

1 **Acute exercise and appetite-regulating hormones in overweight and obese individuals:**

2 **A meta-analysis**

3

4 Jessica Anne Douglas^{1,4}, Kevin Deighton², Jan Maria Atkinson³, Vahid Sari-Sarraf⁵, David John

5 Stensel^{1,4} and Greg Atkinson³

6

7 ¹ School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK

8 ² Institute for Sport, Physical Activity & Leisure, Leeds Beckett University, Leeds, UK

9 ³ Health and Social Care Institute, Teeside University, Middlesbrough, UK

10 ⁴The Leicester-Loughborough Diet, Lifestyle & Physical Activity Biomedical Research Unit based at

11 University Hospitals of Leicester & Loughborough University, UK

12 ⁵ University of Tabriz, Iran

13

14 KD: Institute for Sport, Physical Activity & Leisure, Leeds Beckett University, Headingley Campus,
15 Leeds, LS6 3QS, UK; K.Deighton@leedsbeckett.ac.uk

16

17 JMA: Health and Social Care Institute, Teeside University, Middlesbrough, UK;

18 jan_atkinson@hotmail.com

19

20 VS: Department of Exercise Physiology, Faculty of Physical Education and Sport Sciences, University
21 of Tabriz, Iran; vsarisarraf@yahoo.com

22

23 DJS: School of Sport, Exercise and Health Sciences, Loughborough University, Ashby Road,
24 Loughborough, Leicestershire, LE11 3TU, UK; D.J.Stensel@lboro.ac.uk

25

26 GA: Health and Social Care Institute, Teeside University, Middlesbrough, UK;

27 Greg.Atkinson@tees.ac.uk

28

29 **Address for correspondence**

30 Ms Jessica Anne Douglas

31 School of Sport, Exercise and Health Sciences,

32 Loughborough University,

33 Ashby Road,

34 Loughborough,

35 Leicestershire,

36 LE11 3TU,

37 UK

38 E-mail: J.Douglas@lboro.ac.uk

39 **Abstract**

40 In lean individuals, acute aerobic exercise is reported to transiently suppress sensations of appetite,
41 suppress blood-concentrations of acylated ghrelin (AG) and increase glucagon-like peptide-1 (GLP-1)
42 and peptide-YY (PYY). Findings in overweight/obese individuals have yet to be synthesised.

43 In this systematic review and meta-analysis, we quantified the effects acute exercise has on AG, total
44 PYY and GLP-1 in overweight/obese individuals. The potential for body mass index (BMI) to act as a
45 moderator for AG was also explored.

46 Six published studies (73 participants, 78% male, mean BMI: 30.6 kg.m⁻²) met the inclusion criteria.

47 Standardised mean differences (SMD) and standard errors were extracted for AG, total PYY and
48 GLP-1 concentrations in control and exercise trials and synthesised using a random effects meta-
49 analysis model. BMI was the predictor in a meta-regression for AG.

50 Exercise moderately suppressed AG area-under-the-curve concentrations (pooled SMD -0.34, 95%CI:
51 -0.53 to -0.15). The magnitude of this reduction was greater for higher mean BMIs (pooled meta-
52 regression slope: -0.04 SMD/kg.m⁻² (95%CI: -0.07 to 0.00)). Trivial SMDs were obtained for total PYY
53 (0.10, 95%CI: -0.13 to 0.31) and GLP-1 (-0.03, 95%CI: -0.18 to 0.13).

54 This indicates that exercise in overweight/obese individuals moderately alters AG in a direction that
55 could be associated with decreased hunger and energy intake. (PROSPERO registration:
56 CRD42014006265).

57

58 **Keywords:** Exercise, overweight, obese, appetite, hormones, acylated ghrelin, peptide-YY, glucagon-
59 like peptide-1.

60

61

62

63

64

65

66

67

68

69 **Introduction**

70 Adults with a body mass index (BMI) of equal to or greater than 25 kg.m⁻² are classified as
71 overweight, whilst those with a BMI equal to or greater than 30 kg.m⁻² are classified as obese [1]. In
72 2008, it was estimated that 1.4 billion adults were overweight worldwide. Of these, 200 million men
73 and nearly 300 million women were obese [1]. Obesity is associated with an increased risk of type 2
74 diabetes, coronary heart disease, some types of cancer, as well as strokes [2]. The health risks and
75 financial burden associated with overweight and obesity are causes for concern. Governments are
76 developing schemes and guidelines to help counter overweight and obesity. Alongside limiting energy
77 intake, individuals are advised to take part in regular physical activity. In the UK, healthy adults are
78 advised to perform at least 150 min of moderate intensity aerobic activity per week, and to combine
79 this with muscle strengthening exercise twice a week [3].

80 '*Exercise induced anorexia*' was a term coined in 1994 by King and colleagues, to describe
81 the condition where appetite is suppressed after acute exercise [4]. King et al. [4] showed that appetite
82 was temporarily suppressed during and after high intensity exercise in lean healthy males.
83 Subsequent researchers confirmed these earlier findings [5-9]. At rest, feelings of hunger are
84 mediated by gut hormones such as acylated ghrelin, peptide-YY (PYY) and glucagon-like peptide-1
85 (GLP-1) [10-12]. It has been hypothesised that 'exercise induced anorexia' is mediated by altered
86 concentrations of these hormones. For example, acylated ghrelin (an appetite stimulating hormone)
87 has been found to be suppressed after vigorous exercise [6, 9, 13]. In contrast, circulating
88 concentrations of PYY and GLP-1 (satiety hormones), have been shown to increase after exercise in
89 healthy lean adults [6, 9, 13]. Researchers have also examined the effects that exercise has on
90 energy intake after exercise. The majority of studies indicate that individuals do not compensate for
91 the energy expended during exercise in the immediate hours after exercise [14]. Therefore these
92 individuals are in an energy deficit, and if maintained over time this could result in weight loss.

93 Most studies on exercise and appetite regulation involve crossover designs and relatively
94 small sample sizes. Meta-analyses can be useful to quantify the effects of an intervention with greater
95 precision from a pooled estimate. A standardised mean difference (SMD) is often reported. Recently,
96 the effects of acute exercise on appetite regulatory hormones were examined in lean,
97 overweight/obese individuals [15]. It was concluded that an acute bout of exercise suppresses
98 acylated ghrelin (SMD: 0.20) and increases PYY (SMD: 0.24), GLP-1 (SMD: 0.28) and pancreatic

99 polypeptide (SMD: 0.50). Of the 25 studies included in this review, only two involved
100 overweight/obese individuals. Clearly, there are fewer studies on overweight/obese individuals and no
101 previous systematic review and meta-analysis has been undertaken on this population. Such a review
102 would capture new studies involving overweight/obese individuals, and clarify if they respond in a
103 similar way to their lean counterparts. This in turn could enhance understanding of the role exercise
104 plays in weight maintenance and control. Therefore, we aimed to synthesise this evidence from
105 studies investigating acute exercise bouts and circulating concentrations of acylated ghrelin, total PYY
106 and total GLP-1, measured in overweight/obese participants.

107

108 **Methods**

109 *Data source*

110 A systematic review of peer-reviewed studies was undertaken comparing concentrations of
111 appetite regulatory hormones, quantified as an area under the curve (AUC). The review was
112 registered with the PROSPERO database (CRD42014006265).

113 The literature search was conducted by an information specialist (JA) using commonly-used
114 research databases (Applied Social Sciences Index and Abstracts (ASSIA), Campbell Collaboration,
115 Centre for Review and Dissemination, Database of Promoting Health Effectiveness Reviews
116 (DoPHER), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of
117 Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews or Effects
118 (DARE), EMBASE, NHS Economic Evaluation Database (NHS EED), PROSPERO, PubMed,
119 PsycINFO MEDLINE (Ovid), Sports Discus, SCOPUS, Web of Knowledge and CINAHL). These
120 databases were searched in January 2014 with an update search in June 2014 and October 2016.
121 Keyword searches were performed for 'exercise', 'physical activity', 'energy expenditure', 'energy
122 intake', 'appetite', 'hunger', 'food intake', 'ghrelin', 'acylated ghrelin', 'total ghrelin', 'acyl ghrelin',
123 'peptide YY', 'PYY', 'peptide YY₃₋₃₆', 'PYY₃₋₃₆', 'total PYY', 'glucagon-like peptide-1', 'GLP-1', 'active
124 GLP-1', 'GLP-1(7-36)', 'GLP-1(9-36)', 'obese', 'overweight', and 'appetite hormones'. Details of the
125 search strategy are provided in the supplementary material.

126 *Inclusion criteria*

127 For inclusion, studies were required to meet the following criteria: participants in the study
128 were overweight/obese adults, with no history of diabetes, gastrointestinal, inflammatory, metabolic,

129 cardiovascular or psychological disease; in addition participants were required to be non-smokers.
130 Study selection criteria were not limited by the duration or observation period post-exercise. To
131 maximise search sensitivity, there were also no limitations on the intensity, duration or modality of the
132 acute exercise bout.

133 All studies were required to have a control condition which was completed by the same
134 participants who completed the exercise condition. The control condition was required to be identical
135 to that of the exercise condition, minus the exercise bout.

136 Since the interventions were exercise bouts, investigators were not blinded. Studies were
137 included if they were published in peer-reviewed journals, or were available in conference
138 proceedings, theses or dissertations. A broad range of sources for study inclusion were chosen to
139 minimize the risk of small study effects, which can occur if only published studies are included.

140 *Exclusion criteria*

141 Studies were excluded if they did not measure acylated ghrelin, total PYY or total GLP-1
142 responses to an exercise bout in overweight/obese individuals. Studies were also excluded if they did
143 not include a control trial.

144 *Study selection*

145 Two members of the research team (*JAD* and *KD*) independently selected the studies for
146 inclusion in the meta-analysis and later compared notes to reach a mutual consensus. Potential
147 studies were identified by examining the abstracts and full-text copies were obtained if they met the
148 initial criteria of evaluating appetite hormone changes in response to an acute exercise bout. In the
149 original literature search conducted in January 2014, five studies met the inclusion criteria. Two
150 update searches conducted in June 2014 and October 2016, identified one further study. Together six
151 studies met the inclusion criteria for the current meta-analysis (Figure 1).

152 *Data synthesis*

153 Included studies were assessed for quality and validity independently by two authors (*JAD*
154 and *KD*), using established criteria (Physiotherapy Evidence Database [PEDro],
155 <http://www.pedro.org.au/english/downloads/pedro%20scale/>). Data on the study methods, sample
156 size, participant characteristics, blood analytical methods, exercise intervention information, and
157 hormone ($\text{pmol}\cdot\text{L}^{-1}\text{ h}^{-1}$, $\text{pg}\cdot\text{mL}^{-1}\text{ h}^{-1}$, $\mu\text{U}\cdot\text{mL}^{-1}\text{ h}^{-1}$) and appetite AUC data were extracted for both control
158 and exercise conditions by one author (*JAD*) into a computerised spreadsheet. Data entry was

159 checked by one other author (*KD*), and discrepancies discussed and checked again. If standard error
160 of the mean (SEM) was reported, these were converted to standard deviations [16].

161 *Meta-analysis procedures*

162 Comprehensive Meta-Analysis software (Version 2.2.064; Biostat, Englewood, NJ, USA), was
163 used to conduct a random effects (DerSimonian-Laird inverse variance approach) meta-analysis of
164 the mean difference in acylated ghrelin, total PYY and total GLP-1 during control and exercise trials
165 [16]. The inputted data included sample sizes, AUCs for the control and exercise conditions (with their
166 respective standard deviations) and an imputed correlation coefficient to take into account the fact
167 that all studies were crossover in nature. These correlation coefficients were estimated from prior
168 reliability studies in our laboratory and were as follows; acylated ghrelin; $r=0.93$, total PYY: $r=0.71$ and
169 GLP-1: $r=0.94$. The software calculated the pooled standardised difference in means to determine the
170 effect size [17]. All data are presented as means (95% confidence interval).

171 We interpreted standardised mean difference (SMD) values of <0.2 as trivial, $0.2-0.3$ as
172 small, $0.4-0.8$ as moderate and >0.8 as large [18]. A negative effect size indicates that exercise was
173 associated with decreased hormone concentrations, while a positive effect size indicates that
174 hormone concentrations increased with exercise [19]. Heterogeneity was explored using a *Q*-test, *I*-
175 square statistic and the tau-squared statistic. An *I*-square statistic $>50\%$ was deemed to be indicative
176 of substantial heterogeneity.

177 *Meta-regression analyses for BMI of acylated ghrelin AUC between exercise and control conditions*

178 BMI was used as a moderator in a meta-regression analysis (methods-of-moments model), to
179 determine if BMI could explain the variation in effect size values seen between studies for acylated
180 ghrelin concentrations [17]. Mean BMIs were pooled from studies collected in the current review
181 together with those reported for lean individuals in a recent review by Schubert et al. [15]. Mean BMI
182 was included as a moderating variable, as a negative association exists between study mean BMI
183 and acylated ghrelin concentrations [29]. This analysis was only performed for acylated ghrelin as
184 there were not enough studies ($N < 3$) reporting data for total PYY or total GLP-1 to obtain sufficiently-
185 precise and meaningful estimations of meta-regression slope.

186 *Exploration of small study effects*

187 Small study effects were explored with a funnel plot of standard difference in means vs
188 associated standard errors [20] and by quantifying Egger's linear regression intercept. A large and

189 statistically significant Egger's statistic indicates the presence of a small study effect. This analysis
190 was only performed for acylated ghrelin as there were not enough studies reporting data for a precise
191 exploration of total PYY and total GLP-1.

192

193 **Results**

194 *Overview*

195 Six studies involving a total of 73 participants met the inclusion criteria for the meta-analysis.
196 All of these had been published (or accepted for publication) in peer-reviewed scientific journals. The
197 experimental trials in each study lasted between 2 and 3 h, with exercise conducted in a fasted
198 condition or following a standardised breakfast. Three studies included standardised meals before the
199 exercise bout [13, 21, 22] and four studies included *ad libitum* meals after the exercise bout [13, 21-
200 23]. Blood samples were collected at regular intervals throughout all trials.

201 The included studies are summarised in Table 1. The majority of studies recruited participants
202 of the same sex. One study recruited both males and females [21]. Two of the studies involved more
203 than one exercise intensity trial [21, 23], and are reported in the analysis as "multiple trials".
204 Accounting for these, the total number of trials is 10, each including one control and one exercise
205 condition. Six studies (10 trials) reported acylated ghrelin AUC data, two studies (four trials) reported
206 total PYY AUC data and two studies (four trials) reported total GLP-1 AUC data. Of the 10 trials, one
207 used treadmill walking as the mode of exercise, two used treadmill running and seven used a cycle
208 ergometer. The mean PEDro score for the six studies was 6 ± 0 , rating all studies to have "good"
209 methodological quality.

210 *Participant demographics and exercise intervention characteristics*

211 Of the 73 participants included in the meta-analysis, 57 were men (78%) and 16 were women
212 (22%). BMI values of the 73 participants ranged from 27.7 to 32.7 kg.m⁻² (mean 30.6 kg.m⁻²). Four
213 studies used exercise which was aerobic in nature [13, 22, 23, 25], and two compared aerobic
214 exercise with two variations of high intensity exercise [21, 23]. The exercise interventions lasted
215 between 9 and 60 min (mean 34 min), and exercise intensity was set between 50 and 65% VO₂ peak
216 (mean 58% VO₂ peak, $N = 6$) or 72.5 and 87.5% HR_{max} (mean 79.4 % HR_{max}, $N = 4$). Between 7 and
217 19 participants took part in each study (mean 12 participants) (see Table 1 for summaries of study
218 protocols).

219 *Meta-analysis*

220 Individual study statistics and results for both trials including overweight/obese subjects and
221 lean subjects are summarised in the supplementary material (Tables S1 to S4).

222 *Effect size and moderator variable for acylated ghrelin AUC analysis*

223 In overweight/obese individuals there was a statistically significant moderate suppression in
224 mean acylated ghrelin AUC concentrations in exercise trials compared with resting trials (pooled
225 effect size -0.34, 95% confidence interval -0.533 to -0.146; $N = 10$; $P < 0.001$; Figure 2).
226 Heterogeneity was found to be high between these studies ($I^2 = 87.7\%$; $Q = 73.4$, $T^2 = 0.084$, $d_f = 9$).
227 For this reason a random effects model was chosen to conduct the meta-analyses [26].

228 Sensitivity analysis showed that the study by Gholipour et al. [24] increased the effect size of
229 exercise on mean acylated ghrelin AUC concentrations. The removal of this study decreased the
230 pooled effect size to -0.23 (95% confidence interval -0.35 to -0.11, $P < 0.001$).

231 When data from lean individuals were included into the meta analysis, with that of the
232 previously-reported overweight and obese individuals the pooled standardised effect size of exercise
233 on acylated ghrelin AUC data was reduced to -0.215, 95% confidence interval -0.324 to -0.105; $N =$
234 33; $P < 0.001$).

235 Using BMI as a moderator in a meta-regression model, a higher mean BMI was associated
236 with a greater exercise induced suppression of acylated ghrelin AUC concentration. The slope of
237 regression for BMI was shallow, but significantly negative (95% confidence interval -0.073 to -0.010; P
238 = 0.044; Figure 3). The standardised reduction in acylated ghrelin for exercise vs control conditions
239 was found to be 0.037 units more marked for every 1 kg.m^{-2} increase seen in BMI. Including baseline
240 acylated ghrelin concentrations and BMI into a multiple meta-regression model had little effect on the
241 results; the slope of regression became slightly more negative so that the standardised reduction in
242 acylated ghrelin for exercise vs control was 0.040 units more marked for every 1 kg.m^{-2} increase in
243 BMI (95% confidence interval -0.080 to -0.010; $P = 0.020$).

244 Inspection of the funnel plot (see Figure 4) and Egger's regression intercept revealed that there was
245 little evidence of small study effects (intercept = -3.647, 95% confidence interval -9.080 to 1.785, $P =$
246 0.264).

247

248

249 *Effect size for total PYY AUC analysis*

250 In overweight/obese individuals there was a trivial mean effect of exercise on total PYY
251 (pooled effect size 0.099, 95% confidence interval -0.133 to 0.311; $N = 4$; Figure 5), and this was not
252 significantly different from zero ($P = 0.404$). Heterogeneity was found to be low between these studies
253 ($I^2 = 24.17\%$; $Q = 3.96$, $T^2 = 0.014$, $df = 3$).

254 *Effect size and moderator variable for total GLP-1 AUC analysis*

255 In overweight/obese individuals there was a trivial mean effect of exercise on GLP-1 (Pooled
256 effect size -0.026, 95% confidence interval -0.184 to 0.133; $N = 4$; Figure 6), and this was not
257 significantly different from zero ($P = 0.749$). Heterogeneity was found to be high between these
258 studies ($I^2 = 65.7\%$; $Q = 8.74$, $T^2 = 0.017$, $df = 3$).

259

260 **Discussion**

261 Understanding the responses of appetite regulatory hormones to exercise and consequently
262 the effect they may have on energy intake and appetite could enhance understanding of the role of
263 exercise in weight control. The purpose of this review was to examine the concentration changes of
264 acylated ghrelin, total PYY and total GLP-1 after acute exercise in overweight/obese individuals. We
265 found acylated ghrelin to be moderately suppressed by acute exercise, whilst there were trivial effects
266 of exercise on total PYY and total GLP-1. Ghrelin is an appetite-stimulating hormone [10] and our
267 results suggest that exercise in overweight/obese individuals alters acylated ghrelin in a direction that
268 would be associated with decreased hunger and energy intake. We can only speculate the effects
269 ghrelin has on appetite and food intake as not all studies included these measures in their protocol.
270 Future research should examine energy intake in addition to appetite and appetite regulatory
271 hormone responses to clarify this assumption.

272 The results of the current review appear to mirror those of lean individuals. In a recent review,
273 lean individuals showed a small reduction in acylated ghrelin after exercise, whilst total PYY and total
274 GLP-1 showed small increases [15]. Our findings suggest that overweight/obese individuals show
275 broadly similar appetite hormone responses to exercise in lean individuals, in such a direction that
276 could alter energy intake and achieve weight loss if sustained over prolonged periods of time. Again,
277 this can only be speculated as the studies included in both the review by Schubert et al. [15] and the
278 current review were acute in nature.

279 The present meta-regression demonstrated greater exercise-induced suppression of acylated
280 ghrelin as BMI increased. Although overweight/obese individuals have shown a moderate
281 suppression of acylated ghrelin after exercise, this suppression becomes more prominent as BMI
282 increases from 27.7 to 32.7 kg.m⁻². This finding differed from that of Schubert et al. [15], where BMI
283 was shown to have no influence on appetite regulatory hormones. Schubert [15] included 23 studies
284 examining responses of lean individuals and two studies with overweight/obese individuals. The
285 inclusion of six, rather than two, studies with overweight/obese individuals in the present meta-
286 regression may explain the differences found between the two reviews.

287 The current review found overweight/obese individuals to express a moderate reduction in
288 acylated ghrelin during exercising conditions. Large variations in fasting and postprandial ghrelin
289 concentrations between individuals make it difficult to establish the clinical relevance that exercise
290 has on this hormone. In lean individuals circulating concentrations of acylated ghrelin in the range of
291 40-67 pg/mL may be expected in fasting conditions [27], with obese individuals expressing lower
292 concentrations [28, 29]. We attempted to control for differences in baseline levels of acylated ghrelin
293 between studies by accounting for fasting values observed in resting trials. This had negligible
294 influence on the relationship between increased BMI and acylated ghrelin.

295 The current review found three studies that examined the acute effects of exercise on
296 appetite regulatory hormones in males, two studies in females and one including both males and
297 females. Due to the limited number of studies in this review no conclusions can be drawn upon the
298 effect of exercise and sex on appetite regulatory hormones. It has been hypothesised that exercise
299 could influence acylated ghrelin differently in obese males and females. In one study, after four days
300 of consecutive exercise females experienced an increase in acylated ghrelin, whereas males showed
301 no change [30]. This suggests that females may be prone to increasing energy intake after exercise
302 training. However, after acute exercise lean individuals have shown no sex difference in responses of
303 PYY₃₋₃₆ or acylated ghrelin [31]. Similar relative energy intakes were observed in males and females,
304 suggesting that acute exercise is equally effective for both sexes. Future research is required to
305 understand and compare the responses of males and females.

306 The current review has several limitations. First, only six studies were identified as relevant
307 following our literature searches. We recognise that meta-analyses are not immune from statistical
308 power-related issues, and that the pooling of data from such a small number of studies may still

309 provide relatively low statistical precision (wide confidence interval for pooled effect). For example,
310 despite finding substantial heterogeneity amongst studies in which ghrelin and GLP-1 were
311 measured, precise analyses such as one for the presence of outliers could not be performed due to
312 the small number of studies. We restricted our search to acute exercise trials, further reviews should
313 examine the effects of repeated bouts of exercise and exercise training on appetite regulatory
314 hormones in overweight/obese individuals although at present the literature on this aspect is very
315 limited. The longest trial length in the current review was 3 h, future research should examine what
316 happens to this population later on in the exercising day. Despite trials only lasting 2-3 h protocols
317 differed widely between studies, potentially confounding appetite regulatory AUC estimations.
318 Specifically, the timing of exercise and meal provision within the study protocol. AUC calculations
319 were made over the duration of each trial, irrespective of when exercise occurred. The inclusion of
320 rest periods prior to exercise into AUC calculations could potentially underestimate the effect of
321 exercise on hormone responses. Additionally, studies differed by exercising participants in both fasted
322 and fed states. Further still, studies varied in meal provision (standardised, *ad libitum*, or no meal)
323 after exercise. Together these could further confound the study of hormonal responses to exercise. We
324 meta-regressed the SMD in acylated ghrelin vs. study mean BMI. Such study-level explorations of
325 potential moderators of effect size should be interpreted with caution as within-study relationships can
326 sometimes disagree with between-study relationships [32]. The average BMI of the participants in this
327 review was 30.6 kg.m⁻² (i.e. borderline obese), therefore we cannot generalise the findings of this
328 review to those who fall higher into the obese or severely obese category. Despite our best efforts, we
329 cannot guarantee that we captured all the relevant studies for this review. Finally, we cannot directly
330 link the effects of exercise on appetite regulatory hormones to weight loss and management due to
331 the acute nature of the studies, and the lack of consistency in studies including energy intake and
332 appetite ratings.

333

334 **Conclusions**

335 An evidence synthesis of the six studies on overweight/obese individuals indicated that a
336 moderate reduction in acylated ghrelin occurs after acute exercise. Only trivial effects of exercise
337 were quantified for total PYY and GLP-1.

338

339 **Acknowledgements**

340 The research was supported by the National Institute for Health Research (NIHR) Diet,
341 Lifestyle & Physical Activity Biomedical Research Unit based at University Hospitals of Leicester and
342 Loughborough University. The views expressed are those of the authors and not necessarily those of
343 the NHS, the NIHR or the Department of Health.

344 **References**

- 345 (1) World Health Organisation, Obesity and Overweight, World Health Organisation, Geneva,
346 Switzerland, 2014, <http://www.who.int/mediacentre/factsheets/fs311/en/>.
- 347 (2) National Health Service, Obesity, National Health Service, England, 2014,
348 <http://www.nhs.uk/conditions/Obesity/Pages/Introduction.aspx>.
- 349 (3) World Health Organisation, Global Recommendations on Physical Activity for Health, World Health
350 Organisation, Geneva, Switzerland, 2010,
351 http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf?ua=1.
- 352 (4) N. A. King, V. J. Burley, and J. E. Blundell, "Exercise-induced suppression of appetite: Effects on
353 food intake and implications for energy balance," *European Journal of Clinical Nutrition*, vol. 48, no.
354 10, pp. 715-24, 1994.
- 355 (5) D. R. Broom, R. L. Batterham, J. A. King, and D. J. Stensel, "Influence of resistance and aerobic
356 exercise on hunger, circulating levels of acylated ghrelin, and peptide YY in healthy males," *American*
357 *Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, vol. 296, no. 1, pp. R29-
358 35, 2009.
- 359 (6) D. R. Broom, D. J. Stensel, N. C. Bishop, S. F. Burns and M. Miyashita, "Exercise-induced
360 suppression of acylated ghrelin in humans," *Journal of Applied Physiology*, vol. 102, no. 6, pp. 2165-
361 71, 2007.
- 362 (7) J. A. King, M. Miyashita, L. K. Wasse, and D. J. Stensel, "Influence of prolonged treadmill running
363 on appetite, energy intake and circulating concentrations of acylated ghrelin," *Appetite*, vol. 54, no. 3,
364 pp. 492-8, 2010a.
- 365 (8) J. A. King, L. K. Wasse, D. R. Broom, and D. J. Stensel, "Influence of brisk walking on appetite,
366 energy intake, and plasma acylated ghrelin," *Medicine and Science in Sports and Exercise*, vol. 42,
367 no. 3, pp. 485-92, 2010b.
- 368 (9) J. A. King, L. K. Wasse, J. Ewens, et al., "Differential acylated ghrelin, peptide YY3-36, appetite,
369 and food intake responses to equivalent energy deficits created by exercise and food restriction," *The*
370 *Journal of Clinical Endocrinology and Metabolism*, vol. 96, no. 4, pp. 1114-21, 2011.
- 371 (10) D. E. Cummings, J. Q. Purnell, R. S. Frayo, K. Schmidova, B. E. Wisse, and D. S. Weigle, "A
372 preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans," *Diabetes*, vol.
373 50, no. 8, pp. 1714-9, 2001.
- 374 (11) J. A. Harrold, T. M. Dovey, J. E. Blundell, and J. C. G. Halford, "CNS regulation of appetite,"
375 *Neuropharmacology*, vol. 63, no. 1, pp. 3-17, 2012.
- 376 (12) E. Karra, K. Chandarana, and R. L. Batterham, "The role of peptide YY in appetite regulation and
377 obesity," *The Journal of Physiology*, vol. 587, no. 1, pp. 19-25, 2009.
- 378 (13) S. Y. Ueda, T. Yoshikawa, Y. Katsura, T. Usui, H. Nakao, and S. Fujimoto, "Changes in gut
379 hormone levels and negative energy balance during aerobic exercise in obese young males," *Journal*
380 *of Endocrinology*, vol. 201, no. 1, pp. 151-159, 2009b.
- 381 (14) M. M. Schubert, B. Desbrow, S. Sabapathy, and M. Leveritt, "Acute exercise and subsequent
382 energy intake. A meta-analysis," *Appetite*, vol. 63, pp 92-104, 2013.
- 383 (15) M. M. Schubert, S. Sabapathy, M. Leveritt, and B. Desbrow, "Acute exercise and hormones
384 related to appetite regulation: a meta-analysis," *Sports Medicine*, vol. 44, no. 3, pp. 387-403, 2014.

- 385 (16) J. J. Deeks, J. P. T. Higgins, and D. G. Altman, (eds). Chapter 9: Analysing data and undertaking
386 meta-analyses. In: J. P. T. Higgins, and S. Green, (eds). Cochrane Handbook for Systematic Reviews
387 of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available
388 from www.cochrane-handbook.org.
- 389 (17) J. P. T. Higgins and J. J. Deeks, (eds). Chapter 7: Selecting studies and collecting data. In: J. P.
390 T. Higgins, and S. Green, (eds). Cochrane Handbook for Systematic Reviews of Interventions Version
391 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.
- 392 (18) W. G. Hopkins, and A. M. Batterham, "Error rates, decisive outcomes and publication bias with
393 several inferential methods," *Sports Medicine*, vol. 46, no. 10, pp. 1563-73.
- 394 (19) W. G. Hopkins, S. W. Marshall, A. M. Batterham, and J. Hanin, "Progressive statistics for studies
395 in sports medicine and exercise science," *Medicine and Science in Sports and Exercise*, vol. 41, no. 1,
396 pp. 3-13, 2009.
- 397 (20) J. A. C. Sterne, M. Egger, and D. Moher, (eds). Chapter 10: Addressing reporting biases. In: J. P.
398 T. Higgins, and S. Green, (eds). Cochrane Handbook for Systematic Reviews of Interventions Version
399 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [www.cochrane-](http://www.cochrane-handbook.org)
400 [handbook.org](http://www.cochrane-handbook.org).
- 401 (21) C. Martins, D. Stensvold, G. Finlayson, et al., "Effect of moderate- and high-intensity acute
402 exercise on appetite in obese individuals," *Medicine and Science in Sports and Exercise*, vol. 47, no.
403 1, pp. 40-8, 2015.
- 404 (22) J. L. Unick, A. D. Otto, B. H. Goodpaster, D. L. Helsel, C. A. Pellegrini, and J. M. Jakicic, "Acute
405 effect of walking on energy intake in overweight/obese women," *Appetite*, vol. 55, no. 3, pp. 413-9,
406 2010.
- 407 (23) A. Y. Sim, K. E. Wallman, T. J. Fairchild, and K. J. Guelfi, "High-intensity intermittent exercise
408 attenuates ad-libitum energy intake," *International Journal of Obesity*, vol. 38, no. 3, pp. 417-22, 2014.
- 409 (24) M. Gholipour, M. R. Kordi, M. Taghikhani, A. A. Ravasi, A. A. Gaeini, and A. Tabrizi, "The acute
410 effects of intermittent treadmill running on hunger and plasma acylated ghrelin concentration in
411 individuals with obesity," *Tehran University Medical Journal*, vol. 69, no.2, pp. 125-35, 2011.
- 412 (25) G. Tiryaki-Sonmez, S. Ozen, G. Bugdayci, et al., "Effect of exercise on appetite-regulating
413 hormones in overweight women," *Biology of Sport*, vol. 30, no. 2, pp. 75-80, 2013.
- 414 (26) A. E. Ades, G. Lu, and J. P. T. Higgins, "The Interpretation of Random-Effects Meta-Analysis in
415 Decision Models," *Medical Decision Making*, vol. 25, no. 6, pp. 646-54, 2005.
- 416 (27) T. Sato, Y. Nakamura, Y. Shiimura, H. Ohgusu, K. Kangawa, and M. Kojima, "Structure,
417 regulation and function of ghrelin," *The Journal of Biochemistry*, vol. 151, no. 2, pp. 119-28, 2012.
- 418 (28) M. Tschöp, C. Weyer, P. A. Tataranni, V. Devanarayan, E. Ravussin, and M. L. Heiman,
419 "Circulating ghrelin levels are decreased in human obesity," *Diabetes*, vol. 50, no. 4, pp. 707-9, 2001.
- 420 (29) T. Shiiya, M. Nakazato, M. Mizuta, et al., "Plasma ghrelin levels in lean and obese humans and
421 the effect of glucose on ghrelin secretion," *The Journal of Clinical Endocrinology and Metabolism*, vol.
422 87, no. 1, pp. 240-4, 2002.
- 423 (30) T. A. Hagobian, C. G. Sharoff, B. R. Stephens, et al., "Effects of exercise on energy-regulating
424 hormones and appetite in men and women," *American Journal of Physiology: Regulatory, Integrative
425 and Comparative Physiology*, vol. 296, no. 2, pp. R233-42, 2009.

- 426 (31) T. A. Hagobian, M. Yamashiro, J. Hinkel-Lipsker, K. Streder, N. Evero, and T. Hackney, "Effects
427 of acute exercise on appetite hormones and ad libitum energy intake in men and women," *Applied*
428 *Physiology, Nutrition, and Metabolism*, vol. 38, no. 1, pp. 66-72, 2013.
- 429 (32) E. Petkova, T. Tarpey, L. Huang, and L. Deng, "Interpreting meta-regression: application to
430 recent controversies in antidepressants' efficacy," *Statistics in Medicine*, vol. 32, no. 17, pp. 2875-92,
431 2013.

432 **Tables**433 **Table 1.** Hormone area under the curve (AUC) data for the six studies included in the meta-analysis.

Study	Participants		Intervention	Hormone AUC (pg.mL ⁻¹)		
	N	BMI (kg.m ⁻²)		Acylated Ghrelin	Total PYY	Total GLP-1
Gholipour et al. (24)	9 (male)	32.7 ± 0.8	36 min treadmill run: 10 min, 10 min, 5 min, 2 min at 65% $\dot{V}O_{2max}$, separated by 3 min at 3 km.h ⁻¹	CON: 3512 ± 654 EX: 1935 ± 302*	NM	NM
Martins et al. (21)	12 (7 females and 5 males)	32.3 ± 2.7	Cycling @ 85-90% HR _{max} until 250 kcal expended: 8 s all out sprinting separated by 12 s easy pedalling (average duration, 18 ± 3 min)	CON: 3921 ± 1318 EX: 3315 ± 1219*	NM	CON: 4181 ± 1262 EX: 4272 ± 969
			Cycling @ 70% HR _{max} until 250 kcal expended: continuous cycle (average duration, 27 ± 6 min)	CON: 3921 ± 1318 EX: 3296 ± 1058*	NM	CON: 4181 ± 1262 EX: 4638 ± 1305
Sim et al. (23)	17 (male)	27.7 ± 1.6	30 min continuous cycling @ 60% $\dot{V}O_{2peak}$	CON: 70 ± 37 EX: 69 ± 30	CON: 85 ± 43 EX: 87 ± 37	NM
			30 min cycling: alternating between 60s @ 100% $\dot{V}O_{2peak}$ and 240s @ 50% $\dot{V}O_{2peak}$	CON: 70 ± 37 EX: 62 ± 28	CON: 85 ± 43 EX: 83 ± 40	
			30 min cycling: alternating between 15s @ 170% $\dot{V}O_{2peak}$ and 60s @ 32% $\dot{V}O_{2peak}$	CON: 70 ± 37 EX: 56 ± 26	CON: 85 ± 43 EX: 88 ± 34	
Tiryaki-Sonmez et al. (25)	9 (female)	28.3 ± 1.8	60 min running @ 53% $\dot{V}O_{2max}$	CON: 51 ± 8 EX: 47 ± 5	NM	NM
Ueda et al. (13)	7 (male)	30.0 ± 3.1	60 min cycle @ 50% $\dot{V}O_{2max}$	CON: 15779 ± 10046 EX: 16641 ± 10725	CON: 393 ± 50* EX: 425 ± 46*	NM
Unick et al. (22)	19 (female)	32.5 ± 4.3	Walk @ 70-75% age predicted HR _{max} until 3.0 kcal.kg ⁻¹ of body weight expended (average energy expenditure, 354 ± 72 kcal; average duration 42 ± 8 min)	CON: 6527 ± 2646 EX: 6361 ± 3339	NM	CON: 211400 ± 51600 EX: 201200 ± 49400*

434 BMI; body mass index, CON; resting control trial, EX; exercise trial, GLP-1; glucagon-like peptide-1, HR_{max}; maximum heart rate, NA; AUC data not available, NM; not measured, PYY; peptide YY, $\dot{V}O_{2max}$; maximum oxygen

435 uptake

436 *Significantly different from control ($P < 0.05$) NB Area under the curve values were calculated using hours as the unit of time in some studies and minutes as the unit of time in others.

437 **Figure captions**

438 Figure 1. Flowchart of study selection

439 Figure 2. Forest plot of effect sizes (means \pm 95% confidence intervals [CIs]) for studies evaluating

440 Figure 3. Univariable meta-regression for study mean BMI vs the acylated ghrelin AUC values in

441 response to exercise in overweight and obese individuals SMD for acylated ghrelin. A negative

442 correlation was observed which persisted even when baseline (control) mean ghrelin concentration

443 was added as a covariate.

444 Figure 4. Funnel plot of standard error by standard difference in means for studies evaluating the

445 influence of acute exercise on acylated ghrelin AUC values in overweight/obese individuals.

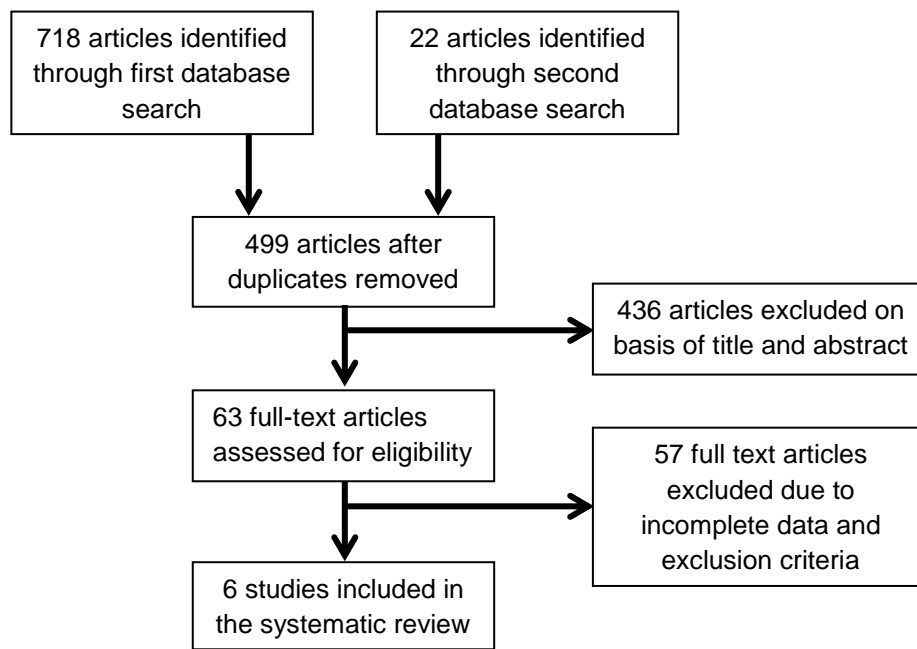
446 Figure 5. Forest plot of effect sizes (means \pm 95% confidence intervals [CIs]) for studies evaluating

447 the influence of acute exercise on total PYY AUC values in overweight and obese individuals.

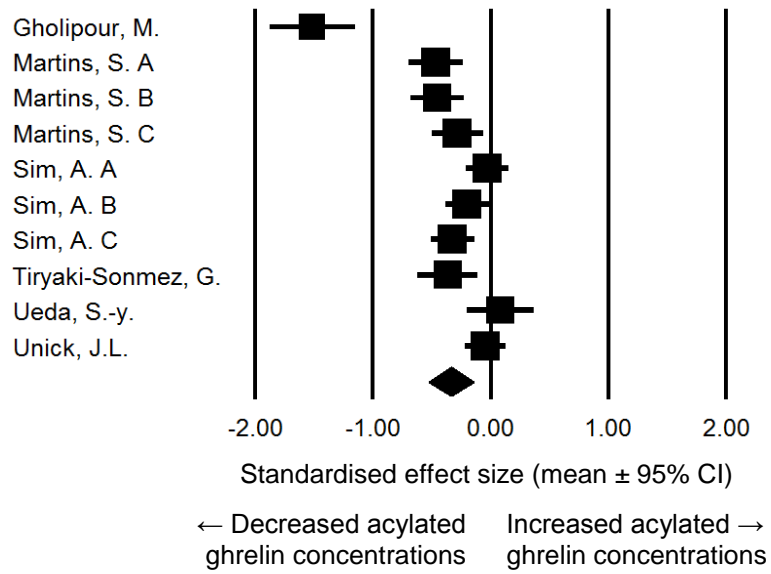
448 Figure 6. Forest plot of effect sizes (means \pm 95 % confidence intervals [CIs]) for studies evaluating

449 the influence of acute exercise on total GLP-1 AUC values in overweight and obese individuals.

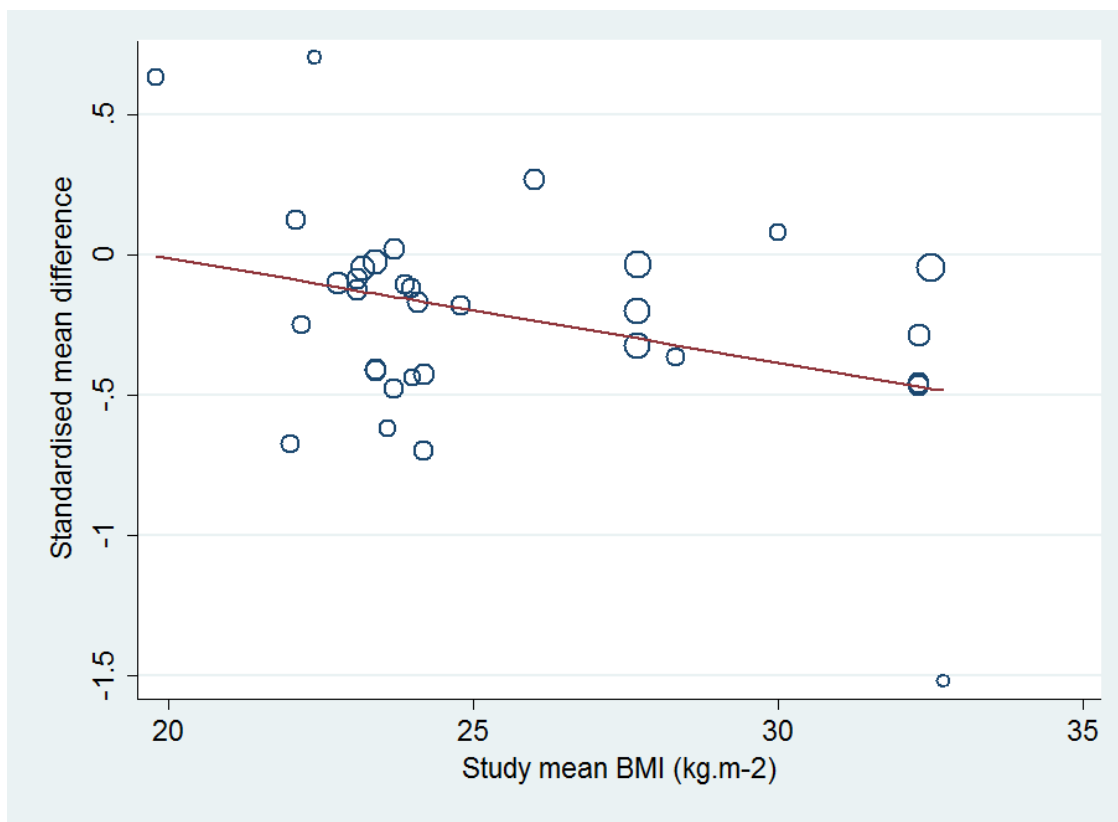
450 **Figure 1.**



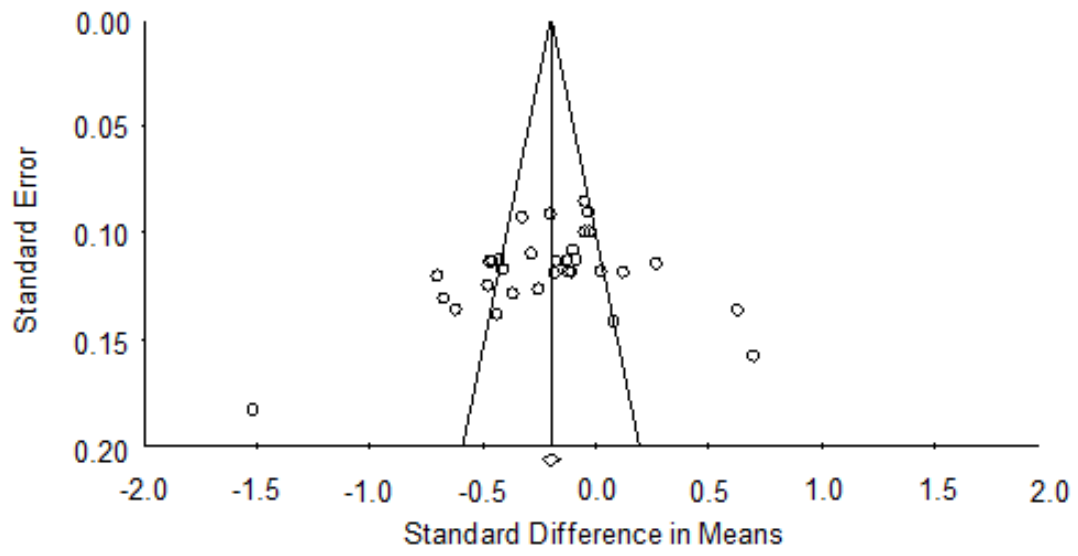
451 **Figure 2.**



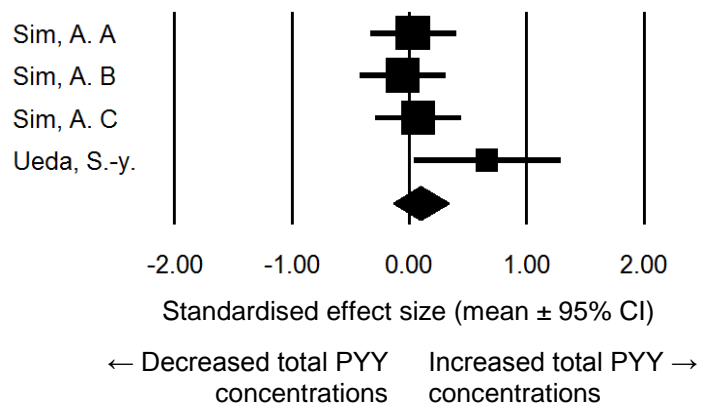
452 **Figure 3.**



453 **Figure 4.**



454 **Figure 5.**



455 **Figure 6.**

