

1 **Effects of peppermint oil (*Mentha piperita* L.) on cardiometabolic and other health**
2 **related outcomes: a parallel placebo randomized controlled trial**

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18
19 **Abstract**

20 Background: There is growing speculation that peppermint may target the mechanisms central
21 to cardiometabolic pathophysiology, though there has yet to be any randomized interventions,
22 examining the efficacy of peppermint supplementation on cardiometabolic outcomes. This trial
23 aimed to examine the effect of peppermint supplementation on cardiometabolic and other
24 health indices following a 20-day supplementation period. Methods: A randomized, placebo-
25 controlled parallel study design was adopted (NCT05071833). Thirty-six healthy adults were

26 assigned into either peppermint or placebo trial arms, of which they drank 50 μ L of either
27 peppermint or peppermint flavoured placebo, diluted in 100 mL of water twice per day for 20
28 days. Participants were blinded to their trial arm assignment, lead investigators and those
29 analyzing the data were blinded until the data were analyzed and those involved in collecting
30 the data were aware of trial arm allocation. The primary outcome was systolic blood pressure,
31 and secondary measurements included anthropometric, energy expenditure, substrate
32 oxidation, blood lipid, diastolic blood pressure/resting heart rate, psychological wellbeing, and
33 sleep efficacy. All measurements were obtained at baseline and after the 20-day intervention
34 period. Results: There were significantly greater reductions in the primary outcome (-
35 4.53mmHg (95% CI = -8.39 - -0.66) $d=-0.81$) and in triglycerides (-0.30mmol/L (95% CI = -
36 0.52 - -0.08) $d=-0.92$) in the peppermint group compared to placebo. Furthermore, both state
37 (-5.43 (95% CI = -11.33 - -0.56) $d=-0.73$) and trait (-5.18 (95% CI = -10.76 - -0.40) $d=-0.74$)
38 anxiety indices improved statistically in the peppermint arm compared to placebo. No other
39 statistically significant findings were observed. Conclusion: As both hypertension and high
40 triglyceride levels are important parameters for the aetiology and severity of cardiometabolic
41 disease, this trial indicates that twice daily peppermint supplementation (50 μ L) may represent
42 an effective means to prophylactically enhance cardiometabolic health. Furthermore, given the
43 negative effects of anxiety on health-related quality of life and psychological wellbeing,
44 peppermint may also be effective in improving both state and trait anxiety.

45 **Keywords:** peppermint; cardiovascular disease; blood pressure; metabolic health

46

47 **1. Introduction**

48 Cardiometabolic disease encompasses a cluster of cardiovascular and metabolic abnormalities,
49 including insulin resistance, hypertension, atherogenic dyslipidemia, low high-density
50 lipoproteins (HDL), high triglycerides, high adiposity, reduced oxidation of lipids, high body

51 mass index, large waist to hip ratio, atherosclerosis and poor glucose regulation [1, 2]. Globally,
52 the incidence of these aforementioned abnormalities is expanding rapidly [3]. Cardiometabolic
53 disease is recognized as the predominant cause of global mortality, associated with significant
54 global healthcare utilization and expenditure [4].

55 Pharmaceutical intervention is the predominant treatment approach for cardiometabolic
56 disease, and angiotensin-converting enzyme inhibitors, betablockers, calcium antagonists,
57 diuretics, and lipid-lowering therapies are the most commonly adopted approaches [5, 6].
58 However, whilst these medicines are unequivocally effective for the treatment of
59 cardiometabolic disease, their long-term efficacy has yet to be established [7], and substantial
60 adverse effects, remain commonplace [8]. These side effects, in addition to global overreliance
61 of daily prescription medication [9], suggest that natural cost-effective approaches are
62 necessary for the management of cardiometabolic disease [10].

63 Dietary practices are considered one of the principal approaches for non-
64 pharmaceutical prevention and management of cardiometabolic disease [11]. However,
65 maintaining effective nutritional patterns have been shown to be difficult to accomplish [12];
66 making dietary supplementation a potentially appealing treatment and prevention modality
67 [10]. Importantly, medicinal plants have received considerable attention in the treatment of risk
68 factors for the development of cardiometabolic disease [13]. Peppermint (*Mentha piperita* L.)
69 is a recurrent flowering plant that cultivates predominantly in western Europe and North
70 America. Peppermint itself is a hybrid amalgamation of both spearmint (*Mentha Spicata*) and
71 water mint (*Mentha Aquatica*). The peppermint plant contains a diverse chemical profile,
72 including menthol, flavonoids, menthone, and menthyl acetate [14]. Peppermint possesses a
73 broad range of biological activities, including digestive, choleric, carminative, antiseptic,
74 antibacterial, antiviral, antispasmodic, antioxidant, anti-inflammatory, myorelaxant,

75 expectorant, analgesic, tonic, and vasodilatory properties [15, 16], and has importantly been
76 shown through toxicology analyses to be safe for ingestion [17].

77 Importantly, owing specifically to its antioxidant, anti-inflammatory, and vasodilatory
78 properties, there is growing speculation that peppermint ingestion may target the mechanisms
79 central to cardiometabolic pathophysiology, and thus confer significant cardiometabolic
80 benefits [18]. To date, very limited analyses have investigated the influence of peppermint
81 supplementation on cardiometabolic outcomes. Barbalho et al. [19] showed that twice daily
82 supplementation of peppermint (20 g of peppermint leaves in 200 mL water) for 30-days,
83 mediated significant reductions in both low-density lipoproteins (LDL) cholesterol and systolic
84 blood pressure. Meamarbashi & Rajabi, [20] revealed that a once daily peppermint oil ingestion
85 (0.05 mL in 500 mL water) for 10-days produced significant reductions in systolic blood
86 pressure, diastolic blood pressure and resting heart rate. However, neither of the
87 aforementioned investigations featured a control group, meaning that it cannot be conclusively
88 determined that the improvements were decisively attributable to peppermint supplementation,
89 as opposed to other external mechanisms.

90

91 *1.1 Rationale*

92 At the current time, there has yet to be any randomized intervention studies, comparatively
93 examining the efficacy of supplementation using peppermint oil on cardiometabolic outcomes.
94 Therefore, with preliminary evidence suggesting a positive effect of peppermint ingestion,
95 further placebo-controlled investigations concerning its influence on cardiometabolic
96 outcomes may be of both practical and clinical relevance.

97

98 *1.2 Aim*

99 The aim of the current study was to investigate the influence of 20-days of twice daily
100 peppermint oil supplementation on cardiometabolic and other health related indices in healthy
101 adults compared to placebo. The primary objective of this randomized trial is to examine the
102 influence of peppermint supplementation on systolic blood pressure relative to placebo. Its
103 secondary objectives are to determine whether peppermint supplementation influences on other
104 risk factors associated with and as a function of cardiometabolic disease.

105 *1.3 Hypotheses*

106 In relation to the primary outcome, it is expected that supplementation with peppermint will
107 mediate significant reductions in systolic blood pressure compared to placebo. Furthermore,
108 for the secondary outcomes, peppermint will produce improvements in cardiometabolic, and
109 other health related parameters compared to placebo.

110 **2. Methods**

111 *2.1 Study design*

112 This investigation represents a 20-day parallel, randomized placebo-controlled trial (Figure 1).
113 Participants were tested on two occasions i.e. baseline and 20-days and randomized by a
114 computer program (Random Allocation Software) to either the peppermint or placebo groups.
115 Participants were blinded to their trial arm assignment, lead investigators and those analyzing
116 the data were blinded until the data were analyzed and those involved in collecting the data
117 were aware of trial arm allocation. The 20-day supplementation period was adopted in
118 accordance with Sinclair et al. [21], and the protocol designed according to the updated
119 guidelines for reporting parallel group randomized trials [22]. All experimental testing took
120 place in the morning in a ≥ 10 h fasted state, with participants having avoided strenuous
121 exercise, alcohol, and nutritional supplements for 24 h and caffeine for 12 h prior to data
122 collection [21]. The study was registered prospectively (NCT05071833) and approved by an
123 institutional ethical review board (HEALTH 0016).

124

125 *2.1.1 Inclusion criteria:*

126 Inclusion criteria were, the capacity to give informed consent, 18 years of age and above, non-
127 smoker and a BMI < 30.

128

129 *2.1.2 Exclusion criteria:*

130 Exclusion criteria were, pregnancy, 65 years of age and above, diabetes or any other
131 metabolic/uncontrolled hypertensive conditions, allergy to peppermint, habitual consumption
132 of peppermint products and not regularly taking medication or antioxidant supplements.

133

134 *2.2 Sample size*

135 Power calculations were performed for the primary outcome variable, i.e., the between-groups
136 change in systolic blood pressure. This showed that a total sample size of 36 was necessary to
137 provide 80% power to detect a minimally important clinical difference (MCID) of 6 mmHg
138 between groups [23], accounting for a loss to follow up rate of 10%.

139

140 *2.3 Participants*

141 The present study was conducted at the University of Central Lancashire in the United
142 Kingdom. Both males and females of diverse race and ethnicities who lived in Preston and the
143 surrounding areas were recruited. Recruiting materials were placed in the local community,
144 public bulletin boards, as well as via social media. Participants were recruited during November
145 2021–July 2022 and formal data collection took place from January 2022–August 2022.
146 Participants attended an eligibility, enrolment, and familiarization session prior to the
147 commencement of formal data collection at the University of Central Lancashire. All
148 participants provided informed consent in written form and completed a Par-Q screening form

149 before taking part, in compliance with principles outlined in the declaration of Helsinki and the
150 Oviedo Convention.

151

152 *2.4 Dietary intervention*

153 After the conclusion of their baseline data collection session, participants were provided with
154 either peppermint oil (*Mentha piperita L.*) or placebo. Participants in the peppermint group
155 were required to consume 50 μ L of peppermint oil (100% essential oil; Piping Rock Health,
156 UK) which was diluted in 100 mL of water twice daily using a dropper: once in the morning
157 and again in the evening [19]. Those in the placebo group consumed 50 μ L of peppermint
158 cordial (Schweppes, Schweppes Geneva) which they diluted into 100 mL of water twice daily
159 using a dropper. This approach to placebo preparation has been shown by previous intervention
160 trials to provide an effective blinding strategy [24]. All supplementation/ placebo was kept
161 refrigerated throughout the 20 days.

162 In accordance with Sinclair et al. [21], participants were encouraged to maintain their
163 habitual diet and exercise routines and asked to refrain from consuming any multivitamin or
164 antioxidant supplements. For their post-intervention data collection session, in order to
165 examine blinding efficacy, all participants were asked whether they felt that they had been
166 allocated to the peppermint or placebo group. In both trial arms, loss to follow up was
167 monitored as were any adverse events. For their post-intervention data collection session, all
168 participants were also asked to return any unused supplementation to determine their %
169 compliance.

170

171 *2.5 Data collection*

172 *2.5.1 Anthropometric measurements*

173 Anthropometric measures of mass (kg) and stature (m) (without shoes) were used to calculate
174 the body mass index (BMI) (kg/m^2). Stature was measured using a stadiometer (Seca,
175 Hamburg, Germany) and mass using weighing scales (Seca 875, Hamburg, Germany). In
176 addition, body composition was examined using a phase-sensitive multifrequency bioelectrical
177 impedance analysis device (Seca mBCA 515, Hamburg, Germany) [25], allowing percentage
178 body fat (%) and fat mass (kg) to be quantified. Finally, waist circumference was measured at
179 the midway point between the inferior margin of the last rib and the iliac crest and hip
180 circumference around the pelvis at the point of maximum protrusion of the buttocks, without
181 compressing the soft tissues [26], allowing the waist-to-hip ratio to be quantified.
182 Anthropometric measures were obtained on three occasions and the mean value extracted for
183 analysis.

184

185 2.5.2 Energy expenditure and substrate oxidation

186 Respiratory gases were collected using a gas analysis system (MetaLyser 3B system, Cortex
187 Biophysic, Leipzig, Germany). The experimental laboratory was maintained using an air-
188 conditioning system at a fixed ambient temperature of 20 °C. To quantify resting energy
189 expenditure and substrate oxidation, participants laid supine for a period of 20 min, and data
190 were extracted and averaged over the final 17 min [27]. Resting fat and carbohydrate oxidation
191 rates (g/min) were quantified using stoichiometric formulae [28] (Equations (1) and (2)),
192 assuming negligible protein utilization. To quantify resting metabolic rate (RMR) (kcal/day)
193 the formula of Weir, [29] was adopted (Equation (3)).

194

$$195 \quad \text{Carbohydrate (g/min)} = (4.55 \times \text{VCO}_2) - (3.21 \times \text{VO}_2) \quad (1)$$

$$196 \quad \text{Fat (g/min)} = (1.67 \times \text{VO}_2) - (1.67 \times \text{VCO}_2) \quad (2)$$

$$197 \quad \text{RMR (kcal/day)} = [(3.941 \times \text{VO}_2) + (1.1106 \times \text{VCO}_2)] \times 1440 \quad (3)$$

198

199 2.5.3 Blood lipid testing

200 Capillary blood samples were also collected via finger-prick using a disposable lancet after
201 cleaning with a 70% ethanol wipe. Capillary triglyceride, total cholesterol, and glucose levels
202 (mmol/L) were immediately obtained using three handheld analyzers (MulticareIn, Multicare
203 Medical, Arezzo, Italy) and capillary hemoglobin levels (g/L) using a single handheld analyzer
204 (HemoCue, Ängelholm, Sweden). From these outcomes, LDL cholesterol (mmol/L) was firstly
205 quantified using the Anandaraja et al. [30] formula with total cholesterol and triglycerides as
206 inputs. In addition, high-density lipoprotein (HDL) cholesterol (mmol/L) was also calculated
207 by re-arranging the Chen et al. [31] equation to make HDL the product of the formulae. Both
208 of these approaches have been shown to have excellent similarity to their associated lipoprotein
209 values examined using immunoassay techniques $r = 0.948 - 0.970$ [32]. The ratios between total
210 and HDL cholesterol and between LDL and HDL cholesterol levels were also determined in
211 accordance with Millán et al. [32]. Finally, the triglycerides and glucose index (TyG index)
212 was calculated as the natural logarithm of the product of plasma glucose and triglycerides
213 divided by two [33].

214

215 2.5.4 Blood pressure and resting heart rate

216 Blood pressure (mmHg) and resting heart rate (beats/min) measurements were undertaken in
217 an up-right seated position at the end of the above-described resting energy expenditure test.
218 Both peripheral measures of systolic and diastolic blood pressure and resting heart rate were
219 measured via a non-invasive, automated blood pressure monitor (OMRON M2, Kyoto, Japan),
220 adhering to the recommendations specified by the European Society of Hypertension [34].
221 Three readings were undertaken, each separated by a period of 1 min [35], and the mean of the
222 last 2 readings used for analysis.

223

224 2.5.5 Questionnaires

225 Sleep quality is diminished in patients with cardiometabolic disease [36], therefore general
226 sleep quality was examined using the Pittsburgh sleep quality index (PSQI) [37], daytime
227 sleepiness using the Epworth Sleepiness Scale ⁴⁴ and symptoms of insomnia via the
228 Insomnia Severity Index [38]. These questionnaires were utilized co-operatively to provide a
229 collective representation of sleep efficacy. The PSQI measure consists of 19 individual items,
230 creating 7 components (subjective sleep quality, sleep latency, sleep duration, sleep efficiency,
231 sleep disturbance, use of sleep medication and daytime dysfunction) that produce one global
232 score ranging from 0 to 21, with lower scores denoting a healthier sleep quality. The Epworth
233 Sleepiness Scale a list of 8 scenarios in which tendency to become sleepy is rated on a scale of
234 0-3. The total score is the sum of these responses and ranges from 0 to 24, with higher scores
235 indicating increased sleepiness. The Insomnia Severity Index features 7 questions in which
236 sleep difficulty is rated on a scale of 0-4. The total score is the sum of these responses and
237 ranges from 0 to 28, with higher scores indicating greater sleep difficulty.

238

239 Furthermore, as psychological wellbeing is lower in those with cardiometabolic disease [39],
240 general psychological wellbeing was examined using the COOP WONCA questionnaire [40],
241 depressive symptoms using the Beck Depression Inventory [41], and state/trait anxiety with
242 the State Trait Anxiety Inventory (STAI) [42]. Once again, these scales were utilized
243 conjunctively to provide a collective depiction of psychological wellbeing. The COOP
244 WONCA questionnaire is comprised of 6 scales (physical fitness, feelings, daily activities,
245 social activities, change in health and overall health) designed to measure functional health
246 status on a scale ranging from 1 to 5. The final score is the mean of the 6 scales, with a higher
247 score indicating reduced functional health. The Beck Depression Inventory is a 21-item

248 questionnaire in which depressive symptoms are rated on a scale of 0-3. The total score is the
249 sum of these responses and ranges from 0 to 63, with higher scores indicating greater
250 depression. Finally, the State Trait Anxiety Inventory uses 20 items to assess trait anxiety and
251 20 to examine state anxiety, rated on a scale of 0-4. The total score for both trait anxiety and
252 state anxiety is the sum of these responses for each component and scores range from 20 to 80,
253 with higher scores denoting greater anxiety.

254

255 *2.6 Statistical analysis*

256 All continuous experimental variables are presented as mean and standard deviations.
257 Comparisons between the two groups in % compliance were undertaken using linear mixed
258 effects models, with group modelled as a fixed factor and random intercepts by participants.
259 All analyses of the intervention-based data were performed on an intention to treat basis. To
260 determine the effects of the intervention on all of the outcome measures, differences in the
261 changes from baseline to 20-days between the two groups were examined using linear mixed
262 effects models with group modelled as a fixed factor and random intercepts by participants
263 adopted. For linear mixed models the mean difference between groups in change from baseline
264 to 20-days (*b*), and 95% confidence intervals of the difference are presented. Effect sizes were
265 calculated for the changes from baseline to 20-days between the two groups, using Cohen's *d*,
266 in accordance with McGough, & Faraone, [43]. Cohen's *d* values were interpreted as 0.2 =
267 small, 0.5 = medium, and 0.8 = large [44].

268 Blinding efficacy was examined using a one-way chi-squared (X^2) goodness of fit test.
269 Finally, changes from baseline to 20-days in the experimental parameters were used to create
270 binary variables i.e. improve/ didn't improve for each participant. Pearson chi-square tests of
271 independence were also used to undertake bivariate cross-tabulation comparisons between the
272 two trial groups, specifically to test differences in the number of participants who exhibited

273 improvements in the experimental outcomes. Probability values for all chi-square analyses in
274 this trial were calculated using Monte-Carlo simulation. All analyses were conducted using
275 SPSS v27 (IBM, SPSS), and statistical significance for all analyses was accepted as the $P \leq 0.05$
276 level.

277

278 **3. Results**

279 *3.1 Baseline characteristics*

280 Characteristics of participants are presented in Table 1.

281 @@@TABLE 1 NEAR HERE@@@

282 *3.2 Loss to follow up, adverse events & compliance*

283 Total loss to follow up in each group were peppermint (n=0) and placebo (n=1), and number
284 of adverse effects were peppermint (n=0), placebo (n=0) (Figure 1). There were no significant
285 differences ($P=0.382$) in compliance between peppermint ($90.03 \pm 6.34\%$), placebo
286 ($88.34 \pm 6.34\%$) groups.

287 @@@FIGURE 1 NEAR HERE@@@

288 *3.3 Blinding efficacy*

289 Of the 35 participants that completed the trial 53% (n=19) correctly identified their designated
290 trial arm, the chi-squared test was non-significant ($\chi^2_{(1)} = 0.26$, $P=0.612$) indicating that an
291 effective blinding strategy was adopted.

292 *3.4 Anthropometric measurements*

293 No statistically significant differences ($P > 0.05$) in anthropometric parameters were found
294 (Table 2).

295 @@@TABLE 2 NEAR HERE@@@

296 *3.5 Energy expenditure and substrate oxidation*

297 No statistically significant differences ($P>0.05$) in energy expenditure and substrate oxidation
298 parameters were found (Table 2).

299 *3.6 Blood lipids*

300 Improvements in triglycerides and TyG index were significantly greater in the peppermint arm
301 compared to placebo (Table 2). For triglycerides the chi-squared test was significant ($X^2_{(1)} =$
302 6.42, $P=0.011$) and 73% and 33% of participants exhibited improvements in the peppermint
303 and placebo groups respectively. No other statistically significant differences ($P>0.05$) in blood
304 lipid values were found.

305 *3.7 Blood pressure and resting heart rate*

306 Improvements in systolic and diastolic blood pressure were significantly greater in the
307 peppermint arm compared to placebo (Table 2). For systolic blood pressure the chi-squared
308 test was significant ($X^2_{(1)} = 5.11$, $P=0.024$) and 83% and 44% of participants exhibited
309 improvements in the peppermint and placebo groups respectively. No other statistically
310 significant differences ($P>0.05$) in blood pressure and resting heart rate values were found.

311 *3.8 Questionnaires*

312 Improvements in STAI trait and STAI state were significantly greater in the peppermint arm
313 compared to placebo (Table 2). No other statistically significant differences ($P>0.05$) in
314 questionnaire values were found.

315 **4. Discussion**

316 The current study aimed to investigate the influence of 20-days of twice daily peppermint
317 supplementation on cardiometabolic and other health-related indices in healthy adults
318 compared to placebo. To date, this represents the first investigation to explore the effects of
319 peppermint on cardiometabolic and other health-related indices using a parallel placebo-
320 randomized controlled trial. The primary aim of this trial was to determine whether peppermint
321 supplementation improved systolic blood pressure compared to placebo, whereas the

322 secondary aim(s) were to explore the effects of peppermint on other risk factors for
323 cardiometabolic disease.

324 In relation to the primary outcome, in agreement with our hypothesis and the findings
325 of both Barbalho et al. [19] and Meamarbashi & Rajabi [20] linear mixed model and chi-square
326 analyses importantly showed that significantly greater improvements in systolic blood pressure
327 were evident in the peppermint group in relation to placebo with a large effect size. It is
328 proposed that this observation was mediated due to the presence of menthol in the peppermint
329 supplementation. As an active agonist of transient receptor potential melastatin 8 (TRPM8)
330 channels present in vascular smooth muscle [45], the vasodilatory effect of menthol mediated
331 as a function of opening of vascular TRPM8 channels. This allows calcium entry into the
332 endothelium [46], which stimulates nitric oxide production [47] and hyperpolarization of
333 vascular smooth muscle cells [48]. Arterial hypertension is the most common preventable risk
334 factor for cardiometabolic disease [49] and represents the greatest single risk factor
335 contributing to the global burden of disease and to global all-cause mortality [50]. Therefore,
336 the observations from this trial appear to have considerable clinical relevance and suggest that
337 peppermint supplementation may be important in the management of hypertension.

338 In addition to the primary outcome, in further support of our hypotheses the findings
339 also confirmed that both triglycerides and the TyG index were significantly attenuated with
340 large effect sizes in the peppermint group in relation to placebo. As no changes in glucose were
341 evident, it is clear that reductions in total TyG index were mediated as a function of the
342 corresponding attenuation in triglycerides values. Previous analyses have shown that
343 peppermint possesses anti-lipidemic benefits [11], although this is the first investigation to
344 show improvements in triglycerides following peppermint supplementation. The mechanism
345 responsible for this observation has not been explored in human participants, however animal
346 models have shown that the antioxidant properties of peppermint decrease lipid peroxidation

347 in the plasma and tissues ¹⁵. Furthermore, animal models have shown that peppermint oil raises
348 hepatic glutathione level, enhance liver function and antioxidant activity which has also been
349 proposed as an underpin mechanism in the hypolipidemic effects of peppermint [51]. Taking
350 into account its positive influence on triglycerides; it is important that future investigations
351 seek to explore and utilize the mechanistic pathways of peppermint supplementation in order
352 to further enhance health-related outcomes.

353 Regardless, elevated triglyceride concentrations contribute to increased risk of
354 cardiometabolic disease [52], and whilst pharmaceutical agents are effective in the
355 management of hypertriglyceridemia, they are associated with substantial side-effects [53] and
356 high levels of global healthcare expenditure. As such, the findings from this investigation lend
357 support to the concept that peppermint supplementation may be important in the preventative
358 management of hypertriglyceridemia.

359 In addition to the improvements in physiological measures of blood pressure and
360 triglycerides shown in the peppermint trial arm. The current investigation also importantly
361 showed that this condition was able to mediate statistical improvements both state and trait
362 anxiety indices with moderate effect sizes. This observation concurs with those of Abdelhalim
363 et al. [54] who also found using a randomized controlled trial that peppermint produced
364 significant improvements in anxiety. The mechanism responsible for the improvements in
365 psychological wellbeing shown in the peppermint group is not currently known and requires
366 further exploration. However, peppermint has been shown to attenuate the secretion of cortisol
367 from the adrenal gland in animal models [55], which has been shown to be linked to the
368 presence of anxiety in humans [56]. Regardless, the observations from the current trial indicate
369 that peppermint supplementation may be important in improving both state and trait anxiety.

370 Overall, the current placebo randomized controlled trial was shown to be associated
371 with a good level of blinding efficacy, higher compliance, a low number of adverse events and

372 a very low dropout rate. These observations, allied to the significant improvements in blood
373 pressure, blood lipid and anxiety indices in the peppermint trial arm indicate that this
374 supplement there appears to represent an effective means to enhance cardiometabolic and
375 psychological wellbeing. However, as with any trial, this investigation is not without
376 limitations. Firstly, whilst this study observed positive effects of peppermint supplementation
377 on cardiometabolic and psychological parameters, it was beyond the scope of the
378 measurements obtained within this trial to elucidate the mechanistic origins for these
379 improvements. It is important therefore that future investigations seek to better understand and
380 potentially utilize these mechanistic pathways of peppermint supplementation to further
381 improve health-related outcomes. Furthermore, although the findings from this investigation
382 indicate that peppermint supplementation may be an effective approach to prophylactically
383 improve cardiometabolic disease risk, as participants in this trial were healthy, it remains
384 unknown as to whether peppermint supplementation would mediate such improvements in
385 patients with existing cardiometabolic disease. Therefore, it is essential that future randomized
386 intervention trials seek to examine the efficacy of peppermint supplementation in pathological
387 populations. Finally, although participants in both arms were instructed to maintain their
388 habitual diet and exercise routines; as many of the experimental variables are influenced by
389 exercise and nutritional status, that physical activity and nutritional intake were not monitored
390 may serve as a limitation to this trial. Therefore, subsequent randomized interventions may
391 seek to quantify the effects of peppermint supplementation whilst at the same time physical
392 activity throughout the intervention period via continuous actigraphy.

393 **5. Conclusion**

394 The current randomized controlled trial aimed to investigate the influence of peppermint
395 supplementation on cardiometabolic, and other health related indices compared to placebo. The
396 current trial supported our primary hypothesis that ingestion of twice daily solution of

397 peppermint oil (50 µL) is able to mediate improved systolic blood pressure compared to
398 placebo and also secondary predictions concerning triglyceride concentrations and anxiety
399 indices. As both hypertension and high triglyceride levels are important parameters for the
400 aetiology and severity of cardiometabolic disease, this trial indicates that peppermint
401 supplementation may represent an effective means to prophylactically enhance
402 cardiometabolic health. Furthermore, given the negative effects of anxiety on health-related
403 quality of life and psychological wellbeing, peppermint may also be effective in improving
404 both state and trait anxiety. Future randomized intervention trials should now seek to explore
405 the efficacy of peppermint supplementation in pathological populations with established
406 cardiometabolic abnormalities at baseline.

407

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410

411 **CRedit authorship contribution statement**

412 Jonathan Sinclair: Conceptualization, Formal analysis, Methodology, Supervision, Writing –
413 review & editing, Heidi Murray: Data curation, Formal analysis, Methodology, Vicki Smith:
414 Data curation, Formal analysis, Methodology, Nevin Tom: Data curation, Formal analysis,
415 Methodology, Tessy Clarence Cruz: Data curation, Formal analysis, Methodology, Paul John
416 Taylor: Formal analysis, Methodology, Supervision, Writing – review & editing, Stephanie
417 Dillon: Formal analysis, Methodology, Supervision, Writing – review & editing, Gareth
418 Shadwell: Formal analysis, Methodology, Supervision, Writing – review & editing, Bobbie
419 Butters: Formal analysis, Methodology, Supervision, Writing – review & editing, Lindsay
420 Bottoms: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review &
421 editing.

422

423 **Disclosures**

424 All authors of this study confirm there are no conflicts of interest to declare. This was an
425 investigator-initiated study, and the design, management, and analysis of this trial was
426 completely independent of anyone other than the authors.

427

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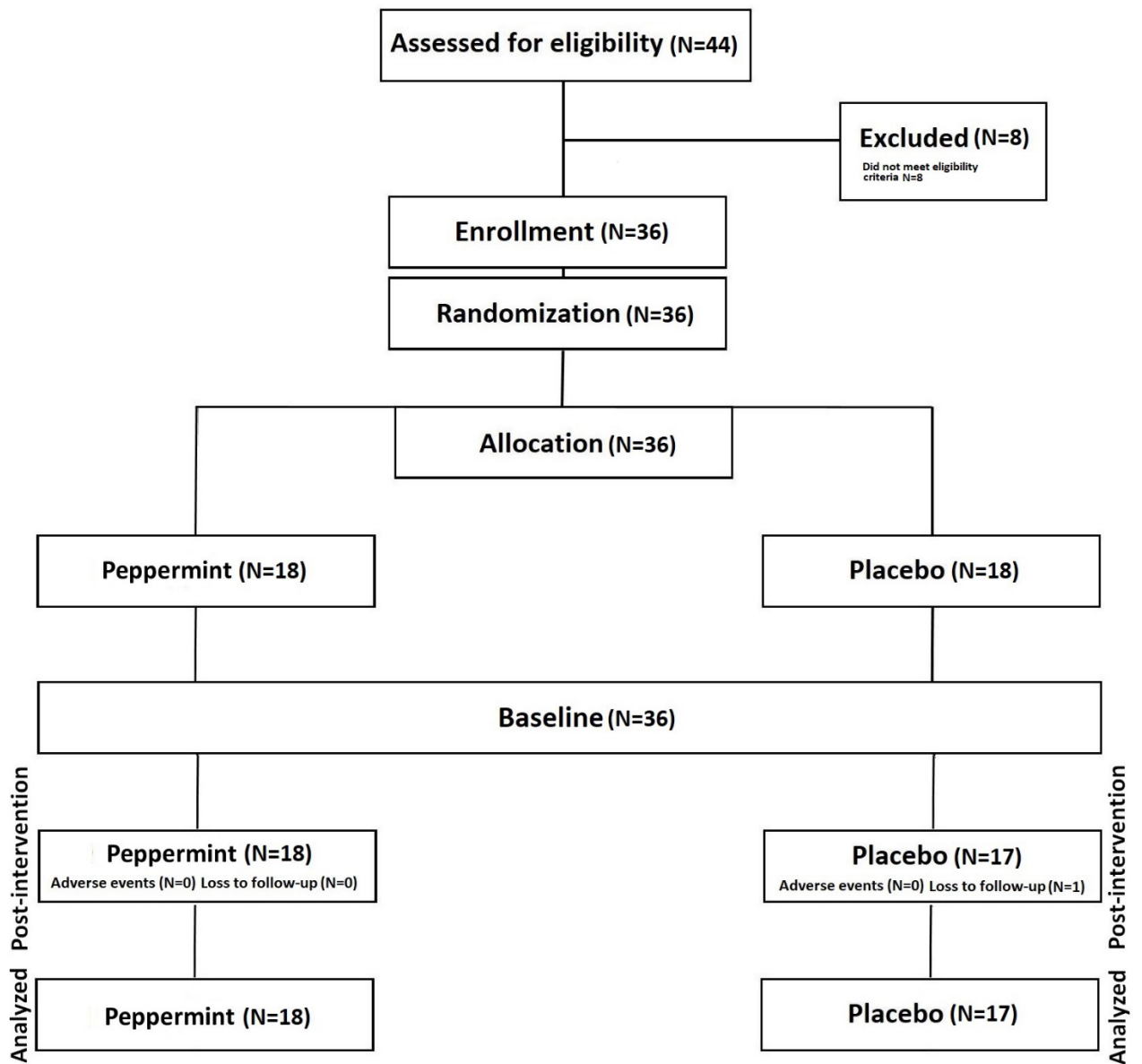


Figure 1: Consort diagram showing of participant flow throughout the study.

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612 Table 1: Baseline characteristics (mean & SD) for both placebo and peppermint groups.

	All		Placebo		Peppermint	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	28.51	9.80	26.59	5.44	30.33	12.53
Mass (kg)	69.49	9.82	71.65	9.96	67.46	9.50
Stature (m)	1.69	0.09	1.70	0.09	1.67	0.09
BMI (kg/m ²)	24.32	2.35	24.61	1.91	24.04	2.73
Sex (m/f)	23/ 12		11/ 6		12/ 6	
Ethnicity	Caucasian = 22 /Asian = 13		Caucasian = 11/Asian = 6		Caucasian = 11 /Asian = 7	

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Table 2: Experimental measurements as a function of each trial arm.

	Placebo				Peppermint				<i>b</i>	95% CI	P-value	<i>d</i>
	Pre		Post		Pre		Post					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Mass (kg)	71.65	9.96	71.55	9.63	67.46	9.50	67.22	9.61	-0.14	-0.73-0.45	0.628	-0.17
Fat mass (kg)	17.68	5.65	17.70	5.08	16.64	5.67	16.89	5.64	0.24	-1.24-1.72	0.742	0.11
BMI (kg/m ²)	24.61	1.91	24.58	1.83	24.04	2.73	23.96	2.84	-0.05	-0.25-0.14	0.593	-0.18
Body fat (%)	24.65	7.89	24.75	7.23	24.74	7.51	25.17	7.29	0.33	-1.69-2.35	0.741	0.11
Waist circumference (m)	84.03	8.09	82.12	7.30	81.14	4.48	79.83	5.36	0.60	-2.49-3.70	0.695	0.13
Waist:hip ratio	0.87	0.13	0.83	0.06	0.83	0.05	0.82	0.06	0.03	-0.04-0.10	0.378	0.30
Resting carbohydrate oxidation (g/min)	0.30	0.07	0.28	0.10	0.26	0.08	0.23	0.09	-0.01	-0.07-0.06	0.851	-0.06
Resting fat oxidation (g/min)	0.03	0.02	0.03	0.02	0.02	0.02	0.03	0.02	0.01	0.00-0.02	0.113	0.55
Resting kcal carbohydrates (kcal/min)	1.19	0.27	1.12	0.40	1.03	0.32	0.92	0.34	-0.04	-0.30-0.23	0.784	-0.09
Resting kcal fats (kcal/min)	0.27	0.19	0.28	0.16	0.20	0.15	0.32	0.23	0.10	-0.01-0.21	0.069	0.64
% Carbohydrate rest (%)	82.42	8.81	79.31	10.37	83.37	9.09	73.98	16.63	-6.28	-14.43-1.87	0.127	-0.53
% Fats rest (%)	17.58	8.81	20.69	10.37	16.63	9.09	26.02	16.63	6.28	-1.87-14.43	0.127	0.53
RMR (kcal)	2106.70	545.34	2011.53	588.03	1776.66	518.37	1773.32	446.46	91.83	-258.82-442.48	0.598	0.18
Cholesterol (mmol/L)	3.56	0.19	3.52	0.10	3.79	0.51	3.48	0.38	-0.27	-0.54-0.00	0.051	-0.68
LDL cholesterol (mmol/L)	1.89	0.49	1.83	0.43	2.08	0.50	1.89	0.17	-0.13	-0.41-0.15	0.348	-0.32
HDL cholesterol (mmol/L)	1.31	0.37	1.33	0.34	1.35	0.15	1.29	0.12	-0.08	-0.16-0.001	0.053	-1.10
Total:HDL ratio	2.88	0.57	2.79	0.50	2.90	0.50	2.83	0.29	0.02	-0.27-0.31	0.891	0.05
LDL:HDL ratio	1.59	0.56	1.50	0.49	1.60	0.46	1.55	0.26	0.04	0.22-0.30	0.751	0.11
Glucose (mmol/L)	4.45	1.05	4.58	1.00	4.22	0.56	4.32	0.73	-0.03	-0.50-0.43	0.879	-0.05
Triglycerides (mmol/L)	1.43	1.03	1.49	0.96	1.49	0.43	1.25	0.33	-0.30	-0.52 - -0.08	0.010	-0.92
TyG index	8.35	0.38	8.44	0.26	8.47	0.30	8.32	0.29	-0.26	-0.46 - -0.06	0.012	-0.90
Haemoglobin (g/L)	148.47	33.34	145.18	23.46	145.94	15.75	153.11	18.15	10.46	-3.96-24.90	0.150	0.50
Systolic blood pressure (mmHg)	118.53	9.53	119.00	10.42	118.44	9.19	114.39	10.70	-4.53	-8.39 - -0.66	0.023	-0.81
Diastolic blood pressure (mmHg)	75.29	9.84	76.18	6.21	76.72	7.04	73.78	7.83	-3.83	-7.45 - -0.21	0.039	-0.73

Resting heart rate (beats/min)	64.41	9.00	65.12	9.05	68.78	13.04	66.56	10.60	-2.93	-7.14-1.28	0.167	-0.48
Beck depression inventory	4.41	4.09	5.24	4.84	3.89	4.36	3.11	4.13	-1.60	-3.92-0.72	0.170	-0.47
COOP WONCA	1.89	0.56	1.95	0.60	1.76	0.47	1.68	0.50	-0.14	-0.46-0.18	0.380	-0.30
STAI state	34.24	10.27	40.06	11.71	31.28	10.09	30.89	11.69	-5.43	-11.33 - -0.56	0.040	-0.73
STAI trait	38.76	10.89	43.00	11.43	34.39	11.10	33.44	11.42	-5.18	-10.76 - -0.40	0.038	-0.74
PSQI	5.29	2.44	4.94	2.22	4.72	2.78	3.78	2.44	-0.59	-1.86-0.68	0.351	-0.32
Insomnia severity index	6.24	4.41	5.71	3.65	5.94	5.43	4.72	4.61	-0.69	-2.76-1.37	0.500	-0.23
Epworth sleepiness scale	6.00	4.02	5.59	3.84	6.72	4.11	5.67	3.46	-0.64	-1.19-0.62	0.307	-0.35

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Notes: bold text = significant difference in the changes from baseline to 20-days between the two groups (negative values denote that reductions in the peppermint group exceeded those in placebo), *b* = mean difference between groups in change from baseline to 20-days, 95% CI = confidence intervals of the mean difference & *d* = Cohen's *d*. **Abbreviations:** RMR = resting metabolic rate, TyG index = Triglyceride-glucose index, STAI = State-Trait Anxiety Inventory questionnaire, BMI = body mass index & PSQI = Pittsburgh Sleep Quality Index questionnaire.

