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PII: S0261-5614(26)00104-4

DOI: <https://doi.org/10.1016/j.clnu.2026.106677>

Reference: YCLNU 106677

To appear in: *Clinical Nutrition*

Received Date: 15 December 2025

Revised Date: 5 April 2026

Accepted Date: 21 April 2026

Please cite this article as: Kamarunzaman NNZ, Le Sayec M, Li Y, Cheok A, Wu H, Zhang Z, Xu Y, Mesnage R, Dalrymple K, Pariante CM, Borsini A, Vauzour D, Bajka B, Rodriguez-Mateos A, Effects of (poly)phenol-rich cranberry on mental health in university students: the CRANMOOD randomised controlled trial, *Clinical Nutrition*, <https://doi.org/10.1016/j.clnu.2026.106677>.

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Effects of (poly)phenol-rich cranberry on mental health in university students: the CRANMOOD randomised controlled trial

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1 **Abstract**

2 **Background and Aims:** Increasing evidence indicate that (poly)phenol-rich foods can have
3 beneficial effects on human brain function. This study investigated whether daily (poly)phenol-
4 rich cranberry supplementation for 12 weeks influences mental health outcomes in university
5 students.

6 **Methods:** A parallel double-blind randomised controlled trial was conducted in 72 young
7 healthy final year university students (20-25 years old). Participants consumed either a
8 (poly)phenol-rich cranberry drink or a placebo drink daily for 12 weeks. The primary outcome
9 was mood, assessed as Total Mood Disturbance (TMD), using the Profile of Mood States
10 questionnaire. Secondary outcomes included stress, anxiety and depression levels, measured
11 using the Perceived Stress Scale (PSS), the Hospital Anxiety Depression Scale (HADS)
12 questionnaire, cognitive function measured using the Online General Cognitive Assessment
13 Battery (CogniFit), and salivary cortisol levels. Blood and urine samples were collected to
14 measure cranberry (poly)phenol metabolites. Dietary intake was assessed via food frequency
15 questionnaires (FFQ), 7-day food diaries (EPIC, European Prospective Investigation into
16 Cancer and Nutrition), and 24-hour online dietary recalls (intake24). Data was analysed using
17 linear mixed-effects models using baseline as covariate.

18 **Results:** No significant differences were observed between groups for the primary outcome,
19 self-reported mood (Total Mood Disturbance), or for secondary self-reported measures of
20 stress, anxiety, or depression. In exploratory secondary analyses, 12 weeks of (poly)phenol-
21 rich cranberry drink consumption significantly lower diurnal area under the curve of salivary
22 cortisol ($p=0.010$) and significantly higher short-term memory ($p=0.024$) and phonological
23 short-term memory ($p=0.014$) compared to placebo. Additionally, plasma and urinary
24 cranberry (poly)phenol metabolites were significantly modulated by cranberry consumption.

25 **Conclusions:** While (poly)phenol-rich cranberry supplementation did not improve self-
26 reported mood, stress, anxiety, or depression in healthy students, it influenced cortisol levels
27 and some aspects of cognitive function, suggesting potential benefits for stress regulation and
28 memory.

29 **Abbreviations:** AUC_G, area under the curve with respect to ground; AUC_I, area under the
30 curve with respect to increase; BMI, body mass index; BP, blood pressure; CAR, cortisol
31 awakening response; EPIC, European Prospective Investigation into Cancer and Nutrition;
32 FFQ, food frequency questionnaire; HADS, Hospital Anxiety and Depression Scale; IPAQ,
33 International Physical Activity Questionnaire; ITT, intention to treat; LC–MS, liquid
34 chromatography–mass spectrometry; PACs, proanthocyanidins; PANAS, Positive and
35 Negative Affect Schedule; POMS, Profile of Mood States; PSS, Perceived Stress Scale; RCT,
36 randomised controlled trial; TMD, Total Mood Disturbance; UHPLC, ultra-high-performance
37 liquid chromatography.

38 **Clinical trial registry:** The National Institutes of Health (NIH)-randomized trial records held
39 on the NIH ClinicalTrials.gov website (NCT05260346).

40 **Keywords:** cranberry (poly)phenol, mood, stress, anxiety, depression, cortisol, cognition,
41 university students

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50 **1. Introduction**

51 The increasing prevalence of mental health issues among university students is becoming a
52 significant concern. A recent study of more than 21,000 students across 140 United Kingdom
53 (UK) universities found that nearly half had experienced a serious psychological issue, and one
54 in five had been diagnosed with a mental health condition (1). Mental health difficulties were
55 significantly associated with students' year of study. First-year students reported the lowest
56 levels of difficulties, which increased significantly in the second year and peaked in the third
57 year. Similarly, the likelihood of a mental health diagnosis was significantly less likely in first
58 year students, with rates rising sharply to peak in the second year, remaining high in the third
59 year, then falling sharply back to first-year levels in the fourth and fifth years (1). Contributing
60 factors include adjustment to a new environment, increasing academic workload, financial
61 pressure, and inadequate social and emotional support (2), leading to outcomes ranging from
62 reduced academic performance and dropout to self-harm and suicide. The complexity of this
63 issue highlights the urgent need for targeted interventions to support student mental health,
64 particularly at university level (2, 3).

65 Recently, non-pharmacological and holistic approaches, including nutrition-based strategies to
66 complement established treatments for the prevention and management of mood disorders,
67 have gained increasing recognition. The transition to university is a period of heightened
68 vulnerability, often associated with the adoption of adverse health behaviours. In this context,
69 students commonly prioritise other challenges over healthy food choices, leading to
70 compromised dietary habits (4, 5). Research from the United States of America (USA) and the
71 UK indicates that university students typically consume diets low in fruits, vegetables, and
72 dairy products but high in saturated fats, refined carbohydrates, salt, and alcohol, patterns
73 generally linked to poorer health outcomes (6-8). Plant-rich diets such as the Mediterranean
74 diet have been shown to be effective strategies to alleviate depression symptoms. These diets

75 are high in plant foods such as fruits, vegetables, whole grains, nuts, seeds, and legumes. Meta-
76 analyses of observational studies revealed that higher adherence to the Mediterranean diet
77 correlated with a 32% lower risk of depression (9), and was associated with better cognitive
78 performance and memory in older adults with and without dementia (10). Similarly, a recent
79 meta-analysis of 5 randomised control trials (RCTs) including 1,507 individuals concluded that
80 Mediterranean diet interventions significantly reduced depressive symptoms among young and
81 middle-aged adults with major depression or mild to moderate depressive symptoms (11).

82 (Poly)phenols are among the most abundant bioactives present in plant foods and plant-rich
83 diets, including the Mediterranean diet, with growing evidence linking their consumption to
84 improved mental health. A systematic review and meta-analysis of nine RCTs found that
85 (poly)phenol-rich cocoa products improved depression, anxiety, and mood in short-term
86 studies but showed inconsistent effects in long-term trials (12). Cocoa is rich in flavan-3-ols,
87 which have neuroprotective and cognitive-enhancing effects: acute intake improved cerebral
88 blood flow and oxygenation, while chronic consumption enhanced cognitive performance and
89 elevated neurotrophin levels (13). A review of 21 studies on green tea, another flavan-3-ol-rich
90 beverage, reported positive effects on cognition, mood, and brain function (14). Cranberries
91 are also rich in flavan-3-ols, though their proanthocyanidin (PAC) profile (15) is distinct from
92 that of other sources, which makes them a unique contributor within the broader spectrum of
93 dietary (poly)phenols. Given cranberries' potential role in modulating brain function (16), this
94 study examined the effects of cranberry (poly)phenol consumption on mental health in a 12-
95 week, double-blind, placebo-controlled parallel intervention in university students.

96 **2. Methods**

97 ***2.1 Intervention study subjects***

98 The CRANMOOD study population consisted of final year Bachelor of Science (BSc) and
99 Master of Science (MSc) university students between 20-25 years old, willing to maintain their
100 normal eating/drinking habits and exercise habits to avoid changes in body weight over the
101 duration of the study; able to understand the nature of the study; willing to give signed written
102 informed consent and comply with all study protocol procedures. Individuals were excluded if
103 they had the following conditions: regularly prescribed medication (including iron for
104 anaemia); subjects who require chronic antimicrobial or antiviral treatment; individuals with
105 hypertension (Blood Pressure $\geq 140/90$ mmHg) or obesity (Body Mass Index ≥ 30 kg/m²);
106 diabetes mellitus; metabolic syndrome, as defined by the World Health Organization (WHO)
107 (17); terminal renal failure and other kidney abnormalities; malignancies; history of cancer,
108 myocardial infarction, cerebrovascular incident; unstable psychological condition (diagnosed
109 with mental health disorders); allergies to berries or other significant food allergy; subjects
110 who took food supplements, dietary supplements or herbal remedies were asked to maintain
111 and advised not to stop taking or begin new supplements during the study; lost more than 10%
112 of their weight in the past 6 months or are currently in a diet; subjects who reported participant
113 in another study within 1 month before the study start; smoking irregular number of cigarettes
114 per day or plan quitting smoking in the next 3 months; pregnant, lactating or planning to
115 become pregnant.

116 ***2.2 Study design***

117 A single-centre, 12-week randomised, double-blinded, placebo-controlled parallel study was
118 conducted at the Department of Nutritional Sciences, King's College London. Individuals who
119 met the inclusion criteria were randomly allocated to a treatment (www.randomizer.org) using
120 blinded treatment codes provided by the manufacturer of both cranberry and placebo juices

121 (Ocean Spray Inc., Lakeville, MA). All research staff involved in the collection and the analysis
122 of the data remained blinded to the treatment randomisation until all aspects of the study,
123 including the statistical analysis, were completed. The intervention consisted of 236 mL of
124 cranberry juice consumed daily for 12 weeks at breakfast, which provided 442 mg of
125 (poly)phenols, including 303 mg proanthocyanidins, 78 mg total flavonoids, 41.4 mg
126 anthocyanins, and 61 mg of phenolic acids per day measured using high-performance liquid
127 chromatography by the manufacturer (see **Supplementary Table 1**). The placebo juice was
128 designed to match colour and taste, and contained water, dextrose, citric acid, malic acid,
129 fumaric acid, colorants, xanthan gum, natural flavour, and emulsion. Participants were asked
130 to maintain their normal dietary and exercise habits throughout the duration of the study, and
131 diet was assessed using 7-days food diaries, 24-hour dietary recalls, and food frequency
132 questionnaires throughout the study.

133 The overall aim of this study was to investigate whether (poly)phenol-rich cranberry improved
134 mood and mental health in university students. The primary outcome was mood, measured as
135 Total Mood Disturbance (TMD) while secondary outcomes included stress levels, anxiety and
136 depression symptoms, cognitive function, cortisol levels, plasma and urinary cranberry
137 (poly)phenol metabolites and assessment of habitual diet and physical activity. Changes in
138 blood pressure, measured as systolic and diastolic blood pressure, and sleeping patterns,
139 measured as bedtime and sleep duration, were also investigated as exploratory outcomes.

140 The study consisted of a total of five visits, with 1 visit every 4 weeks over a total of 12 weeks:
141 a screening visit (V0), a pre-intervention baseline visit (V1), two follow-up visits (V2 & V3),
142 and an end of intervention visit (V4) (**Figure 1**). During the screening visit (V0), volunteers
143 provided informed consent, and body composition, anthropometry, blood pressure, and
144 waist/hip circumference was measured. If volunteers complied with all the inclusion criteria,
145 they were invited to attend a baseline visit (V1), where blood samples were collected to assess

146 general health status of participants (blood lipids, markers of liver and kidney function, urea,
147 uric acid, creatinine, and glucose) (**Figure 1**). The day before each visit (pre-visit), volunteers
148 self-collected a total of 6 saliva samples (0, 15, 30, and 60 min after waking up, 12pm, and
149 8pm) throughout the day to measure daily cortisol levels and cortisol awakening response as a
150 biomarker of stress and mental health. Mental health, sleeping patterns, cognitive function,
151 diet and physical activity were also assessed using self-reported questionnaires, an online
152 cognitive battery test and online 24 h dietary recalls. Seven-day food diaries were also collected
153 at V1 and V4. On the day of each visit, a spot urine sample was self-collected after waking up
154 and before breakfast. All self-collected saliva and urine samples were logged and stored for the
155 relevant study visit, and participants collected new kits for following 4-week period. During
156 V1 and V4, blood samples were taken to measure cranberry (poly)phenol related metabolites.
157 The study was conducted from January to August 2022, and it was registered at
158 clinicaltrials.gov (NCT05260346). The study was conducted according to the guidelines laid
159 down in the Declaration of Helsinki, with all volunteers providing informed consent. All
160 procedures involved were approved by the King's College London Research Ethics Committee
161 (RESC reference: HR/DP-21/22-26721).

162 ***2.3 Mood measures***

163 Volunteers were administered the Profile of Mood States 2nd Edition-Adult (POMS 2-A)
164 (<https://storefront.mhs.com/collections/poms-2>) questionnaire at each visit to provide
165 indications of potential mood disturbance (18, 19). The POMS assessment consists of six
166 scales: Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia,
167 Tension-Anxiety, and Vigor-Activity. The scores from these scales are summed to calculate a
168 Total Mood Disturbance score. Additionally, friendliness was assessed separately. The POMS2
169 is an adjective checklist with instructions to indicate "How have you been feeling over the past
170 week, including today" on a 5-point Likert scale ranging from 0 = Not at all to 4 = Extremely.

171 If the instructions are modified to "how you feel right now," the instrument measures emotional
172 states.

173 ***2.4 Stress, anxiety and depressive symptoms***

174 The Perceived Stress Scale (PSS) (20) was designed and validated for measuring stress levels.
175 It consists of 10 questions ranging from 0 = never to 4 = very often. The PSS score was obtained
176 by summing all items and higher score indicate higher level of perceived stress. The validated
177 Hospital Anxiety and Depression Scale (HADS) (21) was used to evaluate the degree of anxiety
178 and depression symptoms. HADS consisted of 14 items answered on a 4-point Likert scale
179 (range 0-3) with seven items each for anxiety and depression subscales. The total score is the
180 sum of the 14 items, and for each subscale the score is the sum of the respective seven items
181 (ranging from 0–21). The HADS and PSS questionnaires were completed by volunteers at each
182 visit.

183 ***2.5 Cognitive measurements***

184 General Cognitive Assessment Battery (GCAB) by CogniFit™ was used to detect and evaluate
185 cognitive state and abilities through online cognitive tests. GCAB was validated for clinical
186 and scientific use in children age 7+ and adults. It measures various aspects of cognitive
187 performance covering five cognitive domains: memory, attention, perception, coordination,
188 and reasoning (22). CogniFit scores range from 0 to 800 points, where high scores refer to
189 increased cognitive performance. For scores between 0 and 200 (red), cognitive abilities are
190 considered cognitive weaknesses. Participants with scores of 200–400 (yellow) are considered
191 patients with cognitive abilities within what is expected for people of their age and gender.
192 Higher scores in the range of 400–600 (green) mean that cognitive abilities with these scores
193 are in good condition. Cognitive abilities that show scores above 600 (green) are considered
194 strengths or cognitive skills as they exceed those of other people of the same sex and age. In
195 each domain, various sub-skills were assessed, with 22 skills in total included (23).

196 **2.6 Physical activity and sleep**

197 Types of physical activity, intensity and sedentary time was assessed using the International
198 Physical Activity Questionnaire (IPAQ) (24). To estimate energy expenditure from physical
199 activity, MET-minutes/week was used, which consists of open-ended questions that involve
200 individuals remembering the last 7 days of physical activity (25). Sleep quality was assessed
201 using a selection of questions adapted from existing sleep health questionnaires. Participants
202 reported their sleep patterns over the seven days preceding each visit, including the time they
203 fell asleep and the total hours slept, providing an overview of their sleep health (26).

204 **2.7 Biochemical analysis**

205 Blood samples were collected in EDTA tubes (10mL, for plasma (poly)phenols), fluoride
206 oxalate tubes (3mL, for blood glucose level), serum separator tubes (6mL, for blood lipids and
207 liver function). Tubes were centrifuged at 3,000rpm at 4°C for 15 min with serum/plasma
208 stored at -80°C. Additionally, plasma samples for (poly)phenol analysis were spiked with 2%
209 formic acid prior to storage. All clinical chemistry parameters, including total cholesterol,
210 triglycerides, Low-density lipoprotein (LDL) and High-density lipoprotein (HDL) cholesterol,
211 cortisol, glucose, liver enzymes and whole blood count, were analysed according to standard
212 procedures by an accredited laboratory (Affinity Biomarker Laboratories, London, UK).
213 Samples were kept at 4°C and processed on the same day.

214 **2.8 Urine collection**

215 Participants were asked to collect a sample of the first urine of the day before every study
216 visit in a urine sample cup. They were provided with a cooling bag with ice packs to keep the
217 sample at low temperature to avoid degradation of (poly)phenol metabolites. After returning
218 the urine from each visit, a representative sample was saved and centrifuged (3000 rpm, 15
219 min, 4°C). Urine samples for (poly)phenol analysis were spiked with 2% formic acid and
220 frozen at -80°C before further analysis.

221 **2.9 Salivary cortisol**

222 All participants were instructed to collect saliva samples using polymer swabs (Salimetrics
223 Oral Swabs, Salimetrics, PA, USA), which were then inserted into Salivette tubes (Sarstedt;
224 Leicester, UK). Volunteers were asked not to have breakfast or brush their teeth or smoke until
225 the tube at 60 min had been collected while for the other saliva tubes (12:00h and 20:00h),
226 they were asked not to eat, drink or smoke 30 minutes before collecting the saliva (27). All the
227 saliva samples were kept at 4°C to prevent degradation of cortisol until the participants were
228 able to bring it back to the laboratory. Samples were centrifuged at 1,000 x g for 5 min at 20°C
229 before storage at -80°C. Saliva cortisol concentration was measured with a commercial
230 immunoassay kit (High Sensitivity Salivary Cortisol ELISA KIT from Salimetrics) using a
231 recommended procedure in an accredited laboratory (Affinity Biomarkers Laboratories,
232 London, UK). Optical density was read at 450 nm with correction at 620 nm, using a Beckman
233 Coulter (Brea, CA, USA) DTX 880 plate reader, with Multimode Detection Software 2.0.0.12.
234 Cortisol Awakening Response (CAR) was calculated as the area under the curve (AUC) of
235 cortisol concentrations at 0, 15, 30, and 60 minutes post-awakening using Prism's trapezoid
236 rule. Diurnal cortisol AUC was calculated using values from awakening, 12:00 h, and 20:00 h.
237 For both CAR and diurnal profiles, two AUC metrics were computed following Pruessner et
238 al.(28): AUC_G (area under the curve with respect to ground), which reflects total cortisol
239 exposure relative to zero, and AUC_I (area under the curve with respect to increase), which
240 quantifies the dynamic change in cortisol levels relative to baseline.

241 **2.10 Liquid Chromatography-Mass Spectrometry analysis of plasma and urinary**

242 ***(poly)phenol metabolites***

243 Plasma and urine samples were extracted for (poly)phenol metabolites analysis using micro-
244 elution solid phase extraction (m-SPE) and measured by ultra-performance liquid
245 chromatography–triple quadrupole mass spectrometry (UPLC-Q-q-Q MS) by a validated

246 method (29). Before analysis, urine samples were diluted with dilution 1:5 or undiluted plasma
247 samples (1:1) were acidified with 4% phosphoric acid. Each sample (600 μ L) was loaded on
248 Oasis 96-well reversed-phase HLB (hydrophilic-lipophilic balanced) sorbent m-SPE plates
249 (Waters, Eschborn, Germany), washed with HPLC water (200 μ l) and 0.2% acetic acid (200 μ l)
250 and finally eluted with 90 μ L of methanol. Samples were run through UHPLC (ultra-high-
251 performance liquid chromatography) DIONEX Ultimate 3000 fitted with a TSQ Vantage Triple
252 Quadrupole Mass Spectrometer (Thermo Fisher Scientific Inc., San Jose, CA, United States)
253 equipped with a heated-electrospray ionisation source (H-ESI-II; Thermo Fisher Scientific
254 Inc.). Eluted samples (5 mL) were injected through a Raptor Biphenyl column 2.1 x 50 mm,
255 1.8 mm (Restek, Bellefonte, USA) with a compatible Raptor Biphenyl Guard Cartridges 5 x
256 2.1 mm (Restek, Bellefonte, USA) in the UHPLC system. The mobile phase A was water
257 containing 0.1% formic acid and mobile phase B was acetonitrile containing 0.1% formic acid
258 used in this system. The gradient started with 1% B, keeping isocratic conditions for 1 min,
259 reaching 99% at 12 min, followed by 2 min at 99% B and then 2 min equilibration of column.
260 The flow rate was set at 0.35 ml/min, the injection volume was 5 μ L, and the 30°C.
261 Chromatograms, mass spectral data and data processing were performed using Xcalibur
262 software 2.1 (Thermo Fisher Scientific Inc.). Quantification was performed with calibration
263 curves of authentic standards, using Tracefinder software 5.0. Urinary metabolites were
264 normalised to creatinine to account for variability in urine concentration. Total (poly)phenols
265 were calculated as the sum of all quantified (poly)phenol-derived metabolites detected in each
266 biological matrix.

267 ***2.11 Dietary assessment of background diet***

268 In this study, 7-day food diaries, a self-administrated food frequency questionnaire (FFQ), and
269 online 24 h dietary recalls were completed to assess habitual dietary intake. One week prior to
270 the baseline visit (V1) and final visit (V4), participants were given a 7-day food diary (the

271 EPIC-Norfolk 7DD) (30) to record habitual food or drinks consumed in a consecutive 7 days.
272 The 7-day food records were coded into standard food codes and portions by trained coders
273 using the Nutritics software (Nutritics Research Edition v 5.76, Nutritics, Dublin, Ireland). A
274 standard protocol was followed by all coders to minimise coding error and improve the quality
275 and consistency of the data. Participants were asked to record the type and amount of foods
276 and drinks in as much detail as possible. During visit 1, participants completed the EPIC-
277 Norfolk FFQ (31), designed and validated (30) for estimating nutrient and food intake in the
278 past 1 year in UK adults. Microsoft Access software (Access 2019, Microsoft, USA) was used
279 to code the FFQs and transformed into daily food and nutrient intake levels by the FFQ EPIC
280 Tool for Analysis (FETA) software (32). The FFQs analysis is based on nutrient composition
281 from the McCance and Widdowson's "The Composition of Foods (5th edition)" and
282 supplementary materials (33). Online 24 h dietary recalls were recorded prior to each visit
283 remotely by participants (<https://intake24.co.uk/>) where they completed three non-consecutive
284 days dietary recalls including 2 weekdays and 1 weekend. This online dietary recall system
285 was designed for people aged 11 to 88 years (34). The system is based on the multiple-pass 24-
286 h recall (35) and contains a database of over 2500 foods linked to food codes (33). (Poly)phenol
287 intake was assessed using an in-house database which includes the Phenol-Explorer (36) and
288 USDA databases (37), and several published studies (38-57) by matching up the food codes
289 generated from Nutritics software to the available food content data in the (poly)phenols
290 content database. Details of this database have been previously described (58, 59) in which all
291 (poly)phenols content data for compounds bound to sugar moieties were converted to their
292 corresponding aglycone equivalents to allow aggregation with data from other sources.
293 (Poly)phenol intake (mg/day) was estimated by multiplying the daily intake of each food
294 (g/day) by its corresponding (poly)phenol content (mg/100 g), as derived from the in-house
295 database, and dividing the result by 100. Intakes of classes and subclasses of (poly)phenol were

296 calculated by summing all individual compounds within each respective group.

297 ***2.12 Power calculation and statistical analysis***

298 To conduct the power calculation, as this is the first study investigating the effects of
299 (poly)phenol-rich cranberry consumption on Total Mood Disturbance (TMD) scores using the
300 POMS questionnaire, we used published data from a previous RCT of similar design
301 investigating changes in TMD scores after 12 week consumption of another (poly)phenol
302 intervention (curcumin), in healthy older adults (60). Using the reported effect size, with a
303 significant level of 5% and 95% power, the required sample size was estimated at 60
304 participants. To account for a 20% attrition rate, 72 participants were recruited.

305 Linear mixed-effect models (LMM) were used to assess the effectiveness of the intervention
306 with “participant” as a random effect, while time, treatment, and time × treatment group
307 interaction were taken as the principal analysis of effect (fixed effects) with baseline values as
308 covariates followed by post hoc analysis using Bonferroni Test for multiple comparisons (61).
309 Regarding the outcomes that were measured at 2 timepoints (baseline and 12 weeks), including
310 plasma biomarkers and dietary intake measured using food diaries, ANCOVA was used with
311 baseline as covariate. Normality of data was assessed via the skewness-kurtosis test along with
312 the Q-Q plot of residuals. Homogeneity of variance was checked by plotting residuals against
313 the fitted values. If the distribution of data remained non-normal even upon data
314 transformation, the non-parametric Wilcoxon matched-pairs signed-rank test was used instead.
315 Statistical analysis was performed using IBM SPSS Statistics 29 (Statistical Product and
316 Service Solutions; IBM Corp.), and GraphPad Prism 9 on Windows (GraphPad Software) was
317 used for figures. All the statistical tests were applied in the intention to treat (ITT) population
318 unless otherwise stated; per-protocol analyses were performed as sensitivity analyses and
319 showed very similar effects as the ITT analysis. Missing data were minimal and handled within

320 the mixed-effects framework. The significant level for statistical tests was set at $p < 0.05$ and
321 estimates were expressed as means \pm SEMs unless stated otherwise.

322 3. Results

323 3.1 Baseline characteristics of the study population

324 A total of 82 subjects were recruited and screened, with 72 randomised to cranberry juice or
325 placebo as the intention-to-treat (ITT) sample, receiving at least 1 dose of treatment (34 in the
326 cranberry arm, 38 in the placebo arm) (**Figure 1**). The mean age at baseline was 23.2 years
327 (SD= 1.1), 72% of the cohort were of Asian ethnicity, 83% were female and 85% were
328 undertaking an MSc at the time of study recruitment (**Table 1**).

329 Seven-day food diaries collected at baseline and during the final week of the study were
330 analysed using ANCOVA, with no significant differences between the two timepoints, except
331 for carotene intake, which decreased at 12 weeks in comparison with baseline ($-1133 \mu\text{g/d}$; P
332 $= 0.05$) and hydroxyphenylacetic acid (1.35 mg/d ; $P = 0.04$), hydroxyphenylpropanoic acid
333 (0.897 mg/d ; $P = 0.04$), and stilbene intake (1.39 mg/d ; $P = 0.02$), which increased at 12 weeks
334 compared to baseline (**Supplementary Table 2**). In addition to food diaries, online 24-hour
335 dietary recalls recorded before each visit yielded similar results, with no significant differences
336 across visits, indicating that participants maintained a consistent diet throughout the study.

337 Based on food diaries, the daily average baseline for energy intake was $1691.2 \pm 379.4 \text{ kcal/day}$
338 in the cranberry group and $1808.8 \pm 478.8 \text{ kcal/day}$ in the placebo group. Fibre intake was 11.1
339 $\pm 4.5 \text{ mg/day}$ in the cranberry group while $12.6 \pm 3.9 \text{ mg/day}$ in the placebo group. Total
340 (poly)phenol intake was $553.8 \pm 318.9 \text{ mg}$ in the cranberry group and $698.9 \pm 456.8 \text{ mg}$ in the
341 placebo group (See supplementary Table 2). Main contributors to the intake of total
342 (poly)phenols based on the food diaries were coffee (59%), tea (25%), and apples (15%)
343 (**Supplementary Table 3**).

344 **3.2 Effects of (poly)phenol-rich cranberry consumption on mood, stress, anxiety, and**
345 **depression symptoms**

346 No significant differences were observed between the 2 intervention groups after 12 weeks in
347 the primary outcome, TMD score ($P = 0.87$). When looking at each component of TMD score,
348 no significant differences were found between treatments in any of the individual scores.
349 Similarly, no differences between treatments were found in self-reported stress levels ($P =$
350 0.60), anxiety ($P = 0.92$), and depression ($P = 0.98$) symptoms (**Table 2**).

351 **3.3 Effects of (poly)phenol-rich cranberry consumption on salivary cortisol levels**

352 Significant differences in the area under the curve (AUC_G) of salivary cortisol, which reflects
353 diurnal cortisol levels, were found. At visit 2, the cranberry group had a significantly higher
354 AUC_G compared to the placebo group (95% CI: 79.0, 1463; $P = 0.03$). However, after 12 weeks
355 of supplementation, the cranberry group had a significantly lower cortisol AUC_G compared to
356 the placebo group (95% CI: -2449, -358; $P = 0.01$) (**Figure 2**). No significant differences
357 between treatments were found at any timepoint in the area under the curve for cortisol
358 awakening response (CAR), and in diurnal cortisol levels measured as AUC_I (**Table 2**).

359 Comparisons at individual timepoints demonstrated that, at 12 pm, salivary cortisol levels were
360 significantly higher in the cranberry group than placebo at visit 2 (95% CI: 0.243, 4.11; $P =$
361 0.03) but at visit 4, cortisol levels were significantly lower in the cranberry group (95% CI:-
362 5.96, -0.921; $P = 0.01$) compared to placebo. As for cortisol levels at 8 pm, significant
363 differences were only observed at visit 4 (95% CI: -4.94, -0.411; $P = 0.02$) where the cranberry
364 group had significantly lower cortisol levels than the placebo (**Figure 2** and **Table 2**).

365 **3.4 Effects of (poly)phenol-rich cranberry consumption on cognitive function**

366 No significant differences between the cranberry and placebo groups were found on well-being
367 and cognitive profile, memory, reasoning, attention, coordination, and perception domains after
368 12 weeks intervention. However, significant differences were found between treatments for

369 short-term memory (95% CI: 6.67, 160; $P = 0.03$) and phonological short-term (95% CI: 22.6,
370 197; $P = 0.01$) memory, with cranberry group being significantly higher than placebo at visit 4
371 (**Figure 3** and **Table 2**).

372 **3.5 Plasma and urinary (poly)phenol metabolites**

373 A total of 94 phenolic metabolites concentrations were identified and quantified in both plasma
374 and urine. Significant differences were observed between treatments in plasma (poly)phenols
375 measured with LC-MS, in particular changes in total plasma (poly)phenols (95% CI: 3560,
376 47300; $P = 0.02$) and plasma hippuric acid (95% CI: 7783, 41352; $P = 0.01$) (**Figure 4**). In
377 urine, several metabolites concentrations showed significant differences between treatments
378 from baseline to week 12 including 5-(5'-hydroxyphenyl)- γ -valerolactone-3'-sulfate, 5-(3',5'-
379 dihydroxyphenyl)- γ -valerolactone, as well as 7,8-Dihydroxycoumarin, and 3'-
380 methoxycinnamic acid-4'-sulfate (ferulic acid-4'-sulfate) (**Supplementary Figure 1**).
381 Significant inverse correlations were found between changes in total plasma (poly)phenols
382 concentrations and cortisol levels ($\rho = -0.502$; $P = 0.01$) and between plasma hippuric acid
383 and cortisol levels measured as AUC^G awakening response ($\rho = -0.609$; $P = 0.001$), diurnal
384 ($\rho = -0.416$; $P = 0.04$), and AUC^I awakening response ($\rho = -0.425$; $P = 0.02$) after
385 consumption of the cranberry drink for 12 weeks (**Supplementary Figure 2**).

386 **4. Discussion**

387 This study investigated the effects of 12 weeks of daily (poly)phenol-rich cranberry
388 supplementation on mood, anxiety, depression, stress levels, and cognitive function in
389 university students. Our results showed no improvement in the primary outcome, self-reported
390 mood (TMD), or in self-reported stress, anxiety, and depression; however, cranberry
391 consumption reduced diurnal cortisol levels and enhanced certain aspects of cognitive function,
392 particularly short-term and phonological memory.

393 To our knowledge, this is the first study reporting the effects of a (poly)phenol-rich cranberry
394 drink on mood, precluding direct comparison with other cranberry interventions. Although few
395 studies have examined the effects of other berries, such as blueberries, on mood, with mixed
396 results (62), berries such as blueberries are generally richer in anthocyanins than in flavan-3-
397 ols, limiting their suitability for direct comparison with cranberries.

398 In this study, cranberry consumption did not alter mood, as assessed by TMD using the POMS
399 questionnaire. Mixed effects have been reported for cocoa flavan-3-ols: daily consumption of
400 25 g of polyphenol-rich dark chocolate (500 mg/day flavonoids) for 4 weeks had no effect on
401 mood, measured using the Positive and Negative Affect Schedule (PANAS) questionnaire, in
402 healthy individuals (63), whereas consumption of a cocoa drink containing 240 mg flavan-3-
403 ols for 8 weeks significantly lowered TMD in healthy middle-aged Japanese women (64).
404 Additionally, consumption of 30 g/day of 85% dark chocolate, but not 70%, for 3 weeks
405 decreased negative affect in young healthy individuals, also measured using PANAS (65).
406 Besides that, 3 weeks supplementation of Shaded white tea (192 mg of caffeine, 223 mg of
407 flavan-3-ols) in healthy adults showed significantly reduced TMD scores (66). The
408 heterogeneity in study design, mood assessment tools, population characteristics, and flavan-
409 3-ol dose makes direct comparison difficult. Cocoa and tea also contain methylxanthines
410 (caffeine & theobromine) and other bioactives (ie L-theanine), which can influence mood and
411 stress responses. In addition, cranberries have lower levels of flavan-3-ol monomers and are
412 rich in A-type proanthocyanidins, which are less bioavailable than the B-type
413 proanthocyanidins present in cocoa, tea, and other berries (67).

414 Cranberry supplementation also did not alter self-reported stress, anxiety, or depression
415 measured with validated questionnaires. Previous (poly)phenol interventions have shown
416 inconsistent effects, influenced by baseline mental health symptoms, dose, duration, and
417 formulation. Short-term, high-dose cocoa interventions often failed to improve stress or

418 anxiety (68, 69), whereas interventions using bioavailable formulations or combined
419 (poly)phenol diets showed benefits (70-72). The healthy young adult cohort in this study, with
420 moderate stress and low depression and anxiety symptoms, may have had limited potential for
421 observable improvement.

422 A notable finding was the reduction in diurnal cortisol in the cranberry group, particularly in
423 the afternoon and evening measures, while the cortisol awakening response was unchanged,
424 suggesting that the effects occur later in the day. This aligns with delayed appearance of
425 cranberry flavan-3-ol microbially-derived metabolites, such as phenyl- γ -valerolactones, in
426 circulation 4–6 hours post-consumption and among the most abundant cranberry metabolites
427 (73-75). These metabolites can cross the blood-brain barrier (76-78), potentially modulating
428 hypothalamic–pituitary–adrenal axis (HPA) axis activity.

429 Consistent with this interpretation, cranberry supplementation resulted in significant changes
430 in circulating (poly)phenol metabolites concentrations, including increases in total plasma
431 (poly)phenols and hippuric acid. Importantly, total plasma (poly)phenol concentrations and
432 hippuric acid were negatively correlated with diurnal cortisol, further implicating
433 (poly)phenol-derived metabolites in modulating HPA axis activity. While several urinary
434 metabolites differed between treatments over the intervention period, only modest changes
435 were observed for individual compounds (phenyl- γ -valerolactones, 7,8-Dihydroxycoumarin,
436 and ferulic acid-4'-sulfate) likely reflecting extensive metabolism and the timing of spot urine
437 collection more which more than 24 h after cranberry consumption. Similar cortisol-lowering
438 effects have been reported for cocoa (63) and green tea (14), supporting a role for flavan-3-ols
439 in HPA axis regulation. However, these relationships are associative in nature, and causality
440 between specific (poly)phenol metabolites and cortisol outcomes cannot be inferred from the
441 present study. Although between-group differences in cortisol AUC_G were statistically
442 significant, the clinical significance of these changes remains uncertain, as AUC_G lacks

443 established clinical reference ranges or validated thresholds. Accordingly, the findings should
444 be interpreted as reflecting altered HPA axis activity rather than a clinically defined effect. The
445 lack of correlation between cortisol and perceived stress scores is consistent with prior
446 evidence that physiological and subjective stress responses are often uncoupled in healthy
447 populations (79-83).

448 Cranberry supplementation improved short-term and phonological memory, consistent with a
449 previous study in healthy older adults where consumption of a freeze-dried cranberry extract
450 for 12 weeks led to significant improvement in memory performance especially to episodic
451 memory. In that trial, the cranberry powder provided 375 mg of total proanthocyanidins (PACs)
452 per 9 g daily serving, including approximately 59 mg of anthocyanins (16). In the present study,
453 the cranberry intervention delivered 303 mg PACs per 236 mL serving and 41 mg of
454 anthocyanins, which may partly explain the consistency in observed memory-related effects
455 between studies. In contrast, 6 weeks cranberry juice showed no improvement in memory
456 performance (84). Several factors may account for the inconsistent results. The duration of the
457 trial may be crucial for detecting measurable effects on cognitive performance in healthy
458 adults. No effects were observed in other cognitive domains, suggesting domain-specific
459 sensitivity to cranberry (poly)phenols.

460 The baseline diet of participants in this study may have influenced the response to the
461 intervention. Reported fruit and vegetable intake (327 g/day) was below the 400 g/day ("5-a-
462 day") recommendation by the UK Eatwell guide and WHO (85, 86). Fibre intake was
463 considerably lower than recommended, with participants consuming only 11g/day compared
464 to the UK guideline of 30 g/day, indicating a low consumption of plant foods. Furthermore, the
465 average (poly)phenol intake in the study population was 553.8 ± 318.9 mg/day, approximately
466 50% lower than the average reported for similarly aged individuals in the UK National Diet
467 and Nutrition Survey Rolling Programme ($1,035 \pm 545$ mg/day) (87), and significantly below

468 the intake observed in the ‘health-conscious’ group of the UK EPIC study (1521 mg/day) (31).
469 These values suggest that participants had a relatively low habitual intake of (poly)phenols,
470 which may have increased their potential responsiveness to supplementation. Specifically,
471 flavan-3-ol intake was 223 mg/day, falling well short of the recently proposed optimal range
472 of 400–600 mg/day for cardiometabolic health benefits (88). While there are currently no
473 formal dietary recommendations for (poly)phenol intake, these data suggest that participants
474 could have benefitted from a substantial increase in (poly)phenol exposure via the cranberry
475 intervention. Future research should more rigorously account for baseline diet and monitor
476 habitual (poly)phenol intake during interventions. The current lack of such data in many trials
477 limits the ability to compare findings across studies and to draw robust conclusions regarding
478 the efficacy of (poly)phenol supplementation.

479 Strengths of this study include its double-blind randomised design, 12-week controlled
480 intervention, assessment of multiple timepoints for outcomes, comprehensive evaluation of
481 cognitive domains, and multiple measurements of salivary cortisol, allowing detailed
482 characterisation of physiological stress responses.

483 Limitations include that depression, anxiety, cognition, and stress were secondary outcomes,
484 which may have resulted in insufficient statistical power to detect subtle changes. In addition,
485 multiple cognitive subdomains were assessed, and improvements were observed in only two
486 outcomes; therefore, the possibility of type I error due to multiple testing cannot be excluded,
487 and these cognitive findings should be interpreted cautiously. Furthermore, the study
488 population consisted of healthy young adults with low baseline symptoms levels, which likely
489 introduced floor effects and limited the ability to detect improvements in self-reported mental
490 health outcomes. The predominance of Asian and female participants may limit the
491 generalisability of the findings to other populations. Although the intervention provides
492 mechanistic insight under controlled conditions, it does not replicate whole-diet approaches

493 rich in diverse plant foods that deliver a broader spectrum of bioactive compounds. Therefore,
494 the effects observed in this study may not be directly generalisable to habitual dietary patterns.
495 Finally, comparisons with other (poly)phenol interventions are further complicated by
496 variations in bioactive composition and bioavailability.

497 In conclusion, 12 weeks of (poly)phenol-rich cranberry consumption in healthy university
498 students did not affect the primary outcomes, Total Mood Disturbance. Secondary outcomes,
499 including anxiety, depression, stress, diurnal cortisol, and cognitive performance, showed no
500 consistent improvements in self-reported mental health, although exploratory analyses
501 indicated reductions in diurnal cortisol and improvements in short-term memory. These
502 findings provide mechanistic insights into potential links between cranberry-derived
503 (poly)phenol metabolism and modulation of HPA axis, while highlighting the importance of
504 bioactive composition, participant characteristics, baseline mental health status, and
505 methodological factors in determining the efficacy of (poly)phenol interventions. Further
506 research is needed to optimize dosing and formulation, clarify underlying mechanisms, and
507 identify populations most likely to benefit.

508 **Author Disclosures:** None of the authors declared any other conflicts of interest.

509 **Funding:** This work was funded by an unrestricted grant from the Cranberry Institute. The
510 funder of this study had no input on the design, implementation, analysis or interpretation of
511 the data. NNZK is funded by a grant from the Majlis Amanah Rakyat (MARA), Malaysia.

512 **Author contributions and Acknowledgements**

513 The authors' responsibilities were as follows – NNZK, MLS, AB, CP, RM, BB, and ARM:
514 designed the study; NNZK and MLS: carried out data collection; NNZK and MLS: conducted
515 the analysis of the primary and secondary outcomes with support from AC; KD; ZC; YX, DV,
516 and RM: provided support and training for statistical analysis and lab; YL and HW: conducted
517 the dietary assessment analysis of food diaries and questionnaires; DV, ARM and BB shared

518 the primary responsibility for the final content. All authors contributed to the writing, read and
519 approved the final manuscript. No contributor eligible for the authorship has been excluded
520 from the list of authors. The authors would like to thank Tim Wingham, Nicole Callaghan,
521 Emily Stynes Fernandez, Xinyi Zhu and Tuba Astarcioglu for their help during the study, as
522 well as all participants for their time and commitment to the CRANMOOD study.

523 **Data sharing statement:** Data described in this manuscript will be available upon reasonable
524 request, subject to application, approval, and a data sharing agreement.

525 **Ethical approval, study registration and permissions:** All participants provided formal
526 written informed consent to participate in the study. The study protocol was reviewed and
527 approved by the King's College London Research Ethics Committee (RESC reference:
528 HR/DP-21/22-26721).

529 **Declaration of Generative AI and AI-assisted technologies in the writing process:** During
530 the preparation of this manuscript, ChatGPT (OpenAI) was used to assist with language editing
531 and improving clarity. The authors reviewed and edited all content and take full responsibility
532 for the accuracy, originality, and integrity of the work.

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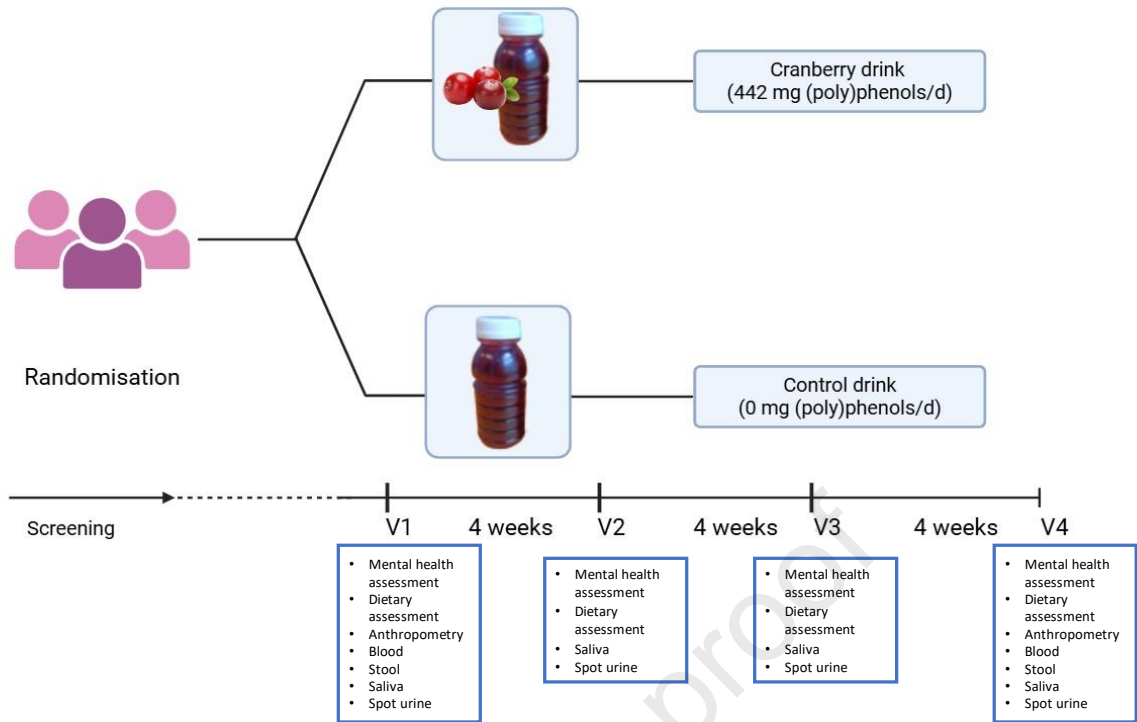
Table 1. Baseline characteristics for both the cranberry and placebo treatments group

	Cranberry group Mean (SD) (N= 34)	Placebo group Mean (SD) (N= 38)
Sex (M/F)	6/28	6/32
Age range	20 - 26	21 - 25
Ethnicity		
Asian	23 (67.6)	29 (76.3)
White	7 (20.6)	8 (21.1)
Black	3 (8.8)	1 (2.6)
Other	1 (2.9)	0 (0)
Education		
BSc	5 (14.7)	6 (15.8)
MSc	29 (85.3)	32 (84.2)
Waist circum. (cm)	71.0 (7.8)	70.0 (7.7)
Height (cm)	166.6 (0.1)	167.1 (0.1)
Hip circum. (cm)	93.8 (7.2)	93.2 (8.6)
Weight (Kg)	58.1 (9.0)	56.6 (11.6)
Body Fat (%)	21.2 (8.3)	22.9 (8.0)
BMI (Kg/m ²)	20.6 (2.4)	20.2 (2.8)
BMR (Kcal)	1380 (205)	1361 (267)
Smoker (n, %)		
Yes	1 (3%)	6 (16%)
Alcohol/week	0.2 (0.0, 1.5)	0.7 (0.0, 1.5)
SBP (mmHg)	109.0 (8.3)	105.5 (10.6)
DBP (mmHg)	71.2 (6.4)	72.4 (6.3)
HR (bpm)	73.8 (11.4)	80.0 (13.3)
Plasma glucose (mmol/L)	4.9 (0.3)	4.9 (0.3)
Total protein (g/L)	72.1 (3.9)	71.4 (4.4)
Albumin (g/L)	48.4 (2.3)	47.4 (3)
Globulins (g/L)	23.7 (2.6)	24.1 (2.6)
Total bilirubin (umol/L)	11.6 (5.5)	11.2 (5.8)
ALP (IU/L)	55.9 (12.8)	53.8 (14.6)
AST (IU/L)	22.1 (4)	25.8 (20.4)
ALT (IU/L)	19.1 (13.3)	19.2 (17.7)
GGT (IU/L)	13.1 (6)	11.8 (3.9)
Urate (umol/L)	304 (65.7)	285 (71.7)
Cholesterol (mmol/L)	4.4 (0.8)	4.1 (0.7)
Triglycerides (mmol/L)	0.8 (0.4)	0.8 (0.3)
HDL cholesterol (mmol/L)	1.6 (0.2)	1.5 (0.3)
LDL cholesterol (mmol/L)	2.6 (0.9)	2.4 (0.7)
Non-HDL cholesterol (mmol/L)	2.8 (0.8)	2.6 (0.6)
Total cholesterol/HDL ratio	2.8 (0.6)	2.8 (0.5)
Physical activity level (n, %)		
LOW	2 (6%)	2 (5%)
MODERATE	17 (50%)	21 (55%)
HIGH	15 (44%)	15 (39%)
PSS (score)	19.1 (5.1)	16.7 (5.3)
HADS- Anxiety (score)	8 (3.1)	7.5 (4)
HADS- Depression (score)	4.7 (2.8)	3.3 (2.4)
TMD (score)	51.7 (10.1)	49 (10.2)
Short-term memory (score)	578 (223)	623 (235)
Phonological short-term memory (score)	570 (255)	652 (204)

BSc, bachelor student; MSc, master student; BMI, body mass index; BMR, basal metabolic rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; GGT, Gamma-glutamyl transferase; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; PSS, Perceived Stress Scale; HADS, Hospital Anxiety and Depression Score; TMD, Total Mood Disturbance. Comparison of demographic between the trial arms, if the outcome of interest was binary or categorical, logistic regression or chi-squared test was used, respectively. Linear regression was used for continuous variables. Binary and categorical variables are presented using counts and percentages. The distribution of continuous variables was assessed using coefficients of skewness and then summarised by mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate.

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A)



B)

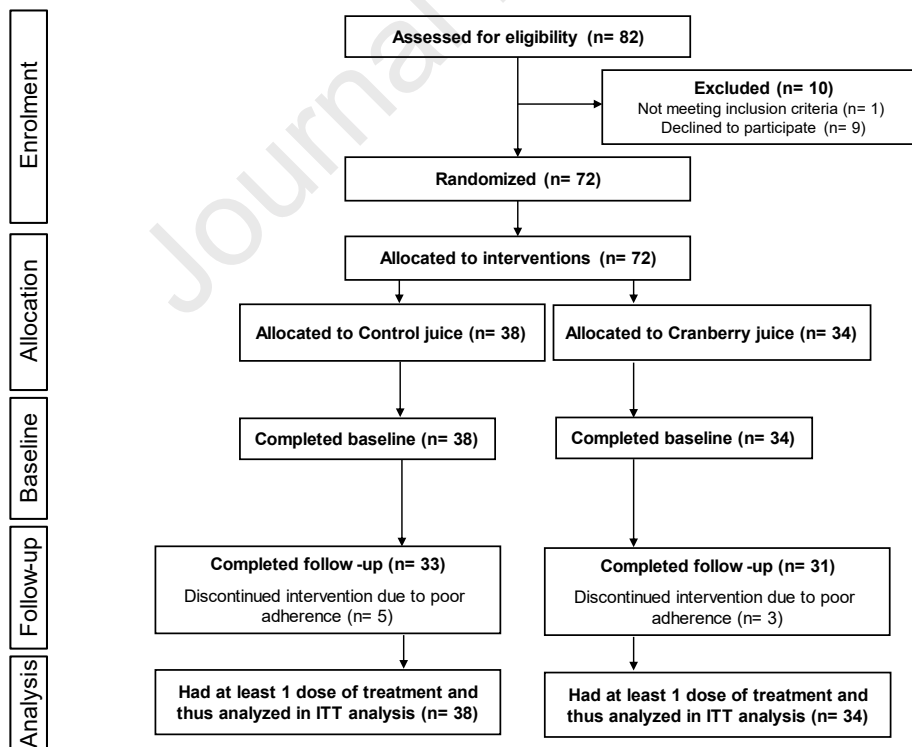


Figure 1. A) Study design of the CRANMOOD study B) Flow diagram outlining study activity and participant numbers throughout the process.

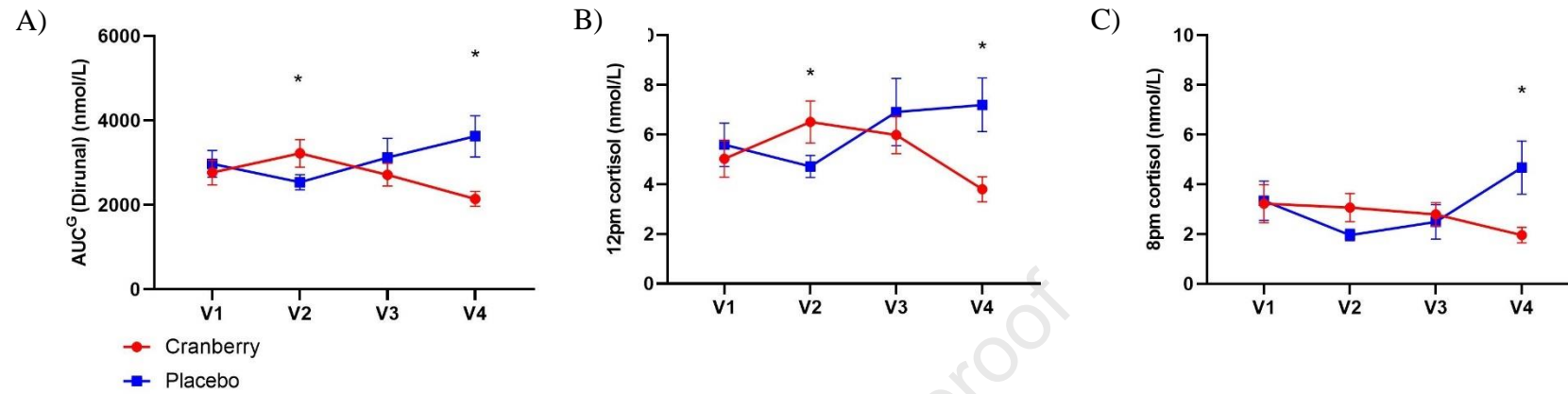


Figure 2: Cortisol levels at baseline (V1), and after 4 weeks (V2), 8 weeks (V3), and 12 weeks (V4) daily consumption of cranberry and placebo drinks, evaluated by linear mixed modeling analysis. Values are expressed as means \pm SEMs. A) Salivary cortisol levels expressed as AUCG, B) 12 pm timepoint and C) 8 pm timepoint. * $P < 0.05$ (Significant between group comparison)

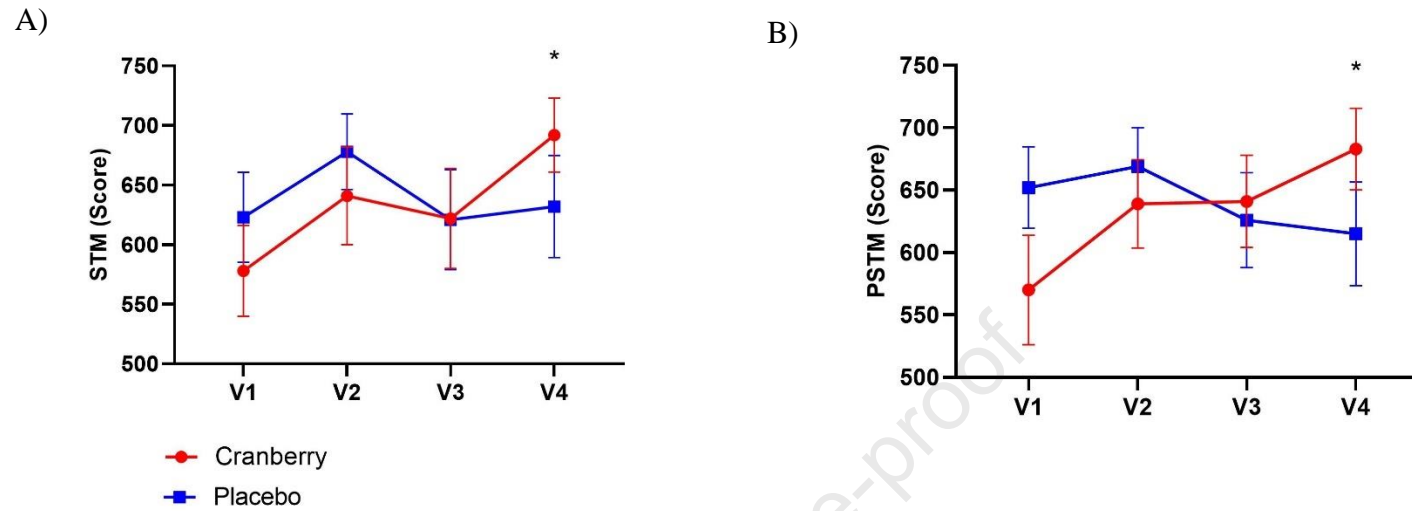
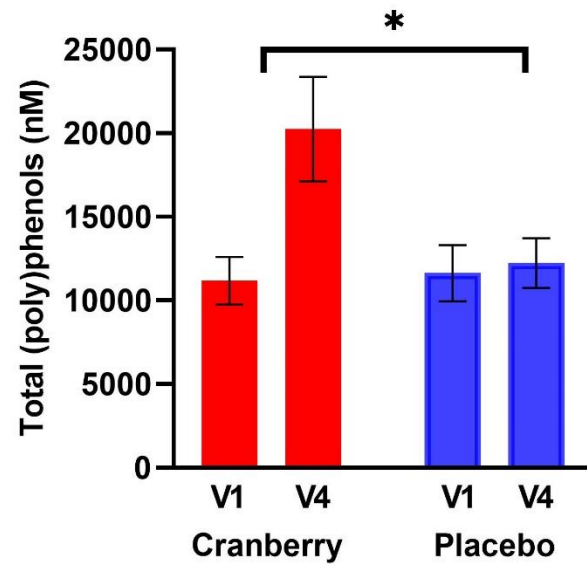


Figure 3: Impact of cognition level after daily consumption of cranberry and placebo at baseline (V1), and after 4 weeks (V2), 8 weeks (V3), and 12 weeks (V4) daily consumption of cranberry and placebo drinks, evaluated by linear mixed modeling analysis. Values are expressed as means \pm SEMs. Absolute value of A) Short-term Memory (STM) (Raw score), and B) Phonological short-term memory (PSTM) (Raw score) at visit 1, 2, 3, and 4 after consecutive consumption of the cranberry and placebo. *P < 0.05 (Significant between group comparison)

A)



B)

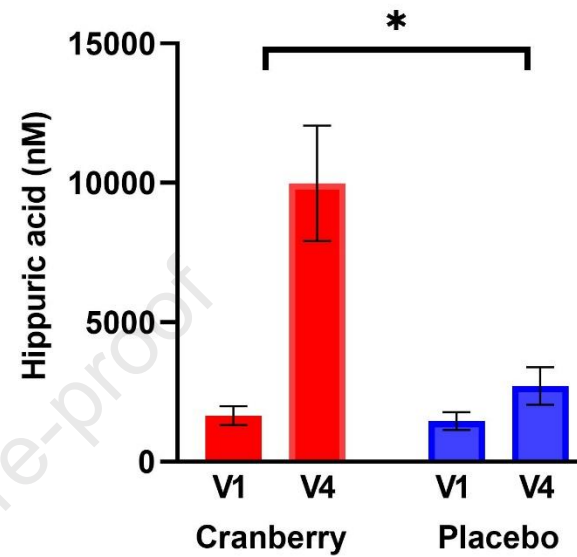


Figure 4: Impact of daily consumption of intervention groups on plasma cranberry (poly)phenol metabolites concentrations evaluated by ANCOVA analysis. Values are expressed as means \pm SEs. A) Total (poly)phenol and B) Hippuric acid changes from baseline after consecutive consumption of treatments cranberry compared to placebo. * $P < 0.05$ (Significant between group comparison)

Table 2. Main outcomes of mental health and cortisol levels following daily consumption of the treatment cranberry and placebo. Linear mixed modelling analysis presented as difference from placebo at visit 2, 3, and 4, using baseline as a covariate. Only results with significant LMM findings are reported (p<0.05)

Variables	V2	V3	V4	P for treatment ¹	P for visit ²	P for interaction ³
TMD (score)						
Cranberry	52.4±1.27	52.4±1.29	50.3±1.59			
Placebo	50.0±1.43	53.3 ±1.60	51.0±1.65	0.87	0.22	0.29
<i>Difference</i> ⁴	2.43(-1.44;6.31)	-0.971(-5.09;3.16)	-0.709(-5.30;3.88)			
<i>p</i> ⁵	0.21	0.64	0.76			
Anger-Hostility (score)						
Cranberry	44.7±0.986	44.2±1.02	43.6±1.00			
Placebo	42.4±0.519	44.5±0.967	44.7±1.11	0.85	0.57	0.09
<i>Difference</i> ⁴	2.25(0.00631;4.49)*	-0.273(-3.09;2.55)	-1.10(-4.09;1.89)			
<i>p</i> ⁵	0.05	0.85	0.46			
Confusion-Bewilderment (score)						
Cranberry	50.9 ±1.26	50.2±1.21	48.5±1.14			
Placebo	3.33(-0.153;6.81)	-0.411(-4.14;3.32)	-0.193(-3.75;3.36)	0.50	0.23	0.13
<i>Difference</i> ⁴	3.33(-0.153;6.81)	-0.411(-4.14;3.32)	-0.193(-3.75;3.36)			
<i>p</i> ⁵	0.06	0.83	0.91			
Depression-Dejection (score)						
Cranberry	49.5±1.11	49.2±1.06	47.3±1.43			
Placebo	46.2±0.858	51.1±1.54	48.3±1.52	0.91	0.05	0.02*
<i>Difference</i> ⁴	3.34(0.526;6.16)*	-1.92(-5.67;1.84)	-1.01(-5.18;3.16)			
<i>p</i> ⁵	0.02	0.31	0.63			
Fatigue-Inertia (score)						
Cranberry	45.9±1.19	46.5±1.11	45.7±1.48			
Placebo	44.8±1.69	46.2±1.22	44.9±1.16	0.60	0.49	0.92
<i>Difference</i> ⁴	1.19(-2.96;5.33)	0.318(-2.99;3.63)	0.757(-3.02;4.54)			
<i>p</i> ⁵	0.59	0.85	0.69			
Tension-Hostility (score)						
Cranberry	48.9 ±1.27	48.7±1.34	46.7±1.48			
Placebo	47.4±1.61	49.2±1.34	48.5±1.43	0.87	0.47	0.36
<i>Difference</i> ⁴	1.57(-2.56;5.71)	-0.480(-4.27;3.31)	-1.82(-5.91;2.29)			
<i>p</i> ⁵	0.45	0.80	0.38			
Vigor-Activity (score)						
Cranberry	49.7±1.04	46.9±1.35	48.6±1.39			
Placebo	47.2±1.31	48.9±1.29	49.2±1.33	0.96	0.69	0.10
<i>Difference</i> ⁴	2.42(-0.979;5.82)	-2.06(-5.79;1.67)	-0.568(-4.41;3.28)			
<i>p</i> ⁵	0.16	0.28	0.77			
Friendliness (score)						

Cranberry	49.2±1.12	46.7±1.19	47.7±1.48			
Placebo	48.2±1.31	47.9±1.42	47.9±1.37	0.90	0.42	0.54
<i>Difference</i> ⁴	1.05(-2.42;4.53)	-1.30(-5.02;2.42)	-0.271(-4.29;3.75)			
<i>p</i> ⁵	0.55	0.49	0.89			
PSS (score)						
Cranberry	19.1± 0.836	18.3±0.873	17.4±1.07			
Placebo	17.9±0.784	17.6±0.865	17.6±0.979	0.60	0.39	0.64
<i>Difference</i> ⁴	1.16(-1.15;3.48)	0.673(-1.79;3.14)	-0.282(-3.19;2.62)			
<i>p</i> ⁵	0.32	0.59	0.85			
HADS anxiety (score)						
Cranberry	7.65±0.511	7.88±0.551	8.03±0.653			
Placebo	7.78±0.414	7.55±0.634	8.04±0.616	0.92	0.75	0.85
<i>Difference</i> ⁴	-0.131(-1.44;1.18)	0.331(-1.35;2.01)	-0.704(-1.79;1.78)			
<i>p</i> ⁵	0.84	0.70	0.99			
HADS depression (score)						
Cranberry	3.87±0.529	4.42±0.441	3.95±0.509			
Placebo	3.75±0.414	4.18±0.502	4.35±0.530	0.98	0.41	0.70
<i>Difference</i> ⁴	0.118(-1.24;1.48)	0.241(-1.11;1.59)	-0.404(-1.88;1.08)			
<i>p</i> ⁵	0.86	0.72	0.59			
AUC^G (Diurnal) (nmol/L)						
Cranberry	3150 ± 311	2630 ± 267	2215 ± 183			
Placebo	2379 ± 146	2731 ± 293	3618 ± 483	0.30	0.76	0.00*
<i>Difference</i> ⁴	771 (79.0;1463)*	-100 (-896;695)	-1403 (-2449;-358)*			
<i>p</i> ⁵	0.03	0.80	0.01			
12pm cortisol (nmol/L)						
Cranberry	6.62 ± 0.874	5.95 ± 0.772	3.81 ± 0.514			
Placebo	4.44 ± 0.398	5.80 ± 0.860	7.26 ± 1.14	0.61	0.87	0.00*
<i>Difference</i> ⁴	2.18 (0.243;4.11)*	0.143 (-2.17;2.46)	-3.44 (-5.96;-0.921)*			
<i>p</i> ⁵	0.03	0.90	0.01			
08pm cortisol (nmol/L)						
Cranberry	3.12 ± 0.593	2.82 ± 0.457	1.99 ± 0.338			
Placebo	1.92 ± 0.227	2.36 ± 0.656	4.67 ± 1.06	0.91	0.51	0.01*
<i>Difference</i> ⁴	1.20 (-0.0791;2.48)	0.467 (-1.14;2.07)	-2.67 (-4.93;-0.411)*			
<i>p</i> ⁵	0.07	0.56	0.02			
PSTM (Raw score)						
Cranberry	658 ± 25.0	672 ± 29.1	703 ± 32.9			
Placebo	648 ± 27.9	608 ± 26.0	593 ± 28.4	0.06	0.78	0.07
<i>Difference</i> ⁴	10.0 (-65.1;85.2)	63.4 (-14.9;142)	110 (22.6;197)*			
<i>p</i> ⁵	0.79	0.11	0.01			
STM (Raw score)						
Cranberry	654 ± 28.2	642 ± 32.8	704 ± 28.1			
Placebo	667 ± 24.3	613 ± 25.7	620 ± 25.8	0.30	0.20	0.04*

<i>Difference</i> ⁴	-13.8 (-88.3;60.7)	29.0 (-54.1;112)	83.2 (6.67;160)*
<i>p</i> ⁵	0.71	0.49	0.03

Values expressed as estimated marginal means \pm SEMs. Analyses were done with baseline values as covariate. ¹Comparison between cranberry and placebo; treatment effect (LMM). ²Comparison between the different visits; visits effects (LMM). ³Comparison between measures obtained throughout the visits with cranberry group and placebo group; carry-over or interaction effect (LMM). ⁴Between group difference; mean difference (lower 95% CI, upper 95% CI). ⁵Between group comparison (LMM followed by multiple comparison with Bonferroni test). TMD, Total mood disturbance; PSS, Perceived Stress Scale; HADS, Hospital Anxiety and Depression Scale; AUCG, area under the curve with respect to the ground; STM, Short-term memory; SWB, Social well-being; PSTM, Phonological short-term memory. *P < 0.05

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Supplementary Table 1. Nutritional and phytochemical content of the cranberry and placebo interventions.

	Cranberry juice (236mL)	Placebo juice (236mL)
Total fat (g)	0	0
Protein (g)	0	0
Total carbohydrates (g)	18	18
Sugar (g)	9	11
Dextrose (%)	3.3	4.6
Fructose (%)	0.7	0
Sucrose (%)	0.02	0
Calories (kcal)	60	60
Dietary fibre, total (g)	1.25	0
Insoluble fibres (g)	0.5	0
Soluble fibre (g)	0.75	0
Total (poly)phenol (mg)	442	0
Proanthocyanidins (mg)	303	0
Total Anthocyanins (mg)	41.4	0
Total flavonoids (mg)	78	0
Myricetin (mg)	1	0
Quercetin (mg)	2	0
Catechin (mg)	27	0
Epicatechin (mg)	2	0
Phenolic acids (mg)	61	0

* Identification and quantification of phenolic compounds in the cranberry juice by HPLC–MS analysis.

Supplementary Table 3. Contribution of food groups and some specific foods to the intake of total (poly)phenol and (poly)phenol classes in the background diet of volunteers from the CRANMOOD study at baseline, assessed using 7-day food diaries.

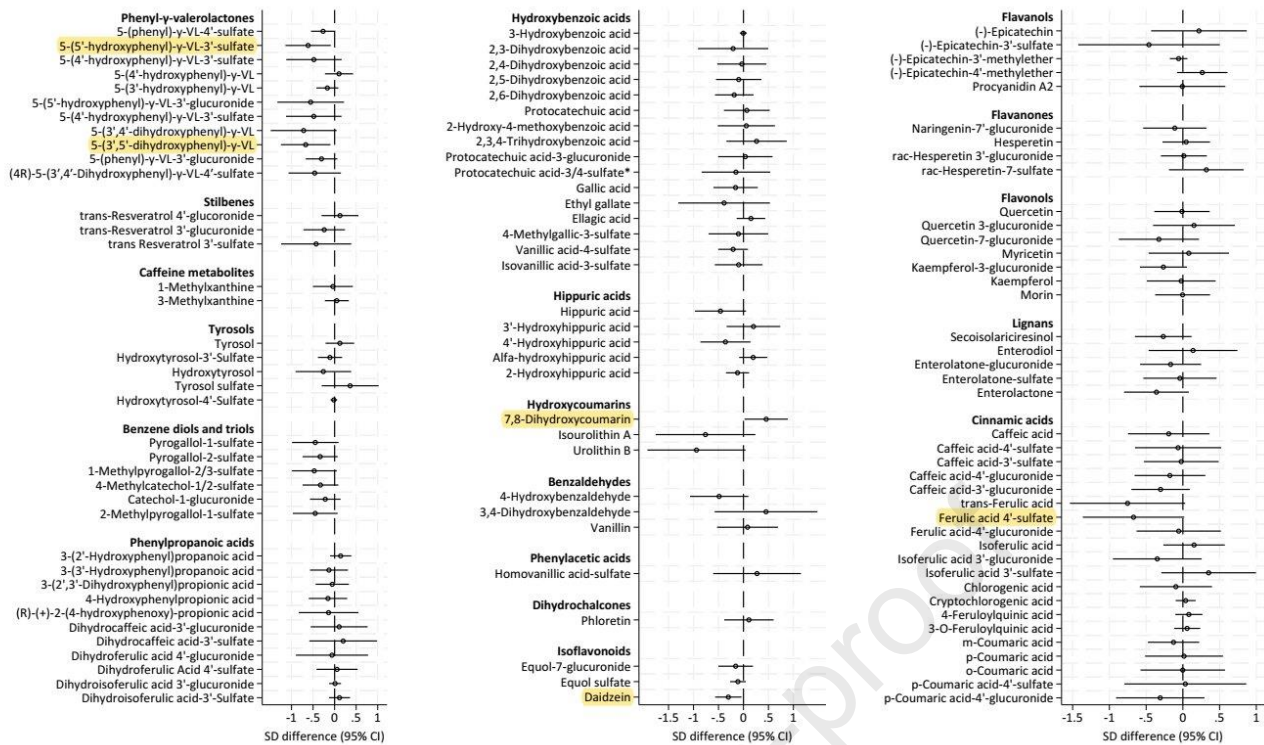
(Poly)phenol	Food category*
Total (poly)phenol	Coffee (59%), tea (25%), and apples (16%)
Total flavonoids	Tea (51%), apples (31%) and strawberries (18%)
Anthocyanins	Aloe vera juice (64%), blueberries (19%) and strawberries (17%)
Flavan-3-ols	Tea (52%), apples (30%), chocolate powder and drinks (17%)
Proanthocyanidins	Apples (49%), chocolate powder and drinks (28%) and strawberries (23%)
Flavanones	Oranges (62%), orange juice (29%) and lemons (10%)
Flavones	Soup (65%), bread (26%) and noodles (10%)
Flavonols	Tomatoes (78%), spinach (17%) and tea (4%)
Isoflavonoids	Tofu (65%), soya milk (21%) and beansprouts (9%)
Lignans	Sesame oil (81%), sesame (16%) and flaxseeds (4%)
Tyrosol	Olive oil (82%), olives (11%) and pesto (7%)
Phenolic acids	Coffee (92%), white rice (5%) and blueberries (3%)
Hydroxybenzoic acids	Chestnuts (40%), tea (34%) and strawberries (26%)
Hydroxycinnamic acids	Coffee (93%), white rice (4%) and blueberries (3%)
Stilbenes	Red wine (74%), strawberries (21%) and grapes (6%)

* Percentages are normalized to the top three contributing food sources only and do not reflect total dietary (poly)phenol intake from all foods.

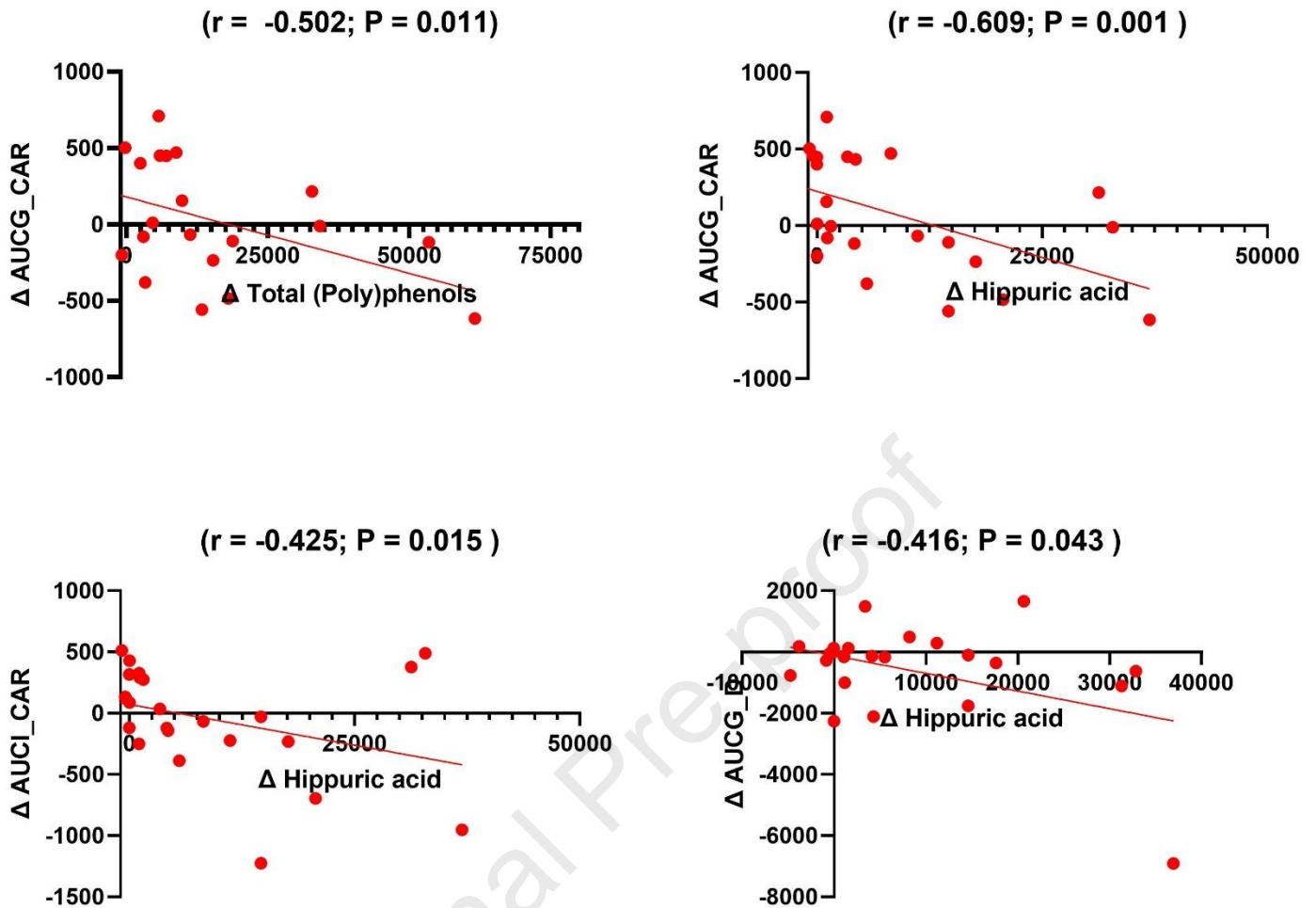
Supplemental Table 2. Average macro-, micronutrient and (poly)phenol intake taken from 7-day diet diaries at baseline and during the 12-week intervention.

	Cranberry (Mean ± SD)			Placebo (Mean ± SD)			Cranberry vs Placebo		
	Visit 1 (n=33)	Visit 4 (n=31)	CFB	Visit 1 (n=32)	Visit 4 (n=31)	CFB	Mean ± SEM	95% CI	P
Energy (kcal)	1691.2 ± 379.4	1637.7 ± 501.0	-79.2±76.1	1808.8 ± 478.8	1677.9 ± 457.6	-134±77.4	55.2±109	-164;274	0.616
Carbohydrates (g)	181.8 ± 46.4	164.5 ± 51.2	-22.5±7.13	203.9 ± 58.4	171.5 ± 40.5	-30.2±7.25	7.67±10.3	-13.0;28.4	0.462
Protein (g)	82.1 ± 24.0	83.9 ± 30.0	1.69±3.99	83.5 ± 37.5	81.1 ± 31.2	-3.04±4.06	4.72±5.69	-6.69;16.1	0.411
Fat (g)	67.9 ± 18.3	69.7 ± 26.5	0.407±4.39	71.4 ± 22.0	70.3 ± 23.5	-1.11±4.46	1.52±6.28	-11.0;14.1	0.809
Fibres (g)	11.1 ± 4.5	10.7 ± 4.8	-0.840±0.647	12.6 ± 3.9	11.5 ± 4.2	-1.14±0.658	0.304±0.930	-1.56;2.17	0.745
Saturated fat (g)	23.8 ± 8.2	22.0 ± 9.7	-2.20±1.64	24.1 ± 9.1	24.1 ± 9.5	-0.455±1.67	-1.74±2.34	-6.43;2.94	0.459
Monounsaturated fat (g)	24.7 ± 7.6	26.4 ± 10.7	0.981±1.89	26.9 ± 8.2	25.1 ± 10.6	-1.29±1.92	2.27±2.71	-3.15;7.69	0.406
Polyunsaturated fat (g)	11.6 ± 4.9	13.0 ± 6.6	1.80±1.15	10.6 ± 4.3	11.9 ± 6.2	0.848±1.17	0.947±1.65	-2.35;4.24	0.568
Vitamin A (µg)	869.8 ± 475.3	605.1 ± 305.6	-15.1±59.5	794.5 ± 563.4	815.6 ± 780.3	45.9±60.4	-60.9±84.8	-231;109	0.475
Retinol (µg)	229.8 ± 112.7	227.4 ± 170.4	-261±95.6	247.9 ± 253.2	289.8 ± 428.2	-15.9±97.2	-245±136	-518;28.2	0.078
Carotene (µg)	3854.1 ± 2858.4	2274.8 ± 1747.6	-1511±390	3309.7 ± 3253.0	3148.9 ± 3388.2	-378±396	-1133±557	-2247;-19.1	0.046*
Vitamin D (µg)	4.5 ± 6.9	3.5 ± 1.7	0.054±0.465	4.7 ± 9.2	4.5 ± 8.9	-0.299±0.473	0.353±0.666	-0.980;1.67	0.598
Vitamin E (mg)	9.0 ± 4.0	9.1 ± 3.8	0.315±0.717	8.2 ± 3.1	8.5 ± 4.3	-0.096±0.729	0.411±1.03	-1.64;2.46	0.69
Vitamin B1 (mg)	1.3 ± 0.4	1.2 ± 0.5	-0.146±0.115	1.4 ± 0.4	1.3 ± 0.7	-0.0141±0.117	-0.132±0.164	-0.461;0.196	0.424
Vitamin B2 (mg)	1.3 ± 0.4	1.3 ± 0.4	-0.106±0.103	1.4 ± 0.6	1.5 ± 0.8	0.128±0.105	-0.234±0.148	-0.530;0.0621	0.119
Vitamin B3 (mg)	35.6 ± 11.4	35.7 ± 13.6	0.188±2.01	35.4 ± 13.2	35.5 ± 13.8	-0.0461±2.04	0.235±2.86	-5.49;5.95	0.935
Vitamin B6 (mg)	1.6 ± 0.5	1.6 ± 0.5	0.0306 ±0.0967	1.6 ± 0.5	1.6 ± 0.6	0.0184 ±0.0983	0.0122±0.138	-0.264;0.288	0.93
Vitamin B9 (µg)	211.7 ± 71.8	199.7 ± 68.6	-15.9±23.2	221.4 ± 83.8	239.2 ± 179.1	18.7±23.6	-34.6±33.1	-101;31.7	0.3
Vitamin B12 (µg)	5.4 ± 2.2	6.7 ± 6.4	1.33±0.960	5.4 ± 2.9	6.4 ± 5.2	1.03±0.976	0.301±1.37	-2.44;3.04	0.827
Vitamin C (mg)	97.5 ± 114.7	105.9 ± 185.6	7.84±25.0	93.4 ± 52.9	82.0 ± 54.4	-16.4±25.4	24.3±35.6	-46.9;95.5	0.498
Sodium (g)	3455.8 ± 4479.1	3010.3 ± 2195.6	-180±212	2381.0 ± 1269.6	2298.0 ± 984.5	-71±215	390±304	-218;999	0.204
Potassium (mg)	2489.0 ± 617.5	2380.2 ± 864.7	-6370±152	14382.1 ± 66125.7	2473.2 ± 797.6	-6258±155	-112±218	-548;324	0.61
Calcium (mg)	670.9 ± 229.4	606.5 ± 235.2	-87.5±34.2	733.1 ± 286.0	681.2 ± 212.6	-45.4±34.8	-42.1±49.0	-140;55.9	0.394
Magnesium (mg)	246.2 ± 76.8	231.4 ± 90.0	-20.7±12.8	269.7 ± 77.6	239.6 ± 77.7	-25.7±12.9	5.02±18.3	-31.6;41.7	0.785
Phosphorus (mg)	1167.3 ± 289.0	1160.8 ± 439.3	-12.0±58.8	1213.3 ± 355.1	1170.9 ± 342.5	-45.3±59.7	33.2±84.0	-135;201	0.694
Iron (mg)	10.3 ± 3.5	10.0 ± 3.7	-0.472±0.619	10.8 ± 3.6	10.6 ± 4.3	-0.226±0.629	-0.246±0.884	-2.02;1.52	0.782
Copper (mg)	1.3 ± 0.7	1.1 ± 0.5	-0.146±0.0882	1.3 ± 0.6	1.2 ± 0.6	-0.0608±0.0896	-0.0861±0.126	-0.337;0.166	0.499
Zinc (mg)	9.3 ± 3.0	8.8 ± 3.7	-0.391±0.576	9.0 ± 3.7	9.4 ± 4.3	0.350±0.585	-0.741±0.821	-2.39;0.902	0.37
Chloride (mg)	4753.3 ± 6699.6	4156.0 ± 3429.3	-284±300	3463.3 ± 1924.9	3134.1 ± 1322.1	-897±306	613±430	-249;1474	0.16
Manganese (mg)	2.8 ± 1.0	2.5 ± 1.0	-0.386±0.144	3.0 ± 1.0	2.7 ± 1.0	-0.262±0.146	-0.124±0.206	-0.536;0.288	0.549
Selenium (µg)	56.6 ± 25.0	60.7 ± 32.6	4.80±4.68	56.4 ± 24.2	53.9 ± 24.1	-2.57±4.78	7.37±6.68	-5.99;20.7	0.274
Iodine (µg)	158.8 ± 209.4	167.6 ± 173.7	19.9±24.5	131.6 ± 66.4	138.0 ± 77.3	-7.39±24.9	27.4±35.1	-42.8;97.6	0.438
Total (poly)phenols (mg)	553.8 ± 318.9	628.5 ± 526.7	-29.9±68.5	698.9 ± 456.8	646.3 ± 352.9	-151±69.6	121±99.6	-78.0;321	0.228
Flavonoids (mg)	270.9 ± 146.9	284.6 ± 212.3	-67.2±32.1	277.3 ± 172.6	307.2 ± 213.5	-53.3±32.6	-13.9±46.0	-106;78.2	0.764
Anthocyanins (mg)	27.4 ± 38.3	35.3 ± 70.4	2.64±13.1	25.9 ± 49.1	41.8 ± 103.7	6.43±13.3	-3.79±18.7	-41.2;33.6	0.84
Flavan-3-ols (mg)	181.5 ± 124.8	192.3 ± 174.9	-59.8±25.8	192.3 ± 146.6	210.5 ± 168.1	-72.3±26.3	12.4±37.5	-62.6;87.4	0.741
Proanthocyanidins (mg)	119.2 ± 87.1	124.8 ± 135.2	-25.1±20.3	129.8 ± 106.3	109.9 ± 94.1	-48.8±20.6	23.7±29.3	-35.0;82.3	0.422
Phenolic acids (all) (mg)	0.1 ± 0.3	0.2 ± 0.6	-0.0533±0.0374	0.1 ± 0.2	0.1 ± 0.2	-0.0352±0.0380	-0.0181±0.0536	-0.125;0.0893	0.737
Hydroxyphenylacetic acids (mg)	1.4 ± 2.2	2.3 ± 3.5	0.647±0.438	2.5 ± 3.1	2.1 ± 1.8	-0.703±0.446	1.35±0.637	0.0739;2.63	0.038*
Hydroxyphenylpropanoic acids (mg)	0.9 ± 1.3	1.6 ± 2.5	0.400±0.292	1.7 ± 1.9	1.4 ± 1.1	-0.497±0.297	0.897±0.423	0.0503;1.74	0.038*
Stilbenes (mg)	0.9 ± 1.7	1.7 ± 3.3	0.825±0.398	1.7 ± 2.4	1.4 ± 1.4	0.825±0.398	1.39±0.579	0.225;2.54	0.02*
Other (poly)phenols‡ (mg)	4.1 ± 6.5	4.7 ± 7.6	-2.77±1.13	5.0 ± 7.0	8.3 ± 12.5	-1.75±1.15	-1.02±1.62	-4.27;2.23	0.531

‡ Other (poly)phenols including chalcones, dihyrochalcones, ellagitannins, theaflavins, and other (poly)phenols as defined in the Phenol Explorer classification (<http://phenol-explorer.eu/compounds/classification>). P- value for difference in change for cranberry and placebo. Changes from baseline (CFB) were calculated from ANCOVA (Bonferroni). *P < 0.05



Supplementary Figure 1. Differences in urinary (poly)phenol metabolites concentration between the cranberry and placebo interventions after 12 week daily consumption. Linear mixed models (LMM) were used to evaluate differences between treatments over time, with baseline metabolite concentrations included as covariates. The models accounted for repeated measures and individual variability, allowing for estimation of treatment effects relative to placebo.



1
Supplementary Figure 2: Correlations between total plasma (poly)phenol and hippuric acid concentration and cortisol levels (n= 34). Plots show correlations between total plasma (poly)phenol and hippuric acid metabolites and changes in cortisol levels showing significant changes from cranberry treatment; AUC CAR and AUC diurnal. *P < 0.05

Table 1. Baseline characteristics for both the cranberry and placebo treatments group

	Cranberry group Mean (SD) (N= 34)	Placebo group Mean (SD) (N= 38)
Sex (M/F)	6/28	6/32
Age range	20 - 26	21 - 25
Ethnicity		
Asian	23 (67.6)	29 (76.3)
White	7 (20.6)	8 (21.1)
Black	3 (8.8)	1 (2.6)
Other	1 (2.9)	0 (0)
Education		
BSc	5 (14.7)	6 (15.8)
MSc	29 (85.3)	32 (84.2)
Waist circum. (cm)	71.0 (7.8)	70.0 (7.7)
Height (cm)	166.6 (0.1)	167.1 (0.1)
Hip circum. (cm)	93.8 (7.2)	93.2 (8.6)
Weight (Kg)	58.1 (9.0)	56.6 (11.6)
Body Fat (%)	21.2 (8.3)	22.9 (8.0)
BMI (Kg/m ²)	20.6 (2.4)	20.2 (2.8)
BMR (Kcal)	1380 (205)	1361 (267)
Smoker (n, %)		
Yes	1 (3%)	6 (16%)
Alcohol/week	0.2 (0.0, 1.5)	0.7 (0.0, 1.5)
SBP (mmHg)	109.0 (8.3)	105.5 (10.6)
DBP (mmHg)	71.2 (6.4)	72.4 (6.3)
HR (bpm)	73.8 (11.4)	80.0 (13.3)
Plasma glucose (mmol/L)	4.9 (0.3)	4.9 (0.3)
Total protein (g/L)	72.1 (3.9)	71.4 (4.4)
Albumin (g/L)	48.4 (2.3)	47.4 (3)
Globulins (g/L)	23.7 (2.6)	24.1 (2.6)
Total bilirubin (umol/L)	11.6 (5.5)	11.2 (5.8)
ALP (IU/L)	55.9 (12.8)	53.8 (14.6)
AST (IU/L)	22.1 (4)	25.8 (20.4)
ALT (IU/L)	19.1 (13.3)	19.2 (17.7)
GGT (IU/L)	13.1 (6)	11.8 (3.9)
Urate (umol/L)	304 (65.7)	285 (71.7)
Cholesterol (mmol/L)	4.4 (0.8)	4.1 (0.7)
Triglycerides (mmol/L)	0.8 (0.4)	0.8 (0.3)
HDL cholesterol (mmol/L)	1.6 (0.2)	1.5 (0.3)
LDL cholesterol (mmol/L)	2.6 (0.9)	2.4 (0.7)
Non-HDL cholesterol (mmol/L)	2.8 (0.8)	2.6 (0.6)
Total cholesterol/HDL ratio	2.8 (0.6)	2.8 (0.5)
Physical activity level (n, %)		
LOW	2 (6%)	2 (5%)
MODERATE	17 (50%)	21 (55%)
HIGH	15 (44%)	15 (39%)
PSS (score)	19.1 (5.1)	16.7 (5.3)
HADS- Anxiety (score)	8 (3.1)	7.5 (4)
HADS- Depression (score)	4.7 (2.8)	3.3 (2.4)

TMD (score)	51.7 (10.1)	49 (10.2)
Short-term memory (score)	578 (223)	623 (235)
Phonological short-term memory (score)	570 (255)	652 (204)

BSc, bachelor student; MSc, master student; BMI, body mass index; BMR, basal metabolic rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; GGT, Gamma-glutamyl transferase; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; PSS, Perceived Stress Scale; HADS, Hospital Anxiety and Depression Score; TMD, Total Mood Disturbance. Comparison of demographic between the trial arms, if the outcome of interest was binary or categorical, logistic regression or chi-squared test was used, respectively. Linear regression was used for continuous variables. Binary and categorical variables are presented using counts and percentages. The distribution of continuous variables was assessed using coefficients of skewness and then summarised by mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate.

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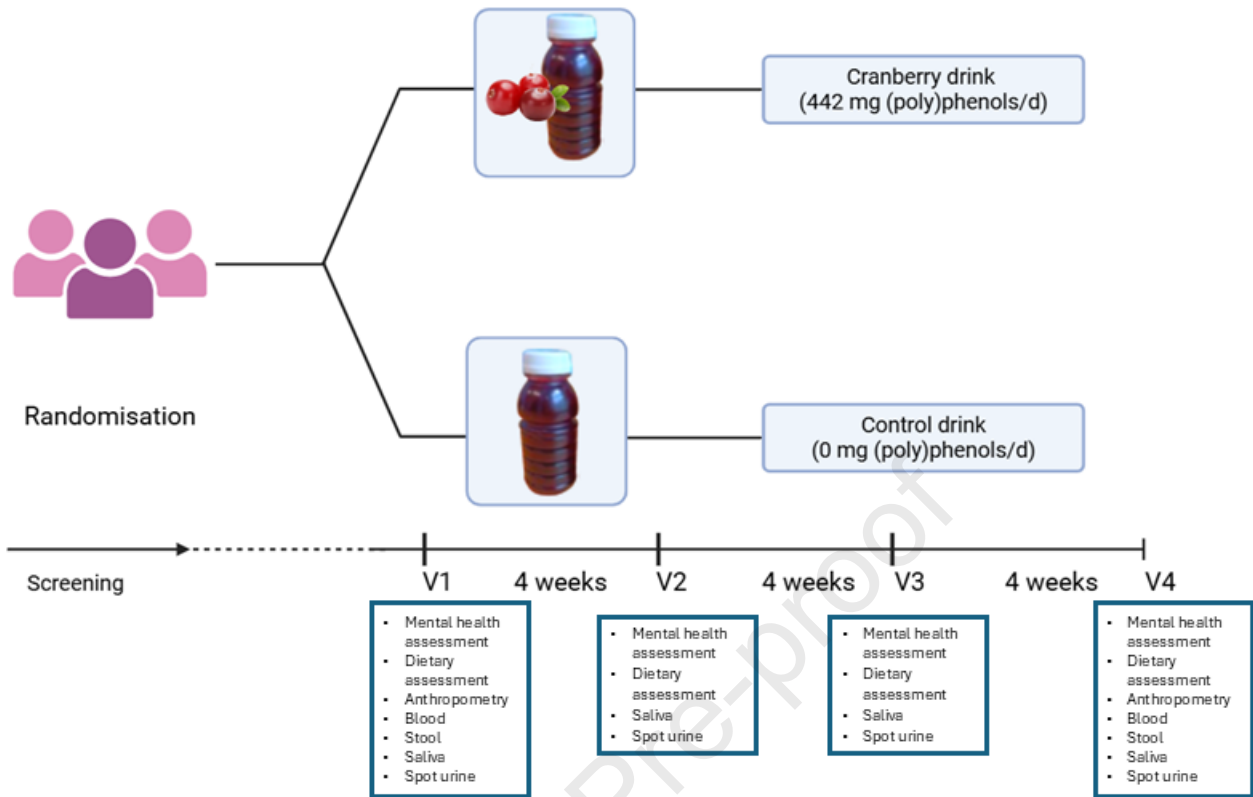
Table 2. Main outcomes of mental health and cortisol levels following daily consumption of the treatment cranberry and placebo. Linear mixed modelling analysis presented as difference from placebo at visit 2, 3, and 4, using baseline as a covariate. Only results with significant LMM findings are reported ($p < 0.05$)

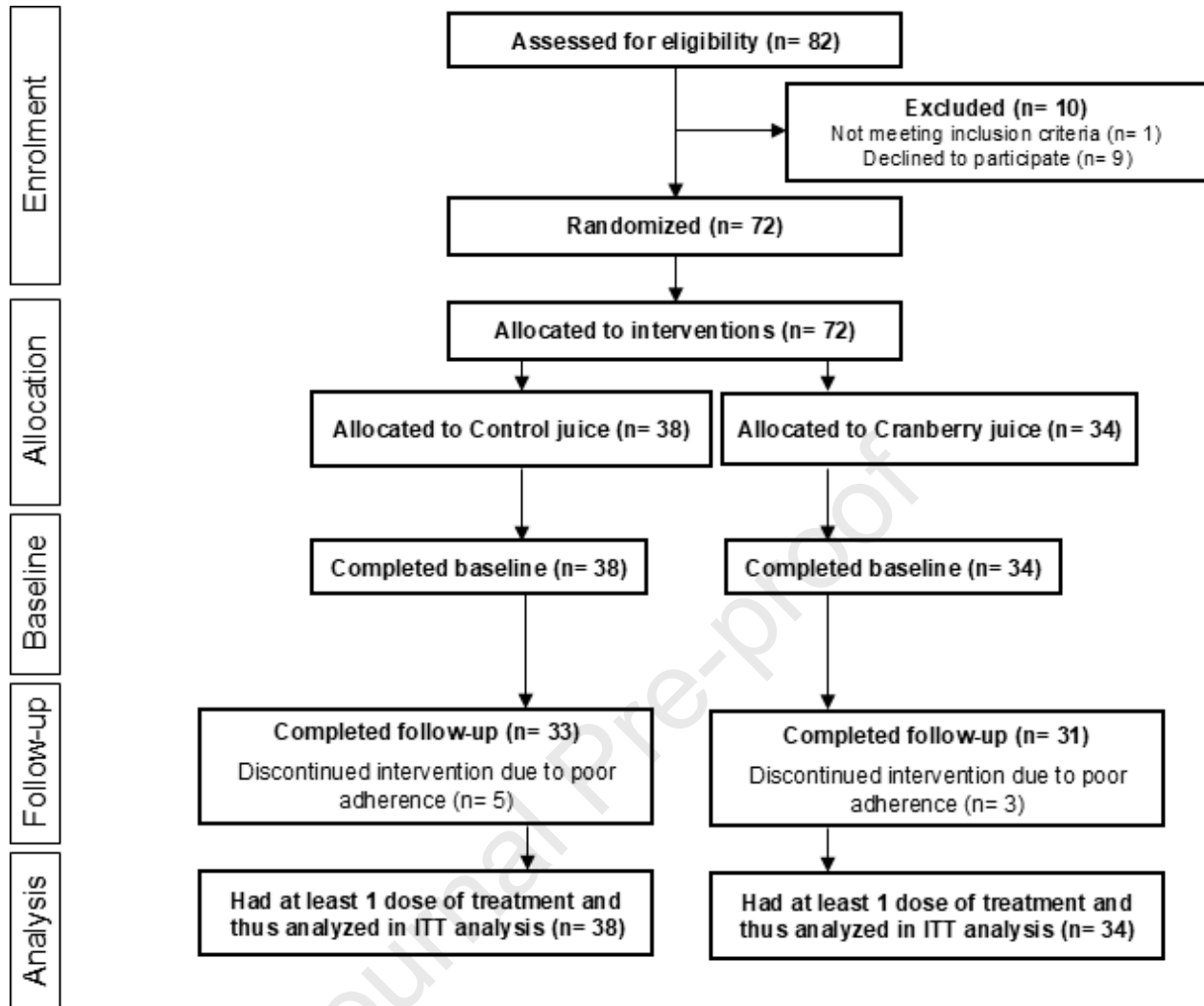
Variables	V2	V3	V4	<i>P</i> for treatment ¹	<i>P</i> for visit ²	<i>P</i> for interaction ³
TMD (score)						
Cranberry	52.4±1.27	52.4±1.29	50.3±1.59			
Placebo	50.0±1.43	53.3 ±1.60	51.0±1.65	0.87	0.22	0.29
<i>Difference</i> ⁴	2.43(-1.44;6.31)	-0.971(-5.09;3.16)	-0.709(-5.30;3.88)			
<i>p</i> ⁵	0.21	0.64	0.76			
Anger-Hostility (score)						
Cranberry	44.7±0.986	44.2±1.02	43.6±1.00			
Placebo	42.4±0.519	44.5±0.967	44.7±1.11	0.85	0.57	0.09
<i>Difference</i> ⁴	2.25(0.00631;4.49)*	-0.273(-3.09;2.55)	-1.10(-4.09;1.89)			
<i>p</i> ⁵	0.05	0.85	0.46			
Confusion-Bewilderment (score)						
Cranberry	50.9 ±1.26	50.2±1.21	48.5±1.14			
Placebo	50.9 ±1.26	50.2±1.21	48.5±1.14	0.50	0.23	0.13
<i>Difference</i> ⁴	3.33(-0.153;6.81)	-0.411(-4.14;3.32)	-0.193(-3.75;3.36)			
<i>p</i> ⁵	0.06	0.83	0.91			
Depression-Dejection (score)						
Cranberry	49.5±1.11	49.2±1.06	47.3±1.43			
Placebo	46.2±0.858	51.1±1.54	48.3±1.52	0.91	0.05	0.02*
<i>Difference</i> ⁴	3.34(0.526;6.16)*	-1.92(-5.67;1.84)	-1.01(-5.18;3.16)			
<i>p</i> ⁵	0.02	0.31	0.63			
Fatigue-Inertia (score)						
Cranberry	45.9±1.19	46.5±1.11	45.7±1.48			
Placebo	44.8±1.69	46.2±1.22	44.9±1.16	0.60	0.49	0.92
<i>Difference</i> ⁴	1.19(-2.96;5.33)	0.318(-2.99;3.63)	0.757(-3.02;4.54)			
<i>p</i> ⁵	0.59	0.85	0.69			
Tension-Hostility (score)						
Cranberry	48.9 ±1.27	48.7±1.34	46.7±1.48			
Placebo	47.4±1.61	49.2±1.34	48.5±1.43	0.87	0.47	0.36
<i>Difference</i> ⁴	1.57(-2.56;5.71)	-0.480(-4.27;3.31)	-1.82(-5.91;2.29)			
<i>p</i> ⁵	0.45	0.80	0.38			

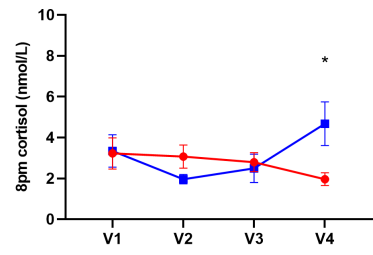
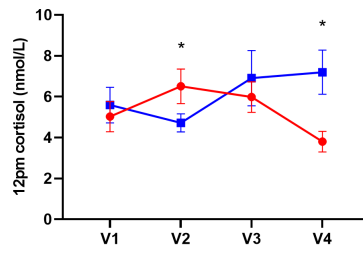
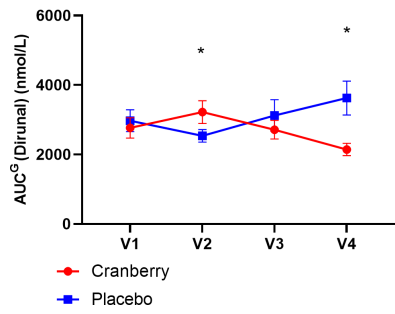
Vigor-Activity (score)						
Cranberry	49.7±1.04	46.9±1.35	48.6±1.39			
Placebo	47.2±1.31	48.9±1.29	49.2±1.33	0.96	0.69	0.10
<i>Difference</i> ⁴	2.42(-0.979;5.82)	-2.06(-5.79;1.67)	-0.568(-4.41;3.28)			
<i>p</i> ⁵	0.16	0.28	0.77			
Friendliness (score)						
Cranberry	49.2±1.12	46.7±1.19	47.7±1.48			
Placebo	48.2±1.31	47.9±1.42	47.9±1.37	0.90	0.42	0.54
<i>Difference</i> ⁴	1.05(-2.42;4.53)	-1.30(-5.02;2.42)	-0.271(-4.29;3.75)			
<i>p</i> ⁵	0.55	0.49	0.89			
PSS (score)						
Cranberry	19.1±0.836	18.3±0.873	17.4±1.07			
Placebo	17.9±0.784	17.6±0.865	17.6±0.979	0.60	0.39	0.64
<i>Difference</i> ⁴	1.16(-1.15;3.48)	0.673(-1.79;3.14)	-0.282(-3.19;2.62)			
<i>p</i> ⁵	0.32	0.59	0.85			
HADS anxiety (score)						
Cranberry	7.65±0.511	7.88±0.551	8.03±0.653			
Placebo	7.78±0.414	7.55±0.634	8.04±0.616	0.92	0.75	0.85
<i>Difference</i> ⁴	-0.131(-1.44;1.18)	0.331(-1.35;2.01)	-0.704(-1.79;1.78)			
<i>p</i> ⁵	0.84	0.70	0.99			
HADS depression (score)						
Cranberry	3.87±0.529	4.42±0.441	3.95±0.509			
Placebo	3.75±0.414	4.18±0.502	4.35±0.530	0.98	0.41	0.70
<i>Difference</i> ⁴	0.118(-1.24;1.48)	0.241(-1.11;1.59)	-0.404(-1.88;1.08)			
<i>p</i> ⁵	0.86	0.72	0.59			
AUC^G (Diurnal) (nmol/L)						
Cranberry	3150 ± 311	2630 ± 267	2215 ± 183			
Placebo	2379 ± 146	2731 ± 293	3618 ± 483	0.30	0.76	0.00*
<i>Difference</i> ⁴	771 (79.0;1463)*	-100 (-896;695)	-1403 (-2449;-358)*			
<i>p</i> ⁵	0.03	0.80	0.01			
12pm cortisol (nmol/L)						
Cranberry	6.62 ± 0.874	5.95 ± 0.772	3.81 ± 0.514			
Placebo	4.44 ± 0.398	5.80 ± 0.860	7.26 ± 1.14	0.61	0.87	0.00*
<i>Difference</i> ⁴	2.18 (0.243;4.11)*	0.143 (-2.17;2.46)	-3.44 (-5.96;-0.921)*			
<i>p</i> ⁵	0.03	0.90	0.01			
08pm cortisol (nmol/L)						
Cranberry	3.12 ± 0.593	2.82 ± 0.457	1.99 ± 0.338			
Placebo	1.92 ± 0.227	2.36 ± 0.656	4.67 ± 1.06	0.91	0.51	0.01*

<i>Difference</i> ⁴	1.20 (-0.0791;2.48)	0.467 (-1.14;2.07)	-2.67 (-4.93;-0.411)*			
<i>p</i> ⁵	0.07	0.56	0.02			
PSTM (Raw score)						
Cranberry	658 ± 25.0	672 ± 29.1	703 ± 32.9			
Placebo	648 ± 27.9	608 ± 26.0	593 ± 28.4	0.06	0.78	0.07
<i>Difference</i> ⁴	10.0 (-65.1;85.2)	63.4 (-14.9;142)	110 (22.6;197)*			
<i>p</i> ⁵	0.79	0.11	0.01			
STM (Raw score)						
Cranberry	654 ± 28.2	642 ± 32.8	704 ± 28.1			
Placebo	667 ± 24.3	613 ± 25.7	620 ± 25.8	0.30	0.20	0.04*
<i>Difference</i> ⁴	-13.8 (-88.3;60.7)	29.0 (-54.1;112)	83.2 (6.67;160)*			
<i>p</i> ⁵	0.71	0.49	0.03			

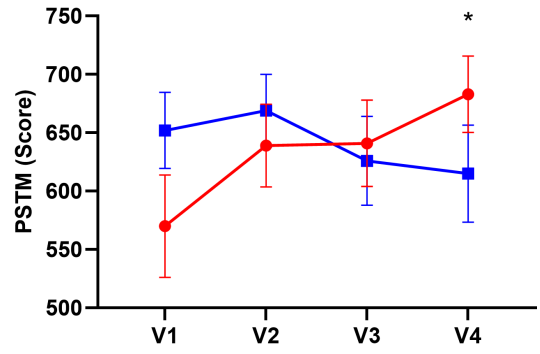
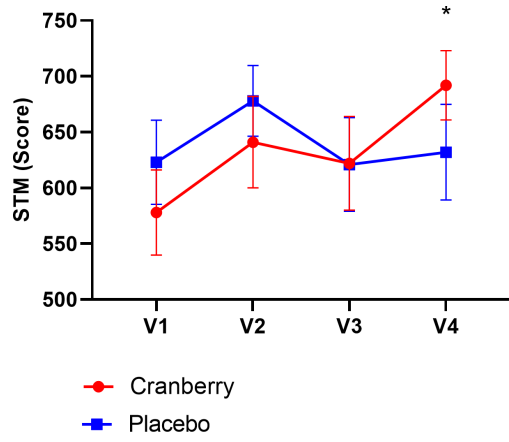
Values expressed as estimated marginal means ± SEMs. Analyses were done with baseline values as covariate. ¹Comparison between cranberry and placebo; treatment effect (LMM). ²Comparison between the different visits; visits effects (LMM). ³Comparison between measures obtained throughout the visits with cranberry group and placebo group; carry-over or interaction effect (LMM). ⁴Between group difference; mean difference (lower 95% CI, upper 95% CI). ⁵Between group comparison (LMM followed by multiple comparison with Bonferroni test). TMD, Total mood disturbance; PSS, Perceived Stress Scale; HADS, Hospital Anxiety and Depression Scale; AUCG, area under the curve with respect to the ground; STM, Short-term memory; SWB, Social well-being; PSTM, Phonological short-term memory. *P < 0.05



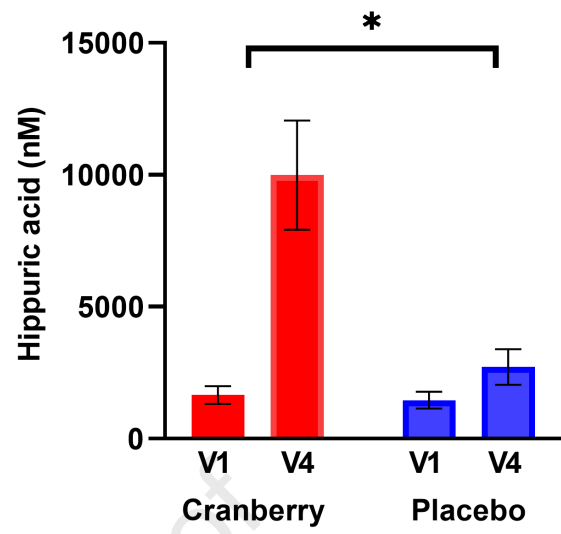
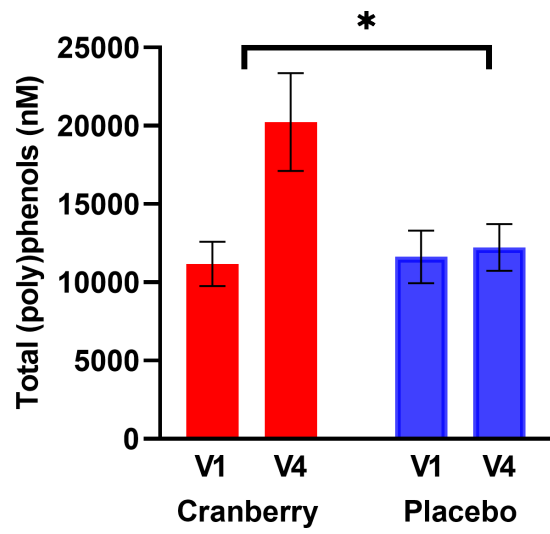




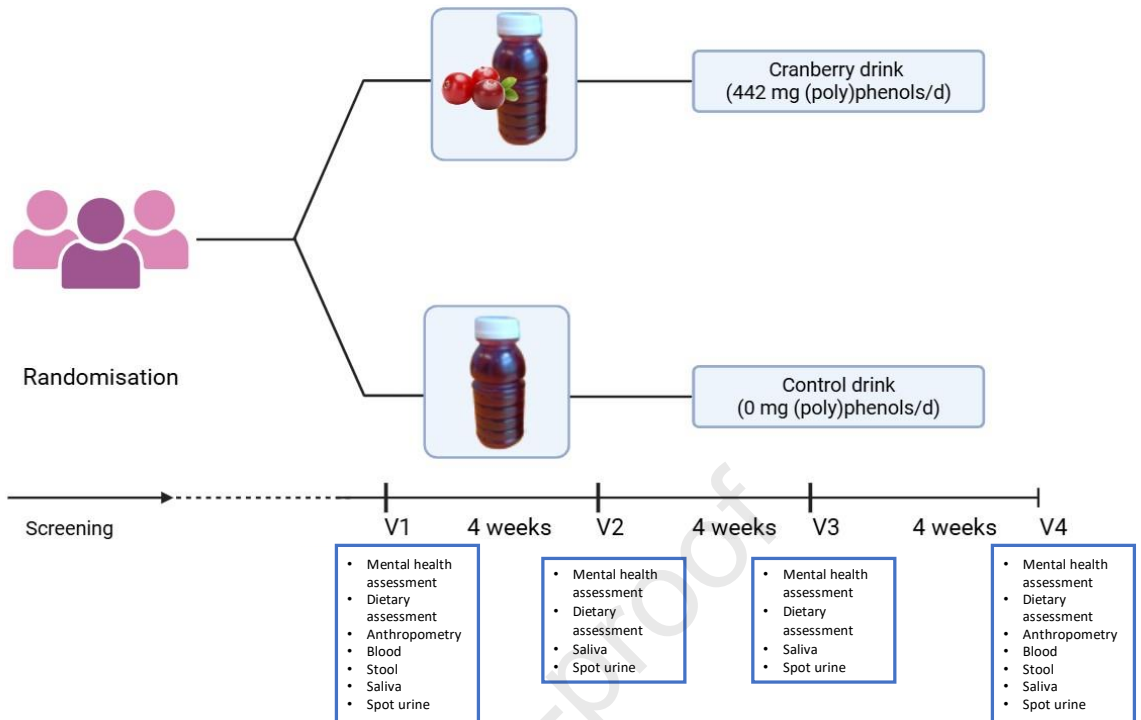
Journal Pre-proof



Journal Pre-proof



A)



B)

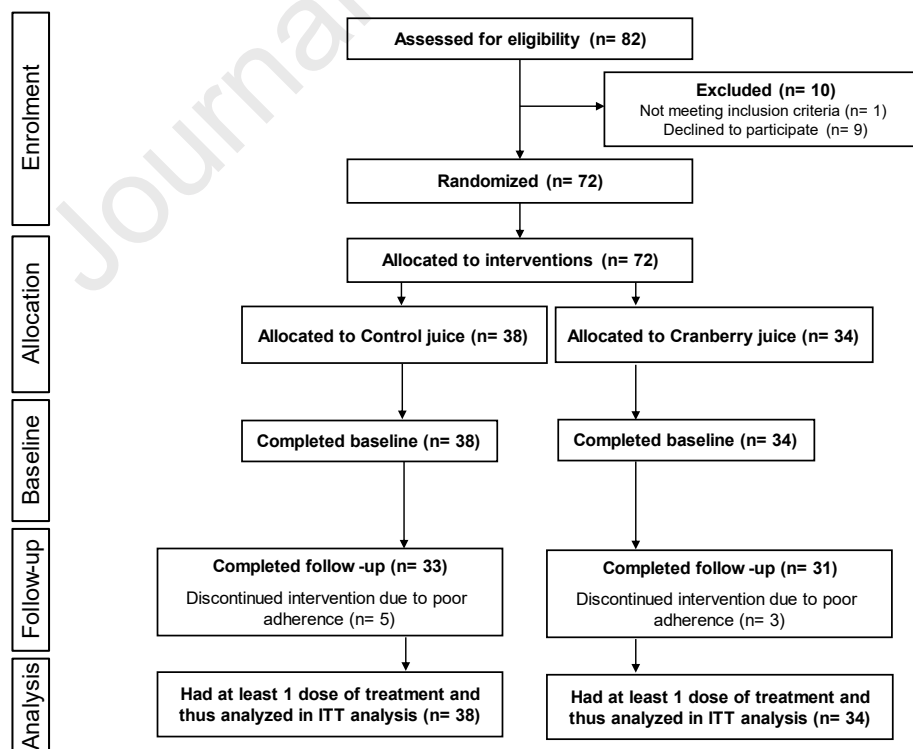


Figure 1. A) Study design of the CRANMOOD study B) Flow diagram outlining study activity and participant numbers throughout the process.