Title: High-intensity interval walking in combination with acute green tea extract
 supplementation reduces postprandial blood glucose concentrations in physically inactive
 participants.

- 4 Authors: Joseph M. Bulmer¹, Thomas R. McBain², Daniel J. Peart¹*
- Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle upon-Tyne, UK
- 7 2. Academy of Sport and Physical Activity, Sheffield Hallam University, Sheffield, UK
- 8 *Correspondence:

9 Dr Daniel J. Peart, Department of Sport, Exercise and Rehabilitation, Northumbria
10 University, Newcastle-upon-Tyne, UK, Email: <u>Daniel.peart@northumbria.ac.uk</u>, Tel: +44
11 (0)191 227 3712
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19 Abstract

Background: Exercise and green tea supplementation have been shown to have the potential
to improve postprandial blood glucose concentrations, but past interventions have not often
investigated attainable and time effective exercise protocols.

Aim: The purpose of this study was to investigate the effects of interval walking exercise and
acute green tea extract supplementation on the glycaemic response to an oral glucose
tolerance test (OGTT).

Methods: Twelve physically inactive participants (9 male, 3 female, age: 22 ± 1 y; body mass: 81.2 ± 16.3 kg; stature: 175.7 ± 9.6 cm; body mass index (BMI; in kg/m²): 26.2 ± 4.3) underwent a 2-hour OGTT immediately following i) no intervention (REST), ii) placebo and exercise (EX-PLAC), ii) green tea extract supplementation and exercise (EX-GTE), in a random order. The walking exercise consisted of 6 x 1-min of brisk walking (7.92 \pm 0.56 km/h) separated by 1-min of slower walking (4.8 km/h). Differences between groups were identified using magnitude based inferences.

Results: The EX-GTE intervention resulted in a ~9% most likely beneficial effect on blood glucose area under the curve response to the OGTT (702.18 \pm 76.90 mmol/L⁻¹.120 min⁻¹) compared to REST (775.30 \pm 86.76 mmol/L⁻¹.120 min⁻¹), and a very likely beneficial effect compared to the EX-PLAC (772.04 \pm 81.53 mmol/L⁻¹.120 min⁻¹).

37 Conclusion: These data suggest that an EX-GTE intervention can reduce postprandial38 glucose concentrations in physically inactive individuals.

39 Key words: Interval training, nutrition, blood glucose, supplement, green tea, walking

41 Introduction

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Glycaemic control is vital in the management and prevention of insulin resistant related 43 diseases such as metabolic syndrome and type 2 diabetes mellitus (T2DM) (American 44 Diabetes Association, 2015). Control of postprandial hyperglycaemia is essential for 45 achieving long-term glycaemic control, defined using recommended HbA_{1c} goals. Peak 46 glucose concentrations typically occur ~60-90 min postprandially and, in individuals with 47 48 insulin resistance, are sustained for several hours (American Diabetes Association, 2015). Glycaemic excursions, such as those following meals, correlate with HbA_{1c} levels and have a 49 detrimental effect, inducing oxidative stress and inflammation (Brownlee, 2005). 50 Furthermore, HbA_{1c} levels are directly associated with increased cardiovascular disease 51 (CVD) risk and all cause-mortality (Brownlee, 2005); with CVD accounting for more than 52 65% of all diabetic deaths (Lloyd-Jones et al., 2009). T2DM prevalence continues to increase 53 54 among the adult population and presents a major public health challenge (Zghebi et al., 55 2017).

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Obesity and a sedentary lifestyle are modifiable risk factors for the development of T2DM. 57 Lifestyle interventions (exercise and diet modification) are therefore obvious cost-effective 58 methods to prevent the development of T2DM and obesity. Both resistance and endurance-59 based exercise increase whole-body glucose uptake (Koopman et al., 2005; Larsen et al., 60 61 1997). However, a major barrier to exercise participation and adherence is reported 'lack of time', regardless of sex, age, socioeconomic status, and fitness level (Trost et al., 2002). 62 63 Low-volume high-intensity interval training (HIT) has been shown to be a time-efficient stimulus to improve blood glucose in healthy and insulin resistant individuals, via a number 64

65 of different modalities (Adams, 2013). Little et al. (2011) conclude that HIT training increases muscle mitochondrial capacity and GLUT-4 protein content, rapidly improving 66 glucose control (10 x 60-s cycling bouts). Additionally, regular HIT training (two weeks 67 cycling intervention) may reduce obesity risk, by increasing energy expenditure and fat 68 oxidation, enhancing weight loss, aiding in the prevention of T2DM (Whyte et al., 2010). 69 Lower intensity interval training, such as interval-walking has also been found to be a 70 71 feasible training method in T2DM participants. Karsoft et al. (2013) report high adherence rates (89 ± 4%) and significant improvements in $\dot{V}O_{2max}$ (16.1 ± 3.7%) and glycaemic control. 72 Moreover, Francois et al. (2014) found that even brief bouts of incline walking (6 x 1 min 73 74 bouts at $\sim 90\%$ HR_{max}) prior to meals significantly improved glycaemic control in individuals 75 with insulin resistance.

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77 Pragmatic lifestyle interventions combining physical activity and diet modifications are effective at promoting weight loss, and improve glycaemic control, potentially reducing the 78 risk of developing T2DM and cardiovascular disease (Hordern et al., 2012). However, there 79 is a need for more research to establish optimal strategies that are both cost-effective and 80 attainable. Interestingly, after investigating diabetic patients' perceptions of illness and 81 82 treatments, Broadbent et al. (2011) report that 86% of patients adhered to medication, whereas, just 22% report to adhere to nutritional advice. Suggesting that nutritional 83 supplementation may be an effective alternative to diet manipulation. Recent research has 84 85 found that green tea catechin (GTC) supplementation in humans may improve risk factors related to metabolic syndrome, including increased insulin sensitivity and reduced cholesterol 86 and adiposity (Bogdanski et al., 2012; Suliburska et al., 2012). An accessible concentrated 87 form of the catechins that are linked to lower disease risk (Kao et al., 2006) can be found in 88 green tea extract (GTE). Specifically, the most biologically active molecule in GTE, 89

90 epigallocatechin gallate (EGCG), is of a high concentration, accounting for ~50-80% of the 91 total catechin content (Khan and Mukhtar, 2007). Importantly, a recent meta-analysis 92 concluded that GTC ingestion lowers fasting blood glucose (-1.48 mg/dL; 95% CI: -2.57, -93 0.40 mg/dL) in human adults (n = 1584) (Zheng et al., 2013), and Venables et al. (2008) have 94 reported that just 24-hrs of green tea extract (GTE) supplementation improves glycaemic 95 control (-15 \pm 4% serum insulin AUC) after an oral glucose load in healthy men (n =11) at 96 rest.

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There is limited research on the use of GTE in combination with exercise. A single study has 98 reported that GTE supplementation attenuates the glucose and insulin responses to an oral 99 100 glucose load 1 hr after a graded exercise test but not at rest (Martin et al., 2016). The exercise employed by Martin et al. (2016) was also appropriate to control workload between 101 102 conditions and analyse substrate oxidation. However the translation of results from such an 103 exercise may be limited, as individuals are unlikely to complete a graded exercise test within 104 their regular physical activity for practical and comfort reasons. Further work is needed to build upon this proof of principle research of Martin et al. (2016), and examine if the results 105 106 from laboratory tests hold true for more attainable and time efficient physical activity such as low-volume interval-walking. The aim of this study was to examine the effect of interval-107 walking exercise, and any additive effects of GTE, on glycaemic control. 108

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115 **Participants**

Twelve participants (9 male, 3 female, age: 22 ± 1 y; body mass: 81.2 ± 16.3 kg; stature: 116 175.7 ± 9.6 cm; body mass index (BMI; in kg/m²): 26.2 ± 4.3) were recruited for the study. 117 All participants were considered to be physically inactive after completing a Global Physical 118 Activity Questionnaire (GPAQ); defined by not meeting national guidelines to achieve a 119 healthy lifestyle – 150 minutes of moderate-intensity exercise per week or 75 minutes of 120 121 vigorous-intensity exercise per week. All participants gave written informed consent to 122 participate in the study, and the study and its protocol received full ethical approval from the Faculty of Health and Life Sciences Research Ethics Committee at Northumbria University. 123 The study contained no drop out of participants. 124

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126 **Preliminary testing**

Basic anthropometric measures were taken, as well as safety measures, including, fasting 127 blood glucose (4.41 \pm 0.17 mmol/L) and systolic blood pressure (SBP; 124.7 \pm 14.3 mmHg) 128 129 (Omron M6 AC Blood Pressure Monitor, Omron, United Kingdom). Fasting blood glucose was collected following an overnight fast (> 8 hr) using finger capillary blood sampling, 130 followed by blood analysis (Biosen 5030 lactate analyser, Cardiff UK). No participants 131 132 presented a blood glucose over 7 mmol/L and/or a systolic blood pressure over 160 mmHg. Following recording of preliminary measures, participants completed a graded exercise test 133 on an incline treadmill (Woodway, Waukeska WI). Participants started at 5 km/h and 4% 134 incline, and gradually increased treadmill speed (1 km/h/min⁻¹) and treadmill incline (1 135

%/min⁻¹) in order to achieve a target RPE of 16 (Borg's Perceived Rate of Exertion).
Participants wore a Polar Electro heart rate monitor (Polar, Finland) throughout preliminary
and intervention exercise testing periods to quantitatively monitor work rate alongside RPE.
Average HR was measured as 170 ± 6 bpm after participants achieved an RPE score of 16.

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141 Study design

A within-groups, double blind, crossover design was used to compare the effects of green tea extract to a placebo, and to a resting condition. A familiarisation visit took place prior to participant completion of three randomly ordered experimental trials. The experimental trials included (1) resting conditions (REST), (2) acute exercise with GTE (EX-GTE), and (3) acute exercise with a placebo (EX-PLAC). All trials were conducted in the morning following an overnight fast (10-12 hrs). At least 3 days separated each trial day (5.7 ± 1.7 days), acting as a washout period.

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150 Supplementation

Participants were provided with capsules prior to each exercise trial of either decaffeinated GTE powder (EGCg Green Tea Extract, Now Foods, Bloomingdale IL) or a plain-flour placebo to colour match the capsules, and then the opposing capsules the following exercise test day.

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Due to the pharmacokinetic evidence that the bioavailability of ingested catechins is greaterin a fasted state (Chow et al., 2005), and considering a half-life of ~4 hr (Lee et al., 2002),

participants were asked to ingest each capsule with 500 ml of water ~1 hr before the provided
dextrose solution, and also ~1 hr before breakfast, lunch and dinner the day prior to each trial
day. Therefore, participants ingested a total of 4 GTE capsules, and 4 PLA capsule each.
Each 400 mg GTE capsule (98% total polyphenols, 80% catechins, 50% EGCG) contained
320 mg of catechins per capsule.

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165 Study controls

Participants were asked to maintain a habitual diet, and to not consume alcohol or excessive amounts of caffeine the day before each trial. A 24-hr food diary was completed by each participants on these days to monitor intake. Participants were also asked not to perform any exercise the day prior to each trial.

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171 Experimental protocol

The resting trial consisted of a 5-minute sitting rest period followed by a 2-hr oral glucose tolerance test (OGTT). OGTT protocol involved a baseline capillary blood sample (minute 0) followed by the ingestion of a 250 ml 75g oral glucose beverage (Dextrose powder, MyProtein Ltd., Cheshire UK) in a fasted state (10-12 hr overnight fast), then capillary blood sampling for 2 hrs following ingestion (at minutes 15, 30, 45, 60, 90, 120).

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178 After preliminary testing, each participant's treadmill speed and incline was noted, after 179 achieving an RPE score of 16 (speed: 7.92 ± 0.56 km/h; incline 6.88 ± 1.17 %). The trial 180 exercise protocol consisted of 6 x 1-min long bouts at a speed that elicited an RPE of 16, interspersed with 'slow' walking (4.8 km/h (3 mph)) for 1-min (total exercise time = 12 181 mins). This exercise protocol was modified from the work of Francois et al. (2014), who 182 183 found 'exercise snacking' to be a time-efficient and effective approach to improve glycaemic control. RPE was used as a simple and inexpensive alternative to HR_{max} as it is easier to 184 measure in a real-world setting. This study aimed for participants to achieve an RPE score of 185 186 16 (hard - very hard) to mimic the research of Francois et al. (2014) which targeted a measure of 90% HR_{max}. A typical RPE response in the Francois et al. (2014) study resulted in the 187 188 mean RPE of 16 in high-intensity bouts 4-6, this is in accordance with the work of Francois and Little (2015) which suggests its take ~3-4 intervals to accurately determine intensity. 189 Following the exercise bout, a baseline blood glucose sample was taken prior to the 190 191 administration of the oral glucose load and 2-hr OGTT.

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193 Statistical analysis

A sample size calculation was conducted using a custom made spreadsheet (Will Hopkins; 194 www.sportsci.org), based on glucose AUC reproducibility data from previous work (Gordon 195 196 et al., 2011), who found increases greater than 63.5 mmol/L⁻¹.120 min⁻¹ and decreases greater than 80.9 mmol/L⁻¹.120 min⁻¹ to exceed daily variation. A between subject standard deviation of 197 100 mmol/L⁻¹.120 min⁻¹ was taken from Venables et al. (2008), and a within subject standard 198 deviation of 98 mmol/L⁻¹.120 min⁻¹ was calculated by taking 13% (upper 95% CI of normal 199 200 daily variation; Gordon et al., 2011) of the average glucose AUC reported by Venables et al. (2008). These values resulted in a sample size of ten being required to achieve 90% power. 201

203 Glucose area under the curve (AUC) was calculated using the incremental method. All data were log-transformed prior to analysis. The descriptive summary for all variables comprised 204 of the geometric mean and dispersion shown as standard deviation (SD) (Hopkins et al., 205 206 2009). An analysis of variance (ANOVA) model was used on peak and AUC glucose data. Following this, a magnitude-based inferences approach (Hopkins et al., 2009), was used to 207 analyse the mean effect of the intervention (EX-GTE), versus placebo (EX-PLAC) and rest 208 (REST). Inferences were based on the disposition of the 90% confidence limits (CL) for the 209 mean difference to the minimal clinically important difference (MCID). Log-transformed 210 211 data were back transformed to provide percent differences between conditions. The probability (percent chances) that differences in glucose AUC between EX-GTE, EX-PLAC 212 and REST were beneficial (>MCID), harmful (>MCID with opposite sign), or trivial (within 213 214 ± MCID) was calculated (Hopkins et al., 2009). Robust clinical data for the MCID on all variables is scarce, therefore, MCID was determined using a standardised mean difference of 215 0.2 times between subjects' standard deviations (Cohen, 1988). Subsequently, the percent 216 chances were defined via probabilistic terms assigned using the following scale; <0.5%, most 217 unlikely or almost certainly not; 0.5 to 5%, very unlikely; 5 to 25%, unlikely or probably not; 218 25 to 75%, possibly; 75 to 95%, likely or probably; 95 to 99.5%, very likely; >99.5%, most 219 likely or almost certainly (Batterham and Hopkins, 2006). Inferences were categorised as 220 clinical, with the default probabilities for declaring an effect clinically beneficial being <0.5% 221 222 (most unlikely) for harm and >25% (possibly) for benefit (Hopkins et al., 2009). 223 Additionally, in the case of an effect being possibly beneficial (>25%) an unacceptable risk of harm (>0.5%) and with an odds ratio for benefit: harm of <66, would be classified as 224 225 unclear.

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230	The heart rate (170 \pm 13 vs. 166 \pm 13 beats.min ⁻¹) and RPE (13 \pm 2 vs. 14 \pm 2) were				
231	comparable between exercise trials. Comparison between conditions for glucose AUC and				
232	peak glucose can be seen in Table 1. When compared to the REST condition (775.30 \pm 86.76				
233	mmol/L ⁻¹ .120 min ⁻¹), there was a most likely beneficial effect of EX-GTE (702.18 \pm 76.90				
234	mmol/L ⁻¹ .120 min ⁻¹) on glucose AUC and a very likely beneficial effect compared to EX-				
235	PLAC (772.04 \pm 81.53 mmol/L ⁻¹ .120 min ⁻¹). The effect was unclear between EX-PLAC and				
236	REST. The average response to the OGTT at all time points is presented in Fig 1. There was				
237	a very likely beneficial effect of EX-GTE (7.51 \pm 0.91 mmom/L) when compared to REST on				
238	peak glucose (8.30 \pm 0.92 mmol/L). The effect was unclear on all other outcomes.				
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240	[Insert Figure 1.]				
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242	Discussion				
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244	This study aimed to investigate the effect of high-intensity walking exercise on glycaemic				
245	control, and any additive effect of an acute GTE supplementation strategy. The main finding				
246	was that the walking exercise alone did not influence the glycaemic response during a 2-h				

OGTT, but the combined walking exercise with GTE had a 'most likely', and 'very likely'

beneficial effect on glucose AUC and peak glucose respectively.

250 Previous research has suggested that high-intensity interval walking may be effective at reducing mean postprandial blood glucose concentrations (Francois et al., 2014; Jakobsen et 251 al., 2016). Francois et al. (2014) reported that 6 x 1 min bouts of inclined interval walking 252 253 (90% HR_{max}) interspersed with periods of slow walking significantly reduced mean 3 hr postprandial glucose before breakfast (-1.4 \pm 1.5 mmol/L, p = 0.02) when compared to 254 traditional continuous exercise (30 min moderate-intensity; 60% HR_{max}), a 17% reduction in 255 256 3 hr post-breakfast AUC (interval walking: $1,090 \pm 178 \text{ mmol/l vs. continuous exercise:}$ $1,307 \pm 337$, p = 0.04). The present study aimed to emulate the exercise protocol of Francois 257 258 et al. (2014) whilst using RPE to measure effort, as opposed to HR_{max}, to give a reliable (Ciolac et al., 2015) but simple and inexpensive method that could be replicated more easily 259 in the real world, to simplify the translation of our findings to practice. However, this study 260 261 did not find a worthwhile effect between postprandial glucose concentrations of exercise alone with placebo and the resting condition. More specifically, we aimed for participants to 262 achieve an RPE score of 16 throughout exercise testing, in an attempt to replicate the 90% 263 264 HR max targeted by Francois et al. (2014). However, average trial RPE failed to give the desired effect (RPE = 16) with an average RPE score of 13.4 ± 1.7 (HR: 170 ± 13.1 bpm) and 265 13.7 ± 1.6 (HR: 165.8 \pm 13 bpm) during the EX-PLAC and EX-GTE trials, respectively. 266 Moreover, the average HR during the high-intensity intervals was 170 ± 6 , ~85% of HR_{max}, 267 lower than the desired 90% of HR_{max} (~178 bpm, p < 0.01). This suggests that the study 268 269 duration, and/or intensity may not have been high enough to induce the desired physiological changes. Similarly, Jakobsen et al. (2016) suggest that altering the intervention to 3 min long 270 bouts of high-intensity walking may improve glycaemic control, specifically, by reducing 271 272 postprandial glucose concentrations. The study found no difference between mean glucose after 1 min walking cycles compared to control, whereas 3 min bouts attenuated glucose 273 response following a 4 hr liquid mixed meal tolerance test. The inclusion of a step test in 274

place of a ramp test would be recommended in future, with sufficient breaks between steps to reduce the effect of cumulative fatigue during the graded exercise test and increase the walking speed at an RPE of 16. Whilst the current study found no benefit to high-intensity interval walking alone for glycaemic control, these results are contrary to the limited previous research.

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The addition of GTE to the walking intervention did reduce postprandial glucose 281 concentrations, and the ~9% reduction in glucose AUC in the EX-GTE trial can be 282 interpreted as being 'most likely beneficial' compared to REST and 'very likely beneficial' 283 compared to exercise alone (Table 1). The effect of this intervention was greater than the 284 285 typical 6% daily variation of OGTT results identified by Gordon et al. (2011). This would suggest that the study intervention may improve insulin sensitivity of the skeletal muscle, 286 agreeing with the work of Martin et al. (2016) who suggest that GTE may alter skeletal 287 muscle glucose uptake in humans. Possibly due to the increased translocation of glucose 288 transporters which is apparent in rodent studies, specifically, green tea has shown to have a 289 290 similar effect to exercise, in that, prolonged consumption increases GLUT-4 translocation in normal and insulin resistant skeletal muscle, in addition to increased adipocyte insulin-291 receptor binding (Wu et al., 2004). 292

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A limitation of the present study is the absence of a GTE group without the exercise intervention to give further context to the combined effect of GTE and exercise, however, previous research has indicated that GTE alone may not sufficiently reduce postprandial glucose concentrations. As mentioned, Martin et al. (2016) state that GTE attenuated glucose response to an oral glucose load following acute exercise, however, the study found no effect

under resting conditions (Glucose AUC: GTE = 394 ± 70 , PLA = $409 \pm 78 \text{ mmol/L}^{-1} \cdot 60 \text{ min}^{-1}$ 299 ¹, p = 0.51). Venables et al. (2008) also found that GTE significantly lowered insulin AUC (-300 $15 \pm 4\%$, p < 0.01) and increased insulin sensitivity (insulin sensitivity index (ISI): $13 \pm 4\%$, 301 302 p < 0.05), albeit with no difference in glucose concentrations (p > 0.05). Furthermore, a combined intervention should be recommended where possible due to the further reaching 303 benefits of physical activity. Importantly, this study presents evidence that a combined 304 walking and GTE intervention can improve glycaemic control. This offers insight in to a 305 potentially more real world applicable and achievable exercise in physically inactive people 306 307 than has been researched in the past, as previous studies have for example used higher intensity cycling protocols (Little et al., 2011; Whyte et al., 2010). It should also be 308 considered when interpreting our results that although the participants were physically 309 310 inactive, their glycaemic control was good under all testing conditions, and fasted blood glucose was 4.41 ± 0.17 mmol/L. The results may be different in populations with poorer 311 glycaemic control, and further research is warranted in this area. 312

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In conclusion low-volume interval-walking exercise combined with GTE supplementation was found to reduce postprandial glucose concentrations in physically inactive individuals. A combined walking and green tea routine may be an achievable and translatable intervention for physically inactive people.

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322 Authors' contributions

323 XXX and XXX conceived the study. XXX recruited participants and collected the data. XXX 324 performed the statistical analysis. XXX, XXX and XXX contributed to drafts of the manuscript, and 325 all authors have read and approved the final version of the manuscript, and agree with the order of 326 presentation of the authors.

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329 Availability of data and materials

330 The datasets used and/or analysed during the current study are available from the331 corresponding author on reasonable request.

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333 Declaration of conflicting interests

334 The authors declared no potential conflicts of interest with respect to the research, authorship,

and/or publication of this article.

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434	Figure caption
435	Fig 1. Average post-prandial blood glucose (mmol/L) response at each time point of the OGTT
436	for the REST, EX-PLAC and EX-GTE conditions. Error bars for EX-PLAC have been removed for
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		groups	intervention being	
			mer venuon being	
		(% mean; 90%CL)	beneficial / trivial /	
			harmful	
Glucose AUC	EX-GTE to REST	-9.4 ±4.9	99.8 / 0.1 / 0.1	Most likely beneficial
(mmol.min ⁻¹)	EX-GTE to EX-PLAC	-9.1 ±7.1	98.0 / 0.0 / 2.0	Very likely beneficial
	EX-PLAC to REST	-0.37 ±50	50.5 / 0.0 / 2.0	Unclear
Peak glucose	EX-GTE to REST	-9.8 ±7.5	98.2 / 0.0 / 1.7	Very likely beneficial
(mmol/l)	EX-GTE to EX-PLAC	-7.23 ±12	84.1 / 0.2 / 15.2	Unclear
	EX-PLAC to REST	-2.79 ±50	53.7 / 0.1 / 46.2	Unclear

454 Table 1 Clinical inferences of differences in glycaemic control between treatment groups

AUC = area under the curve; REST = resting condition; EX-PLAC = exercise intervention with placebo; EX-GTE

exercise intervention with green tea extract supplementation