Interrupting prolonged sitting with intermittent walking increases postprandial gut hormone responses

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Abstract

Introduction: Continuous exercise can increase postprandial gut hormone such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) responses but it is unknown whether interrupting prolonged sitting with intermittent walking elicits this effect. **Method:** Ten participants with central overweight/obesity (7 men and 3 postmenopausal women, 51 ± 5 y; mean ± SD) completed a randomized crossover study in which they consumed breakfast and lunch in the laboratory whilst either sitting continuously for the entire 5.5-hour period (SIT) or with the prolonged sitting interrupted every 20 minutes by walking briskly (6.4 $km \cdot h^{-1}$) for 2 minutes every 20 minutes (BREAKS). Blood samples were collected at regular intervals to examine postprandial plasma GLP-1, PYY and glucose-dependent insulinotropic polypeptide (GIP) concentrations. Adipose tissue samples were collected at baseline and at the end of the trials to examine changes in net dipeptidyl peptidase 4 (DPP-4) secretion from primary explants. **Results:** Mean (95% confidence interval [CI]) postprandial GLP-1 and PYY iAUCs were elevated by 26% and 31% in the BREAKS trial *versus* SIT (8.4 [0.7, 16.1] *versus* 6.7 [−0.8, 14.2], p=0.001 and 26.9 [8.1, 45.6] *versus* 20.4 [5.1, 35.8] $nmol \cdot 330\ min \cdot L^{-1}$, p=0.024, respectively) but without any such effect on GIP (p=0.076) or net adipose tissue DPP-4 secretion (p>0.05). **Conclusions:** Interrupting prolonged sitting with regular short bouts of brisk walking increases postprandial GLP-1 and PYY concentrations in healthy middle-aged men and women with central adiposity.

Key words: glucagon-like peptide 1, peptide YY, glucose-dependent insulinotropic polypeptide, sedentary, prolonged sitting, incretin

Introduction

Prolonged sitting contributes to increased adiposity (i.e., overweight/obesity), impaired appetite control (e.g., gut hormones dysfunction), reduced insulin sensitivity and glucose tolerance, and greater likelihood of suffering from metabolic-related diseases (1, 2). Studies have shown that gut hormones such as glucagon-like peptide 1 (GLP-1), peptide YY (PYY) and glucose-dependent insulinotropic polypeptide (GIP) can regulate appetite, glycaemic control and insulin secretion, gut motility and/or nutrient digestion/absorption (3-6). For example, elevated GLP-1 and PYY concentrations have been shown to inhibit gastric emptying and suppress energy consumption (7). Within the context of obesity, these responses are considered beneficial by contributing to a negative energy balance. However, individuals with greater adiposity often exhibit abnormal circulating gut hormone concentrations compared to lean individuals (8, 9). This typically manifests as lower postprandial GLP-1 and PYY concentrations (8), but higher GIP concentrations in those with overweight/obesity (10). Since gut hormones play important roles in metabolism and energy balance regulation, normalizing gut hormone concentrations may contribute to better metabolic control and/or weight management.

Clinical strategies, such as medication (e.g., GLP-1 analogues and dipeptidyl peptidase-4 [DPP-4] inhibitor) and surgery (e.g., bariatric surgery) have been shown to enhance gut hormones concentrations (e.g., GLP-1 and PYY) (11, 12). However, these approaches have potential side effects, highlighting the need for less invasive and/or non-pharmacological strategies. Studies have revealed that continuous exercise at moderate-intensity (13, 14) and low volume high-intensity/sprint interval training (15) elevate gut hormone concentrations in individuals with overweight/obesity. However, the effect of less strenuous or prolonged modalities of physical activity on gut hormone concentrations in people with

obesity is not known. This is particularly relevant in people with overweight/obesity as lower-intensity physical activity may be better tolerated than more strenuous exercise.

At present, only two studies have investigated the responses of any gut hormones in response to breaking sitting, and these have only determined PYY responses (16, 17). These studies found that breaking prolonged sitting does not alter PYY concentrations in young individuals with and without obesity (16, 17). GLP-1 and GIP are two key gut hormones with therapeutic potential in relation to glucose and weight control (18, 19), but neither were measured in those studies. Moreover, the meals provided during trials had low external validity (e.g., liquid diet with only carbohydrate and fat, and small meals every 2 hours) (16, 17). Thus, the purpose of current study was to investigate whether breaking up prolonged sitting can affect gut hormones responses (GLP-1, PYY and GIP) to feeding in middle-aged people with central overweight/obesity.

MATERIALS AND METHODS

Participants

Participants were required to be healthy (e.g., without any cardiovascular and metabolic diseases), aged between 35 and 64 years, centrally overweight with a waist circumference of >80 cm for postmenopausal women or >94 cm for men, and weight stable (no self-reported change in weight ± 3%) for at least 3 months (20). Smokers, pre-menopausal women and volunteers using any medication which could influence metabolic and inflammatory responses were excluded. Once participants consented to take part, a Physical Activity Readiness Questionnaire (PAR-Q) and a health questionnaire were completed to exclude any existing cardiometabolic related diseases and to ensure that participants were able to walk on the treadmill without any safety issues. Due to problems

cannulating one participant, ten participants (7 men and 3 post-menopausal women) were included in this analysis. A summary of participants' physical characteristics is shown in **Table 1**.

Table 1. Participant characteristics

Characteristics	Mean ± SD (n = 10)
Age (years)	51 ± 5
Body mass (kg)	96 ± 21
Height (m)	1.74 ± 0.08
Body mass index ($kg \cdot m^{-2}$)	31.9 ± 6.7
Waist circumference (cm)	109 ± 15
Hip circumference (cm)	111 ± 12
Fat mass (%)	34.2 ± 6.4
Fat mass (kg)	32.6 ± 10.7
Fat in L1-L4 region (kg; DEXA)	4.8 ± 2
Systolic blood pressure (mmHg)	136 ± 13
Diastolic blood pressure (mmHg)	89 ± 8
Physical activity level (PAL)	1.47 ± 0.17

Fat mass in L1-L4 region was assessed as described previously (21).

Experimental design

Two experimental conditions (SIT = prolonged sitting; BREAKS = breaking prolonged sitting with regular short bouts of brisk walking), in a randomised crossover fashion, were conducted with a 3–4 week wash-out period. On main trial days, breakfast and lunch (identical meals) were provided based on participants' total body mass. Venous blood samples were taken regularly during the main trials. Studies have shown that DPP-4, an adipokine, is mainly secreted by adipose tissue and regulates the function of gut hormones (e.g., GLP-1, GIP and PYY) (22). Therefore, in addition to determining plasma concentrations of gut hormones, abdominal subcutaneous adipose biopsies were also

collected at baseline and at the end of each visit for the measurement of DPP-4. The study protocol was approved by the Bristol NHS Research Ethics Committee (reference number: 13/SW/0321). All participants provided written informed consent before taking part.

Pre-trial assessments

All participants were asked to walk on a treadmill for 2 minutes at the pre-determined speed of 6.4 $km \cdot h^{-1}$ to ensure that they were able to complete the study protocol safely. Body mass was assessed using digital scales post-void (TANITA corp., Tokyo, Japan). Waist and hip circumferences were assessed following World Health Organisation standard operating procedures (23). Body composition was accessed via Dual Energy X-ray Absorptiometry (DEXA; Discovery, Hologic, Bedford, UK) and a central region between L1-L4 was used to estimate abdominal subcutaneous and visceral adipose tissue mass (21). Then, habitual physical activity level was recorded using a combined heart rate/accelerometer monitor for 24 hours per day for continuously 7 days (Actiheart^{TM}, Cambridge Neurotechnology Ltd., Cambridge, UK) except during showering/bathing/swimming (24).

Pre-trial standardization

In the 72 hours prior to each laboratory visit, participants were asked to refrain from all types of strenuous exercise. In addition, to eliminate any acute effects from recent physical activity, in the 48 hours prior to the main trials, participants were asked to restrict steps to <4,000 per day to mimic a sedentary lifestyle (25). Adherence was measured using a pedometer (Yamax, Japan). Meanwhile, a weighed food and fluid record was completed and alcohol/caffeine intake was not permitted in the 48 hours leading to the first and second trial. Participants replicated their diets for 48 hours prior to their second main trial.

Trial days

On main trial days, participants reported to the laboratory between 0800–0900 AM after a 12-hour overnight fast. Anthropometric assessments (i.e., height, weight, and waist and hip circumferences, Table 1) were obtained, followed by two 5-minute expired air samples using Douglas bags (Hans Rudolph, MO, USA) to determine resting metabolic rate (RMR) (26) from substrate oxidation (27).

A cannula (BD, Venflon™ Pro) was then inserted into an antecubital forearm vein and a 10-mL baseline venous blood sample was collected and aliquoted into tubes with ethylenediaminetetraacetic acid (EDTA). Plasma samples were centrifuged immediately at 3465 *g* at 4°C for 10 minutes. Approximately 1 g of subcutaneous abdominal adipose tissue was obtained under local anaesthetic (1% lidocaine) from the area around the waist approximately 5 cm lateral to the umbilicus with a 14-gauge needle using an aspiration technique (28). Adipose tissue was then cleaned and processed as previously described (29).

After taking the baseline samples (blood and adipose tissue), breakfast was consumed, followed by lunch 3 hours afterwards. Breakfast and lunch (identical meals) were consumed within a 15-minute period in both SIT and BREAKS trials. The test meal was prescribed according to total body mass (provided 0.35 g fat, 1.17 g carbohydrate, 0.29 g protein and 37 kJ energy per kilogram body mass) and the percentage of energy from macronutrients was 52% carbohydrate, 35% fat and 13% protein. The meal comprised white bread (Hovis; soft white bread, medium sliced), sliced cheese (Sainsbury; cheese slices, basic), butter (Unilever; I can't believe it's not butter), mayonnaise (Hellmann; light mayonnaise), lettuce (Sainsbury; Iceberg lettuce), tomato (Sainsbury; tomatoes, basics), ham (Sainsbury; British

157 honey roast), whole milk (Sainsbury; British), cocoa powder (Nesquik; cocoa powder), and
158 yoghurt (Müller; fruit corner strawberry).
159
160 **Prolonged sitting and breaking sitting trials**
161 In the BREAKS trial, participants walked on a treadmill at 6.4 $km \cdot h^{-1}$ speed for 2 minutes
162 every 20 minutes, accumulating a total 30 minutes of brisk walking (15 x 2 minutes bouts of
163 walking) over 300 minutes. For the remainder of the time participants remained seated. In
164 the SIT trial, participants sat on a chair throughout. During sitting in both trials, participants
165 were allowed to read, use a laptop or watch television but were otherwise asked to keep as
166 still as possible throughout (including specific instructions to avoid fidgeting). In the first trial,
167 participants were allowed to consume water *ad libitum* and the volume ingested was
168 replicated for the second trial. A wheelchair was used to assist participants if toilet breaks
169 were needed to minimise physical activity. The study protocol is shown in **Figure 1**.
170
171 Ratings of perceived exertion (RPE) and heart rate were collected in the last 30 seconds of
172 each 2-minute bout of walking during the BREAKS trial. During the BREAKS trial, two, 1-
173 minute expired air samples were collected during the last minute of walking (the 7^{th} and 15^{th}
174 bout) to estimate energy expenditure and substrate utilization (30). In addition, expired air
175 samples were taken in both SIT and BREAKS trials using Douglas bags (Hans Rudolph,
176 MO, USA) during two 5-minute periods of sitting (90 minutes after the 1^{st} and the 2^{nd} meal
177 consumption) to estimate total energy expenditure under resting conditions. In each main
178 trial, baseline blood samples were collected before breakfast and hourly for the remaining 5
179 hours. Two additional blood samples were taken every 30 minutes for the first hour after
180 meals. A total of 8 blood samples were collected for each trial **(Figure 1).**

Figure 1

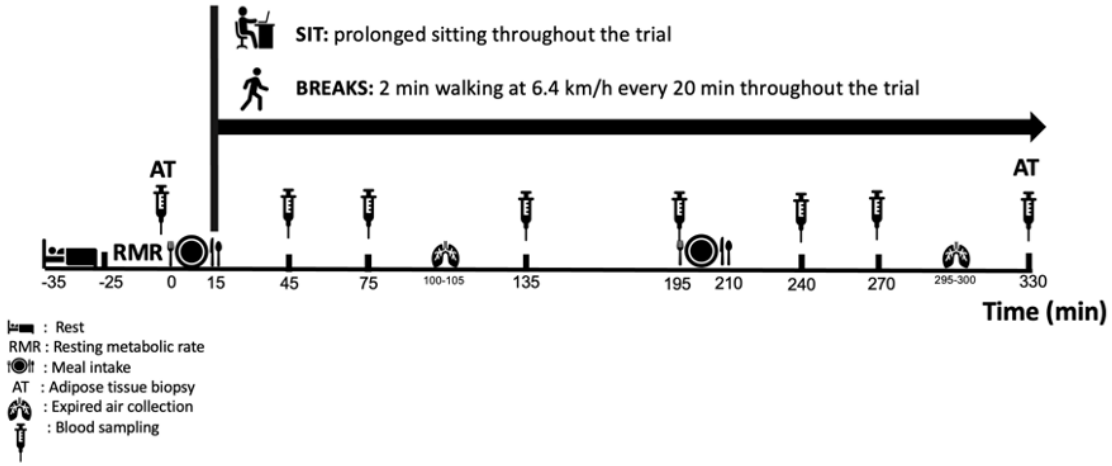

Figure 1 − Experimental protocol in prolonged sitting and breaking sitting trials. In the prolonged sitting trial, participants sat on a chair throughout. In the breaking sitting trial, participants walked on a treadmill at 6.4 $km \cdot h^{-1}$ for 2 minutes every 20 minutes.

Adipose tissue culture

Adipose tissue was directly placed in sterile culture plates in duplicate (Nunc, Roskilde, Denmark) with endothelial cell basal media (ECBM) (Promocell, Germany) containing 0.1% fatty acid-free bovine serum albumin 100 $U \cdot mL^{-1}$ penicillin and 0.1 $mg \cdot mL^{-1}$ streptomycin (Sigma–Aldrich, Gillingham, UK). Samples were incubated at 37°C, 5% CO_2 and 95 ± 5 % relative humidity for 3 hours (MCO-18A1C CO_2 incubator; Sanyo, Osaka, Japan) with a final ratio of 100 mg tissue per 1 mL ECBM media (29). After the 3-hour incubation, cultured adipose media was transferred to sterile eppendorfs and stored at −80°C for future analyses.

Biochemical analyses

Adipose explant secretion of dipeptidyl peptidase 4 (DPP-4) (abcam systems) and plasma $GLP\text{-}1_{Total}$, GIP_{Total} and PYY_{Total} (ELISA; all from Merck Millipore Ltd. Watford, UK) were

198 measured using commercially available enzyme-linked immunosorbent assays. Intra-assay
199 coefficients of variation were less than 5% for GLP-1, PYY and GIP.
200
201 **Statistical analysis**
202 Descriptive data are presented in text and tables as means ± standard deviation (SD);
203 variance bars on figures are presented as means and 95% confidence intervals (CIs). Time-
204 series data were examined using a two-way ANOVA (Trial*Time) with repeated measures
205 using SPSS version 22 (IBM, Armonk, NY, USA). Greenhouse–Geisser corrections were
206 applied to intra-individual contrasts where $\varepsilon < 0.75$; however, for less severe asphericity the
207 Huynh-Feldt correction was selected (31). Incremental area under curve (iAUC) was
208 calculated using the trapezoid method (32) and the differences in summative scores
209 between trials were analysed using paired *t-tests*. Data for iAUC represent the period from
210 the consumption of the first meal to the conclusion of the second meal (330 minutes).
211 Statistical significance was set at $p \leq 0.05$.
212
213 **RESULTS**
214 **Plasma GLP-1, GIP and PYY in SIT and BREAKS trials**
215 The iAUC for GLP-1 was greater in the BREAKS trial than in the SIT trial (8.4, 95% CI 0.7,
216 16.1 *versus* 6.7, 95% CI −0.8, 14.2 nmol·330 min·L^{-1}) (**Figure 2D**, $p = 0.001$). In addition,
217 iAUC for PYY was higher in SIT compared BREAKS (26.9, 95% CI 8.1, 45.6 *versus* 20.4,
218 95% CI 5.1, 35.8 nmol·330 min·L^{-1}, respectively, $p = 0.024$, **Figure 2F**). There was no
219 difference for GIP-1 iAUC between trials (179, 95% CI 138, 221 *versus* 154, 95% CI 123,
220 184 nmol·330 min·L^{-1}, respectively, $p = 0.076$, **Figure 2B**).
221

222 iAUCs were further separated to SIT- and BREAKS-morning ($iAUC_{Baseline\text{-}M1180\ min}$) and SIT-
223 and BREAKS-afternoon ($iAUC_{M1180\text{-}M2120\ min}$). There was no difference in SIT- and BREAKS-
224 morning for all gut hormones (all, $p > 0.05$, **Figure 2**), but all demonstrated greater difference
225 between BREAKS- compared to SIT-afternoon (all, $p < 0.05$, **Figure 2**).
226
227 In terms of temporal patterns, plasma GIP concentrations increased after each meal (time
228 effect, $p = 0.002$), and to a greater extent in BREAKS *versus* SIT (time * trial interaction
229 effect, $p = 0.002$, **Figure 2A**). Neither trial * time nor time effects were found for plasma
230 GLP-1 responses (both $p > 0.1$, **Figure 2C**). Plasma PYY concentrations increased after
231 each meal (time effect, $p = 0.031$), without differences between trials (time * trial interaction
232 effect, $p = 0.099$, **Figure 2E**).

Figure 2

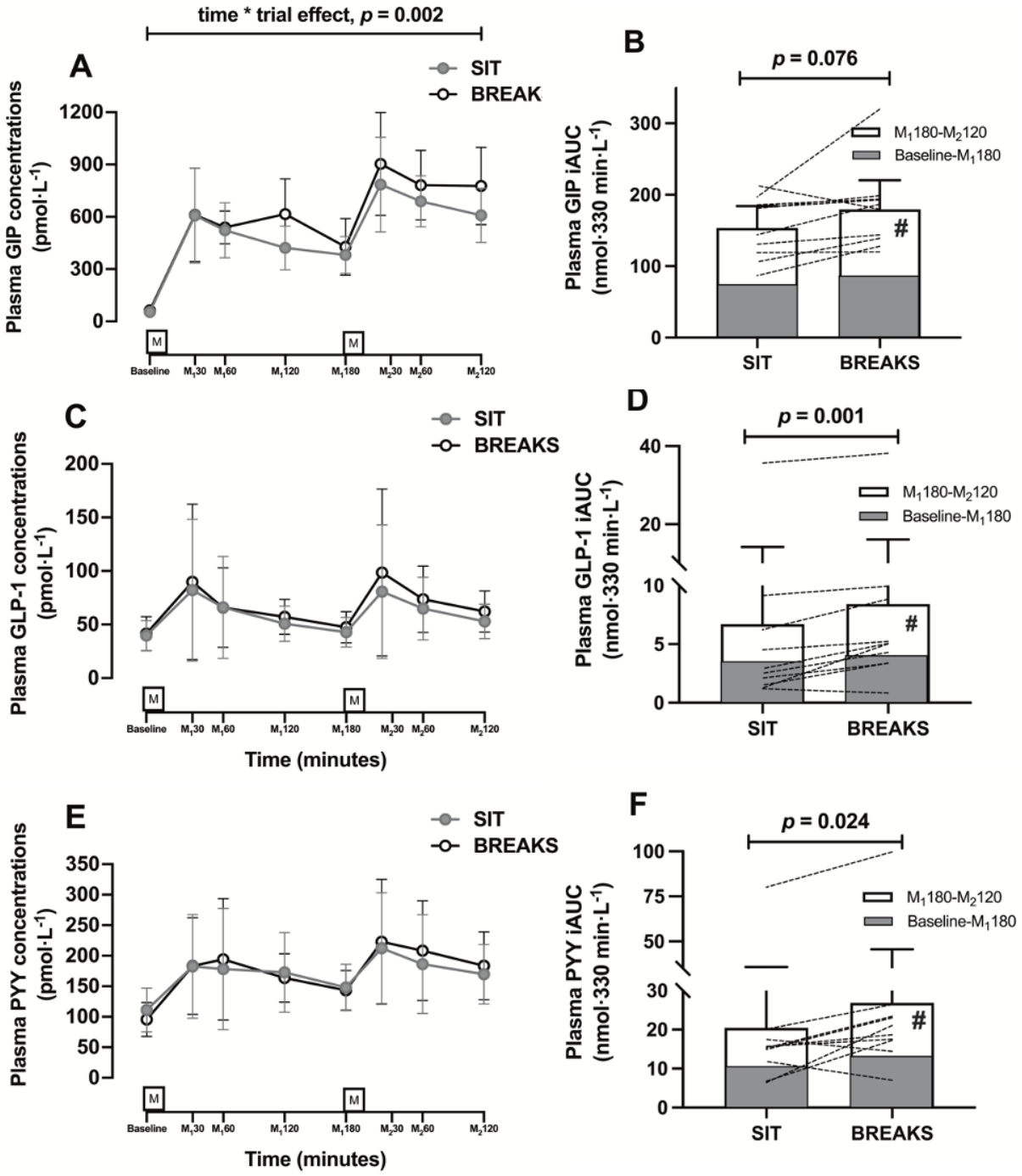

Figure 2. Plasma GIP (A), GLP-1 (C), and PYY (E) concentrations in prolonged sitting (SIT) and breaking sitting (BREAKS) trials. iAUC for GIP (B), GLP-1 (D), and PYY (F). The sample size is n = 10. Values are presented as mean ± 95 % confidence intervals. M denotes meal time. # denotes BREAKS greater than SIT for iAUC $M_1$180-$M_2$120 period.

Adipose DPP-4 and glucose in SIT and BREAKS trials

There was no difference in net DPP-4 secretion from adipose tissue explants between SIT and BREAKS trials (**Figure 3**).

Figure 3

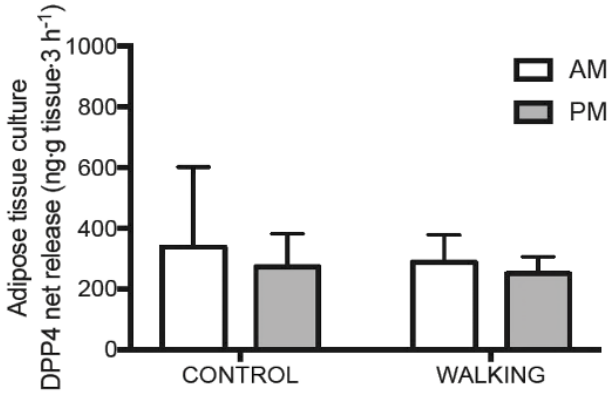

Figure 3. Net secretion of dipeptidyl peptidase 4 (DPP-4) from adipose tissue explants at baseline (AM) and at end of the trial (PM) (all n = 8, due to lack of sufficient tissue samples for one male and one female participant).

Physiological responses during the BREAKS trial

During the 15 two-minute bouts of walking, the average heart rate was 136 (95% CI 129, 144) beats·min^{-1} with an RPE (Borg, 6–20 scale) of 10 (95% CI, 9, 12).

DISCUSSION

This is the first study to investigate gut hormone responses to prolonged sitting with and without regular activity breaks in middle-aged men and women with central adiposity. We found that breaking up prolonged sitting with short bouts of intermittent walking elevated postprandial GLP-1 (~26%) and PYY (~31%) iAUCs compared to prolonged sitting. Thus, our results demonstrate that breaking up sitting time with intermittent walking increases gut hormones similar to previously-reported effects for continuous aerobic exercise.

257

258 Targeting gut hormones (e.g., to increase GLP-1 and PYY concentrations to those seen in
259 people without obesity) has been suggested as a potential therapy for obesity (33). In
260 accordance with previous findings in moderate-intensity (~50–70% $\dot{V}O_{2peak}$) continuous
261 exercise (13, 14) and low volume high-intensity/sprint interval training (15), our results
262 demonstrate that interrupting prolonged sitting via regular short bouts of brisk walking is an
263 alternative strategy to increase GLP-1 and PYY concentrations individuals with
264 overweight/obesity. Performing short bouts of brisk walking could be a highly feasible or
265 preferable mode of physical activity for individuals with central adiposity. Bariatric surgery,
266 and GLP-1 receptor analogues and DPP-4 inhibitors to augment gut hormones
267 availability/action (e.g., GLP-1 and PYY) are of great interest for the prevention/treatment of
268 obesity and obesity-related diseases (11, 34). The magnitude of the observed effect from
269 the physical activity used in the present study is, however, modest compared with Roux-en-
270 Y gastric bypass surgery where GLP-1 can increase from ~20 pmol·L^{-1} to ~100 pmol·L^{-1}
271 during oral glucose tolerance test 1 month post-surgery (35) and from ~15 pmol·L^{-1} to ~140
272 pmol·L^{-1} in a mixed-nutrient meal 6 months post-surgery (36). However, surgical strategies
273 are invasive and expensive and might have potential side effects that make them unsuitable
274 for some individuals. Interestingly, the results from the current study indicate that the effects
275 of breaking sitting are almost instantaneous (i.e., evident within the first few hours), with
276 peak GLP-1 concentrations increased from ~80 pmol·L^{-1} to ~100 pmol·L^{-1} with breaking
277 sitting. We do not know if the effects would become more or less pronounced over weeks
278 or months – or whether the effect would remain constant. Our results demonstrate that
279 breaking sitting is a potential non-pharmacological strategy to acutely increase GLP-1 and
280 PYY.

281

Interestingly, our PYY results contrast with previous findings (16, 17). Holmstrup et al. (17) showed that hourly 5-minute walking breaks did not increase postprandial PYY_{total} concentrations in young individuals with obesity. Similarly, despite identical walking patterns (2 minutes walking in every 20 minutes) and a similar accumulated walking period (28 minutes *versus* 30 minutes), Bailey et al. (16) found that neither slow (3.2 $km \cdot h^{-1}$) nor fast speed walking (5.8−7.9 $km \cdot h^{-1}$) impacted upon postprandial PYY_{total} concentrations in young healthy individuals. Both studies recruited healthy sedentary individuals, but participants in the present study were older than the participants in both these previous studies. Ageing has been reported to modulate gut postprandial hormone responses (37). In addition, despite the walking speed being similar to Bailey, Broom (16), it is likely that absolute intensity was greater in our study due to a lower maximum oxygen uptake. Neither of the previous studies measured GLP-1 or GIP concentrations (16, 17), so it is unclear whether these other gut hormones responded similarly or differently to the present study. However, based on the findings for PYY, it is possible that the effects of breaking sitting are influenced by age and/or fitness. Previous reports have indicated that participant characteristics influence the effect of breaking sitting (38).

We further compared iAUCs between morning-BREAKS (baseline to prior to lunch intake, $iAUC_{Baseline\text{-}M1180\ min}$) and afternoon-BREAKS (beginning of lunch intake to the end of the trial, $iAUC_{M1180\text{-}M2120\ min}$). The results showed that GLP-1, PYY and GIP iAUCs did not increase in the morning-BREAKS compared to the SIT trial. Interestingly, all three gut hormones were increased in the afternoon-BREAKS, suggesting that most of the effect overall was accounted for by a difference in response to the second meal.

306 Gut hormones play a powerful role in the regulation of appetite (i.e., eating behaviour) (39).
307 The present study was not originally designed to investigate the effects of breaking
308 prolonged sitting on eating behaviour and so appetite-related measures were not assessed.
309 Eating behaviour has been reported to be unaffected by breaking sitting in young lean
310 individuals (16, 40), although this may be partly explained by the previously-discussed lack
311 of effect on gut hormone responses in some of these studies (16). Therefore, further
312 research in this population is required to determine whether eating behaviour and *ad libitum*
313 energy intake would be altered by the changes to gut hormones observed in the current
314 study.
315
316 In the current study, our results showed that there was no difference in *ex vivo* subcutaneous
317 adipose tissue DPP-4 secretion between conditions. Studies have shown that DPP-4 is
318 mainly secreted by adipose tissue and secretion is more pronounced in obese and insulin-
319 resistant patients (22). Gut hormones (i.e., GLP-1, GIP and PYY), once released into the
320 circulation, are rapidly degraded by endogenous proteases like DPP-4, giving a very short
321 half-life of 2−3 minutes. Consequently, only 10–15% of gut hormones reaches the circulation
322 intact (41). We found no difference in *ex vivo* subcutaneous adipose tissue DPP-4 secretion
323 between the SIT and BREAK trials, suggesting that greater circulating GLP-1 and PYY
324 concentrations when breaking sitting were not due to lower adipose tissue DPP-4 secretion.
325
326 **Conclusion**
327 This is the first study to demonstrate that breaking up prolonged sitting with regular short
328 bouts of walking enhances postprandial gut hormones concentrations (i.e., GLP-1, and PYY)
329 in healthy middle-aged men and women with central adiposity. This type of intervention
330 (breaking sitting with 2-minute bouts of walking every 20 minutes) could be readily

incorporated into real-world settings, and further work is required to examine whether this translates into improved energy balance regulation over weeks and months.

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Authors contributions

YCC was responsible funding, study design and conduct, data collection, data analysis, data interpretation, statistical analysis, draft written and manuscript revision. JAB was responsible for study design and manuscript revision. JPW, AH and JTG assisted with technical support and manuscript revision. DT was responsible for funding, study design, data interpretation, and manuscript revision.

Conflict of Interest

The authors declare no competing interests. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The results of this study are presented clearly, honestly, and without fabrications, falsification, or inappropriate data manipulation.

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