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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Consumption of certain berries appears to slow postprandial glucose absorption, attributable to polyphenols, which may benefit exercise and cognition, reduce appetite and/or oxidative stress. This randomized, cross-over, placebo-controlled study determined whether polyphenol-rich fruits added to carbohydrate-based foods produce a dose-dependent moderation of postprandial glycemic, glucoregulatory hormone, appetite, and ex-vivo oxidative stress responses. Twenty participants (18M/2F; 24±5 yr; BMI: 27±3 kg/m <sup>2</sup> ) consumed one of five cereal bars (~88% carbohydrate) containing no fruit ingredients (reference), freeze-dried black raspberries (10% or 20% total weight; LO-R and HI-R, respectively), and cranberry extract (0.5% or 1% total weight; LO-C and HI-C), on trials separated by ≥5 d. Postprandial peak/nadir from baseline (Δ <sub>max</sub> ) and incremental postprandial area-under-the-curve (AUC) over 60- and 180-min, for glucose and other biochemistries were measured. Fortification with freeze-dried black-raspberries (~25 g, containing 1.2 g of polyphenols) seems to slightly improve the glucoregulatory hormone and glycemic responses to a high-carbohydrate food item in young adults, but did not affect appetite or oxidative stress responses.					
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# **U.S. Army Research Institute of Environmental Medicine**

*Natick, Massachusetts*

**TECHNICAL REPORT NO. T19-09**

**DATE: 1 APRIL 2019**

**GLYCEMIC REGULATION, APPETITE, AND EX-VIVO OXIDATIVE STRESS IN  
YOUNG ADULTS FOLLOWING CONSUMPTION OF HIGH CARBOHYDRATE  
CEREAL BARS FORTIFIED WITH POLYPHENOL-RICH BERRIES**

**Approved for Public Release; Distribution Is Unlimited**

**United States Army  
Medical Research & Materiel Command**

**1 ABSTRACT**

2 Consumption of certain berries appears to slow postprandial glucose absorption, attributable to  
3 polyphenols, which may benefit exercise and cognition, reduce appetite and/or oxidative stress.  
4 This randomized, cross-over, placebo-controlled study determined whether polyphenol-rich  
5 fruits added to carbohydrate-based foods produce a dose-dependent moderation of postprandial  
6 glycemic, glucoregulatory hormone, appetite, and ex-vivo oxidative stress responses. Twenty  
7 participants (18M/2F; 24±5 yr; BMI: 27±3 kg/m<sup>2</sup>) consumed one of five cereal bars (~88%  
8 carbohydrate) containing no fruit ingredients (reference), freeze-dried black raspberries (10% or  
9 20% total weight; LO-R and HI-R, respectively), and cranberry extract (0.5% or 1% total weight;  
10 LO-C and HI-C), on trials separated by ≥5 d. Postprandial peak/nadir from baseline ( $\Delta_{\max}$ ) and  
11 incremental postprandial area-under-the-curve (AUC) over 60- and 180-min, for glucose and  
12 other biochemistries were measured to examine dose-dependent effects. Glucose AUC<sub>0-180mins</sub>  
13 trended towards being higher (43%) after HI-R versus LO-R (P=0.06), with no glucose  
14 differences between the raspberry and reference bars. Relative to reference, HI-R resulted in a  
15 17% lower  $\Delta_{\max}$  insulin, 3% lower C-peptide (AUC<sub>0-60mins</sub>) and 3% lower GIP (AUC<sub>0-180mins</sub>)  
16 p<0.05. No treatment effects were observed for the cranberry bars regarding glucose and  
17 glucoregulatory hormones, nor were any treatment effects noted for either berry-type regarding  
18 ex-vivo oxidation, appetite mediating hormones, or appetite. Fortification with freeze-dried  
19 black-raspberries (~25 g, containing 1.2 g of polyphenols) seems to slightly improve the  
20 glucoregulatory hormone and glycemic responses to a high-carbohydrate food item in young  
21 adults, but did not affect appetite or oxidative stress responses at doses or with methods studied  
22 herein. **Clinical Trials Registration Number:** NCT02763020

23 **Key words:** polyphenols, tannins, glycemia, appetite, oxidative stress, young adults

24  
25 A sustained postprandial glycemic response is advantageous for facilitating physical and  
26 cognitive performance <sup>(1; 2; 3; 4; 5)</sup>. Working memory and selective attention, for example, were  
27 improved in the later postprandial period following consumption of a food item (bread enriched  
28 with guar gum) that elicited higher net glucose availability in the postprandial period compared  
29 to a reference food item (bread without guar gum). Additionally, evidence suggests that  
30 consuming moderate glycemic index foods 1-2 hours prior to exercise better maintains  
31 euglycemia and maximizes carbohydrate oxidation during endurance exercise versus high  
32 glycemic index foods which result in lower net glucose availability during the postprandial  
33 period <sup>(1; 2; 3)</sup>. Additionally, slowing glucose absorption prevents postprandial hyperinsulinemia,  
34 which in turn causes a rapid drop in blood glucose to below fasting concentrations. The resulting  
35 relative hypoglycemia initiates a counter-regulatory hormone response that promotes  
36 gluconeogenesis, glycogenolysis, free fatty acid release, and oxidative stress <sup>(6)</sup>. Given the  
37 popularity of foods high in rapidly-digested carbohydrate and the advantages of promoting a  
38 sustained glycemic response to promote physical and cognitive performance, there is substantial  
39 interest in developing food products that moderate postprandial glycemic responses <sup>(7)</sup>.

40 Polyphenols are a heterogeneous group of phytochemicals found in plant-based foods,  
41 many of which display antioxidant and anti-inflammatory properties, but which are also thought  
42 to modulate carbohydrate metabolism <sup>(7)</sup>. In support, some studies have shown that whole  
43 berries, berry extracts, apple extract or juice, and a mixture of polyphenol and fibre-rich foods  
44 (e.g., green tea, apple peel and freeze-dried berry powders) modulate the glycemic response  
45 following consumption of sugar water or starch-based food items <sup>(8; 9; 10; 11; 12; 13; 14)</sup>. For example,  
46 Torronen et al. <sup>(13; 14)</sup> demonstrated that consuming polyphenol-rich berry nectars or berry purees  
47 with a high-carbohydrate food favorably modulated postprandial glycemia in healthy adults by

48 slowing glucose absorption, and enhancing insulin and glucagon-like peptide-1 (GLP-1)  
49 secretion. However, an acknowledged limitation of those studies was a higher dietary fiber  
50 content and viscosity of the berry interventions relative to control, as both fiber and viscosity  
51 influence postprandial glycemia and endocrine responses. In contrast, studies by Castro-Acosta  
52 (2016 and 2017) observed a blunted glycemic response when a starchy meal was provided with  
53 polyphenol-rich apple and blackcurrant extracts (i.e., devoid of fiber). With regard to  
54 mechanisms of the glycemic and glucoregulatory hormone modulation, *in vitro* and animal  
55 studies suggest that polyphenols, including those found in berries and in extracts of polyphenol-  
56 rich foods, can inhibit the carbohydrate digestive enzymes  $\alpha$ -amylase and  $\alpha$ -glucosidase, slow  
57 glucose absorption, modulate secretion of insulin and/or the incretin hormones glucose-  
58 dependent insulintropic polypeptide (GIP) and GLP-1<sup>(9; 14; 15)</sup>, and stimulate glucose uptake into  
59 insulin-sensitive tissues through increased activation of insulin receptors<sup>(7)</sup>. As such, polyphenol  
60 fortification of high carbohydrate foods may help improve postprandial glycemic control. This  
61 could have the added benefits of reducing free fatty acid release and oxidative stress<sup>(16)</sup>, and  
62 preventing increases in appetite that may result from rapid drops in blood glucose concentrations  
63<sup>(7)</sup>.

64 Our group and others have previously reported that cranberry and black raspberry  
65 polyphenols inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase activities *in vitro*<sup>(17; 18; 19)</sup>. The primary  
66 objective of this study was to translate those findings to human metabolism by determining dose-  
67 response effects of fortifying a high carbohydrate food with freeze-dried black raspberries or  
68 with cranberry extract on postprandial glycemia (i.e., glucose incremental area under the curve  
69 with respect to baseline, AUC, 0-180 mins) in healthy adults. Fortified and non-fortified cereal  
70 bars were created that were approximately matched for fiber, macronutrients, and

71 physicochemical characteristics. Secondary objectives were to determine effects on postprandial  
72 glucoregulatory hormone responses, appetite, and ex-vivo oxidative stress. We hypothesized  
73 that polyphenol fortification would result in a dose-dependent improvement in postprandial  
74 metabolic profiles, and reduce appetite and ex-vivo oxidative stress.

75

## 76 **Materials and methods**

### 77 *Participants*

78 Participants were military and civilian personnel assigned to Natick Soldier Systems Center,  
79 Natick, MA. Twenty of the 21 participants who were enrolled and began the study completed data  
80 collection and were included in the data analyses. One participant was withdrawn from the study  
81 prior to consuming any of the cereal bars due to multiple failed catheter placements. Data collection  
82 occurred from January to November 2016 at the U.S. Army Research Institute of Environmental  
83 Medicine (Natick, MA). Each participant gave their written, informed consent after an oral  
84 explanation of the study. Men and women were included if they were 18-39 yr, were generally  
85 healthy, and had no history of liver disease, alcoholism, impaired glucose metabolism, thyroid  
86 disease, bleeding disorders, or GI-related conditions that may impact glucose absorption, and had no  
87 allergy or aversion to any of the test foods. The study was approved by the Institutional Review  
88 Board, U.S. Army Research Institute of Environmental Medicine. Investigators adhered to the  
89 policies for protection of human subjects as prescribed DOD Instruction 3216.02 and the research  
90 was conducted in adherence with the provisions of 32 CFR Part 219. The Clinicaltrials.gov  
91 identifier is NCT02763020.

92

### 93 *Design*

94

95 This was a randomized, placebo-controlled, cross-over trial, conducted over five  
96 experimental sessions each separated by  $\geq 5$ d ( $9.5 \pm 5.2$  days). Participants were assigned to  
97 experimental conditions using on-line software, Research Randomizer ([www.randomizer.org](http://www.randomizer.org)).  
98 Flavor profile and color of the bars provided some indication of the fruit contents, however,  
99 participants were unaware of which bars contained high versus low doses of the fruit ingredients.  
100 Study participants received written and verbal instructions to consume a low-polyphenol diet for two  
101 consecutive days prior to each session. Participants also consumed a provided dinner meeting  
102 approximately 1/3 of their estimated weight maintenance energy requirements the evening before  
103 testing.

104 On test days, participants arrived following a  $\geq 12$ hr overnight fast. Adherence to pre-trial  
105 dietary restrictions and consumption of the standardized dinner meal was verified using food records  
106 which were reviewed by research dietitians during each session. Following IV catheter placement,  
107 participants consumed one of five cereal bars in  $\leq 15$ min. After bar consumption, overall  
108 acceptability was rated on a Likert scale ranging from 1 (dislike extremely) to 9 (like extremely).  
109 Blood samples were collected and appetite was rated before and periodically for 180min after bar  
110 consumption, in order to detect both the early and late postprandial responses of the outcome  
111 measures and to facilitate the ad libitum lunch test by providing a more realistic time frame between  
112 the “breakfast” and lunch meals.. During the 180min postprandial period participants remained  
113 seated and supervised, and were not provided additional food or beverages other than 360 g of water.  
114 After 180min, energy intake was measured during an *ad libitum* lunch.

#### 115 *Description of high-carbohydrate snack bars*

116

117 Five different fiber and macronutrient-matched high-carbohydrate cereal bars were tested  
118 (*Table 1*). The placebo bar contained no freeze-dried fruit or fruit extract. Two bars contained

119 freeze-dried black raspberries [10% (LOW-Rasp) or 20% (HIGH-Rasp) total weight], and two  
120 bars contained cranberry extract [0.5% (LOW-Cran) or 1.0% (HIGH-Cran) total weight]. The  
121 base bar consisted of rice crisp cereal, marshmallows, butter, and vanilla extract. The bar was  
122 loosely modeled after a Rice Krispie Treat (Kellogg Company, Battle Creek, MI), in an effort to  
123 promote palatability and to provoke marked glycemia, which was necessary for testing the  
124 efficacy of polyphenol supplementation to moderate the glycemic response.

125 Fructose powder, glucose powder or wheat bran was added to the bars, in order to  
126 approximately match sugar and fiber content between bars. The cranberry extract and raspberry  
127 powder were chosen based on their polyphenolic content and previous work by members of our  
128 group and others suggesting that the polyphenol components (e.g., anthocyanins and  
129 proanthocyanidines) in these fruits effectively inhibited  $\alpha$ -amylase and glucoamylase activity *in*  
130 *vitro* <sup>(17; 18; 19)</sup>. The LOW-Rasp and HI-Rasp bars contained approximately 0.6 and 1.2 g of total  
131 polyphenols, respectively, based on gram weight of the bars (Table 1) and data indicating that  
132 black raspberries contain 0.98 g of polyphenols per 100 g of whole fruit<sup>(20)</sup> (i.e., or ~5.1 g  
133 polyphenols per 100 g of freeze-dried black raspberry powder). The LOW-Cran and HI-Cran  
134 bars contained 0.3 and 0.6 g of polyphenols, respectively, based on gram weight of the bars  
135 (Table 1) and data indicating that the cranberry extract contains 45 g of polyphenols per 100 g of  
136 extract<sup>(21)</sup>. The polyphenols contained within HI-R and LO-R were mostly anthocyanins,  
137 ellagitannins, ellagic acid and quercetin<sup>(20; 22)</sup>, while the HI-C and LO-C mainly consisted of  
138 flavanols (e.g., epicatechin), flavonols (e.g., quercetin) and phenolic acids (e.g., benzoic acid and  
139 chlorogenic acid), in addition to other polyphenolic compounds<sup>(21)</sup>. The highest dose of each fruit  
140 was based on the maximum dose that could be incorporated without compromising organoleptic  
141 properties of the bars. The lower doses were included to assess dose-response effects.

142 *Blood sampling*

143

144 An indwelling catheter was placed in the participants' forearm or antecubital space upon

145 arrival to the testing site. Blood samples were taken after catheter placement and every 15 mins

146 for the first hour and every 30-min thereafter (up to 180 minutes) following bar consumption.

147 Whole blood was collected into serum tubes for measurement of glucose, insulin, and C-peptide,

148 and chilled EDTA tubes for measurement of GIP, GLP-1, and acylated ghrelin. EDTA tubes

149 contained 4-(2-aminoethyl)-benzenesulfonyl fluoride, hydrochloride (100 mM; 50  $\mu$ L/mL whole150 blood), dipeptidyl peptidase inhibitor IV (10  $\mu$ L/mL whole blood), and aprotinin (500 KIU/mL

151 whole blood). Following serum and plasma separation, samples were stored at -80°C until

152 analysis.

153 Glucose was measured on a Siemens Dimension Xpand Plus clinical chemistry analyzer,

154 while insulin and C-peptide were measured on a Siemens Immulite 2000 immunoassay system.

155 GIP, active GLP-1, and acylated ghrelin were measured using the Milliplex MAP human

156 metabolic hormone panel (Millipore; Billerica, MA) according to manufacturer instructions.

157 Assay sensitivity was 0.6 pg/mL for GIP, 1.2 pg/mL for GLP-1, and 13 pg/mL for acylated

158 ghrelin.

159 *Ex-vivo LDL resistance against Cu<sup>2+</sup>-induced oxidation*

160

161 Postprandial oxidative stress is regarded as a secondary response to postprandial

162 hyperglycemia and hypertriglyceridemia<sup>(23)</sup>. While there are many markers for assessment of

163 oxidative stress, LDL oxidation was selected as a biomarker because of the involvement of

164 oxidized LDL in the development of atherosclerosis. For example, Natella et al. reported that

165 postprandial LDL was more susceptible to metal-catalyzed oxidation than the homologous

166 baseline LDL after an ethanol meal<sup>(24)</sup>. It was anticipated that postprandial hyperglycemia may

167 have the same impact on LDL susceptibility to oxidation as acute hyperglycemia-induced  
168 oxidative stress in healthy people<sup>(25)</sup>.

169 Plasma was mixed with sucrose (0.6% final concentration), aliquoted, and stored at -80°C.  
170 An ex-vivo LDL oxidation assay was performed within 2 months of the sample collection. LDL  
171 (1.019-1.063 g/mL) was collected from the frozen plasma according to Chung et al. using a  
172 Beckman NVT-90 rotor (or similar) in a Beckman L8-M centrifuge (or similar) (Palo Alto, CA)  
173 <sup>(26)</sup>. After salt removal using a desalting PD-10 column (Bio-Rad, Hercules, CA), the concentration  
174 of LDL was determined using a BCA protein assay kit (Pierce; Rockford, IL or similar). Ex-vivo  
175 LDL oxidation induced by Cu<sup>2+</sup> was performed according to the method described by Chen et al.  
176 <sup>(16)</sup>. Formation of conjugated dienes was monitored by absorbance at 234 nm at 37°C for 6-h using  
177 a Shimadzu UV1800 spectrophotometer (Japan) equipped with a 6-position automated sample  
178 changer. The results of the assay are expressed as lag time, the intercept at the abscissa in the  
179 diene-time plot.

#### 180 *Plasma flavonoids and phenolic acids*

181  
182 Flavonoids (including the flavanols catechin and epicatechin and the flavonols quercetin,  
183 myricetin, and isorhamnetin) and phenolic acids (including protocatechuic, phenylacetic, gentisic  
184 acid, benzoic acid, sinapic, caffeic, ferulic, vanillic, and p-coumaric acids) in plasma were  
185 determined according to Chen et al. (2005), in order to provide insight into oxidative stress  
186 results <sup>(16)</sup>. Briefly, plasma was incubated with vitamin C-EDTA and β-glucuronidase/sulfatase at  
187 37°C for 45 min. Phenolic acids and flavonoids in the resulting mixture were extracted with  
188 acetonitrile, dried under purified N<sub>2</sub> gas, and reconstituted with mobile phase A for HPLC  
189 analysis using a ESA CoulArray System (ESA, Inc. Chelmsford, MA). Analyte separation was  
190 achieved using a Zorbax ODS C18 column (4.6 x 250 mm, 3.5 μm). Quantification of phenolic

191 acids and flavonoids in unknown samples were calculated based on standard curves constructed  
192 using authentic standards with adjustment for the internal standard (4'-hydroxy-3'-  
193 methoxyacetophenone).

#### 194 *Appetite testing*

195  
196 Two separate visual analog scales were administered before each blood sample collection  
197 to measure self-perceived appetite<sup>(27)</sup>. Participants rated their levels of hunger and fullness by  
198 marking anywhere on a 10-cm scale anchored by phrases representing opposite extremes of a  
199 spectrum (e.g., “not at all hungry” and “extremely hungry”).

200 An *ad libitum* lunch was served within 10min after the final blood sample to provide an  
201 objective measure of appetite<sup>(28; 29)</sup>. The meal consisted of Stouffer’s lasagna (41%  
202 carbohydrate, 36% fat, 23% protein) and 240g water. Participants were served  $1653 \pm 57$ g and  
203 instructed to eat until “comfortably full”. The amount of uneaten lasagna was weighed to  
204 calculate energy intake.

#### 205 *Statistical analysis*

206 Sample size estimates based on peak postprandial glucose concentrations, and using  
207 mean and variance data from Torronen et al.<sup>(13; 14; 30)</sup> indicated that 20 participants would allow  
208 detection of a 0.9 mmol/L (~15 mg/dL) difference in peak glucose between trials with power =  
209 0.8 and  $\alpha = 0.01$  to account for multiple comparisons.

210 Statistical analyses were conducted using the IBM SPSS statistical package version 24.0  
211 (IBM Inc., Armonk, New York). Data were examined for outliers both quantitatively and  
212 graphically, and normal distribution of data was examined via the Shapiro-Wilk test. All data,  
213 except glucose, appetite ratings, energy intake, and LDL lag were  $\log_{10}$ -transformed for analysis  
214 to normalize distributions. Values that were below the assay limits of detection (13% of values

215 for GLP-1, 2% for ghrelin, 4% for insulin) were replaced with the lowest detectable limit for that  
216 assay prior to analysis.

217 Time to peak (i.e., for glucose, insulin, GLP-1, GIP, C-peptide) or nadir (i.e., for ghrelin)  
218 concentrations, change from baseline (time 0) to peak (i.e., for glucose, insulin, GLP-1, GIP, C-  
219 peptide, fullness) or nadir (i.e., for ghrelin, hunger) concentrations ( $\Delta_{\max}$ ), and incremental area  
220 under the curve with respect to baseline (AUC) from 0-60min and 0-180min were computed for  
221 all outcomes to standardize the results and used in the analyses to detect any differences between  
222 bars with regards to initial (AUC 0-60) and overall (AUC 0-180) postprandial responses.

223 Analyses were run separately for the raspberry and cranberry interventions because the study  
224 objective was to assess dose-response effects within each intervention type and not to compare  
225 interventions. Data were analyzed using marginal models to test for main effects of treatment.  
226 Baseline (i.e., time 0min) values were entered as covariates in the models, and carry-over effects  
227 were assessed by including terms for treatment order and its interaction with treatment. These  
228 terms were removed from the model if not significant. When significant main effects of  
229 treatment were observed all possible t-tests were conducted using the Bonferroni correction to  
230 adjust for multiple comparisons. The Kruskal-Wallis test was used to test for main effects of  
231 treatment on plasma flavonoid/phenolic acid content, because transformations did not normalize  
232 the data distribution. When significant main effects of treatment were observed, Mann-Whitney  
233 tests were conducted using Bonferroni corrections to adjust for multiple comparisons. Results are  
234 presented as mean  $\pm$  SD, unless otherwise noted. Two-tailed p-values  $\leq 0.05$  were considered  
235 statistically significant, and p-values  $\leq 0.10$  were considered trends.

## 236 **Results**

237

238 *Participant characteristics*

239

240 Eighteen men and two women completed the study (age:  $24 \pm 5$  years; BMI:  $26.8 \pm 3.5$   
241  $\text{kg/m}^2$ ) (**Figure 1**). Energy and macronutrient intake in the two days before each trial, and in the  
242 evening meal prior to each trial, did not differ across trials ( $P > 0.6$ ) (*Table 1*). Body weight, and  
243 fasting glucose and insulin concentrations did not differ across trials ( $P > 0.3$ ) (*Table 2*). Relative to  
244 the reference, overall acceptability of the bars was rated lower for HI-Rasp, and both cranberry bars  
245 (main effect of treatment,  $P \leq 0.02$ ) (*Table 3*).

#### 246 *Glucose*

247  
248 Within the raspberry treatments, there was a significant treatment effect on the overall  
249 glucose response ( $P = 0.04$ ) wherein a trend for a higher glucose  $\text{AUC}_{0-180\text{min}}$  was observed  
250 during HI-Rasp versus LO-Rasp ( $P = 0.06$ ; *Figure 2A*). Glucose  $\Delta_{\text{max}}$ , time to peak and  $\text{AUC}_{0-}$   
251  $_{60\text{min}}$  was not affected by treatment (*Table 4*).

252 The cranberry treatments had no effect on the postprandial glucose response (*Table 4 and*  
253 *Figure 2B*).

#### 254 *Insulin*

255  
256 Within the raspberry treatments, there was a significant treatment effect on insulin  $\Delta_{\text{max}}$   
257 ( $P = 0.02$ ), wherein the HI-Rasp response was lower relative to the reference (*Table 4 & Figure*  
258 *3*). There were no effects of the raspberry treatments on time to peak insulin or insulin  $\text{AUC}_{0-}$   
259  $_{60\text{min}}$  or  $\text{AUC}_{0-180\text{min}}$  (*Table 4 and Figure 2C*).

260 The cranberry treatment had no effects on the postprandial insulin response (*Table 4*  
261 *Figure 2D*).

#### 262 263 *C-peptide*

264  
265 Within the raspberry treatments (*Figure 2E*), there was a significant treatment effect ( $P =$   
266  $0.01$ ), wherein participants C-peptide  $\text{AUC}_{0-60}$  was lower during HI-Rasp ( $247 \pm 117$  ng/dL)

267 compared to the reference ( $279 \pm 243$  ng/dL), but there was no effect on  $AUC_{0-180}$  or time to  
268 peak C-peptide (*Table 4*)

269 The cranberry treatments had no effects on the postprandial C-peptide response (*Table 4*  
270 *and Figure 2F*).

271  
272 *Glucagon-like peptide-1 (GLP-1)*

273  
274 Within the raspberry treatments, there was a trend for a treatment effect ( $P = 0.09$ ),  
275 wherein GLP-1  $\Delta_{max}$  trended towards being lower during HI-Rasp relative to the reference  
276 (*Table 4 & Figure 3A*). No differences in time to peak GLP-1,  $AUC_{0-60min}$  or  $AUC_{0-180min}$  were  
277 observed (*Figure 3A*).

278 Within the cranberry treatment, a carryover effect was noted for GLP-1  $AUC_{0-180min}$ .  
279 After removing the treatment sequence responsible for the carryover effect, no differences across  
280 treatments were observed. No differences in time to peak GLP-1 or GLP-1  $\Delta_{max}$  were observed  
281 (*Table 4*).

282 *Glucose-dependent insulinotropic polypeptide (GIP)*

283  
284 Within the raspberry treatments, there were significant treatment effects on the overall  
285 GIP response ( $p < 0.05$ ), wherein  $AUC_{0-60}$  and  $AUC_{0-180}$  for GIP was significantly lower  
286 following consumption of the HI-Rasp versus LO-Rasp and/or reference bar (*Figure 3C*). There  
287 was also a significant treatment effect ( $P = 0.01$ ), wherein GIP  $\Delta_{max}$  was lower after participants  
288 consumed HI-Rasp versus LO-Rasp, but no effect on time to peak GIP was observed (*Table 4*).

289 The cranberry treatment had no effect on postprandial GIP response (*Table 4 and Figure*  
290 *3D*).

291 *Ghrelin*

292  
293 The raspberry treatments had no effects on the postprandial acylated ghrelin response  
294 (*Table 4 and Figure 3E*).

295           Within the cranberry treatment, there was a trend ( $P = 0.07$ ) for a treatment effect  
296 wherein the acylated ghrelin  $AUC_{0-180min}$  trended towards being more negative (i.e., larger  
297 decrease) during HI-Cran relative to LO-Cran ( $P = 0.08$ ). There was no effect of cranberry  
298 treatment on the maximal decrease in acylated ghrelin from baseline or time to nadir (*Table 4 &*  
299 *Figure 3F*).

### 300 *Ex-vivo LDL resistance against Cu<sup>2+</sup>-induced oxidation*

301  
302           There was no treatment effect when the raspberry bars were compared to one another  
303 and/or the reference bar (*Figure 4A*).

304           There were no treatment, time or treatment x time interactions when the cranberry bars  
305 were compared to one another and/or the reference bar (*Figure 4B*).

### 306 *Flavonoids and phenolic acids*

307  
308           The raspberry treatment had no effects on plasma concentrations of measured flavonoids  
309 or phenolic acids (select phenolic acids shown in *Figures 5 & 6*).

310           Within the cranberry treatment, there were significant treatment effects on the plasma  
311 concentrations of phenolic acids (i.e., gentisic, vanillic, caffeic, coumaric, ferulic and sinapic  
312 acids,  $p < 0.05$ ), but not flavonoids. Most notably, post-hoc testing indicated that gentisic acid was  
313 significantly higher after HI-cran versus LO-cran and/or the reference bar; coumaric, ferulic and  
314 sinapic acids were significantly higher after consumption of HI-cran and LO-cran compared to  
315 the reference bar; and, vanillic acid and caffeic acid were significantly higher after LO-cran or  
316 HI-cran, respectively, versus the reference bar ( $p < 0.02$ ) (*Figures 5 & 6*).

### 317 *Appetite*

318  
319           Within the raspberry treatments, there was a trend for a main effect of treatment on *ad*  
320 *libitum* energy intake ( $P = 0.10$ ), but post hoc testing did not indicate significant differences

321 between treatments. The raspberry treatments did not impact postprandial hunger or fullness  
322 ratings (*Table 5*).

323         Within the cranberry treatments, there was a trend for a main effect of treatment on  
324 fullness AUC<sub>0-180min</sub> (P=0.06) with post hoc comparisons indicating a trend for lower fullness  
325 during HI-Cran relative to the reference bar (P = 0.06). A trend for a main effect of treatment on  
326 the peak change in fullness (P = 0.08) was also observed, but post hoc testing did not indicate  
327 significant differences between treatments. The cranberry treatments did not impact hunger  
328 ratings or *ad libitum* energy intake (*Table 5*).

### 329 **Discussion**

330         The main findings of this study were that fortifying a high-carbohydrate cereal bar with a  
331 high-dose, but not a smaller-dose, of freeze-dried raspberries blunted postprandial peak insulin  
332 and incretin hormone responses compared to an unfortified bar, and tended to increase  
333 postprandial glucose AUC, but not peak concentrations. Together, these findings suggest that  
334 fortifying a high-carbohydrate bar with a high dose, but not a smaller dose, of freeze-dried black  
335 raspberry powder attenuated postprandial insulinemia and slowed glucose absorption. These  
336 results are supported by reduced GIP concentrations following consumption of the high-dose  
337 raspberry bar, as GIP is a sensitive marker of intestinal glucose uptake and no differences in  
338 plasma glucose concentrations were observed in the 60-min postprandial period when the  
339 predominant influence on blood glucose is absorption rate). These effects did not result in  
340 differences in appetite or ex-vivo LDL resistance against oxidation, and fortification with a  
341 polyphenol-rich cranberry extract did not elicit similar effects.

343         Our findings demonstrate that the high-dose raspberry bar favorably modulated  
344 postprandial glucose and glucoregulatory hormone responses. The 43% higher postprandial

345 glucose AUC, but no difference in peak glucose concentrations, following consumption of the  
346 high-dose compared to the low-dose raspberry bar suggests delayed glucose absorption or uptake  
347 into peripheral tissues. The former response could reduce the postprandial insulin demand <sup>(7; 31)</sup>,  
348 while the latter could be driven by lower postprandial insulin concentrations. Although  
349 diminished postprandial insulinemia was not observed when comparing the high-dose to low-  
350 dose raspberry bar, the high-dose bar did show a modest blunting of postprandial insulin, C-  
351 peptide and glucoregulatory hormones responses when compared to the reference bar which is  
352 consistent with other studies <sup>(14; 15)</sup>. The insulinemic response to the high dose black raspberry  
353 bar, compared to the reference, is consistent with the observation that C-peptide was lower in the  
354 60 minutes following consumption of the high-dose black raspberry bar compared to the  
355 reference. C-peptide is not used by the liver and other organs, thus it is a more sensitive  
356 biomarker for endogenous insulin secretion compared to insulin itself due to unknown variability  
357 in tissue clearance of insulin<sup>(32)</sup>. *In-vitro* studies demonstrating that polyphenols extracted from a  
358 variety of flavanol-rich foods inhibit digestive enzymes—specifically *α*-amylase, *α*-glycosidase,  
359 and glucoamylase—during the breakdown of dietary carbohydrates into glucose <sup>(17)</sup> provide a  
360 plausible mechanism. For example, recent *in vitro* studies demonstrate the inhibitory effects of  
361 different plants/extracts (e.g., grapeseed extract and African pear fruit) on *α*-amylase and *α*-  
362 glycosidase <sup>(11; 33; 34; 35; 36)</sup>. Additionally, the raspberry powder used in the current study has  
363 exhibited similar effects *in vitro*, and these actions would be expected to inhibit starch digestion  
364 and slow glucose absorption <sup>(7; 13; 14; 19)</sup>. Alternately, the blunted GIP and GLP-1 responses  
365 following the high-dose fortification could underpin the lower postprandial C-peptide and insulin  
366 concentrations which could slow glucose uptake into peripheral tissues. Regardless of the  
367 mechanism, previous studies suggest that one possible advantage of slowed glucose absorption

368 and/or uptake is improved physical and cognitive performance, especially during exercise <sup>(1; 2; 3; 4;</sup>  
369 <sup>5)</sup>.

370 We acknowledge the inconsistency of not finding evidence for delayed glucose  
371 absorption when comparing the high-dose raspberry and reference bar despite the blunted insulin  
372 and glucoregulatory hormone responses. However, consistent with our results three prior studies  
373 reported that the initial insulin response to a glucose beverage or starch-based food (i.e., bread)  
374 was attenuated by berries with little or no appreciable effect on glycemic response <sup>(37; 38; 39; 40)</sup>.  
375 These findings suggest an alternative mechanism whereby postprandial glucose metabolism may  
376 require less insulin when polyphenol-rich foods are consumed with high carbohydrate foods,  
377 compared to high carbohydrate foods alone <sup>(37; 39; 40; 41; 42)</sup>. Although the underpinning  
378 mechanisms have not been clearly defined, polyphenols may possibly act acutely to improve  
379 insulin sensitivity in peripheral tissue <sup>(7; 31; 39; 40)</sup>. We also acknowledge the inconsistency in the  
380 observation that the overall glucose response ( $AUC_{0-180 \text{ min}}$ ) was higher following consumption  
381 of HI-R versus LO-R, in the absence of a higher overall insulin response. This suggest a lack of  
382 compensatory insulin secretion, possibly secondary to a lower overall GIP response given that  
383 GIP is an incretin hormone. Indeed, inhibition of GIP has been observed in response to  
384 anthocyanin-rich black-currents <sup>(8)</sup>. As suggested by others, this effect may be attributable to  
385 delayed glucose uptake in response to polyphenols as GIP is secreted from the proximal region  
386 of the small intestine, whereas glucose absorption may be occurring more distally because of the  
387 polyphenols <sup>(8; 10)</sup>.

388 The observed effects of fortifying high-carbohydrate foods with polyphenol-rich foods on  
389 postprandial glycemia were similar in magnitude (with regard to AUC) to a recent study that  
390 supplemented starch (i.e., white bread) with a mixture of polyphenol and fibre-rich foods (e.g.,

391 green tea powder, apple peel, blackberry, blackcurrent, and strawberry freeze-dried powders)<sup>(11)</sup>,  
392 but less pronounced than those reported in other studies <sup>(13; 14; 30)</sup>. While the estimated amounts  
393 of total polyphenols were similar between this study and those of Torronen et al , it is possible  
394 that the type of polyphenols provided, as well as the fiber content and viscosity of the test meals,  
395 may be partially responsible for this discrepancy. For example, prior trials demonstrating a  
396 substantially altered glycemic response used whole berries or berry purees consisting mainly of  
397 anthocyanins and proanthocyanidins <sup>(13; 14; 30)</sup>, whereas the current study used freeze-dried  
398 raspberry powder which contained mostly anthocyanins, ellagitannins, ellagic acid and quercetin.  
399 Further, the polyphenol-rich foods used in those studies contained more soluble fiber and were  
400 more viscous than their control foods. Authors of those studies asserted that the modified  
401 glucose response they observed was not solely attributed to differences in the soluble fiber  
402 content of the berry meals (up to 1.5 g), however, it may partially explain their results since  
403 soluble fiber increases viscosity and mitigates postprandial glycemic response to high  
404 carbohydrate foods <sup>(43)</sup>. In contrast, the polyphenol-rich and reference bars used in the current  
405 study contained no soluble fiber and did not differ in viscosity. Indeed, similar to the current  
406 study, Castro-Acosta (2016 and 2017) removed fiber as a potential confounding variable (i.e., by  
407 testing apple and blackcurrant extracts), and observed that the fruit extract modulated the  
408 glycemic response to fruit juice and white bread with apricot jam<sup>(8; 9)</sup>. Differential findings  
409 between the aforementioned and current study may be attributable to the type of fruits, and their  
410 polyphenolic constituents, that were tested.

411 Contrary to our hypothesis, polyphenol fortification did not suppress appetite, and did not  
412 dose-dependently potentiate postprandial increases in GLP-1 or postprandial decreases in  
413 acylated ghrelin, both appetite-mediating hormones. Although relatively few studies have

414 evaluated the acute effects of polyphenol-rich foods on appetite and associated hormones <sup>(44)</sup>,  
415 several have reported that consuming polyphenol-rich foods may alter appetite-mediating  
416 hormones in a direction that would be expected to suppress appetite. For example, in separate  
417 studies, adding a polyphenol-rich berry puree to sugar water potentiated postprandial increases in  
418 the appetite-suppressing hormone GLP-1 <sup>(14)</sup>, while adding polyphenol-rich soluble carob fiber to  
419 a liquid meal potentiated the postprandial suppression of the appetite-stimulating hormone  
420 acylated ghrelin <sup>(45)</sup>. *In vitro* and animal studies suggest that certain polyphenols may directly  
421 modulate GLP-1 and ghrelin secretion, and interact with hormones known to influence their  
422 biological activity <sup>(44)</sup>. However, the effects of polyphenols on GLP-1 and acylated ghrelin  
423 appear to vary by polyphenol type <sup>(46; 47)</sup>, and the food matrix in which polyphenols are  
424 consumed <sup>(45; 48; 49)</sup>. Importantly, studies demonstrating effects of polyphenol-rich foods on GLP-  
425 1 and/or ghrelin in a direction that would be expected to suppress appetite could not separate  
426 effects of polyphenols from the fiber and viscosity of the test meals <sup>(14; 45)</sup>, which are both factors  
427 also thought to influence appetite-mediating hormone responses <sup>(50)</sup>. Additionally, a recent study  
428 found no acute effect of consuming 0.5-1.5g of polyphenol-rich grape seed extract on appetite <sup>(51)</sup>  
429 despite the extract having been shown to inhibit  $\alpha$ -amylase and  $\alpha$ -glucosidase *in vitro* <sup>(52)</sup>, similar  
430 to the polyphenols used in the present study. Collectively, these findings do not support an  
431 appetite suppressing effect of berry polyphenols within the doses studied when fiber intake and  
432 viscosity are matched across fortified and non-fortified food products. Nonetheless, an impact of  
433 polyphenols on appetite is biologically plausible given evidence for roles of various polyphenols  
434 in modulating glucose metabolism, and the concentrations of appetite-regulating neuropeptides  
435 and enteroendocrine hormones <sup>(7; 44; 46; 53)</sup>. As such, these results may not pertain to other  
436 polyphenol forms or sources administered in different doses or other food matrices.

437 Findings from the current study indicate that neither of the fruit ingredients, in the  
438 doses provided, enhanced the ex-vivo resistance of LDL lipids to oxidation following  
439 consumption of a high carbohydrate snack bar. This is not surprising, given there was little effect  
440 of the reference bar on LDL oxidation. Postprandial oxidative stress, as a sub-form of nutritional  
441 oxidative stress, ensues from sustained postprandial hyperlipidemia and/or hyperglycemia and is  
442 associated with a higher risk for cardiometabolic diseases<sup>(54)</sup>. Even though absorbed  
443 polyphenols, including flavonoids and phenolic acids, may confer anti-oxidative protection to  
444 LDL against oxidation during the postprandial state, we speculated that the protection of LDL  
445 against oxidation might be mainly attributed to diminished postprandial glucose response derived  
446 from lower glucose absorption in the GI tract. Thus, the interpretation of LDL oxidation data  
447 cannot solely focus on polyphenol bioavailability. Additionally, this study only measured one  
448 biomarker to evaluate the effect of antioxidants within cranberry and black-raspberry on  
449 oxidative stress, while a complete assessment of oxidative stress status from antioxidant  
450 interventions requires application of an array of biomarkers, including antioxidants (e.g.,  
451 enzymes and small molecular antioxidants) and free radical-derived oxidized products.  
452 Altogether, future studies should consider assessing the effect of fortifying a high fat food item  
453 with raspberry or cranberry polyphenols on LDL oxidation, using ex-vivo or more robust in-vivo  
454 methods, or in populations with increased susceptibility to oxidative stress such as the obese and  
455 elderly.

456 The raspberry and cranberry treatments produced differential effects on plasma  
457 concentrations of flavonoids and phenolic acids. Specifically, the raspberry treatment had no  
458 effect on circulating flavonoids or phenolic acid concentrations, whereas the cranberry treatment  
459 increased postprandial concentrations of several phenolic acids. These differences are likely

460 attributable to the type of polyphenolic constituents within the berries and the methods of  
461 detection used in the current study. For example, anthocyanins are a main polyphenolic  
462 constituent of cranberries and black raspberries which are not quantified using the method  
463 described herein. Further, the bioavailability of polyphenols is also dependent on a number of  
464 factors which may have limited their detection in plasma, e.g., chemical structure of the food  
465 matrix, intestinal absorption, interaction with gut microbiota and inter-subject differences in  
466 physiological, genetic, and biochemical conditions <sup>(55)</sup>.

#### 467 *Limitations*

468  
469 While the cereal bars were formulated to contain similar sugar and fiber composition,  
470 post-production chemical analysis revealed slight differences in fructose, sucrose and insoluble  
471 fiber content between the bars. However, these discrepancies are minor and unlikely to explain  
472 the differences we observed in glycemic, insulinemic and glucoregulatory hormone responses  
473 between the bars. Further, while polyphenol types within the bars were not measured, this data is  
474 reported in Phenol-Explorer <sup>(56)</sup> by Wada et al (2002), and a detailed characterization of the  
475 cranberry extract was published by Martín et al, 2015. Additionally, the cyclical reproductive  
476 hormones for the two female participants were not considered and the study was not powered to  
477 assess differences between male and females. Lastly, we did not measure plasma anthocyanins  
478 due to cost constraints and instead chose to focus on flavonoids and phenolic acids, since the  
479 assay allowed measurement of more polyphenolic compounds. Despite these limitations, this  
480 was a comprehensive, highly controlled study examining the glycemic, insulinemic,  
481 glucoregulatory hormone and ex-vivo oxidative stress responses following consumption of  
482 polyphenol-fortified, high carbohydrate cereal bars.

#### 483 *Conclusion*

484

485 Fortification with a high-dose of freeze-dried black raspberries blunted postprandial peak insulin  
486 and incretin hormone responses compared to the reference bar, and tended to increase  
487 postprandial glycemia compared to the low-dose raspberry bar. Together, these findings suggest  
488 that fortifying a high-carbohydrate bar with ~25 g raspberry powder, which contained ~1.2 g of  
489 total polyphenols, modulated postprandial glycemia and insulinemia in a dose-dependent  
490 manner, thus maintaining glucose availability in the postprandial period. Further research is  
491 warranted to determine whether this response has practical benefits in certain scenarios, e.g.,  
492 when the food item is consumed prior to endurance exercise or to maximize cognitive  
493 performance during the later postprandial period. However, these glyceemic effects did not  
494 translate into meaningful changes in appetite or ex-vivo oxidation of LDL within the immediate  
495 postprandial period at the dose consumed and/or with the method used to assess appetite.

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501  
502 The authors' contributions are as follows – TJS designed the study, collected data,  
503 conducted analyses and drafted the manuscript; JPK contributed to study design, collected data,  
504 conducted analyses, drafted portions of the manuscript related to satiety and revised the article  
505 for important intellectual content;. MW and CW collected data and assisted in data analyses; CW  
506 also assisted in drafting the manuscript. AB and NFF conceived of the study, assisted in study  
507 design and revised the article for important intellectual content; C-YOC assessed LDL oxidation  
508 and plasma polyphenolic concentrations, and revised the article for important intellectual  
509 content; SM contributed to study design and revised the article for important intellectual content.  
510 All authors reviewed, edited, and approved the final manuscript.

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## References

- 511 1. Kirwan JP, Cyr-Campbell D, Campbell WW *et al.* (2001) Effects of moderate and high  
512 glycemic index meals on metabolism and exercise performance. *Metabolism: clinical and*  
513 *experimental* **50**, 849-855.
- 514 2. Kirwan JP, O'Gorman D, Evans WJ (1998) A moderate glycemic meal before endurance  
515 exercise can enhance performance. *Journal of applied physiology (Bethesda, Md : 1985)* **84**, 53-  
516 59.
- 517 3. Kirwan JP, O'Gorman DJ, Cyr-Campbell D *et al.* (2001) Effects of a moderate glycemic meal  
518 on exercise duration and substrate utilization. *Medicine and science in sports and exercise* **33**,  
519 1517-1523.
- 520 4. Nilsson A, Radeborg K, Bjorck I (2009) Effects of differences in postprandial glycaemia on  
521 cognitive functions in healthy middle-aged subjects. *European journal of clinical nutrition* **63**,  
522 113-120.
- 523 5. Nilsson A, Radeborg K, Bjorck I (2012) Effects on cognitive performance of modulating the  
524 postprandial blood glucose profile at breakfast. *European journal of clinical nutrition* **66**, 1039-  
525 1043.
- 526 6. Ludwig DS (2002) The glycemic index: physiological mechanisms relating to obesity,  
527 diabetes, and cardiovascular disease. *Jama* **287**, 2414-2423.
- 528 7. Hanhineva K, Torronen R, Bondia-Pons I *et al.* (2010) Impact of dietary polyphenols on  
529 carbohydrate metabolism. *International journal of molecular sciences* **11**, 1365-1402.
- 530 8. Castro-Acosta ML, Smith L, Miller RJ *et al.* (2016) Drinks containing anthocyanin-rich  
531 blackcurrant extract decrease postprandial blood glucose, insulin and incretin concentrations. *The*  
532 *Journal of nutritional biochemistry* **38**, 154-161.
- 533 9. Castro-Acosta ML, Stone SG, Mok JE *et al.* (2017) Apple and blackcurrant polyphenol-rich  
534 drinks decrease postprandial glucose, insulin and incretin response to a high-carbohydrate meal  
535 in healthy men and women. *The Journal of nutritional biochemistry* **49**, 53-62.
- 536 10. Johnston KL, Clifford MN, Morgan LM (2002) Possible role for apple juice phenolic  
537 compounds in the acute modification of glucose tolerance and gastrointestinal hormone secretion  
538 in humans. *Journal of the Science of Food and Agriculture* **82**, 1800-1805.
- 539 11. Nyambe-Silavwe H, Williamson G (2016) Polyphenol- and fibre-rich dried fruits with green  
540 tea attenuate starch-derived postprandial blood glucose and insulin: a randomised, controlled,  
541 single-blind, cross-over intervention. *The British journal of nutrition* **116**, 443-450.

- 542 12. Schulze C, Bangert A, Kottra G *et al.* (2014) Inhibition of the intestinal sodium-coupled  
543 glucose transporter 1 (SGLT1) by extracts and polyphenols from apple reduces postprandial  
544 blood glucose levels in mice and humans. *Molecular nutrition & food research* **58**, 1795-1808.
- 545 13. Torronen R, Kolehmainen M, Sarkkinen E *et al.* (2012) Postprandial glucose, insulin, and  
546 free fatty acid responses to sucrose consumed with blackcurrants and lingonberries in healthy  
547 women. *The American journal of clinical nutrition* **96**, 527-533.
- 548 14. Torronen R, Sarkkinen E, Niskanen T *et al.* (2012) Postprandial glucose, insulin and  
549 glucagon-like peptide 1 responses to sucrose ingested with berries in healthy subjects. *The*  
550 *British journal of nutrition* **107**, 1445-1451.
- 551 15. Williamson G (2013) Possible effects of dietary polyphenols on sugar absorption and  
552 digestion. *Molecular nutrition & food research* **57**, 48-57.
- 553 16. Chen CY, Milbury PE, Lapsley K *et al.* (2005) Flavonoids from almond skins are  
554 bioavailable and act synergistically with vitamins C and E to enhance hamster and human LDL  
555 resistance to oxidation. *The Journal of nutrition* **135**, 1366-1373.
- 556 17. Barrett A, Ndou T, Hughey CA *et al.* (2013) Inhibition of alpha-amylase and glucoamylase  
557 by tannins extracted from cocoa, pomegranates, cranberries, and grapes. *Journal of agricultural*  
558 *and food chemistry* **61**, 1477-1486.
- 559 18. Martín MA, Ramos S, Mateos R *et al.* (2015) Chemical characterization and chemo-  
560 protective activity of cranberry phenolic powders in a model cell culture. Response of the  
561 antioxidant defenses and regulation of signaling pathways. *Food research international* **71**, 68-  
562 82.
- 563 19. Barrett AH FN, Fortier JS, Apostolidis E (2015) Glucosidase Inhibition Effectiveness of  
564 Various Fruit Extracts and Their Acceptance in Performance Bar Products. *Institute of Food*  
565 *Technologists Annual Meeting*
- 566 20. Wada L, Ou B (2002) Antioxidant activity and phenolic content of Oregon caneberries.  
567 *Journal of agricultural and food chemistry* **50**, 3495-3500.
- 568 21. Martín MA, Ramos S, Mateos R *et al.* (2015) Chemical characterization and chemo-  
569 protective activity of cranberry phenolic powders in a model cell culture. Response of the  
570 antioxidant defenses and regulation of signaling pathways. *Food Research International* **71**, 68-  
571 82.
- 572 22. Gu J, Ahn-Jarvis JH, Riedl KM *et al.* (2014) Characterization of black raspberry functional  
573 food products for cancer prevention human clinical trials. *Journal of agricultural and food*  
574 *chemistry* **62**, 3997-4006.
- 575 23. Ceriello A, Genovese S (2016) Atherogenicity of postprandial hyperglycemia and  
576 lipotoxicity. *Reviews in endocrine & metabolic disorders* **17**, 111-116.
- 577 24. Natella F, Ghiselli A, Guidi A *et al.* (2001) Red wine mitigates the postprandial increase of  
578 LDL susceptibility to oxidation. *Free radical biology & medicine* **30**, 1036-1044.
- 579 25. Marfella R, Quagliaro L, Nappo F *et al.* (2001) Acute hyperglycemia induces an oxidative  
580 stress in healthy subjects. *The Journal of clinical investigation* **108**, 635-636.
- 581 26. Chung BH, Wilkinson T, Geer JC *et al.* (1980) Preparative and quantitative isolation of  
582 plasma lipoproteins: rapid, single discontinuous density gradient ultracentrifugation in a vertical  
583 rotor. *Journal of lipid research* **21**, 284-291.
- 584 27. Blundell J, de Graaf C, Hulshof T *et al.* (2010) Appetite control: methodological aspects of  
585 the evaluation of foods. *Obesity reviews : an official journal of the International Association for*  
586 *the Study of Obesity* **11**, 251-270.

- 587 28. Karl JP, Young AJ, Montain SJ (2011) Eating rate during a fixed-portion meal does not  
588 affect postprandial appetite and gut peptides or energy intake during a subsequent meal.  
589 *Physiology & behavior* **102**, 524-531.
- 590 29. O'Connor KL, Scisco JL, Smith TJ *et al.* (2016) Altered Appetite-Mediating Hormone  
591 Concentrations Precede Compensatory Overeating After Severe, Short-Term Energy Deprivation  
592 in Healthy Adults. *J Nutr* **146**, 209-217.
- 593 30. Torronen R, Sarkkinen E, Tapola N *et al.* (2010) Berries modify the postprandial plasma  
594 glucose response to sucrose in healthy subjects. *The British journal of nutrition* **103**, 1094-1097.
- 595 31. Kim DJ, Jeong YJ, Kwon JH *et al.* (2008) Beneficial effect of chungkukjang on regulating  
596 blood glucose and pancreatic beta-cell functions in C75BL/KsJ-db/db mice. *Journal of medicinal*  
597 *food* **11**, 215-223.
- 598 32. Saisho Y (2016) Postprandial C-Peptide to Glucose Ratio as a Marker of  $\beta$  Cell Function:  
599 Implication for the Management of Type 2 Diabetes. *International journal of molecular sciences*  
600 **17**, 744.
- 601 33. Miao M, Jiang H, Jiang B *et al.* (2014) Phytonutrients for controlling starch digestion:  
602 evaluation of grape skin extract. *Food chemistry* **145**, 205-211.
- 603 34. Oboh G, Ademosun A, Olasehinde T *et al.* (2014) *Effect of processing methods on the*  
604 *antioxidant properties and inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase by African pear*  
605 *(Dacryodes edulis) fruit.*
- 606 35. Sarikurkcu C (2015) An alternative antioxidative and enzyme inhibitory agent from Turkey:  
607 Robinia pseudoacacia L. *Industrial crops and products* v. **78**, pp. 110-115-2015 v.2078.
- 608 36. Tong WY, Wang H, Waisundara VY *et al.* (2014) Inhibiting enzymatic starch digestion by  
609 hydrolyzable tannins isolated from Eugenia jambolana. *LWT - Food Science and Technology* **59**,  
610 389-395.
- 611 37. Torronen R, Kolehmainen M, Sarkkinen E *et al.* (2013) Berries reduce postprandial insulin  
612 responses to wheat and rye breads in healthy women. *The Journal of nutrition* **143**, 430-436.
- 613 38. Clegg ME, Pratt M, Meade CM *et al.* (2011) The addition of raspberries and blueberries to a  
614 starch-based food does not alter the glycaemic response. *The British journal of nutrition* **106**,  
615 335-338.
- 616 39. Coe S, Ryan L (2016) White bread enriched with polyphenol extracts shows no effect on  
617 glycemic response or satiety, yet may increase postprandial insulin economy in healthy  
618 participants. *Nutrition research (New York, NY)* **36**, 193-200.
- 619 40. Xu J, Jönsson T, Plaza M *et al.* (2018) Probiotic fruit beverages with different polyphenol  
620 profiles attenuated early insulin response. *Nutrition Journal* **17**, 34.
- 621 41. Leinonen K, Liukkonen K, Poutanen K *et al.* (1999) Rye bread decreases postprandial insulin  
622 response but does not alter glucose response in healthy Finnish subjects. *Eur J Clin Nutr* **53**, 262-  
623 267.
- 624 42. Juntunen KS, Laaksonen DE, Autio K *et al.* (2003) Structural differences between rye and  
625 wheat breads but not total fiber content may explain the lower postprandial insulin response to  
626 rye bread. *The American journal of clinical nutrition* **78**, 957-964.
- 627 43. Wood PJ (2007) Cereal  $\beta$ -glucans in diet and health. *Journal of Cereal Science* **46**, 230-238.
- 628 44. Pinent M, Blay M, Serrano J *et al.* (2017) Effects of flavanols on the enteroendocrine system:  
629 Repercussions on food intake. *Critical reviews in food science and nutrition* **57**, 326-334.
- 630 45. Gruendel S, Garcia AL, Otto B *et al.* (2006) Carob pulp preparation rich in insoluble dietary  
631 fiber and polyphenols enhances lipid oxidation and lowers postprandial acylated ghrelin in  
632 humans. *The Journal of nutrition* **136**, 1533-1538.

- 633 46. Serrano J, Casanova-Marti A, Depoortere I *et al.* (2016) Subchronic treatment with grape-  
634 seed phenolics inhibits ghrelin production despite a short-term stimulation of ghrelin secretion  
635 produced by bitter-sensing flavanols. *Molecular nutrition & food research* **60**, 2554-2564.
- 636 47. Serrano J, Casanova-Marti A, Gil-Cardoso K *et al.* (2016) Acutely administered grape-seed  
637 proanthocyanidin extract acts as a satiating agent. *Food & function* **7**, 483-490.
- 638 48. Gruendel S, Garcia AL, Otto B *et al.* (2007) Increased acylated plasma ghrelin, but improved  
639 lipid profiles 24-h after consumption of carob pulp preparation rich in dietary fibre and  
640 polyphenols. *The British journal of nutrition* **98**, 1170-1177.
- 641 49. Gruendel S, Otto B, Garcia AL *et al.* (2007) Carob pulp preparation rich in insoluble dietary  
642 fibre and polyphenols increases plasma glucose and serum insulin responses in combination with  
643 a glucose load in humans. *The British journal of nutrition* **98**, 101-105.
- 644 50. Wanders AJ, van den Borne JJ, de Graaf C *et al.* (2011) Effects of dietary fibre on subjective  
645 appetite, energy intake and body weight: a systematic review of randomized controlled trials.  
646 *Obesity reviews : an official journal of the International Association for the Study of Obesity* **12**,  
647 724-739.
- 648 51. Shin HS, Kindleysides S, Yip W *et al.* (2015) Postprandial effects of a polyphenolic grape  
649 extract (PGE) supplement on appetite and food intake: a randomised dose-comparison trial.  
650 *Nutrition journal* **14**, 96.
- 651 52. Yilmazer-Musa M, Griffith AM, Michels AJ *et al.* (2012) Grape seed and tea extracts and  
652 catechin 3-gallates are potent inhibitors of alpha-amylase and alpha-glucosidase activity. *Journal*  
653 *of agricultural and food chemistry* **60**, 8924-8929.
- 654 53. Panickar KS (2013) Effects of dietary polyphenols on neuroregulatory factors and pathways  
655 that mediate food intake and energy regulation in obesity. *Molecular nutrition & food research*  
656 **57**, 34-47.
- 657 54. Sies H, Stahl W, Sevanian A (2005) Nutritional, dietary and postprandial oxidative stress.  
658 *The Journal of nutrition* **135**, 969-972.
- 659 55. Cassidy A, Minihane AM (2017) The role of metabolism (and the microbiome) in defining  
660 the clinical efficacy of dietary flavonoids. *The American journal of clinical nutrition* **105**, 10-22.
- 661 56. Neveu V, Perez-Jimenez J, Vos F *et al.* (2010) Phenol-Explorer: an online comprehensive  
662 database on polyphenol contents in foods. *Database : the journal of biological databases and*  
663 *curation* **2010**, bap024.

**Table 1.** Pre-trial Energy and Macronutrient Intake

<b>Pre-Trial Intake<sup>1</sup></b>				
<b>Bar Type</b>	<b>Energy (kcal)</b>	<b>Fat (g)</b>	<b>CHO (g)</b>	<b>PRO (g)</b>
Reference	2280 ± 490	85 ± 27	261 ± 63	117 ± 30
Black Raspberry Low	2380 ± 740	92 ± 34	255 ± 87	131 ± 44
Black Raspberry High	2360 ± 710	88 ± 34	260 ± 94	134 ± 35
Cranberry Low	2400 ± 690	93 ± 31	263 ± 85	130 ± 39
Cranberry High	2300 ± 620	87 ± 32	252 ± 65	126 ± 32
<b>Pre-Trial Evening Meal</b>				
<b>Bar Type</b>	<b>Energy (kcal)</b>	<b>Fat (g)</b>	<b>CHO (g)</b>	<b>PRO (g)</b>
Reference	970 ± 120	29 ± 4	125 ± 16	54 ± 7
Black Raspberry Low	990 ± 170	30 ± 4	128 ± 17	54 ± 7
Black Raspberry High	990 ± 110	30 ± 4	130 ± 5	54 ± 7
Cranberry Low	980 ± 120	30 ± 5	127 ± 16	54 ± 7
Cranberry High	1000 ± 170	31 ± 7	130 ± 22	54 ± 7

All data is mean ± SD.

<sup>1</sup>Indicates average daily intake in the two days prior to each trial.

**Table 2.** Baseline body weight, glucose and insulin

	Black raspberry			Cranberry	
	Reference	Low <sup>1</sup>	High <sup>2</sup>	Low <sup>3</sup>	High <sup>4</sup>
Body Weight (kg)	82.0 ± 13.9	81.9 ± 14.1	81.7 ± 13.8	82.1 ± 14.0	82.1 ± 13.9
Glucose (mg/dL)	90.6 ± 8.0	88.8 ± 7.9	88.6 ± 7.9	89.8 ± 7.3	90.6 ± 9.7
Insulin (uIU/mL)	6.8 ± 5.5	7.3 ± 6.5	6.3 ± 6.2	5.9 ± 4.7	6.2 ± 5.5

Values are mean ± SD; there were no significant difference between treatments at baseline ( $p > 0.3$ ).

<sup>1</sup>Contains 10% freeze-dried black raspberry powder per total weight

<sup>2</sup>Contains 20% freeze-dried black raspberry powder per total weight

<sup>3</sup>Contains 0.5% cranberry extract per total weight

<sup>4</sup>Contains 1% cranberry extract per total weight

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**Table 3.** Nutritional Composition and Acceptability of Cereal bars<sup>1</sup>

	Reference	Black-Raspberry		Cranberry	
		Low <sup>2</sup>	High <sup>3</sup>	Low <sup>4</sup>	High <sup>5</sup>
<b>Weight (g)</b>	124	122.9	121.6	124.9	125.5
<b>Energy (kcal)</b>	459	458.4	451.1	460.9	465.6
<b>Carbohydrates (g)</b>	100	100.7	99	101.7	102.2
Total Sugars (g)	45	45.5	44	45.3	45.4
Fructose (g)	3.9	5.8	4.1	4	4.3
Sucrose (g)	17.3	14.4	15.2	11.7	15.7
Glucose (g)	14.5	15.9	15.8	19.9	16.3
Maltose (g)	9.3	9.5	8.9	9.7	9.2
Total Fiber (g)	6.4	7.9	7.1	9.1	7.3
Soluble Fiber (g)	0	0	0	0	0
Insoluble Fiber (g)	6.4	7.9	7.1	9.1	7.3
Starch (g) <sup>6</sup>	48.6	47.3	47.9	47.3	49.5
Carbohydrates (% total kcal)	87	88	88	88	88
<b>Fat (g)</b>	3.7	3.7	3.4	3.5	3.5
Fat (% total kcal)	7	7	7	7	7
<b>Protein (g)</b>	6.2	5.5	5.9	5.7	6.1
Protein (% total kcal)	5	5	5	5	5
Overall acceptability	7.4 ± 1.2	6.9 ± 1.5	6.6 ± 1.5 <sup>a</sup>	5.2 ± 2.3 <sup>a</sup>	5.8 ± 1.6 <sup>a</sup>

<sup>1</sup>All bars were chemically analyzed for nutritional content (Covance Laboratories, Inc., Madison, WI).

<sup>2</sup>Contains 10% freeze-dried black raspberry powder per total weight

<sup>3</sup>Contains 20% freeze-dried black raspberry powder per total weight

<sup>4</sup>Contains 0.5% cranberry extract per total weight

<sup>5</sup>Contains 1% cranberry extract per total weight

<sup>6</sup>Starch content calculated as total carbohydrates minus total fiber and total sugar.

<sup>a</sup>Marginal model with Bonferroni corrections. Significantly different from reference  $P \leq 0.01$ .

**Table 4.** Time to peak or nadir, and change from baseline to postprandial peak or nadir, blood concentrations of glucose, insulin, glucoregulatory and appetite-mediating hormones.

	Reference	Black raspberry		Cranberry	
		Low <sup>4</sup>	High <sup>5</sup>	Low <sup>6</sup>	High <sup>7</sup>
Glucose $\Delta$ Max (mmol/L)	2.9 $\pm$ 1.2	2.8 $\pm$ 0.9	2.9 $\pm$ 0.9	2.9 $\pm$ 1.0	3.3 $\pm$ 1.1
Time to peak glucose (mins)	38 $\pm$ 11	38 $\pm$ 15	38 $\pm$ 17	42 $\pm$ 24	38 $\pm$ 9
Insulin $\Delta$ Max (uIU/mL) <sup>1</sup>	90 $\pm$ 64	78 $\pm$ 55	75 $\pm$ 53 <sup>a</sup>	84 $\pm$ 58	82 $\pm$ 52
Time to peak insulin (mins)	49 $\pm$ 25	50 $\pm$ 21	54 $\pm$ 32	48 $\pm$ 20	50 $\pm$ 22
GLP-1 $\Delta$ Max (pg/mL) <sup>2</sup>	25 $\pm$ 15	21 $\pm$ 14	18 $\pm$ 13 <sup>b</sup>	27 $\pm$ 25	19 $\pm$ 14
Time to peak GLP-1 (mins)	41 $\pm$ 40	33 $\pm$ 26	26 $\pm$ 14	45 $\pm$ 40	38 $\pm$ 26
GIP $\Delta$ Max (pg/mL) <sup>3</sup>	201 $\pm$ 103	211 $\pm$ 82	162 $\pm$ 97 <sup>c</sup>	180 $\pm$ 64	188 $\pm$ 88
Time to peak GIP (mins)	78 $\pm$ 31	95 $\pm$ 42	71 $\pm$ 36	60 $\pm$ 24	74 $\pm$ 33
C-peptide $\Delta$ Max (mg/dL)	8 $\pm$ 3	8 $\pm$ 3	8 $\pm$ 3	9 $\pm$ 4	9 $\pm$ 4
Time to peak C-peptide (mins)	49 $\pm$ 15	71 $\pm$ 31	62 $\pm$ 27	65 $\pm$ 36	59 $\pm$ 23
Ghrelin $\Delta$ Max (pg/mL)	-64 $\pm$ 51	-63 $\pm$ 50	-59 $\pm$ 58	-59 $\pm$ 48	-72 $\pm$ 51
Time to nadir glucose (mins)	58 $\pm$ 22	68 $\pm$ 31	67 $\pm$ 28	65 $\pm$ 25	70 $\pm$ 20

Values are mean  $\pm$  SD.  $\Delta$ Max, change from baseline to peak glucose, insulin, Glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), c-peptide concentrations or nadir acylated ghrelin concentrations.

Data analyzed using marginal models with Bonferroni corrections.  $\Delta$ Max analyses included fasting blood concentrations as a covariate.

<sup>1</sup>Significant main effect of bar within raspberry treatment (P = 0.02). <sup>a</sup>P = 0.03 versus reference.

<sup>2</sup>Trend for main effect of bar within raspberry treatment (P = 0.09). <sup>b</sup>P = 0.09 versus reference.

<sup>3</sup>Significant main effect of bar within raspberry treatment (P = 0.01). <sup>c</sup>P = 0.01 versus LO-Rasp.

<sup>4</sup>Contains 10% freeze-dried black raspberry powder per total weight.

<sup>5</sup>Contains 20% freeze-dried black raspberry powder per total weight.

<sup>6</sup>Contains 0.5% cranberry extract per total weight.

<sup>7</sup>Contains 1% cranberry extract per total weight.

**Table 5.** Appetite and ad libitum energy intake following consumption of fortified and reference cereal bars.

	Reference	Black raspberry		Cranberry	
		Low <sup>3</sup>	High <sup>4</sup>	Low <sup>5</sup>	High <sup>6</sup>
AUC <sub>0-180 min</sub> (cm*min)					
Hunger	-530 ± 372	-386 ± 418	-451 ± 448	-409 ± 388	-432 ± 428
Fullness <sup>1</sup>	509 ± 459	423 ± 353	470 ± 359	402 ± 385	408 ± 379 <sup>a</sup>
ΔMax (cm)					
Hunger	-4.8 ± 2.7	-4.7 ± 2.7	-4.6 ± 2.9	-4.6 ± 2.1	-4.4 ± 3.1
Fullness <sup>1</sup>	4.7 ± 3.2	4.6 ± 2.3	4.6 ± 2.8	4.4 ± 2.3	4.1 ± 2.9
<i>Ad libitum</i> energy intake (kcal) <sup>2</sup>	1177 ± 438	1093 ± 390	1169 ± 492	1226 ± 420	1189 ± 437

Values are mean ± SD. ΔMax, change from baseline to peak fullness or the hunger nadir. Data analyzed using marginal models with Bonferroni corrections. AUC and ΔMax analyses included fasting hunger or fullness as a covariate.

<sup>1</sup>Trend for main effect of bar within cranberry treatment (P ≤ 0.08). <sup>a</sup>P = 0.06 versus reference.

<sup>2</sup>Trend for main effect of bar within raspberry treatment (P = 0.10). No significant post hoc differences.

<sup>3</sup>Contains 10% freeze-dried black raspberry powder per total weight

<sup>4</sup>Contains 20% freeze-dried black raspberry powder per total weight

<sup>5</sup>Contains 0.5% cranberry extract per total weight

<sup>6</sup>Contains 1% cranberry extract per total weight

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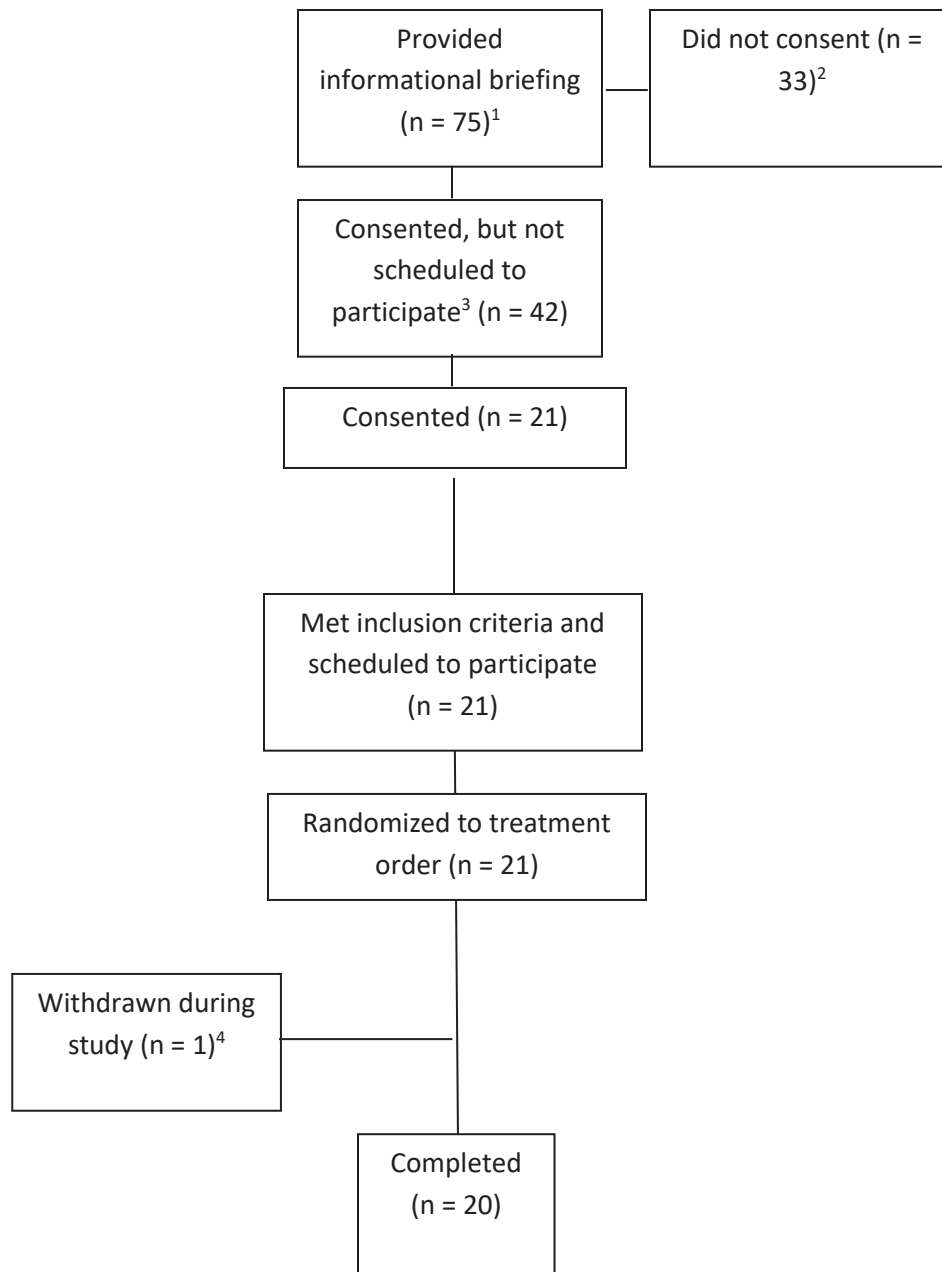


Figure 1. Participant Disposition. <sup>1</sup>Potential volunteers attended the briefing after seeing informational flyers or as part of their voluntary assignment in the Natick Soldier, Research, Development and Engineering Center's Human Volunteer Detachment (Natick, MA); <sup>2</sup>Two individuals verbally indicated that they did not meet inclusion criteria; <sup>3</sup>Not scheduled to participate due to scheduling conflicts; <sup>4</sup>Withdrawn due to multiple failed catheter attempts.

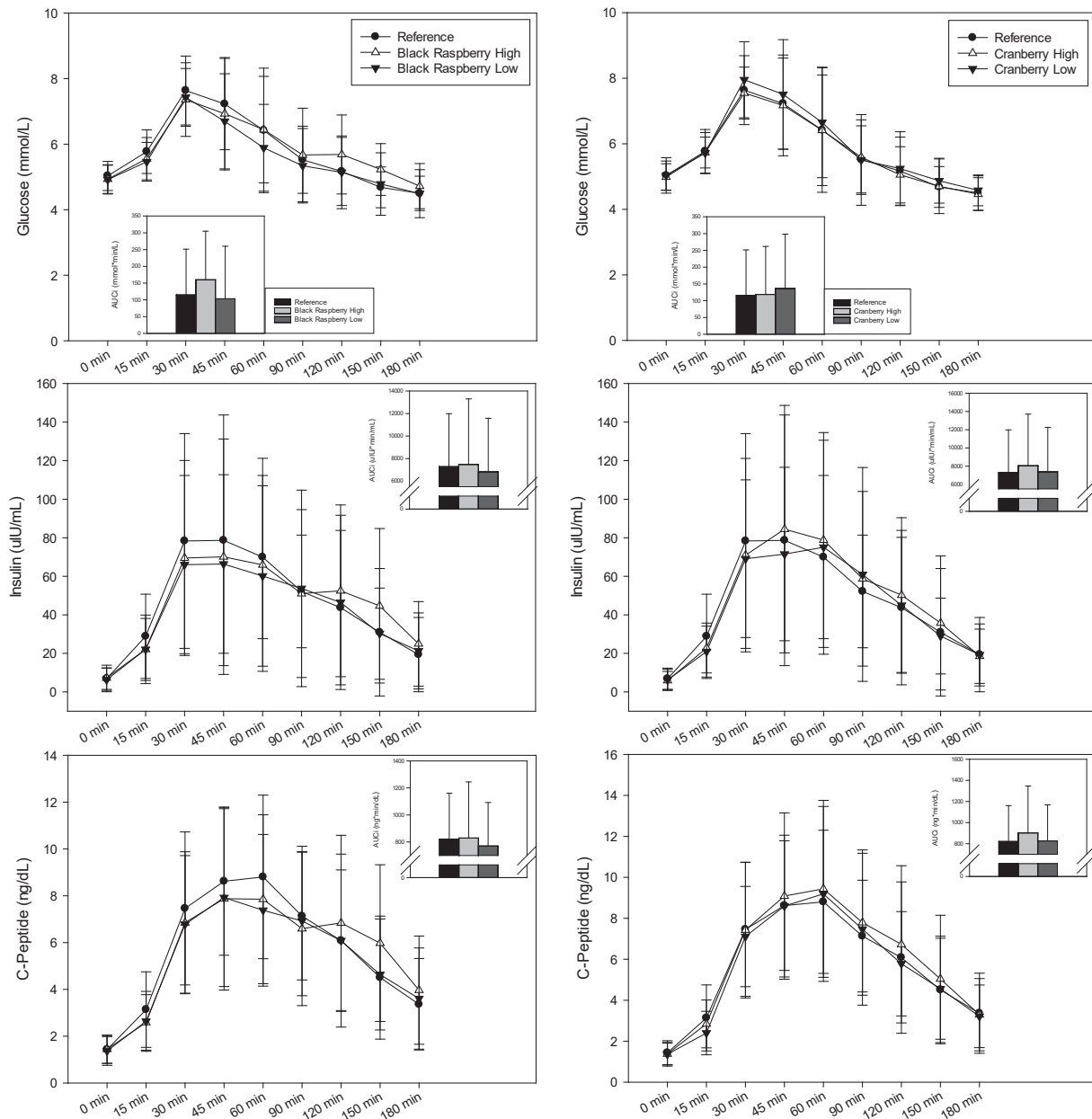


Figure 2. Baseline and post-prandial glucose (A, B), insulin (C, D), and c-peptide (E, F) concentrations. Note: Error bars represent standard deviations. AUC<sub>i</sub> inset represents incremental area under the curve 0-180 mins post-prandial. Treatment effect on glucose AUC<sub>0-180min</sub> response (P=0.04): trend for higher glucose following consumption of black raspberry high versus black raspberry low (P=0.06).

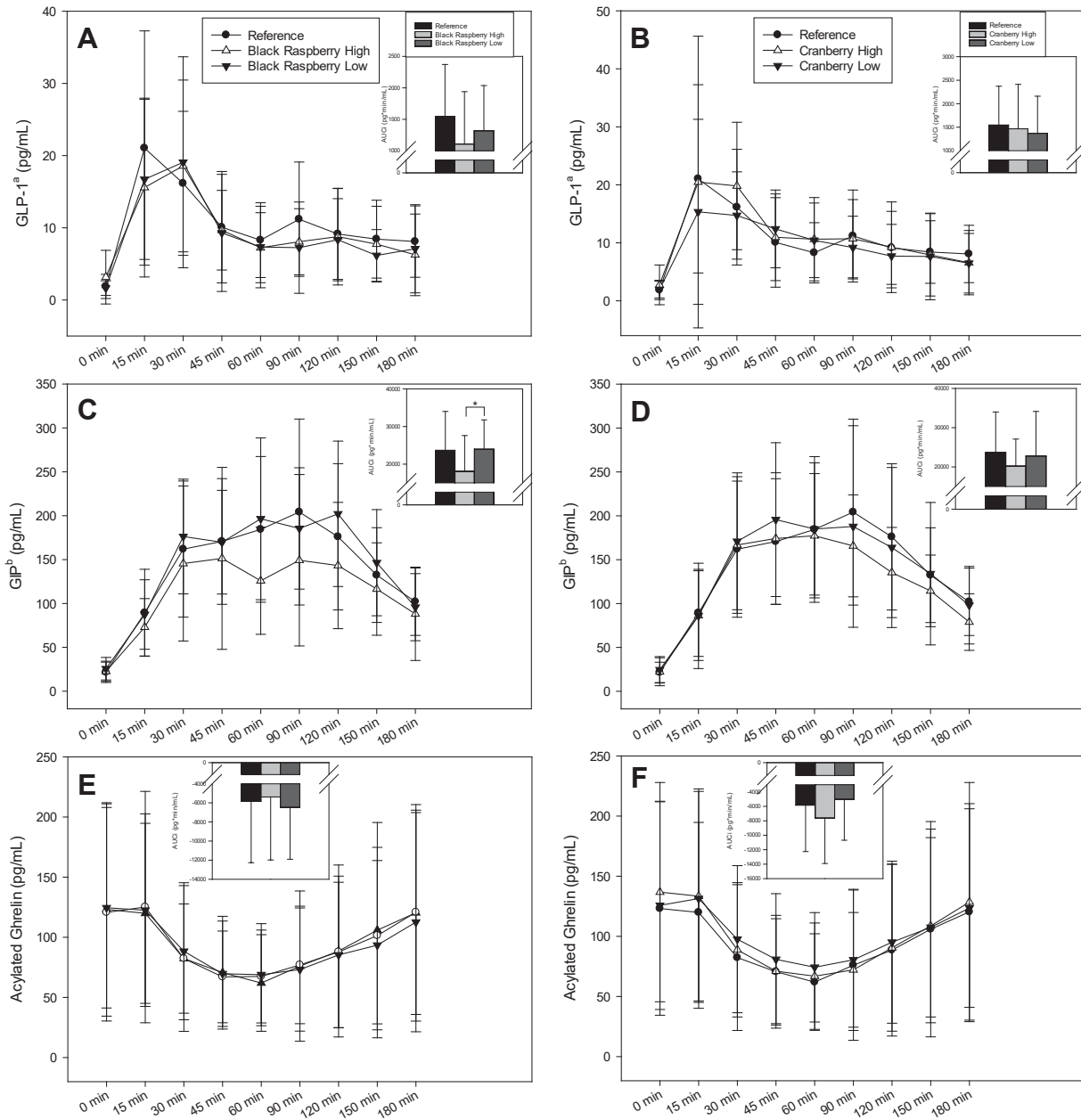


Figure 3: Baseline and post-prandial GLP-1 (A, B), GIP (C, D) and acylated ghrelin (E, F) concentrations. Note: Error bars represent standard deviations. AUC<sub>i</sub> inset represents incremental area under the curve 0-180 mins post prandial. \*indicates significant difference between groups,  $p < 0.05$ . <sup>a</sup>glucose-dependent insulinotropic polypeptide. <sup>b</sup>glucagon-like peptide-1. Treatment effect on GIP AUC<sub>0-180min</sub> response ( $P=0.001$ ): GIP lower following consumption of black raspberry high versus reference ( $P=0.014$ ) and black raspberry low ( $P=0.003$ ).

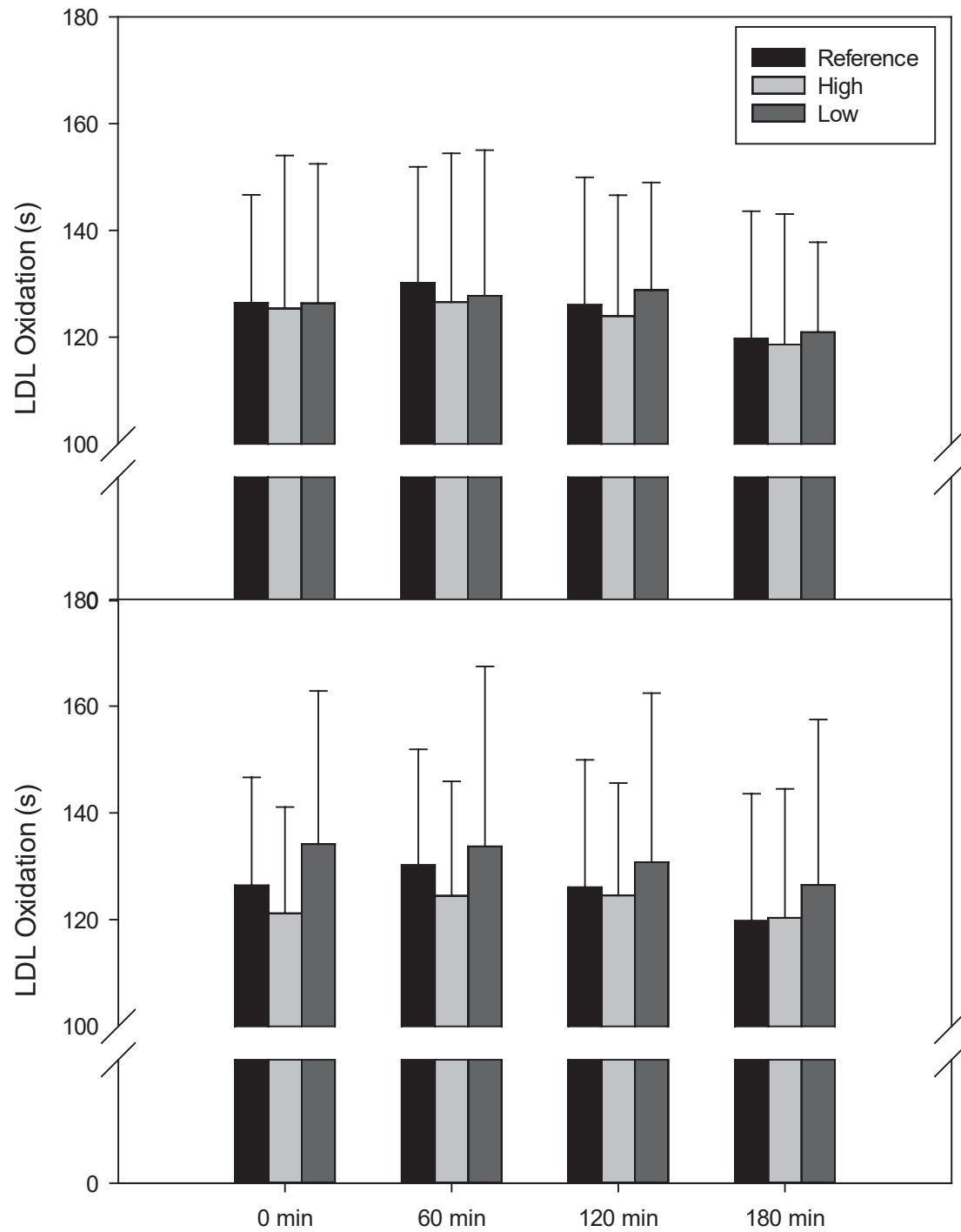


Figure 4: Ex-vivo LDL oxidation (lag time, seconds) of A) Reference vs black raspberry fortified bars and B) Reference vs cranberry fortified bars. Error bar represent standard deviations.

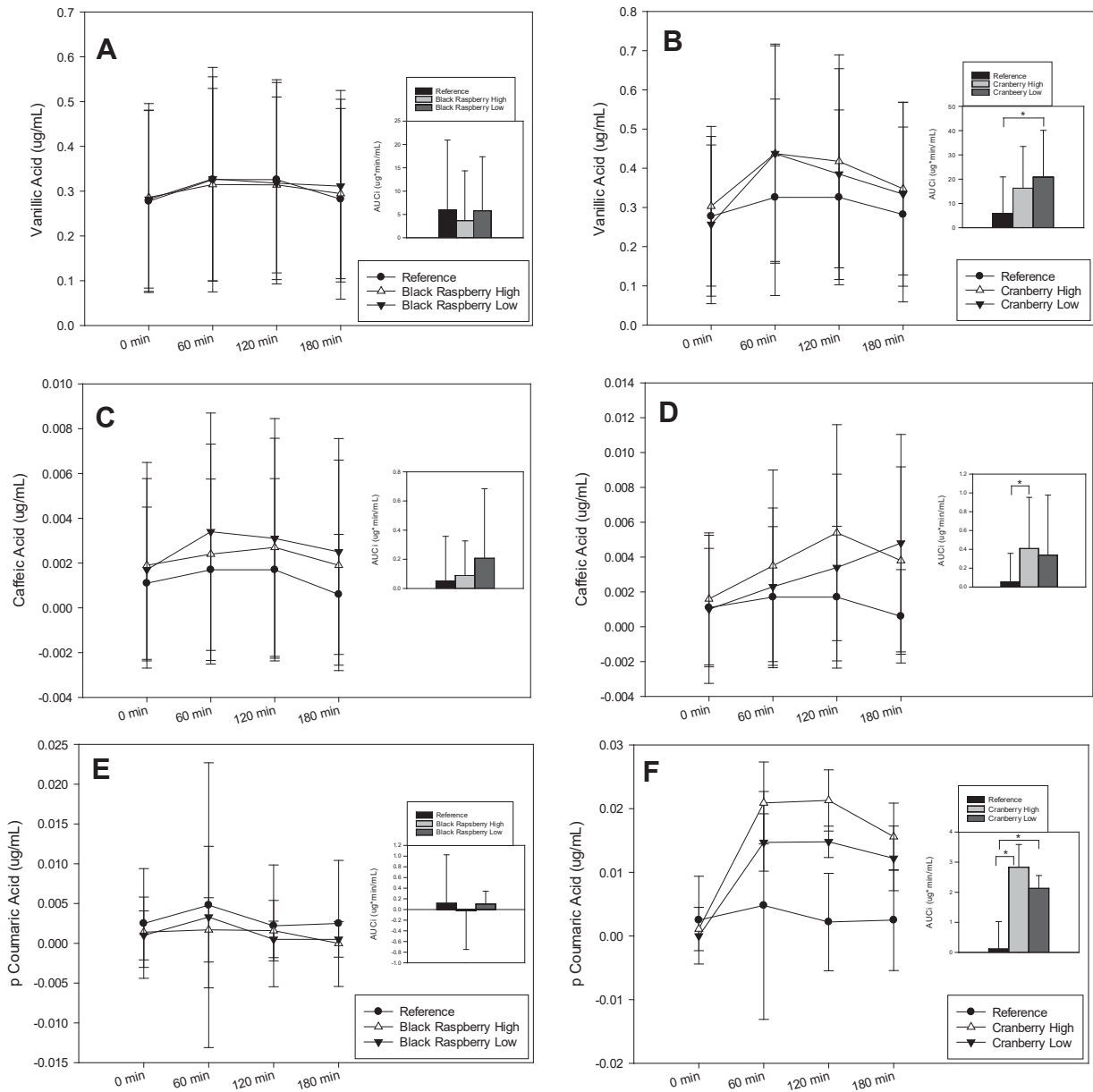


Figure 5: Baseline and Post-prandial concentrations of vanillic acid (A, B), caffeic acid (C, D) and coumaric acid (E, F). Note: Error bar represent standard deviations. AUCi inset represents incremental area under the curve 0-180 mins post prandial. \*indicates significant difference between groups,  $p < 0.05$ .

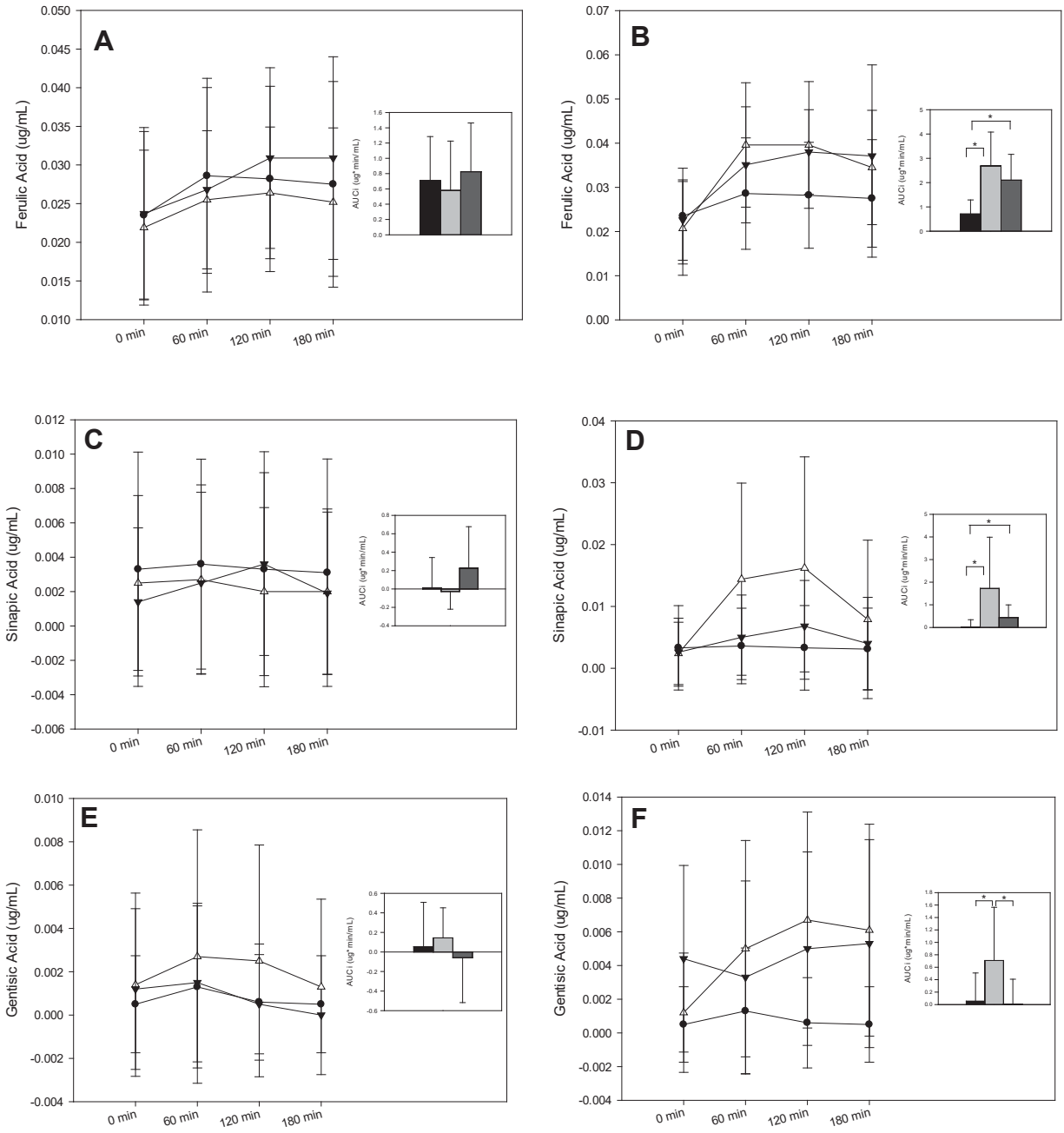


Figure 6: Baseline and Post-prandial concentrations of ferulic acid (A, B), sinapic acid (C, D) and gentisic acid (E, F). Note: Error bar represent standard deviations. AUCi inset represents incremental area under the curve 0-180 mins post prandial. \*indicates significant difference between groups, p < 0.05.