement in FMD after four weeks of potassium supplementation with potassium chloride and potassium bicarbonate, with an increase in mean 24 h potassium excretion of 45 and 48 mmol/d, respectively. We have previously demonstrated that a 36 mmol potassium increase is sufficient to protect FMD in the postprandial state [7], and this study provides more evidence that a potassium increase of about 40 mmol/d is required to achieve a benefit in FMD.

Variations in endogenous oestrogen production throughout the menstrual cycle have been reported to potentially influence the vasodilatory response due to increased endothelial NO synthase activity [12], however in the present study there was no effect of oestrogen grouping on FMD.

There were increases of 20–30% in carbohydrate, sugar, fibre, folate, magnesium, and iron intake following the high potassium diet. These changes were not expected based on dietary modelling of the prescribed diets. However these relatively small differences were not correlated with the change in FMD and are not likely to be responsible for the findings.

There was a small significant reduction in E-selectin following the high potassium diet. E-selectin has been shown to be a predictor of atherosclerotic burden [17], and is negatively associated with FMD [18]. Studies have demonstrated E-selectin is also associated with endothelium-independent vasodilation in a hypertensive population [19] and it has been shown that smooth muscle can influence the expression of E-selectin by endothelial cells. Smooth muscle can also express E-Selectin [20]. We did not measure endothelium-independent vasodilation and therefore can only speculate the reduction in E-selectin could have been influenced by a change in smooth muscle function. We speculate that increased potassium intake down regulates E-selectin production. We found no changes in serum levels of ICAM-1, ADMA or endothelin-1. Conversely, Berry et al. [6] reported that a 40 mmol/day increase in dietary potassium significantly reduced ICAM-1 in female participants.

We hypothesise that increasing potassium intake transiently increases serum potassium within the physiological range. This may directly affect the small and intermediate calcium-activated potassium channels of the endothelial cells which are then electrically coupled to the smooth cells – i.e. an endothelium derived hyperpolarizing factor effect [21]. Increased serum potassium may increase NO release, as cellular studies have demonstrated an increase in release of nitrites (an index of NO release) in response to increased extracellular potassium [22]. Increased potassium intake may increase potassium uptake through inward rectifying potassium channels as demonstrated in skeletal muscle cells [23]. Altering the intracellular potassium concentration of endothelial and smooth muscle cells may lead to an increased potassium release into the sub-endothelial space following flow stimulation of the endothelial cell, increasing the smooth muscle response [24].

There were no differences in measures of vascular stiffness despite sufficient power to see a change of 3% in PWV and 6% in AI. This is consistent with a previous study showing no change in PWV following a dietary potassium intervention [6]. In contrast, Matthesen et al. [25] found a moderate increase in PWV following four weeks of 100 mmol/d potassium chloride supplementation. This increase in PWV was accompanied by an increase in plasma aldosterone, which has previously been directly associated with PWV [26]. Another study demonstrated a 64 mmol/d potassium supplement increased serum aldosterone levels [27], but this did not evoke changes in vascular function. Previous studies have shown a decrease in PWV following potassium supplementation which was not large enough to provoke a change in plasma aldosterone concentrations [5]. AI was unchanged in our study and this replicates previous findings showing no change in AI following potassium supplementation [6,25,27].

No change was seen in blood pressure measurements between the diets. Previous studies investigating the effects of potassium interventions on blood pressure have reported inconsistent findings. A recent meta-analysis suggested that increasing potassium intake is effective in reducing blood pressure in hypertensive but not non-hypertensive populations, particularly in the short term [28]. The Trials of Hypertension Prevention (TOHPI) demonstrated no change in blood pressure following 60 mmol/day potassium supplementation [29] and Matthesen et al. [25] found no changed in central blood pressure despite an increase in PWV with a 100 mol/day increase in potassium in normotensive populations. Our study excluded people with blood pressure above 130/90 mmHg and the duration was short, therefore little change was expected. However blood pressure was not a primary outcome and we were underpowered to detect any changes.

Limitations of the study include that the 48 mmol/d difference in potassium excretion between the diets was smaller than the planned difference (70 mmol/d). While statistically significant the increase in FMD on the high potassium diet (0.6 ± 1.5%) was smaller than the 1.3% expected. We did not measure the endothelium-independent response and can therefore not exclude the possibility that the high potassium diet improved smooth muscle responsiveness. The lack of data relating to shear rate and the hyperaemic response is a limitation in interpreting FMD results [30]. Post-hoc analysis revealed the study was underpowered to detect differences in some secondary endpoints.

In conclusion, a high potassium diet improved endothelial function assessed by FMD, and reduced serum E-selectin concentrations. This suggests potassium intake may have protective effects on vascular function although the mechanisms for this effect remain unclear.

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## Author's contributions

JBK and PMC developed the hypotheses tested in the study and designed the research (project conception, development of overall research plan, and study oversight). NB contributed to study design, planned and conducted the study, performed the vascular measurements (hands-on conduct of the experiments and data collection), performed the initial statistical analyses and drafted the manuscript. KSP assisted in conducting the study, performed some vascular measurements (hands-on conduct of the experiments and data collection) and performed the initial dietary analyses. SRW assisted in conducting analysis (laboratory analysis). JBK and PMC contributed to statistical analyses, interpretation of the data and critically reviewed the manuscript.

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