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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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Abstract

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

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

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

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

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

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

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

1. Introduction

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

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

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

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

2. Methods

2.1 Intervention study subjects

The CRANMOOD study population consisted of final year Bachelor of Science (BSc) and Master of Science (MSc) university students between 20-25 years old, willing to maintain their normal eating/drinking habits and exercise habits to avoid changes in body weight over the duration of the study; able to understand the nature of the study; willing to give signed written informed consent and comply with all study protocol procedures. Individuals were excluded if they had the following conditions: regularly prescribed medication (including iron for anaemia); subjects who require chronic antimicrobial or antiviral treatment; individuals with hypertension (Blood Pressure ≥140/90 mmHg) or obesity (Body Mass Index ≥30 kg/m^2); diabetes mellitus ; metabolic syndrome, as defined by the World Health Organization (WHO) (17); terminal renal failure and other kidney abnormalities; malignancies; history of cancer, myocardial infarction, cerebrovascular incident; unstable psychological condition (diagnosed with mental health disorders); allergies to berries or other significant food allergy; subjects who took food supplements, dietary supplements or herbal remedies were asked to maintain and advised not to stop taking or begin new supplements during the study; lost more than 10% of their weight in the past 6 months or are currently in a diet; subjects who reported participant in another study within 1 month before the study start; smoking irregular number of cigarettes per day or plan quitting smoking in the next 3 months; pregnant, lactating or planning to become pregnant.

2.2 Study design

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

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

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

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

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

2.3 Mood measures

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

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

2.4 Stress, anxiety and depressive symptoms

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

2.5 Cognitive measurements

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

2.6 Physical activity and sleep

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

2.7 Biochemical analysis

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

2.8 Urine collection

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

2.9 Salivary cortisol

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

2.10 Liquid Chromatography-Mass Spectrometry analysis of plasma and urinary (poly)phenol metabolites

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

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

2.11 Dietary assessment of background diet

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

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

calculated by summing all individual compounds within each respective group.

2.12 Power calculation and statistical analysis

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

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

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

3. Results

3.1 Baseline characteristics of the study population

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

Seven-day food diaries collected at baseline and during the final week of the study were analysed using ANCOVA, with no significant differences between the two timepoints, except for carotene intake, which decreased at 12 weeks in comparison with baseline (-1133 μg/d; P = 0.05) and hydroxyphenylacetic acid (1.35 mg/d; P = 0.04), hydroxyphenylpropanoic acid (0.897 mg/d; P = 0.04), and stilbene intake (1.39 mg/d; P = 0.02), which increased at 12 weeks compared to baseline (**Supplementary Table 2**). In addition to food diaries, online 24-hour dietary recalls recorded before each visit yielded similar results, with no significant differences across visits, indicating that participants maintained a consistent diet throughout the study. Based on food diaries, the daily average baseline for energy intake was 1691.2 ± 379.4 kcal/day in the cranberry group and 1808.8 ± 478.8 kcal/day in the placebo group. Fibre intake was 11.1 ± 4.5 mg/day in the cranberry group while 12.6 ± 3.9 mg/day in the placebo group. Total (poly)phenol intake was 553.8 ± 318.9 mg in the cranberry group and 698.9 ± 456.8 mg in the placebo group (See supplementary Table 2). Main contributors to the intake of total (poly)phenols based on the food diaries were coffee (59%), tea (25%), and apples (15%) (**Supplementary Table 3**).

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

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

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

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

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

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

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

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

3.5 Plasma and urinary (poly)phenol metabolites

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

4. Discussion

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

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

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

Cranberry supplementation also did not alter self-reported stress, anxiety, or depression measured with validated questionnaires. Previous (poly)phenol interventions have shown inconsistent effects, influenced by baseline mental health symptoms, dose, duration, and 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

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

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

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

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

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

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

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

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

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

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

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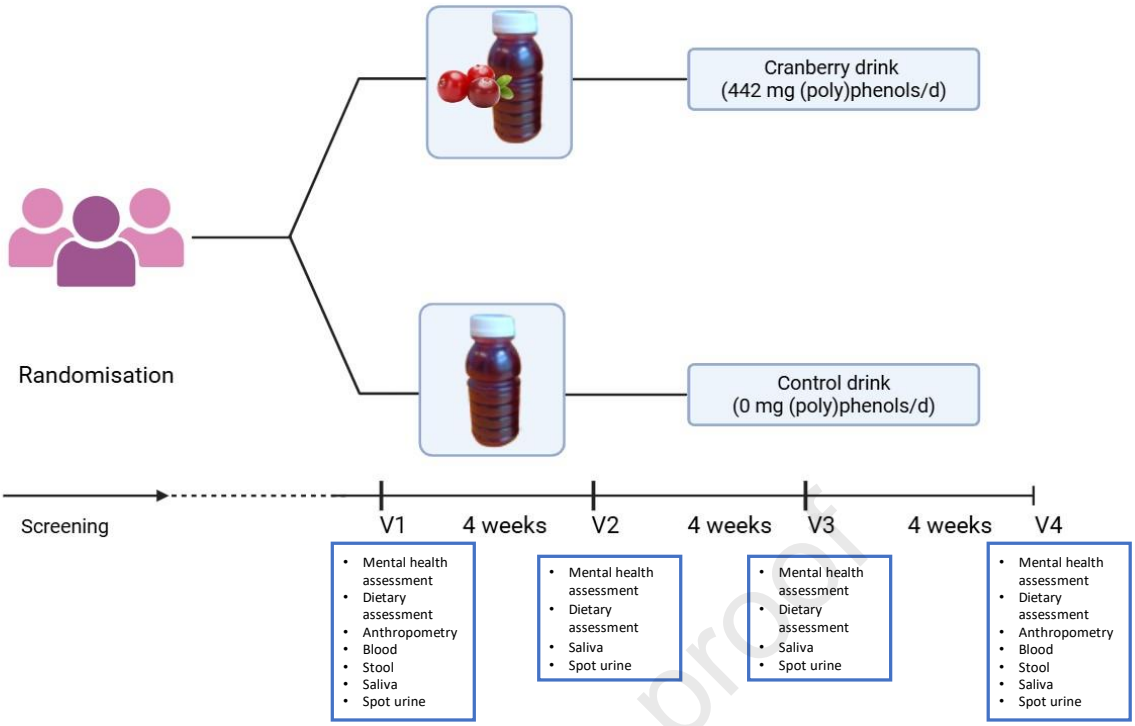
Table 1. Baseline characteristics for both the cranberry and placebo treatments group

	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.

A)



B)

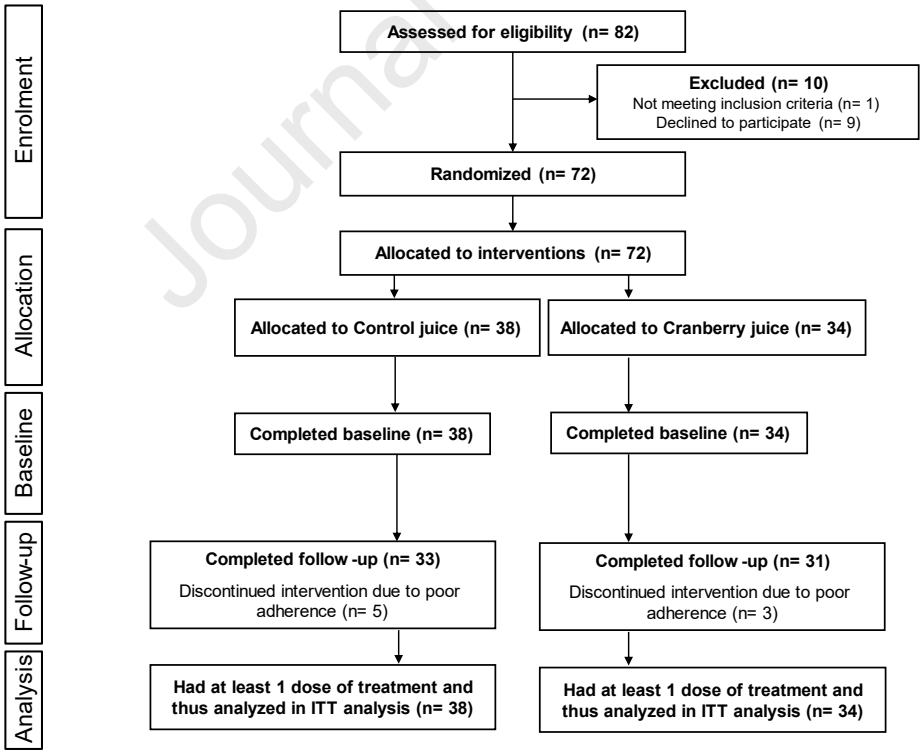


Figure 1. A) Study design of the CRANMOOD study B) Flow diagram outlining study activity and participant numbers throughout the process.

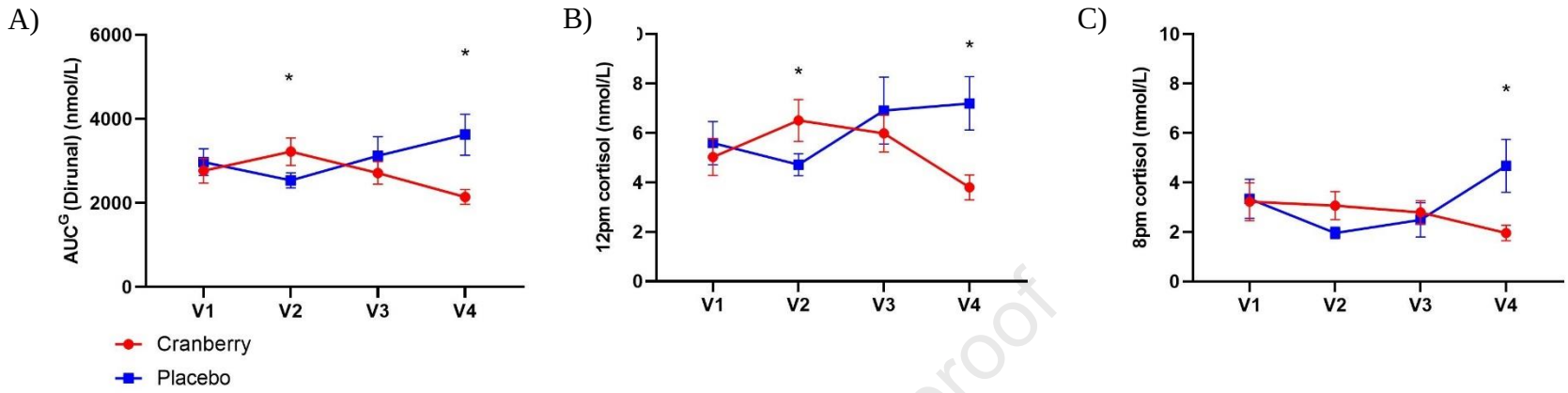


Figure 2: Cortisol levels at baseline (V1), and after 4 weeks (V2), 8 weeks (V3), and 12 weeks (V4) daily consumption of cranberry and placebo drinks, evaluated by linear mixed modeling analysis. Values are expressed as means ± SEMs. A) Salivary cortisol levels expressed as AUCG , B) 12 pm timepoint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

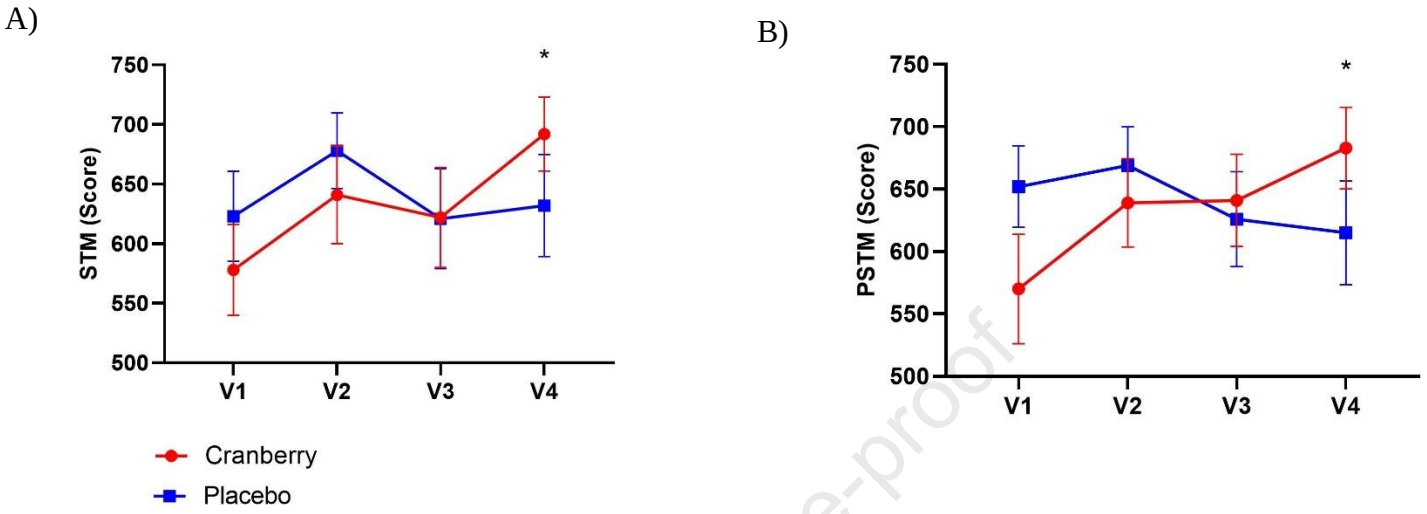


Figure 3: Impact of cognition level after daily consumption of cranberry and placebo at baseline (V1), and after 4 weeks (V2), 8 weeks (V3), and 12 weeks (V4) daily consumption of cranberry and placebo drinks, evaluated by linear mixed modeling analysis. Values are expressed as means ± SEMs. Absolute 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)

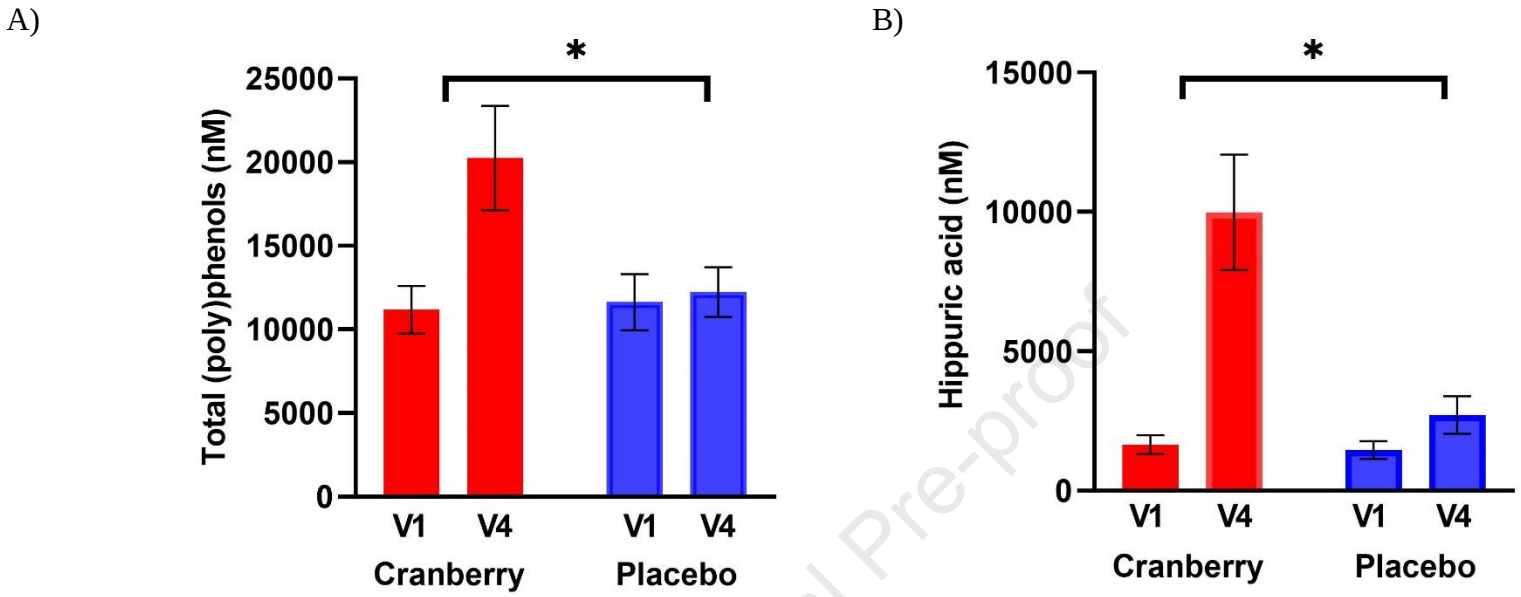


Figure 4: Impact of daily consumption of intervention groups on plasma cranberry (poly)phenol metabolites concentrations evaluated by ANCOVA analysis. Values are expressed as means ± SEs. A) Total (poly)phenol and B) Hippuric acid changes from baseline after consecutive consumption of treatments cranberry 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
Difference[4]	2.43(-1.44;6.31)	-0.971(-5.09;3.16)	-0.709(-5.30;3.88)			
P[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
Difference[4]	2.25(0.00631;4.49)*	-0.273(-3.09;2.55)	-1.10(-4.09;1.89)			
P[5]	0.05	0.85	0.46			
Confusion-Bewilderment (score)						
Cranberry	50.9 ±1.26	50.2±1.21	48.5±1.14			
Difference[4]	3.33(-0.153;6.81)	-0.411(-4.14;3.32)	-0.193(-3.75;3.36)	0.50	0.23	0.13
P[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***
Difference[4]	3.34(0.526;6.16)*	-1.92(-5.67;1.84)	-1.01(-5.18;3.16)			
P[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
Difference[4]	1.19(-2.96;5.33)	0.318(-2.99;3.63)	0.757(-3.02;4.54)			
P[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
Difference[4]	1.57(-2.56;5.71)	-0.480(-4.27;3.31)	-1.82(-5.91;2.29)			
P[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
Difference[4]	2.42(-0.979;5.82)	-2.06(-5.79;1.67)	-0.568(-4.41;3.28)			
P[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
Difference[4]	1.05(-2.42;4.53)	-1.30(-5.02;2.42)	-0.271(-4.29;3.75)			
P[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
Difference[4]	1.16(-1.15;3.48)	0.673(-1.79;3.14)	-0.282(-3.19;2.62)			
P[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
Difference[4]	-0.131(-1.44;1.18)	0.331(-1.35;2.01)	-0.704(-1.79;1.78)			
P[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
Difference[4]	0.118(-1.24;1.48)	0.241(-1.11;1.59)	-0.404(-1.88;1.08)			
P[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***
Difference[4]	771 (79.0;1463)*	-100 (-896;695)	-1403 (-2449;-358)*			
P[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***
Difference[4]	2.18 (0.243;4.11)*	0.143 (-2.17;2.46)	-3.44 (-5.96;-0.921)*			
P[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***
Difference[4]	1.20 (-0.0791;2.48)	0.467 (-1.14;2.07)	-2.67 (-4.93;-0.411)*			
P[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
Difference[4]	10.0 (-65.1;85.2)	63.4 (-14.9;142)	110 (22.6;197)*			
P[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***

Difference[4]	-13.8 (-88.3;60.7)	29.0 (-54.1;112)	83.2 (6.67;160)*
P[5]	0.71	0.49	0.03

Values expressed as estimated marginal means ± SEMs. Analyses were done with baseline values as covariate. [1]Comparison between cranberry and placebo; treatment effect (LMM). [2]Comparison between the different visits; visits effects (LMM). [3]Comparison between measures obtained throughout the visits with cranberry group and placebo group; carry-over or interaction effect (LMM). [4]Between group difference; mean difference (lower 95% CI, upper 95% CI). [5]Between 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

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.

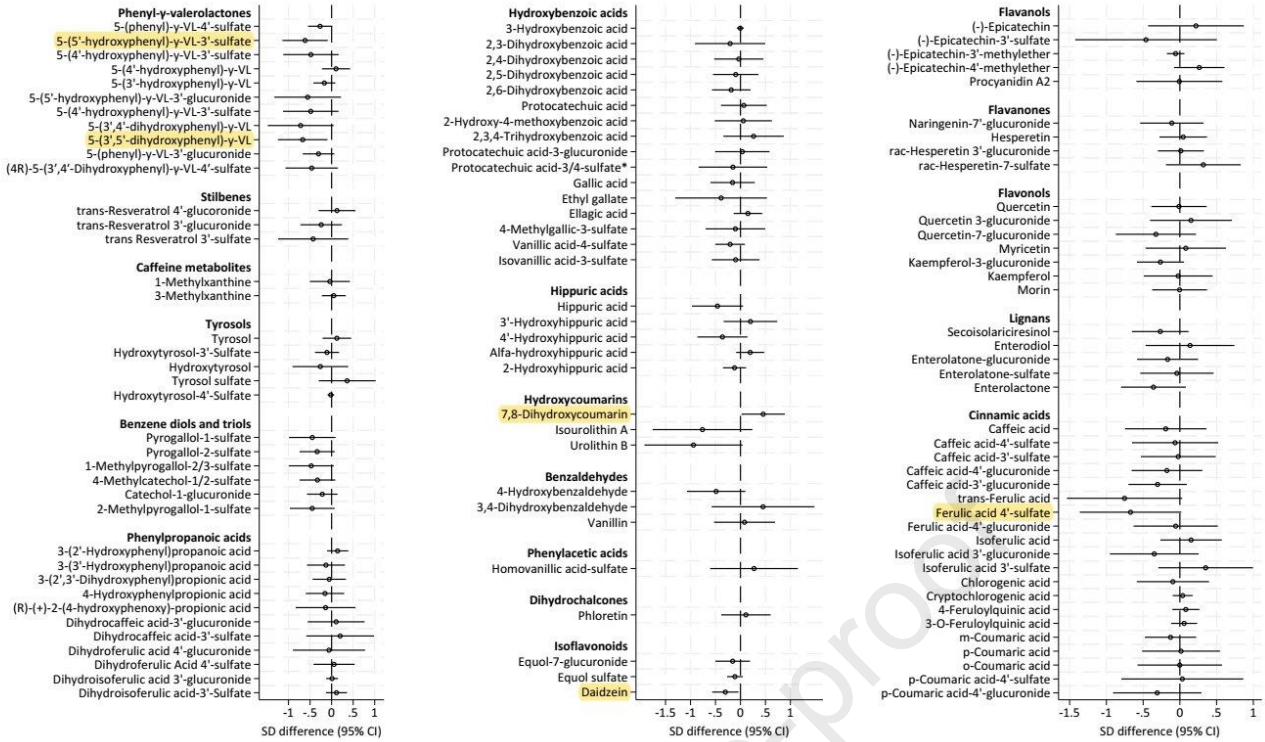
(Poly)phenol	Food category*
Total (poly)phenol	Coffee (59%), tea (25%), and apples (16%)
Total flavonoids	Tea (51%), apples (31%) and strawberries (18%)
Anthocyanins	Aloe vera juice (64%), blueberries (19%) and strawberries (17%)
Flavan-3-ols	Tea (52%), apples (30%), chocolate powder and drinks (17%)
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.

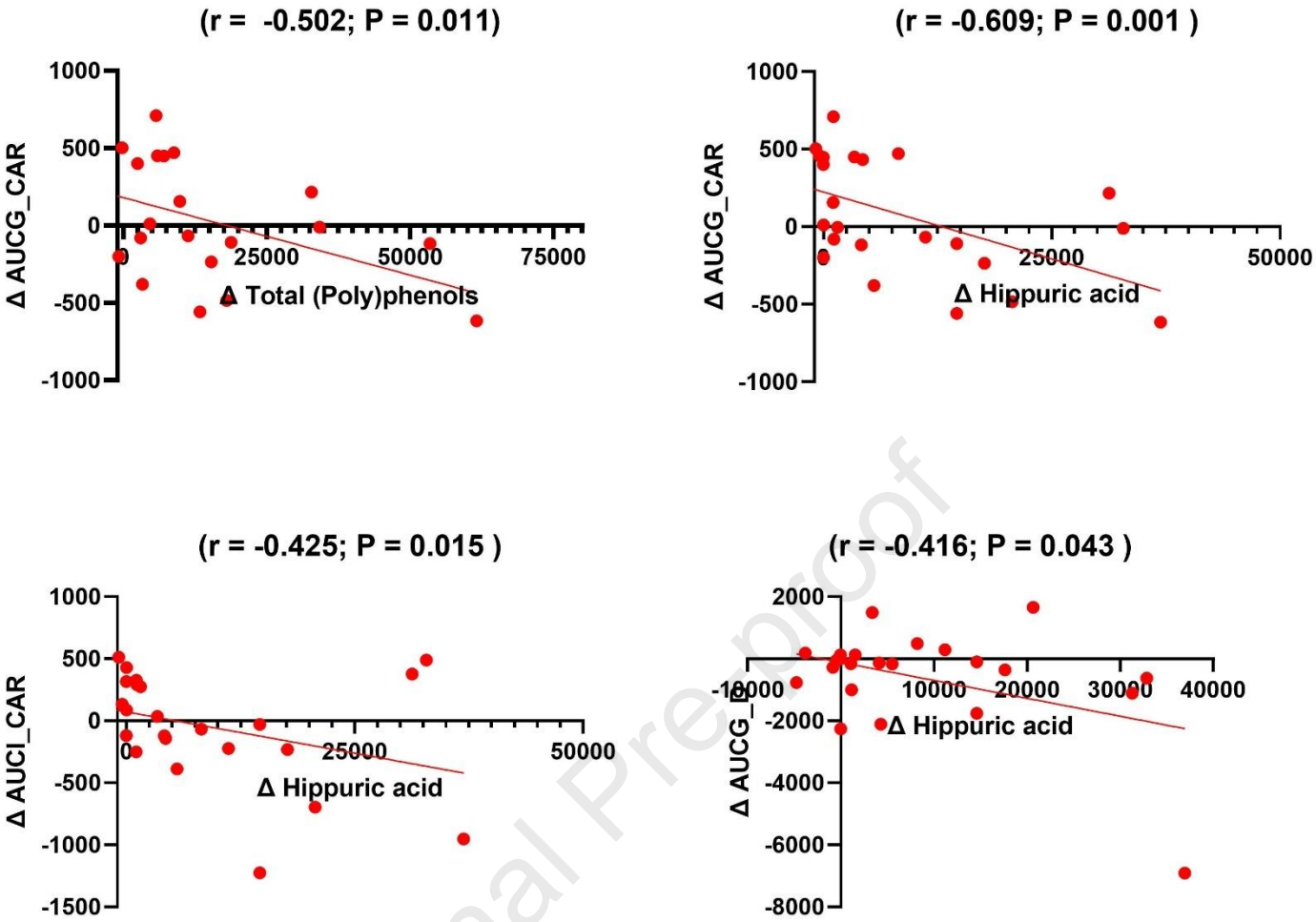
Supplemental Table 2. Average macro-, micronutrient and (poly)phenol intake taken from 7-day diet diaries at baseline and during the 12-week intervention.

	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
Polyunstaurated 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	0.0541±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	-0.0961±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	-571±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, ellagitanins, 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.



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.

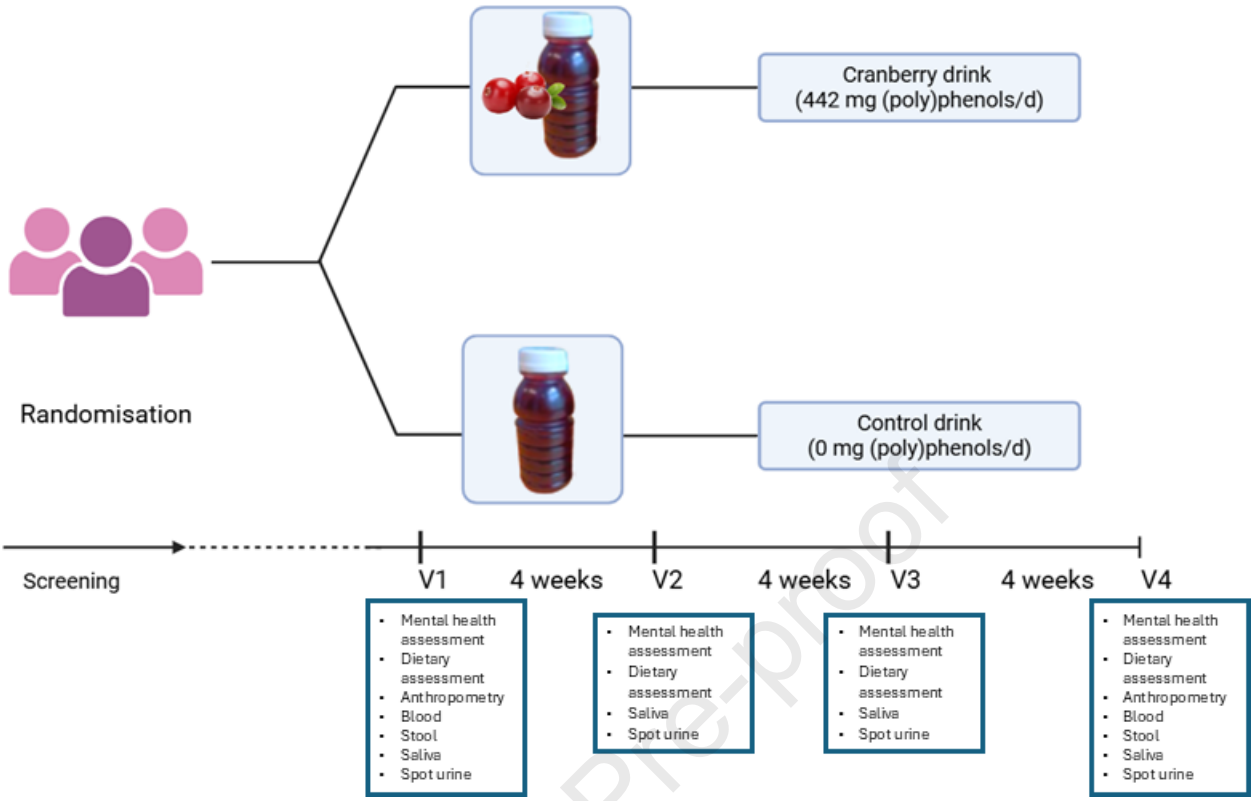
Table 2. Main outcomes of mental health and cortisol levels following daily consumption of the treatment cranberry and placebo. Linear mixed modelling analysis presented as difference from placebo at visit 2, 3, and 4, using baseline as a covariate. Only results with significant LMM findings are reported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

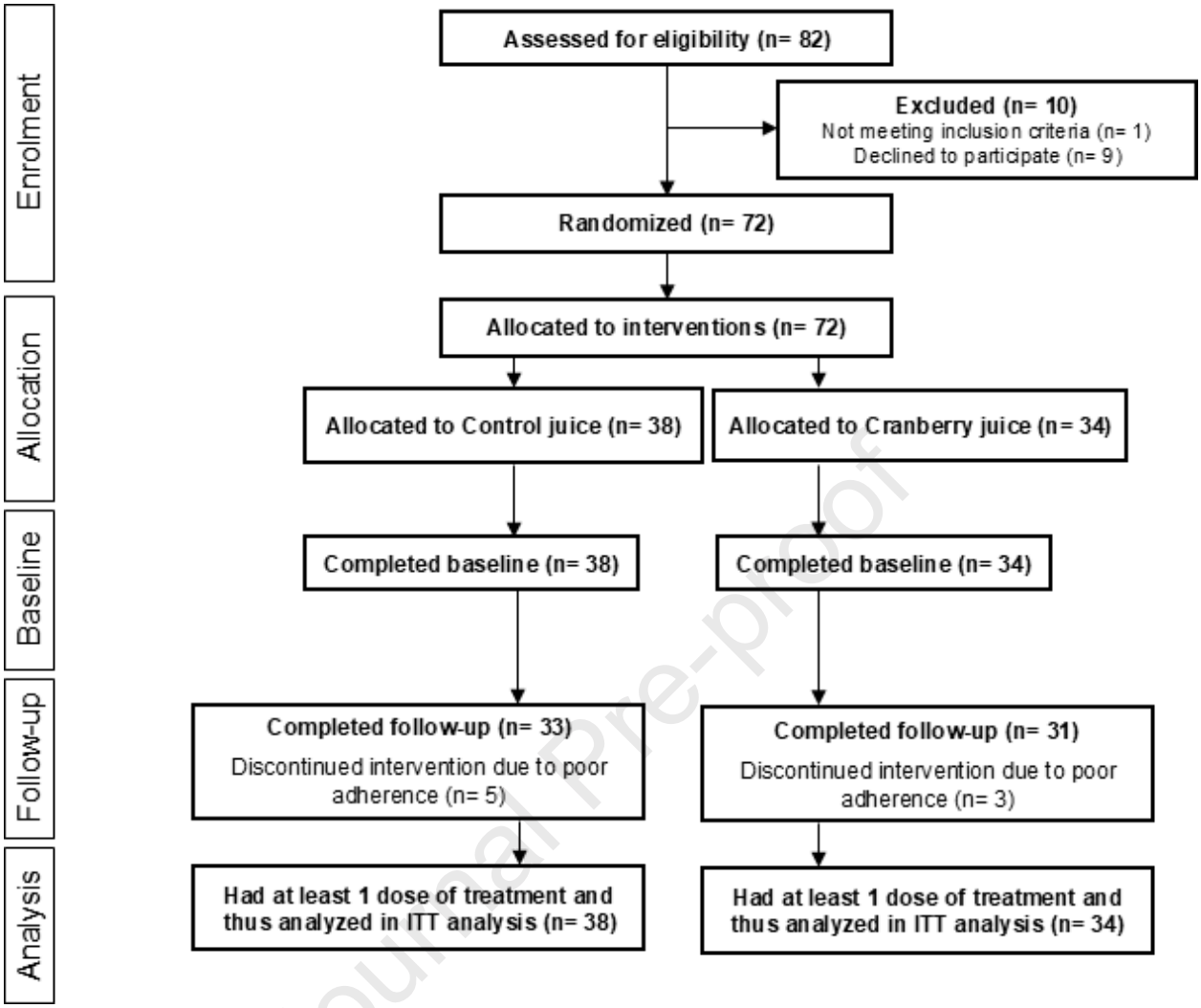
Variables	V2	V3	V4	*P* for treatment[1]	*P* for visit[2]	*P* for interaction[3]
TMD (score)						
Cranberry	52.4±1.27	52.4±1.29	50.3±1.59			
Placebo	50.0±1.43	53.3 ±1.60	51.0±1.65	0.87	0.22	0.29
Difference[4]	2.43(-1.44;6.31)	-0.971(-5.09;3.16)	-0.709(-5.30;3.88)			
P[5]	0.21	0.64	0.76			
Anger-Hostility (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
Difference[4]	2.25(0.00631;4.49)*	-0.273(-3.09;2.55)	-1.10(-4.09;1.89)			
P[5]	0.05	0.85	0.46			
Confusion-Bewilderment (score)						
Cranberry	50.9 ±1.26	50.2±1.21	48.5±1.14			
Difference[4]	3.33(-0.153;6.81)	-0.411(-4.14;3.32)	-0.193(-3.75;3.36)	0.50	0.23	0.13
P[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***
Difference[4]	3.34(0.526;6.16)*	-1.92(-5.67;1.84)	-1.01(-5.18;3.16)			
P[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
Difference[4]	1.19(-2.96;5.33)	0.318(-2.99;3.63)	0.757(-3.02;4.54)			
P[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
Difference[4]	1.57(-2.56;5.71)	-0.480(-4.27;3.31)	-1.82(-5.91;2.29)			
P[5]	0.45	0.80	0.38			

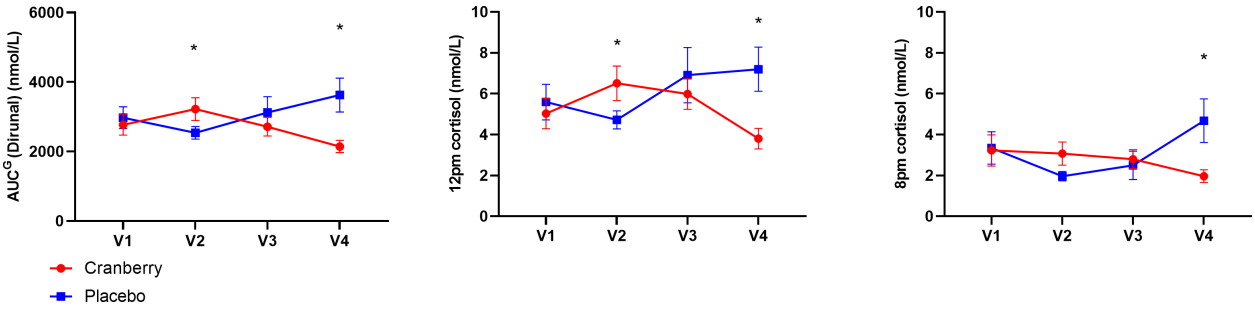
Vigor-Activity (score)						
Cranberry	49.7±1.04	46.9±1.35	48.6±1.39			
Placebo	47.2±1.31	48.9±1.29	49.2±1.33	0.96	0.69	0.10
Difference[4]	2.42(-0.979;5.82)	-2.06(-5.79;1.67)	-0.568(-4.41;3.28)			
P[5]	0.16	0.28	0.77			
Friendliness (score)						
Cranberry	49.2±1.12	46.7±1.19	47.7±1.48			
Placebo	48.2±1.31	47.9±1.42	47.9±1.37	0.90	0.42	0.54
Difference[4]	1.05(-2.42;4.53)	-1.30(-5.02;2.42)	-0.271(-4.29;3.75)			
P[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
Difference[4]	1.16(-1.15;3.48)	0.673(-1.79;3.14)	-0.282(-3.19;2.62)			
P[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
Difference[4]	-0.131(-1.44;1.18)	0.331(-1.35;2.01)	-0.704(-1.79;1.78)			
P[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
Difference[4]	0.118(-1.24;1.48)	0.241(-1.11;1.59)	-0.404(-1.88;1.08)			
P[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***
Difference[4]	771 (79.0;1463)*	-100 (-896;695)	-1403 (-2449;-358)*			
P[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***
Difference[4]	2.18 (0.243;4.11)*	0.143 (-2.17;2.46)	-3.44 (-5.96;-0.921)*			
P[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***

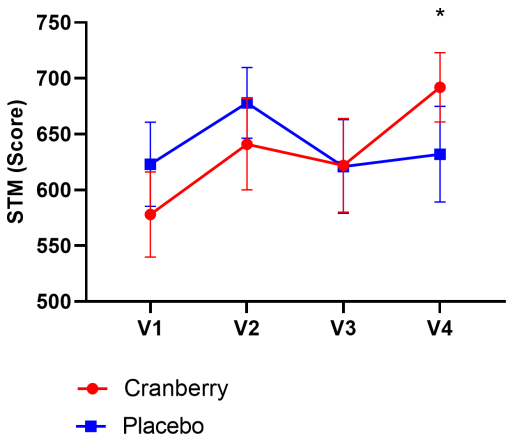
Difference[4]	1.20 (-0.0791;2.48)	0.467 (-1.14;2.07)	-2.67 (-4.93;-0.411)*			
P[5]	0.07	0.56	0.02			
PSTM (Raw score)						
Cranberry	658 ± 25.0	672 ± 29.1	703 ± 32.9			
Placebo	648 ± 27.9	608 ± 26.0	593 ± 28.4	0.06	0.78	0.07
Difference[4]	10.0 (-65.1;85.2)	63.4 (-14.9;142)	110 (22.6;197)*			
P[5]	0.79	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***
Difference[4]	-13.8 (-88.3;60.7)	29.0 (-54.1;112)	83.2 (6.67;160)*			
P[5]	0.71	0.49	0.03			

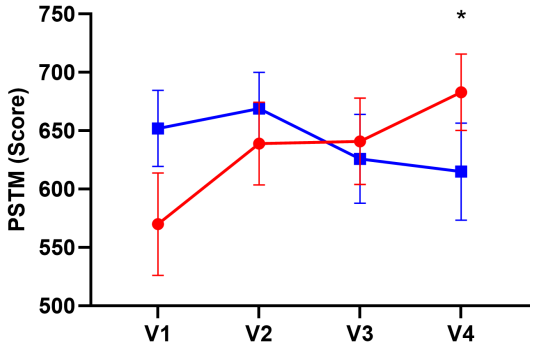
Values expressed as estimated marginal means ± SEMs. Analyses were done with baseline values as covariate. [1]Comparison between cranberry and placebo; treatment effect (LMM). [2]Comparison between the different visits; visits effects (LMM). [3]Comparison between measures obtained throughout the visits with cranberry group and placebo group; carry-over or interaction effect (LMM). [4]Between group difference; mean difference (lower 95% CI, upper 95% CI). [5]Between 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

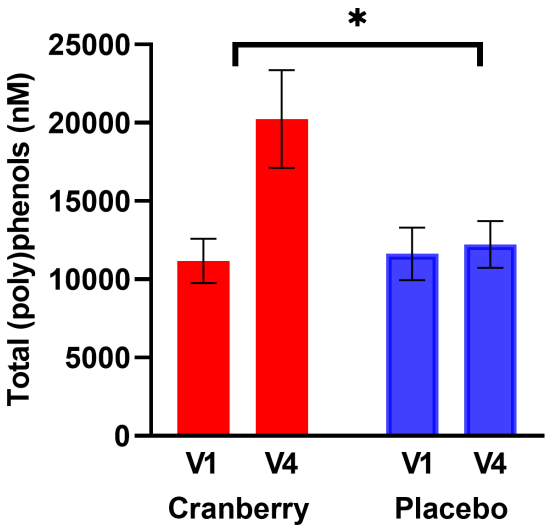


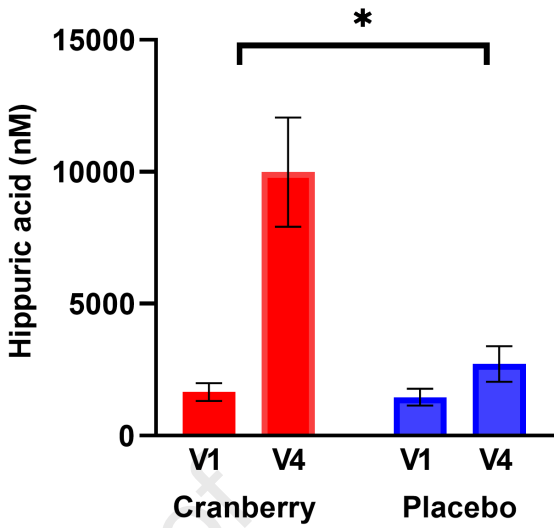












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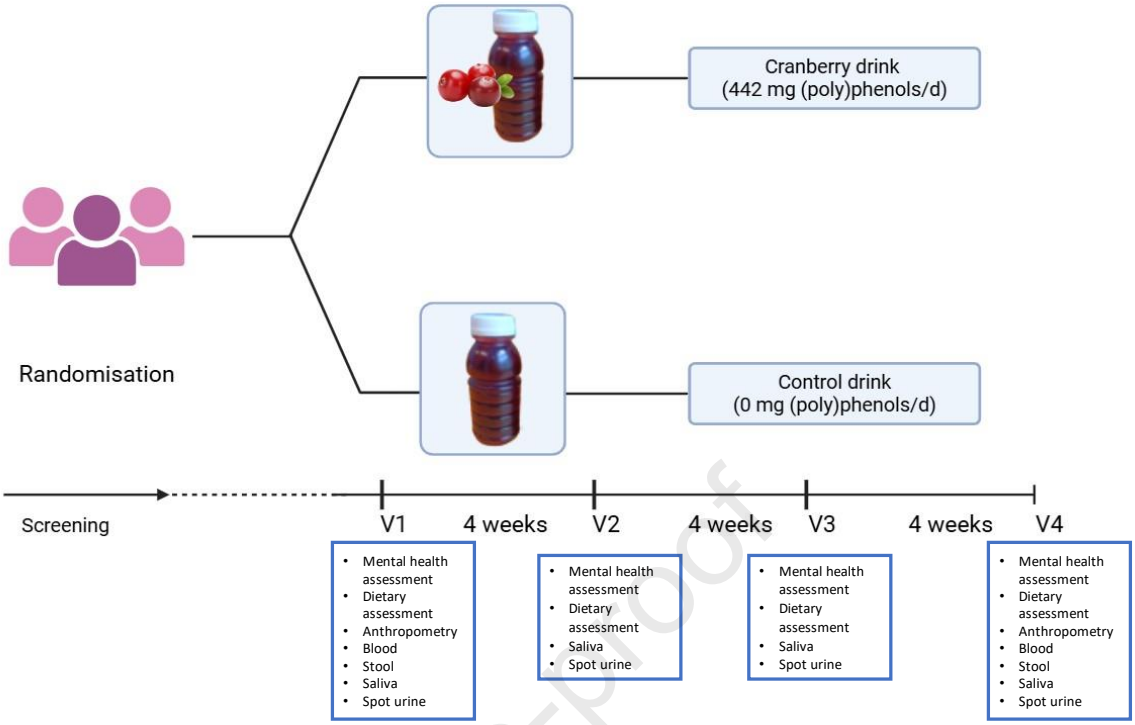

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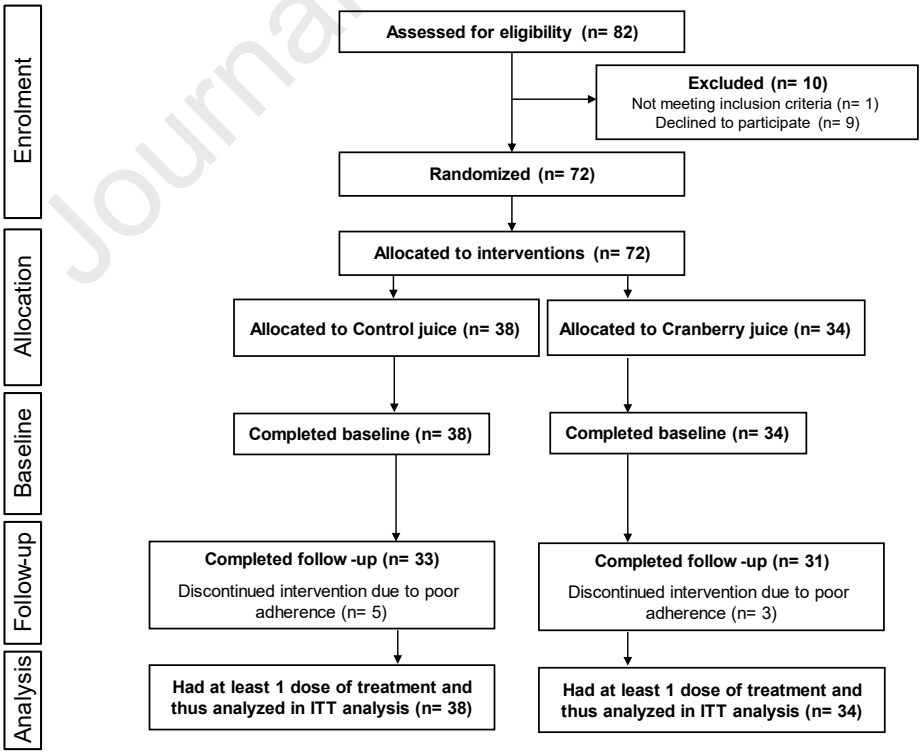

Figure 1. A) Study design of the CRANMOOD study B) Flow diagram outlining study activity and participant numbers throughout the process.