

1 **Title:** The effects of hypoxia on hunger perceptions, appetite-related hormone concentrations,
2 and energy intake: a systematic review and meta-analysis

3 **Authors names:** Jamie Matu,¹ Javier T. Gonzalez,² Theocharis Ispoglou,¹ Lauren
4 Duckworth¹ and Kevin Deighton¹

5 **Department and institution:**

6 ¹Institute for Sport Physical Activity & Leisure, Leeds Beckett University, Leeds, United
7 Kingdom

8 ²Department for Health, University of Bath, Bath, UK

9 **Corresponding author:** Dr Kevin Deighton, Institute for Sport Physical Activity & Leisure,
10 Leeds Beckett University, Leeds, LS6 3QS, United Kingdom (email:
11 K.Deighton@leedsbeckett.ac.uk, telephone number: +44 (0)113 8123582).

12 **Shortened title:** Effects of hypoxia on appetite

13 **Keywords:** Appetite; altitude; ghrelin; insulin

14

15

16 **Abstract**

17 Exposure to hypoxia appears to depress appetite and energy intake, however the mechanisms
18 are not fully understood. The aim of this review was to determine the magnitude of changes in
19 hunger and energy intake in hypoxic compared with normoxic environments, and establish any
20 alterations in appetite-related hormone concentrations. PubMed and The Cochrane Library as
21 well as MEDLINE, SPORTDiscus, PsycINFO and CINAHL, via EBSCOhost, were searched
22 through 1st April 2017 for studies that evaluated hunger, energy intake and/or appetite-related
23 hormones in normoxia and during hypoxic exposure in a within-measures design. A total of 28
24 studies (comprising 54 fasted and 22 postprandial comparisons) were included. A random-
25 effects meta-analysis was performed to establish standardised mean difference (SMD) with
26 95% confidence intervals. Hypoxic exposure resulted in a trivial but significant decrease in
27 postprandial hunger scores (SMD: -0.15, 95% CI: -0.29 to -0.01; $n=14$; $p=0.043$) and a
28 moderate decrease in energy intake (SMD: -0.50, 95% CI: -0.85 to -0.15; $n=8$; $p=0.006$).
29 Hypoxic exposure resulted in a decrease (albeit trivial) in postprandial acylated ghrelin
30 concentrations (SMD: -0.16, 95% CI: -0.25 to -0.08; $n=7$; $p<0.0005$), and a moderate increase
31 in fasted insulin concentrations (SMD: 0.41, 95% CI: 0.17 to 0.65; $n=34$; $p=0.001$). Meta-
32 regression revealed a decrease in postprandial acylated ghrelin concentrations ($p=0.010$) and
33 an increase in fasted insulin concentrations ($p=0.020$) as hypoxic severity increased. Hypoxic
34 exposure reduces hunger and energy intake, which may be mediated by decreased circulating
35 concentrations of acylated ghrelin and elevated insulin concentrations. PROSPERO
36 registration number: CRD42015017231.

37

38

39 **Introduction**

40 Chronic exposure to hypoxia is associated with a decrease in body mass (Pulfrey & Jones,
41 1996; Rose et al., 1988; Sergi et al., 2010; Zaccagni et al., 2014), with as much as 67% of body
42 mass losses coming from reductions in fat-free mass (Rose et al., 1988). Such losses of lean
43 mass at altitude are likely to have deleterious consequences for altitude sojourners by impairing
44 physical capabilities (Sergi et al., 2010) and suppressing immune function (Mazzeo, 2005).
45 These changes in body mass and composition appear to be the result of a chronic negative
46 energy balance due to reductions in appetite and *ad-libitum* energy intake (Aeberli et al., 2013;
47 Matu et al., 2017a; Wasse et al., 2012), in combination with potential increases in resting
48 energy expenditure (Butterfield et al., 1992; Matu et al., 2017a), compared with sea level.
49 Developing a better understanding of the changes in appetite and energy intake that occur
50 during hypoxic exposure is vital in designing interventions to minimise energy deficits.

51 Despite a substantial amount of recent research (Debevec, 2017), the mechanisms
52 underlying reductions in appetite during hypoxic exposure are not well understood.
53 Historically, studies have attributed the loss of appetite to acute mountain sickness (AMS),
54 however this is unlikely to be the sole cause, as symptoms of anorexia persist when AMS has
55 subsided (Tschop & Morrison, 2001), and others have found appetite suppression in individuals
56 without symptoms of AMS (Matu et al., 2017a). Appetite is regulated, in part, by the
57 neuroendocrine system (Murphy & Bloom, 2006), and multiple hormones have been
58 implicated as mediators of hunger and satiety in hypoxia (Bailey et al., 2015; Debevec et al.,
59 2014a; Debevec et al., 2016; Matu et al., 2017a; Sierra-Johnson et al., 2008; Shulka et al., 2005;
60 Tschop et al., 1998). Acylated ghrelin has been hypothesized to act physiologically to signal
61 hunger and initiate eating, and has received growing attention in hypoxic research during recent
62 years (Bailey et al., 2015; Matu et al., 2017a; Morishima & Goto, 2016; Wasse et al., 2012).
63 Current evidence suggests that appetite and acylated ghrelin are concomitantly suppressed
64 during exposure to high, but not moderate, simulated altitude, which suggests a potential
65 mediating role of this hormone in altitude-induced anorexia (Matu et al., 2017a). However, due
66 to the complex chemical preparation required for accurate acylated ghrelin measurements
67 (Hosoda et al., 2004), total ghrelin concentrations have been more commonly measured in
68 response to hypoxic exposure and the findings remain equivocal (Benso et al., 2007; Debevec
69 et al., 2014a; Debevec et al., 2016; Mekjavic et al., 2016; Riedl et al., 2012; Riepl et al., 2012;
70 Shulka et al., 2005).

71 The role of circulating leptin concentrations as a mediator of appetite and energy intake
72 changes at altitude has been a topic of great interest and controversy. Leptin is an adipocytokine
73 that has been proposed to express regulatory physiological effects on appetite and
74 metabolism (Klok et al., 2007). It is well known that exposure to altitude stimulates hypoxia-
75 inducible factor 1 (HIF-1) (Semenza, 2012). HIF-1 can transactivate the human leptin gene
76 promoter, potentially increasing circulating leptin concentrations (Grosfeld et al., 2002). On
77 the contrary, altitude exposure is often associated with a significant loss of adiposity due to
78 increased energy expenditure and/or decreased energy intake (Rose et al., 1988; Zaccagni et
79 al., 2014). This would therefore reduce leptin expression in adipose tissue. Consequently, the
80 effects of hypoxic exposure on leptin concentrations remain ambiguous (Sierra-Johnson et al.,
81 2008), and several confounding factors may regulate leptin concentrations in hypoxia, such as
82 the completion of varying amounts of physical activity (Yu et al., 2017), as well as the duration
83 and severity of hypoxic exposure. Other hormones which have been investigated in relation to
84 appetite suppression during hypoxic exposure include glucagon-like peptide-1 (GLP-1) (Bailey
85 et al., 2004; Bailey et al., 2015; Debevec et al., 2014a; Debevec et al., 2016; Matu et al., 2017a;
86 Mekjavic et al., 2016; Morishima & Goto, 2016; Snyder et al., 2008), pancreatic polypeptide
87 (PP) (Matu et al., 2017a; Riepl et al., 2012), peptide YY (PYY) (Bailey et al., 2015; Debevec
88 et al., 2014a; Debevec et al., 2016; Mekjavic et al., 2016; Wasse et al., 2012), cholecystokinin
89 (CCK) (Aeberli et al., 2013; Riepl et al., 2012) and insulin (Debevec et al., 2014a; Matu et al.,
90 2017a; Mekjavic et al., 2016). The results of these studies are equivocal, possibly due to a wide
91 variety of methodologies employed.

92 A clear understanding of the dose-response and underlying regulation of hypoxia-
93 induced appetite suppression in humans requires the equivocal results of previous studies to be
94 explained. In an attempt to resolve these discrepancies, our objective was to conduct a
95 systematic review and meta-analysis of within-measures studies which have investigated the
96 effect of hypoxia on hunger, energy intake and/or hormone concentrations implicated in
97 appetite regulation. Using post-hoc subgroup analyses and meta-regression, we also aimed to
98 identify any study characteristics which could help to explain the observed results.

99

100 **Methods**

101 This systematic review and meta-analysis was performed in accordance with the PRISMA
102 (Preferred Reporting Items for Systematic Review and Meta-analyses) guidelines (Liberati et

103 al., 2009) and was prospectively registered with the PROSPERO database
104 (CRD42015017231).

105

106 *Literature Search*

107 PubMed and The Cochrane Library as well as MEDLINE, SPORTDiscus, PsycINFO and
108 CINAHL, via EBSCOhost, were searched from 3rd March 2015 through 1st April 2017.
109 Keyword searches were performed for: 'altitude', 'hypoxia', 'hypoxic', 'mountaineering',
110 'appetite', 'appetite hormones', 'ghrelin', 'acylated ghrelin', 'glp-1', 'glucagon like peptide-
111 1', 'peptide YY', 'PYY', 'leptin', 'pancreatic polypeptide', 'insulin', 'hunger', 'satiety',
112 'energy intake', 'food intake', 'energy balance' (details of the search strategy are outlined in
113 the Supplementary Material). This gave a total of 68 combinations. Reference lists of eligible
114 studies and review articles were also searched. If only the abstract or partial data were published
115 then the author was contacted for the full data set. No language or date of publication
116 restrictions were applied during the searches.

117

118 *Inclusion Criteria*

119 For inclusion, studies were required to meet the following criteria: participants in the studies
120 were between 18 and 65 years old, non-smokers, not pregnant and had no history of diabetes,
121 gastrointestinal, inflammatory, metabolic, cardiovascular, neurological or psychological
122 disease(s). Studies were included if they were published in peer-review journals or were
123 available as published conference proceedings, theses or dissertations, to minimise the effect
124 of any potential publication bias.

125 All studies were required to contain at least one of the following measures: subjective
126 hunger perceptions measured via visual analogue scales; measurements of blood acylated
127 ghrelin, total ghrelin, leptin, GLP-1, PYY and/or insulin concentrations; and/or energy intake
128 measured by the researcher as the weight of food or kJ/kcal (i.e. not self-reported). Hunger was
129 used as opposed to other subjective appetite measures, as hunger is the most commonly utilised
130 scale and therefore allowed for the inclusion of more studies.

131 All studies were required to contain the required measure(s) during a hypoxic exposure.
132 Hypoxic exposure interventions were defined as original investigations including exposure to

133 a true altitude via geographical location (e.g. mountaineering) or a simulated normobaric or
134 hypobaric exposure (e.g. hypoxic chamber, hypoxic tent or breathing mask). Exposures were
135 required to be $\geq 1000\text{m}$ in altitude (or a simulated hypoxic equivalent) and be of ≥ 30 minutes
136 in duration. Studies were also required to contain an appropriate within-subjects control, i.e.
137 the equivalent measure(s) in normoxic conditions prior to the hypoxic exposure or a separate
138 control (normoxic) condition.

139 Two researchers (JM and KD) independently assessed studies for inclusion and later
140 compared notes to reach a mutual consensus. Disagreements about the eligibility of any
141 particular studies were resolved by a third reviewer (TI). Potential studies that could be
142 included based on their title or abstract were retrieved in full-text and reviewed against the
143 inclusion/exclusion criteria independently by two researchers (JM and KD) with a third
144 researcher (TI) used to settle any disputes. In total, 28 studies met the inclusion criteria and
145 were included in this meta-analysis (supplementary figure 1). For a variable to be included in
146 the meta-analysis a minimum of three studies, measuring the respective variable, were required
147 to meet the inclusion criteria.

148

149 *Data abstraction*

150 Data were extracted independently by two researchers (JM and KD) into a standardised
151 spreadsheet, which included (i) characteristics of articles valid for review; (ii) the Cochrane
152 Collaboration's tool for assessing risk of bias and (iii) outcome data suitable for successive
153 analysis based on mean, SD and sample size. Additional data were collected for study design,
154 participant characteristics, severity and duration of hypoxic exposure, acclimatisation status
155 and activity status of participants. Participants were deemed to be passive if no exercise was
156 conducted during the hypoxic exposure (e.g. bedrest, or ascent to altitude by vehicle).
157 Participants were deemed to be active if exercise was conducted during the hypoxic exposure
158 (e.g. exercise capacity tests, or trekking to altitude). When studies employed multiple measures
159 of the same variable in the same hypoxic severity then the first measure and chronologically
160 final measure were used for analysis. This ensured that single studies were not weighted too
161 highly due to multiple measures whilst still accounting for the effect of acute and chronic
162 hypoxic exposure.

163 Where blood analyte values were reported in $\text{pmol}\cdot\text{L}^{-1}$, values were converted to $\text{pg}\cdot\text{mL}^{-1}$
164 ¹ as follows: multiplied by 4 for total PYY, 3.297 for total GLP-1, 3.37 for acylated and total

165 ghrelin, and 16 for leptin. Insulin was converted from $\text{pmol}\cdot\text{L}^{-1}$ to $\mu\text{U}\cdot\text{mL}^{-1}$. where necessary by
166 dividing by six. Where values were only presented in figure form, the figure was digitized
167 using graph digitizer software (DigitizeIt, Germany) and the means and SD/SEM were
168 measured manually at the pixel level to the scale provided on the figure. If area under the curve
169 values were reported rather than mean values, the authors of the relevant studies were contacted
170 to obtain the raw dataset and mean values were subsequently calculated.

171

172 *Assessment of risk of bias in included studies*

173 To assess the risk of bias in included studies The Cochrane Collaboration's tool for assessing
174 risk of bias (Higgins et al., 2011) was used independently by two reviewers (JM and LD). Each
175 study was assessed in the following six domains: sequence generation, allocation concealment,
176 blinding of participants, personnel and outcome assessors, incomplete outcome data, selective
177 outcome reporting, and other sources of bias (e.g. has been claimed to have been fraudulent).
178 A judgement was made on each of the domains by the two independent researchers as to
179 whether they were 'high risk' or 'low risk'. When insufficient detail was reported then the
180 judgement of 'unclear risk' was made. Disagreements were solved initially via discussion
181 between the two independent reviewers however a third reviewer (TI) was consulted for dispute
182 resolution. 'Risk of bias graphs' were computed in Review Manager (RevMan) 5.3 (The
183 Cochrane Collaboration) to include low, unclear and high risk for each domain.

184

185 *Statistical analysis*

186 Missing standard deviations were calculated from standard errors or confidence intervals.
187 Outcome measures were converted into the standardised mean difference (SMD) with 95%
188 confidence intervals (CI) and were used as the summary statistic. The SMD represents the size
189 of the effect of the intervention relative to the variability observed in that intervention. A
190 random-effects meta-analysis was performed by JM, JG and KD using Comprehensive Meta-
191 Analysis Software (version 3, Biostat, Englewood, NJ, USA). A random-effects model was
192 chosen over a fixed effects model due to unexplained heterogeneity in the included studies
193 (Ades et al., 2005). The inputted data included sample sizes, outcome measures with their
194 respective standard deviations, and a correlation coefficient for within-subject measurements.
195 These correlation coefficients were estimated from prior studies in our laboratory and other

196 published studies, and were as follows: fasted hunger $r = 0.52$, postprandial hunger $r = 0.61$,
197 energy intake $r = 0.51$, postprandial acylated ghrelin $r = 0.97$, fasted total ghrelin $r = 0.40$,
198 postprandial total ghrelin $r = 0.53$, fasted leptin $r = 0.32$, fasted GLP-1 $r = 0.94$, postprandial
199 GLP-1 $r = 0.95$, fasted PYY $r = 0.70$, postprandial PYY $r = 0.86$, fasted insulin $r = 0.43$ and
200 postprandial insulin $r = 0.53$.

201 We interpreted SMD values of <0.20 as trivial, $0.20-0.39$ as small, $0.40-0.80$ as
202 moderate and >0.80 as large (Cohen, 1969). A negative SMD indicates that hypoxic exposure
203 was associated with a decrease in the respective outcome variable while a positive SMD
204 indicates that hypoxic exposure was associated with an increase in the respective outcome
205 variable. Heterogeneity between trials was assessed using the I-squared statistic, where $0-40\%$
206 suggests heterogeneity might not be important, $30-60\%$ may represent moderate heterogeneity,
207 $50-90\%$ may represent substantial heterogeneity and $75-100\%$ represents substantial
208 heterogeneity (Higgins & Thompson, 2002). This measure of heterogeneity was complimented
209 by also reporting the Tau-squared statistic and the Chi-squared statistic. To examine whether
210 any conclusions were dependent on a single study, sensitivity analyses was employed for each
211 variable by repeating the analyses with each study omitted in turn.

212 Where significant effects of hypoxic exposure were observed, post-hoc meta-regression
213 analysis (method-of-moments model) was performed. This analysis was used to determine
214 whether continuous data, including duration or severity of hypoxic exposure, could explain the
215 variation in the SMD values observed between studies for a respective outcome measure.
216 Where data were available, subgroup meta-analysis was performed for categorical variables
217 including acclimatisation status, method of achieving hypoxic exposure and physical activity
218 status.

219

220 *Exploration of small study effects*

221 Small study effects were explored with funnel plots of standard difference in means versus
222 standard errors (Sterne et al., 2011) and by quantifying Egger's linear regression intercept. A
223 large and statistically significant Egger statistic indicates the presence of a small study effect.

224

225 **Results**

226 *Overview*

227 Supplementary figure 1 outlines the flowchart of study selection. In total, 28 studies met the
228 inclusion criteria for the meta-analysis. All included studies had been published (or accepted
229 for publication) in peer-reviewed scientific journals at the time of inclusion. Within the 28
230 included studies a total of 54 fasted and 22 postprandial comparisons were included between
231 normoxic and hypoxic conditions. Comparisons were segregated into fasted (see
232 supplementary table 1) and postprandial (see supplementary table 2) responses to differentiate
233 between findings during these two distinct periods of appetite regulation. Fasted comparisons
234 represent comparisons of single time points obtained after an overnight fast. Eleven out of the
235 12 studies which reported postprandial comparisons provided standardised meals to
236 participants with an energy content of 1347 - 3205 kJ (mean: 2128 kJ) and an observation
237 period of 50 – 420 minutes (mean: 210 minutes). The remaining study which assessed
238 postprandial comparisons measured hunger responses to ad libitum feeding during the waking
239 hours of an entire day (Westerterp-Platenga et al., 1999). All studies involving postprandial
240 comparisons provided mixed macronutrient meals, with seven studies providing this in the
241 form of solid foods and five studies providing this in a liquid form. Visual inspection of the
242 data suggests that the composition of meals provided and observation periods employed did
243 not dictate the outcomes of postprandial variables.

244

245 *Participant demographics and hypoxic exposure characteristics*

246 A total of 407 participants (351 men and 56 women; 86% men) were included in this meta-
247 analysis. Mean age was reported in 22 out of the 28 studies and ranged from 21 to 44 years
248 (mean: 29 years). Mean BMI was reported in 18 out of the 28 studies and ranged from 20.7 to
249 25.0 kg·m⁻² (mean: 23.4 kg·m⁻²). For all comparisons hypoxic severity ranged from 2134 to
250 7753m (mean: 4302m) and duration of hypoxic exposure ranged from 50 minutes to two
251 months (mean: 10 days).

252

253 *Meta-Analysis*

254 Individual study statistics and results for each outcome variable are summarised in
255 supplementary tables 3 - 15.

256

257 *Standardised mean difference and moderator variables for hunger scores*

258 Hypoxic exposure resulted in a small decrease in fasted hunger scores (SMD: -0.35, 95% CI: -
259 0.76 to 0.07; $n = 15$; $p = 0.102$). The degree of heterogeneity may be substantial between these
260 studies ($I^2 = 81.6\%$; $Q = 76.0$, $\tau^2 = 0.521$, $d_f = 14$). Sensitivity analysis revealed that the removal
261 of one comparison (Aeberli et al. 2013-2) further decreased the SMD to -0.43 (95% CI: -0.85
262 to -0.01; $p = 0.045$). Inspection of the funnel plot and Egger's regression intercept revealed that
263 there was evidence of small study effects (intercept = -5.522, 95% CI: -9.25 to -1.79; $p = 0.007$).

264 Hypoxic exposure resulted in a trivial decrease in postprandial hunger scores (SMD: -
265 0.15, 95% CI: -0.29 to -0.01; $n = 14$; $p = 0.043$; Figure 1). The degree of heterogeneity was
266 found to be low between these studies ($I^2 = 5.2\%$; $Q = 13.7$, $\tau^2 = 0.004$ and $d_f = 13$). Sensitivity
267 analysis revealed that the removal of eight single comparisons in turn moderated the statistical
268 interpretation of the results; for example the removal of the comparison with the largest
269 negative SMD (Wasse et al., 2012) would increase the SMD to -0.11 (95% CI: -0.25 to 0.03;
270 $p = 0.118$). Subgroup analysis indicated a difference between active and passive participants
271 ($p = 0.049$), with postprandial hunger being suppressed to a greater extent in passive
272 participants (Table 1). Utilising a meta-regression model, neither hypoxic severity nor duration
273 of exposure were associated with postprandial hunger scores. Inspection of the funnel plot and
274 Egger's regression intercept revealed that there was evidence of small study effects (intercept
275 = -3.332, 95% CI: -6.06 to -0.60; $p = 0.021$).

276 [Insert Figure 1 near here]

277

278 *Standardised mean difference and moderator variables for energy intake*

279 Hypoxic exposure resulted in a moderate decrease in energy intake (SMD: -0.50, 95% CI: -
280 0.85 to -0.15; $n = 8$; $p = 0.006$; Figure 2). The degree of heterogeneity may be substantial
281 between these studies ($I^2 = 64.5\%$; $Q = 19.7$, $\tau^2 = 0.159$ and $d_f = 7$). Sensitivity analysis revealed
282 minor changes only, and these changes did not substantially alter the overall mean effect. Using
283 duration of exposure as a moderator in a meta-regression model, a shorter duration of exposure
284 tended to be associated with a larger decrease in energy intake. The slope of the regression
285 tended to be positive ($p = 0.056$; Table 1), with a standardised increase in energy intake of
286 0.051 units for every one day of hypoxic exposure. Inspection of the funnel plot and Egger's

287 regression intercept revealed that there was little evidence of small study effects (intercept = -
288 4.065, 95% CI: -10.04 to 1.91; $p = 0.147$).

289 [Insert Figure 2 near here]

290

291 *Standardised mean difference and moderator variables for acylated ghrelin concentrations*

292 Hypoxic exposure resulted in a trivial decrease in postprandial acylated ghrelin concentrations
293 (SMD: -0.16, 95% CI: -0.25 to -0.08; $n = 7$; $P < 0.0005$; Figure 3). The degree of heterogeneity
294 was found to be moderate between these studies ($I^2 = 56.7\%$; $Q = 13.9$, $\tau^2 = 0.007$ and $d_f = 6$).
295 Sensitivity analysis revealed minor changes only, and these changes did not substantially
296 impact the overall mean effect. Using hypoxic severity as a moderator in a meta-regression
297 model, a higher degree of hypoxia was associated with a larger decrease in acylated ghrelin
298 concentrations (Figure 4). The slope of the regression was negative (slope: -0.0001, 95% CI -
299 0.0002 to -0.0000; $p = 0.010$; Table 1), with a standardised decrease in acylated ghrelin of 0.1
300 units for every 1000m increase in hypoxic severity. Inspection of the funnel plot and Egger's
301 regression intercept revealed that there was little evidence of small study effects (intercept = -
302 5.431, 95% CI: -21.82 to 10.96; $p = 0.467$).

303 [Insert Figure 3 and 4 near here]

304

305 *Standardised mean difference and moderator variables for total ghrelin concentrations*

306 Hypoxic exposure resulted in trivial changes in fasted (SMD: 0.00, 95% CI: -0.33 to 0.34; $n =$
307 14; $p = 0.987$) and postprandial (SMD: 0.02, 95% CI: -0.37 to 0.41; $n = 5$; $p = 0.920$) total
308 ghrelin concentrations. The degree of heterogeneity may be substantial for fasted comparisons
309 ($I^2 = 74.7\%$; $Q = 51.3$, $\tau^2 = 0.284$ and $d_f = 13$) and low for postprandial comparisons ($I^2 =$
310 33.4%; $Q = 6.0$, $\tau^2 = 0.064$ and $d_f = 4$). Sensitivity analysis revealed only minor changes in the
311 SMDs for both fasted and postprandial total ghrelin concentrations. Inspection of the funnel
312 plot and Egger's regression intercept revealed that there was little evidence of small study
313 effects for both fasted (1.104, 95% CI: -2.82 to 5.03; $p = 0.552$) and postprandial (-3.503, 95%
314 CI: -10.62 to 3.61; $p = 0.215$) total ghrelin concentrations.

315

316 *Standardised mean difference and moderator variables for GLP-1 concentrations*

317 Hypoxic exposure resulted in a trivial increase in fasted (SMD: 0.03, 95% CI: -0.11 to 0.17; n
318 = 8; $p = 0.684$) and postprandial (SMD: 0.03, 95% CI: -0.05 to 0.11; $n = 10$; $p = 0.474$) GLP-
319 1 concentrations. The degree of heterogeneity may be substantial for fasted comparisons ($I^2 =$
320 62.1%; $Q = 18.5$, $\tau^2 = 0.024$ and $d_f = 7$) and was moderate for postprandial comparisons ($I^2 =$
321 39.2%; $Q = 14.8$, $\tau^2 = 0.006$ and $d_f = 9$). Sensitivity analysis revealed only minor changes in
322 the SMDs for both fasted and postprandial GLP-1 concentrations. Inspection of the funnel plot
323 and Egger's regression intercept revealed that there was little evidence of small study effects
324 for both fasted (intercept = 5.819, 95% CI: -4.71 to 16.35; $p = 0.225$) and postprandial (intercept
325 = 4.524, 95% CI: -3.73 to 12.78; $p = 0.242$) GLP-1 concentrations.

326

327 *Standardised mean difference and moderator variables for leptin concentrations*

328 Hypoxic exposure resulted in a trivial decrease in fasted leptin concentrations (SMD: -0.09,
329 95% CI: -0.40 to 0.23; $n = 25$; $p = 0.588$). The degree of heterogeneity was found to be
330 substantial between these studies (studies ($I^2 = 82.8\%$; $Q = 139.8$, $\tau^2 = 0.493$ and $d_f = 24$).
331 Sensitivity analysis revealed minor changes only, and these changes did not impact the overall
332 mean effect. Inspection of the funnel plot and Egger's regression intercept revealed that there
333 was little evidence of small study effects (intercept = 0.953, 95% CI: -1.97 to 3.87; $p = 0.506$).

334

335 *Standardised mean difference and moderator variables for PYY concentrations*

336 Hypoxic exposure resulted in a trivial increase in fasted (SMD: 0.02, 95% CI: -0.18 to 0.21; n
337 = 7; $p = 0.865$) and postprandial (SMD: 0.02, 95% CI: -0.14 to 0.18; $n = 8$; $p = 0.810$) PYY
338 concentrations. The degree of heterogeneity was low for fasted comparisons ($I^2 = 0.0\%$; $Q =$
339 3.2, $\tau^2 = 0.000$ and $d_f = 6$) and moderate for postprandial comparisons ($I^2 = 44.2\%$; $Q = 12.6$,
340 $\tau^2 = 0.023$ and $d_f = 7$). Sensitivity analysis revealed only minor changes in the SMDs for both
341 fasted and postprandial PYY concentrations. Inspection of the funnel plot and Egger's
342 regression intercept revealed that there was some evidence of small study effects for fasted
343 PYY concentrations (-9.938, 95% CI: -7.87 to 0.00; $p = 0.050$) but little evidence for
344 postprandial PYY concentrations (-2.485, 95% CI: -14.86 to 9.89; $p = 0.641$).

345

346 *Standardised mean difference and moderator variables for insulin concentrations*

347 Hypoxic exposure resulted in a moderate increase in fasted insulin concentrations (SMD: 0.41,
348 95% CI: 0.17 to 0.65; $n = 34$; $p = 0.001$; Figure 4). The degree of heterogeneity may be
349 substantial between these studies ($I^2 = 70.6\%$; $Q = 112.1$, $\tau^2 = 0.323$, $df = 33$). Sensitivity
350 analysis revealed minor changes only, and these changes did not impact the overall mean effect.
351 Subgroup analysis indicated a difference between the acclimatisation status of the participants
352 ($p < 0.0005$), with acclimatised individuals experiencing a larger increase in insulin
353 concentrations. Additionally, there was a difference between the methods of achieving hypoxia
354 ($p < 0.0005$), with simulated hypobaric hypoxia inducing the largest increases in insulin
355 concentrations (Table 1). Using hypoxic severity as a moderator in a meta-regression model, a
356 higher degree of hypoxia was associated with a greater increase in insulin concentration (Figure
357 6). The slope of the regression was positive (slope: 0.0003, 95% CI 0.0000 to 0.0005; $p =$
358 0.020; Table 1), with a standardised increase in insulin of 0.3 units for every 1000m increase
359 in hypoxic severity. Inspection of the funnel plot and Egger's regression intercept revealed that
360 there was evidence of small study effects (intercept = 2.617, 95% CI: 0.78 to 4.46; $p = 0.007$).

361 Hypoxic exposure resulted in a small decrease in postprandial insulin concentrations
362 (SMD: -0.035, 95% CI: -0.22 to 0.15; $n = 11$; $p = 0.707$). The degree of heterogeneity was
363 found to be low between these studies ($I^2 = 0.00\%$; $Q = 9.5$, $\tau^2 = 0.00$ and $df = 10$). Sensitivity
364 analysis revealed minor changes only, and these changes did not impact the overall mean effect.
365 Inspection of the funnel plot and Egger's regression intercept revealed that there was evidence
366 of small study effects (intercept = -5.36, 95% CI: -9.03 to -1.69; $p = 0.009$).

367 [Insert Figure 5 and 6 near here]

368 [Insert Table 1 near here]

369

370 *Risk of bias*

371 Since many of the studies included were high altitude expeditions, certain biases were often
372 unavoidable, such as blinding of participants and personnel (Figure 7).

373 [Insert Figure 7 near here]

374

375 **Discussion**

376 The purpose of this meta-analysis was to examine the effect of hypoxic exposure on hunger
377 and energy intake responses, and to investigate changes in appetite-related hormones as
378 potential mechanistic variables. We observed decreases in postprandial hunger scores and
379 energy intake during hypoxic exposure compared with normoxia. Furthermore, we found
380 postprandial acylated ghrelin concentrations to be suppressed and fasted insulin concentrations
381 to be elevated during hypoxic exposure compared with normoxia. The observed reductions in
382 postprandial hunger and energy intake accord with the hypothesised orexigenic effects of
383 acylated ghrelin (Monteiro & Batterham, 2017) and anorexigenic effects of insulin (Air et al.,
384 2002; Hallschmid et al., 2012). We did not find any significant effects of hypoxic exposure,
385 compared with normoxia, on circulating total ghrelin, GLP-1, leptin or PYY concentrations,
386 which suggests that these hormones are unlikely to play a role in altitude-induced anorexia.

387 Interestingly, the reductions observed in postprandial hunger during hypoxia compared
388 with normoxia do not appear to be moderated by the duration of hypoxic exposure. This
389 speculation aligns with previous research that has observed significant reductions in appetite
390 with both acute (Matu et al., 2017a; Wasse et al., 2012) and chronic (Westerterp et al., 1994;
391 Westerterp-Platenga et al., 1999) hypoxic exposures. However, reductions in energy intake
392 tended to be associated with a shorter duration of hypoxic exposure, signifying a possible
393 acclimatisation response during prolonged exposures. No other variables were found to be
394 moderated by the duration of hypoxic exposure, therefore suggesting that other factors may be
395 involved in the regulation of energy intake at altitude. Surprisingly, subgroup analysis revealed
396 that hypoxic exposure was associated with a smaller reduction in postprandial hunger in the
397 studies involving the completion of physical activity than those involving passive exposure to
398 hypoxia. This finding may seem unexpected considering the longstanding evidence that
399 strenuous exercise ($\geq 60\%$ of maximum oxygen uptake) induces a transient suppression of
400 appetite known as exercise-induced anorexia (Deighton & Stensel, 2014). Although it is
401 difficult to provide a precise explanation for this observation, it seems feasible that any
402 exercise-induced appetite suppression during normoxic trials may have reduced the *relative*
403 decrease in hunger during matched hypoxic trials due to a baseline effect. It must also be
404 acknowledged that subgroup and meta-regression analyses are observational, in contrast to the
405 main analysis and summary effect which represent the impact of the hypoxic interventions.
406 Subsequently, it is feasible that the moderating effect of activity status on postprandial hunger
407 is confounded by other factors within the study designs such as the participant characteristics
408 or the nature of the hypoxic exposure (type, duration, severity of hypoxia etc.).

409 It must be noted that appetite perceptions and hormonal regulation are just two aspects
410 of a multifaceted system controlling energy intake in humans. Hypoxia has been shown to
411 degrade the taste of food in both humans (Matu et al., 2017b) and rodents (Ettinger & Staddon,
412 1982), and this could potentially alter food reward (Berthoud, 2006). Furthermore, individuals
413 exposed to chronic altitude may consciously attempt to maintain energy balance to avoid illness
414 and fatigue (Matu et al., 2017b). This behavioural regulation of energy intake may confound
415 the observed reductions in energy intake during chronic hypoxic exposure. It is also possible
416 that the initial body composition and fitness levels of the participants included in the current
417 review may alter their hormonal responses to altitude. For example, an increased adiposity can
418 lead to a decrease in insulin and leptin sensitivity (Adam et al., 2009). However, not enough
419 studies reported these data for them to be included as moderator variables.

420 The current review found an inverse association between hypoxic severity and changes
421 in acylated ghrelin concentrations. This finding concords with those of Matu et al. (2017a),
422 who found that acylated ghrelin was suppressed with high but not moderate simulated altitude
423 exposure. The findings of this meta-analysis demonstrate that acylated ghrelin is suppressed in
424 hypoxia compared with normoxia but that total ghrelin concentrations remain unchanged. Total
425 ghrelin consists of the combined levels of des-acyl ghrelin and acylated ghrelin, and recent
426 research has found that des-acyl ghrelin can inhibit the orexigenic effects of acylated ghrelin
427 by targeting the arcuate nucleus, independently of the growth hormone secretagogue receptor
428 (Fernandez et al., 2016). The opposing effects of these hormones suggest that physiologically
429 relevant changes in ghrelin constituents may be masked by the measurement of total ghrelin. It
430 would therefore be beneficial for further research in this area to differentiate between the
431 ghrelin constituents.

432 Fasting insulin concentrations were found to be elevated with hypoxic exposure
433 compared with normoxia, and this effect was positively associated with the severity of
434 hypoxia. Additionally, a larger effect was observed in acclimatised participants than in
435 unacclimatised participants. However, this observation may be confounded by the fact that
436 studies that tend to recruit acclimatised participants often use higher altitudes. These higher
437 altitudes may be the factor causing the larger increase in insulin concentrations, which is
438 supported by the meta-regression between hypoxic severity and changes in insulin
439 concentrations. Such increases in insulin concentration may contribute to the observed
440 reductions in hunger during hypoxic exposure but could also represent a reduction in insulin
441 sensitivity. An increase in fasted, but not postprandial insulin concentrations, suggests that

442 hepatic insulin sensitivity is more heavily influenced by hypoxia than peripheral insulin
443 sensitivity (Matsuda & DeFronzo, 1999; Radziuk, 2014). Hypoxia has been shown to induce
444 whole-body insulin resistance in mice (Murphy et al., 2017). Furthermore, the use of a
445 hyperinsulinaemic, euglycaemic clamp in humans has demonstrated that an acute 30-min
446 hypoxic exposure (resulting in a blood oxygen saturation of ~75%) rapidly reduces whole-
447 body insulin sensitivity by ~15% (Oltmanns et al., 2004). The reduction in insulin sensitivity
448 could be due to catecholamine responses, adipose tissue inflammation, and/or HIF signalling
449 (Murphy et al., 2017; Oltmanns et al., 2004). This reduction in insulin sensitivity may be
450 transient, as others have shown that following an acute hypoxic exposure, insulin sensitivity
451 under normoxia is *increased* compared to continuous normoxia. Therefore, hypoxia may
452 acutely reduce insulin sensitivity, with a subsequent “rebound” upon return to normoxia.
453 Further work is required to establish whether chronic, sustained hypoxia reduces hepatic
454 and/or peripheral insulin sensitivity.

455 Interestingly, subgroup analysis revealed a larger increase in fasted insulin
456 concentrations under conditions of simulated hypobaric hypoxia than terrestrial altitude or
457 simulated normobaric hypoxia. Although further research is required, some evidence suggests
458 that simulated hypobaric hypoxia induces greater physiological stress than simulated
459 normobaric hypoxia (Coppel et al., 2015), which may contribute to the larger increases in
460 fasted insulin levels under this condition. It also seems feasible that simulated hypobaric
461 hypoxia may be a more potent physiological stressor than terrestrial altitude due to the
462 immediacy of the hypoxic exposure (i.e., walking through the door of an environmental
463 chamber rather than ascending more gradually to terrestrial altitude by transport or trekking).
464 Despite these potential effects, other differences between the studies assessing fasted insulin
465 concentrations may also have contributed to this observation, including the severity of
466 hypoxia induced in the different experiments.

467 The findings of the current review provide support for the notion that leptin
468 concentrations are not consistently affected by hypoxic exposure. From the studies included in
469 this review it appears that shorter duration studies utilising simulated altitudes result in
470 elevations of leptin concentrations compared with normoxia (Mekjavic et al., 2016; Snyder et
471 al., 2008), whereas longer duration studies at terrestrial altitude result in reductions in leptin
472 levels compared with normoxia (Benso et al., 2007; Castell et al., 2010; Vats et al., 2004).
473 These observations concur with the hypothesis that hypoxia stimulates HIF-1, which can
474 increase leptin concentrations. However chronic hypoxic exposure can suppress leptin

475 concentrations by reducing adiposity. This explains the lack of an overall effect in the current
476 meta-analysis. Due to multiple confounding factors in the included studies, which were not
477 possible to account for in the current analysis (e.g. sleep, cold, smoking status), further well
478 designed research would be beneficial to elucidate the effects of hypoxia *per se* on circulating
479 leptin concentrations in humans.

480 In the current review the only hormones investigated which aligned with the observed
481 reductions in hunger and energy intake were acylated ghrelin and insulin. Each of the other
482 appetite-related hormones were not found to change significantly in hypoxia compared with
483 normoxia. One recent study found that a high fat breakfast directly increased postprandial
484 acylated ghrelin and reduced postprandial insulin concentrations at simulated altitude,
485 compared with a high carbohydrate breakfast (Matu et al., 2017c). These alterations in hormone
486 concentrations were associated with increased appetite perceptions during an exercise bout that
487 simulated trekking activity. This research supports the conclusions of this review, and suggests
488 that it may be beneficial for further future studies to focus on interventions to minimise altitude-
489 induced changes in acylated ghrelin and insulin concentrations in an attempt to augment energy
490 intake, particularly during prolonged periods of hypoxic exposure.

491 Some notable limitations must be acknowledged in this meta-analysis. First, the
492 postprandial comparisons included within this review included a range of feeding protocols
493 and observation durations. Although these factors did not appear to have any noticeable effect
494 on the direction of the overall findings, it is possible that these factors may have influenced the
495 findings of each individual study. For example, the studies that provided meals containing
496 higher energy content or in the form of solid food would be expected to induce greater
497 reductions in hunger than lower energy or liquid meals (Tieken et al., 2007). It remains unclear
498 whether this would alter the effects of hypoxic exposure on the variables measured in this
499 review when compared with a matched normoxic trial, but this remains an important
500 consideration and an avenue for future investigation. Second, the hormones PP and CCK are
501 proposed to exert anorexigenic effects but these hormones were not included in this meta-
502 analysis as only two studies met the inclusion criteria for each hormone. These studies both
503 reported that hypoxic exposure suppressed concentrations of PP (Matu et al., 2017a; Riepl et
504 al., 2012) and CCK (Aeberli et al., 2013; Riepl et al., 2012) in the fasted and postprandial states,
505 suggesting that neither hormone plays a role in altitude-induced anorexia, as suppression of
506 these hormones would be expected to increase hunger. Third, we decided to exclude self-
507 reported energy intake data and only include energy intake data from studies where it was

508 measured by the research team. In total 27 studies were excluded for this reason, and thus it
509 may be argued that conclusions from this meta-analysis may be biased. However, this decision
510 was made *a-priori* due to the various limitations associated with self-report methods (Hill &
511 Davies, 2001) and recent conclusions that self-reported energy intake should not be used as a
512 measure of energy intake in scientific research (Dhurandhar et al., 2016; Subar et al., 2015).
513 Fourth, the statistical power of the analysis must be considered when interpreting the results,
514 particularly with regard to the subgroup analysis. As few as two comparisons were included in
515 some subgroups for analysis, and therefore may be underpowered. Fifth, as shown in Figure 7,
516 many of the included studies were classified as high risk for random sequence generation,
517 allocation concealment and blinding. However, it is important to note this this appraisal does
518 not necessarily mean the studies were methodologically flawed as these factors are often not
519 possible to incorporate during high altitude trekking studies. Finally, despite an extensive
520 search returning 2834 records, we cannot guarantee that our search was completely exhaustive
521 of the relevant literature. However, having searched the reference lists of all included studies
522 we are confident to have included all available relevant studies.

523 In conclusion, this meta-analysis reveals that exposure to hypoxia decreases hunger and
524 energy intake compared with normoxia, and that these reductions are associated with depressed
525 acylated ghrelin concentrations and elevated insulin concentrations. Given the hypothesised
526 roles of these hormones in the control of appetite, these changes are plausible neuroendocrine
527 signals mediating altitude-induced anorexia. It may be beneficial for future research to
528 investigate interventions that increase acylated ghrelin concentrations and decrease insulin
529 concentrations at altitude, with the aims of maintaining insulin sensitivity, and increasing
530 appetite and energy intake to assist with the maintenance of energy balance.

531

532 **Financial Support**

533 This research received no specific grant from any funding agency, commercial or not-for-profit
534 sectors.

535

536 **Conflict of Interest**

537 The authors declare no conflicts of interest.

References

- Adam TC, Toledo-Corral C, Lane CJ et al. (2009) Insulin sensitivity as an independent predictor of fat mass gain in Hispanic adolescents. *Diabetes care* 32, 2114-2115.
- *Aeberli I, Erb A, Spliethoff K et al. (2013) Disturbed eating at high altitude: influence of food preferences, acute mountain sickness and satiation hormones. *Eur J Nut* 52, 625-635.
- Air EL, Benoit SC, Blake Smith KA et al. (2002) Acute third ventricular administration of insulin decreases food intake in two paradigms. *Pharmacol Biochem Behav* 72, 423-429.
- Ades AE, Lu G, Higgins JP (2005) The interpretation of random-effects meta-analysis in decision models. *Med Decis Mak* 25, 646-654.
- *Bailey DM, Ainslie PN, Jackson SK et al. (2004) Evidence against redox regulation of energy homeostasis in humans at high altitude. *Clin Sci* 107, 589-600.
- *Bailey DP, Smith LR, Christmas BC et al. (2015) Appetite and gut hormone responses to moderate-intensity continuous exercise versus high-intensity interval exercise, in normoxic and hypoxic conditions. *Appetite* 89, 237-245.
- *Benso A, Broglio F, Aimaretti G et al. (2007) Endocrine and metabolic responses to extreme altitude and physical exercise in climbers. *Eur J Endocrinol* 157, 733-740.
- Berthoud HR (2006) Homeostatic and non-homeostatic pathways involved in the control of food intake and energy balance. *Obesity* 14, 197-200.
- *Braun B, Rock PB, Zamudio S et al. (2001) Women at altitude: short-term exposure to hypoxia and/or alpha(1)-adrenergic blockade reduces insulin sensitivity. *J Appl Physiol* 91, 623-631.
- Butterfield GE, Gates J, Fleming S et al. (1992) Increased energy intake minimizes weight loss in men at high altitude. *J Appl Physiol* 72, 1741-1748.
- *Castell LM, Thake CD, Ensign W (2010) Biochemical markers of possible immunodepression in military training in harsh environments. *Mil Med* 175, 158-165.
- Cohen J (1969) *Statistical power analysis for the behavioural sciences*. Hillsdale (NJ): Lawrence Erlbaum Associates.
- Coppel J, Hennis P, Gilbert-Kawai E, Grocott MPW (2015) The physiological effects of hypobaric hypoxia versus normobaric hypoxia: a systematic review of crossover trials. *Extrem Physiol Med* 4, 2.
- *Debevec T, Simpson EJ, Macdonald IA et al. (2014a) Exercise training during normobaric hypoxic confinement does not alter hormonal appetite regulation. *PloS one* 9, e98874.
- *Debevec T, Bali TC, Simpson EJ et al. (2014b) Separate and combined effects of 21-day bed rest and hypoxic confinement on body composition. *Eur J Appl Physiol* 114, 2411-2425.

*Debevec T, Simpson EJ, Mekjavic IB et al. (2016) Effects of prolonged hypoxia and bed rest on appetite and appetite-related hormones. *Appetite* 107, 28-37.

Debevec T (2017) Hypoxia-Related Hormonal Appetite Modulation in Humans during Rest and Exercise: Mini Review. *Front Physiol* 8, 366.

Deighton K, Stensel DJ (2014) Creating an acute energy deficit without stimulating compensatory increases in appetite: is there an optimal exercise protocol? *Proc Nutr Soc* 73, 352-358.

Dhurandhar NV, Brown AW, Thomas D et al. (2016) We Agree That Self-Reported Energy Intake Should Not Be Used as a Basis for Conclusions about Energy Intake in Scientific Research. *J Nut* 146, 1141-1142.

Ettinger RH, Staddon JE (1982) Decreased feeding associated with acute hypoxia in rats. *Physiol Behav* 29, 455-458.

Fernandez G, Cabral A, Cornejo MP et al. (2016) Des-Acyl Ghrelin Directly Targets the Arcuate Nucleus in a Ghrelin-Receptor Independent Manner and Impairs the Orexigenic Effect of Ghrelin. *J Neuroendocrinol* 28, 12349.

Grosfeld A, Andre J, Hauguel-De Mouzon S et al. (2002) Hypoxia-inducible factor 1 transactivates the human leptin gene promoter. *J Biol Chem* 277, 42953-42957.

Hallschmid M, Higgs S, Thienel M, Ott V, Lehnert H (2012) Postprandial administration of intranasal insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes* 61, 782-789.

Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Medicine* 21, 1539-1558.

Higgins JP, Altman DG, Sterne JA (2011) Chapter 8: Assessing risk of bias in included studies in *Cochrane Handbook for Systematic Reviews of Interventions*. vol. Version 5.1.0. Chichester, West Sussex Hoboken NJ : John Wiley & Sons, [2008] ©2008.

Hill RJ, Davies PS (2001) The validity of self-reported energy intake as determined using the doubly labelled water technique. *Brit J Nut* 85, 415-430.

Hosoda H, Doi K, Nagaya N et al. (2004) Optimum collection and storage conditions for ghrelin measurements: octanoyl modification of ghrelin is rapidly hydrolyzed to desacyl ghrelin in blood samples. *Clin Chem* 50, 1077-1080.

Klok MD, Jakobsdottir S, Drent ML (2007) The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev* 8, 21-34.

*Larsen JJ, Hansen JM, Olsen NV et al. (1997) The effect of altitude hypoxia on glucose homeostasis in men. *J Physiol* 504, 241-249.

Liberati A, Altman DG, Tetzlaff J et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 339.

Matsuda M, DeFronzo RA (1999) Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes care* 22, 1462-1470.

*Matu J, Deighton K, Ispoglou T et al. (2017a) The effect of moderate versus severe simulated altitude on appetite, gut hormones, energy intake and substrate oxidation in men. *Appetite* 113, 284-292.

Matu J, O'Hara J, Hill N et al. (2017b) Changes in appetite, energy intake, body composition, and circulating ghrelin constituents during an incremental trekking ascent to high altitude. *Eur J Appl Physiol* 117, 1917–1928.

Matu J, Deighton K, Ispoglou T et al. (2017c) A high fat breakfast attenuates the suppression of appetite and acylated ghrelin during exercise at simulated altitude. *Physiol Behav* 179, 353-360.

Mazzeo RS (2005) Altitude, exercise and immune function. *Ex Immun Rev* 11, 6-16.

*Mekjavic IB, Amon M, Kölegård R et al. (2016) The effect of normobaric hypoxic confinement on metabolism, gut hormones and body composition. *Front Physiol* 7, 202.

Monteiro MP, Batterham RL (2017) The Importance of the Gastrointestinal Tract in Controlling Food Intake and Regulating Energy Balance. *Gastroenterology* 152, 1707-1717.

*Morishima T, Goto K (2016) Ghrelin, GLP-1, and leptin responses during exposure to moderate hypoxia. *Appl Physiol, Nutrition, Metab* 41, 375-381.

Murphy AM, Thomas A, Crinion SJ et al. (2017) Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. *Eur Respir J* 49, DOI: 10.1183/13993003.01731-2016.

Murphy KG, Bloom SR (2006) Gut hormones and the regulation of energy homeostasis. *Nat* 444, 854-859.

Oltmanns KM, Gehring H, Rudolf S et al. (2004) Hypoxia Causes Glucose Intolerance in Humans. *Am J Respir Crit Care Med* 169, 1231-1237.

Pulfrey SM, Jones PJ (1996) Energy expenditure and requirement while climbing above 6,000 m. *J Appl Physiol* 81, 1306-1311.

Radziuk J (2014) Homeostatic model assessment and insulin sensitivity/resistance. *Diabetes* 63, 1850-1854.

*Riedl S, Kluge M, Schweitzer K et al. (2012) Adaptation of ghrelin and the GH/IGF axis to high altitude. *Eur J Endocrinol* 166, 969-976.

*Riepl RL, Fischer R, Hautmann H et al. (2012) Influence of acute exposure to high altitude on basal and postprandial plasma levels of gastroenteropancreatic peptides. *PloS one* 7, e44445.

Rose MS, Houston CS, Fulco CS et al. (1988) Operation Everest. II: Nutrition and body composition. *J Appl Physiol* 65, 2545-2551.

*Sawhney RC, Malhotra AS, Singh T et al. (1986) Insulin secretion at high altitude in man. *Int J Biometeorol* 30, 231-238.

*Sawhney RC, Malhotra AS, Singh T (1991) Glucoregulatory hormones in man at high altitude. *Eur J Appl Physiol Occup Physiol* 62, 286-291.

Semenza GL (2012) Hypoxia-inducible factors in physiology and medicine. *Cell* 148, 399-408.

Sergi G, Imoscopi A, Sarti S et al. (2010) Changes in total body and limb composition and muscle strength after a 6-8 weeks sojourn at extreme altitude (5000-8000 m). *J Sports Med Phys Fit* 50, 450-455.

Sierra-Johnson J, Romero-Corral A, Somers VK et al. (2008) Last word on viewpoint: effect of altitude on leptin levels, does it go up or down? *J Appl Physiol* 105, 1691.

*Shukla V, Singh SN, Vats P et al. (2005) Ghrelin and leptin levels of sojourners and acclimatized lowlanders at high altitude. *Nut Neurosci* 8, 161-165.

*Simpson EJ, Debevec T, Eiken O, Mekjavic I, Macdonald IA (2016) PlanHab: the combined and separate effects of 16 days of bed rest and normobaric hypoxic confinement on circulating lipids and indices of insulin sensitivity in healthy men. *J Appl Physiol* 120, 947-955.

*Smith JD, Cianflone K, Martin J et al. (2011) Plasma adipokine and hormone changes in mountaineers on ascent to 5300 meters. *Wilderness Environ Med* 22, 107-114.

*Snyder EM, Carr RD, Deacon CF et al. (2008) Overnight hypoxic exposure and glucagon-like peptide-1 and leptin levels in humans. *Appl Physiol, Nut, Metab* 33, 929-935.

*Spliethoff K, Meier D, Aeberli I et al. (2013) Reduced insulin sensitivity as a marker for acute mountain sickness? *High Alt Med Biol* 14, 240-250.

Sterne JAC, Egger M, Moher D (2011) Chapter 10: Addressing reporting biases in *Cochrane Handbook for Systematic Reviews of Interventions*. vol. Version 5.1.0. Chichester, West Sussex Hoboken NJ : John Wiley & Sons, [2008] ©2008.

Subar AF, Freedman LS, Tooze JA et al. (2015) Addressing Current Criticism Regarding the Value of Self-Report Dietary Data. *J Nut* 145, 2639-2645.

Tieken SM, Leidy HJ, Stull AJ et al. (2007) Effects of solid versus liquid meal-replacement products of similar energy content on hunger, satiety, and appetite-regulating hormones in older adults. *Horm Metab Res* 39, 389-94.

Tschop M, Morrison KM (2001) Weight loss at high altitude. *Adv Exp Med Biol* 502, 237-247.

Tschop M, Strasburger CJ, Hartmann G et al. (1998) Raised leptin concentrations at high altitude associated with loss of appetite. *Lancet* 352, 1119-1120.

*Tschop M, Strasburger CJ, Topfer M et al. (2000) Influence of hypobaric hypoxia on leptin levels in men. *Int J Obes Rel Metab Disord* 24, 151.

*Vats P, Singh SN, Shyam R et al. (2004) Leptin may not be responsible for high altitude anorexia. *High Alt Med Biol* 5, 90-92.

*Wasse LK, Sunderland C, King JA et al. (2012) Influence of rest and exercise at a simulated altitude of 4,000 m on appetite, energy intake, and plasma concentrations of acylated ghrelin and peptide YY. *J Appl Physiol* 112, 552-559.

Westerterp KR, Kayser B, Wouters L et al. (1994) Energy balance at high altitude of 6,542 m. *J Appl Physiol* 77, 862-866.

*Westerterp-Plantenga MS, Westerterp KR, Rubbens M et al. (1999) Appetite at "high altitude" [Operation Everest III (Comex-'97)]: a simulated ascent of Mount Everest. *J Appl Physiol* 87, 391-399.

*Young PM, Rose MS, Sutton JR et al. (1989) Operation Everest II: plasma lipid and hormonal responses during a simulated ascent of Mt. Everest. *J Appl Physiol* 66, 1430-1435.

Yu N, Ruan Y, Gao X et al. (2017) Systematic Review and Meta-Analysis of Randomized, Controlled Trials on the Effect of Exercise on Serum Leptin and Adiponectin in Overweight and Obese Individuals. *Horm Metab Res* 49, 164-173.

Zaccagni L, Barbieri D, Cogo A et al. (2014) Anthropometric and body composition changes during expeditions at high altitude. *High Alt Med Biol* 15, 176-182.

*Zaccaria M, Ermolao A, Bonvicini P et al. (2004) Decreased serum leptin levels during prolonged high altitude exposure. *Eur J Appl Physiol* 92, 249-253.

*** denotes that the study is included within the meta-analysis.**

Figure 1. Forest plot of standardised mean differences (means \pm 95% confidence intervals [CIs]) for studies evaluating the influence of hypoxic exposure on postprandial hunger scores compared with sea level. The size of each circle represents the relative weight of each comparison. The diamond represents a SMD (mean \pm 95% CI) for the model.

Figure 2. Forest plot of standardised mean differences (means \pm 95% confidence intervals [CIs]) for studies evaluating the influence of hypoxic exposure on energy intake compared with sea level. The size of each circle represents the relative weight of each comparison. The diamond represents a SMD (mean \pm 95% CI) for the model.

Figure 3. Forest plot of standardised mean differences (means \pm 95% confidence intervals [CIs]) for studies evaluating the influence of hypoxic exposure on postprandial acylated ghrelin concentrations compared with sea level. The size of each circle represents the relative weight of each comparison. The diamond represents a SMD (mean \pm 95% CI) for the model.

Figure 4. Univariable meta-regression for hypoxic severity versus the postprandial acylated ghrelin concentration responses to hypoxic exposure expressed as standardised mean difference (SMD).

Figure 5. Forest plot of standardised mean differences (means \pm 95% confidence intervals [CIs]) for studies evaluating the influence of hypoxic exposure on fasted insulin concentrations compared with sea level. The size of each circle represents the relative weight of each comparison. The diamond represents a SMD (mean \pm 95% CI) for the model.

Figure 6. Univariable meta-regression for hypoxic severity versus fasted insulin concentration responses to hypoxic exposure expressed as standardised mean difference (SMD).

Figure 7. Risk of bias across expressed as a percentage across all included studies. White, grey and black bars indicate low, unclear and high risk of bias, respectively.

Table 1. Summary of moderator variable analysis for postprandial hunger, energy intake, postprandial acylated ghrelin and fasted insulin meta-analysis by subgroup and meta-regression

Moderator Variable	<i>p</i> value	Comparison
Postprandial hunger		
Acclimatisation status	0.183	Acclimatised (<i>n</i> = 3; SMD -0.382, 95% CI -0.749 to -0.015) Unacclimatised (<i>n</i> = 11; SMD -0.110, 95% CI -0.270 to 0.050)
Hypoxic method	0.396	Simulated hypobaric (<i>n</i> = 3; SMD -0.382, 95% CI -0.749 to -0.015) Simulated normobaric (<i>n</i> = 9; SMD -0.151, 95% CI -0.330 to 0.028) Terrestrial altitude (<i>n</i> = 2; SMD -0.001, 95% CI -0.457 to 0.455)
Activity status	0.049	Passive (<i>n</i> = 6; SMD -0.350, 95% CI -0.598 to -0.103) Active (<i>n</i> = 8; SMD -0.051, 95% CI -0.216 to 0.114)
Hypoxic severity	0.175	Meta-regression of altitude height vs. SMD (slope -0.0001, 95% CI -0.0002 to 0.0000)
Duration of exposure	0.889	Meta-regression of duration of exposure vs. SMD (slope -0.0017, 95% CI -0.0224 to 0.0258)
Energy intake		
Hypoxic method	0.833	Simulated normobaric (<i>n</i> = 6; SMD -0.531, 95% CI -1.014 to -0.047) Terrestrial altitude (<i>n</i> = 2; SMD -0.448, 95% CI -1.045 to 0.149)
Activity status	0.970	Passive (<i>n</i> = 2; SMD -0.489, 95% CI -1.207 to 0.230) Active (<i>n</i> = 6; SMD -0.505, 95% CI -0.941 to -0.069)
Hypoxic severity	0.289	Meta-regression of altitude height vs. SMD (slope -0.0003, 95% CI -0.0007 to 0.0002)
Duration of exposure	0.056	Meta-regression of duration of exposure vs. SMD (slope 0.0509, 95% CI -0.0014 to 0.1031)
Postprandial acylated ghrelin		
Activity status	0.450	Passive (<i>n</i> = 2; SMD -0.207, 95% CI -0.321 to -0.092) Active (<i>n</i> = 5; SMD -0.145, 95% CI -0.258 to -0.031)
Hypoxic severity	0.010	Meta-regression of hypoxic severity vs. SMD (slope -0.0001, 95% CI -0.0002 to -0.0000)
Duration of exposure	0.293	Meta-regression of duration of exposure vs. SMD (slope -0.4196, 95% CI -1.2018 to 0.3625)
Fasted insulin		
Acclimatisation status	<0.0005	Acclimatised (<i>n</i> = 12; SMD 1.016, 95% CI 0.582 to 1.450) Unacclimatised (<i>n</i> = 22; SMD 0.121, 95% CI -0.121 to 0.363)
Hypoxic method	<0.0005	Simulated hypobaric (<i>n</i> = 6; SMD 1.052, 95% CI 0.638 to 1.467) Simulated normobaric (<i>n</i> = 7; SMD -0.215, 95% CI -0.913 to 0.361) Terrestrial altitude (<i>n</i> = 21; SMD 0.443, 95% CI 0.162 to 0.724)
Activity status	0.107	Passive (<i>n</i> = 16; SMD 0.619, 95% CI 0.184 to 1.055) Active (<i>n</i> = 18; SMD 0.211, 95% CI -0.027 to 0.450)
Hypoxic severity	0.020	Meta-regression of hypoxic severity vs. SMD (slope 0.0003, 95% CI 0.0000 to 0.0005)
Duration of exposure	0.377	Meta-regression of duration of exposure vs. SMD (slope 0.0079, 95% CI -0.0096 to 0.0255)

Figure 1

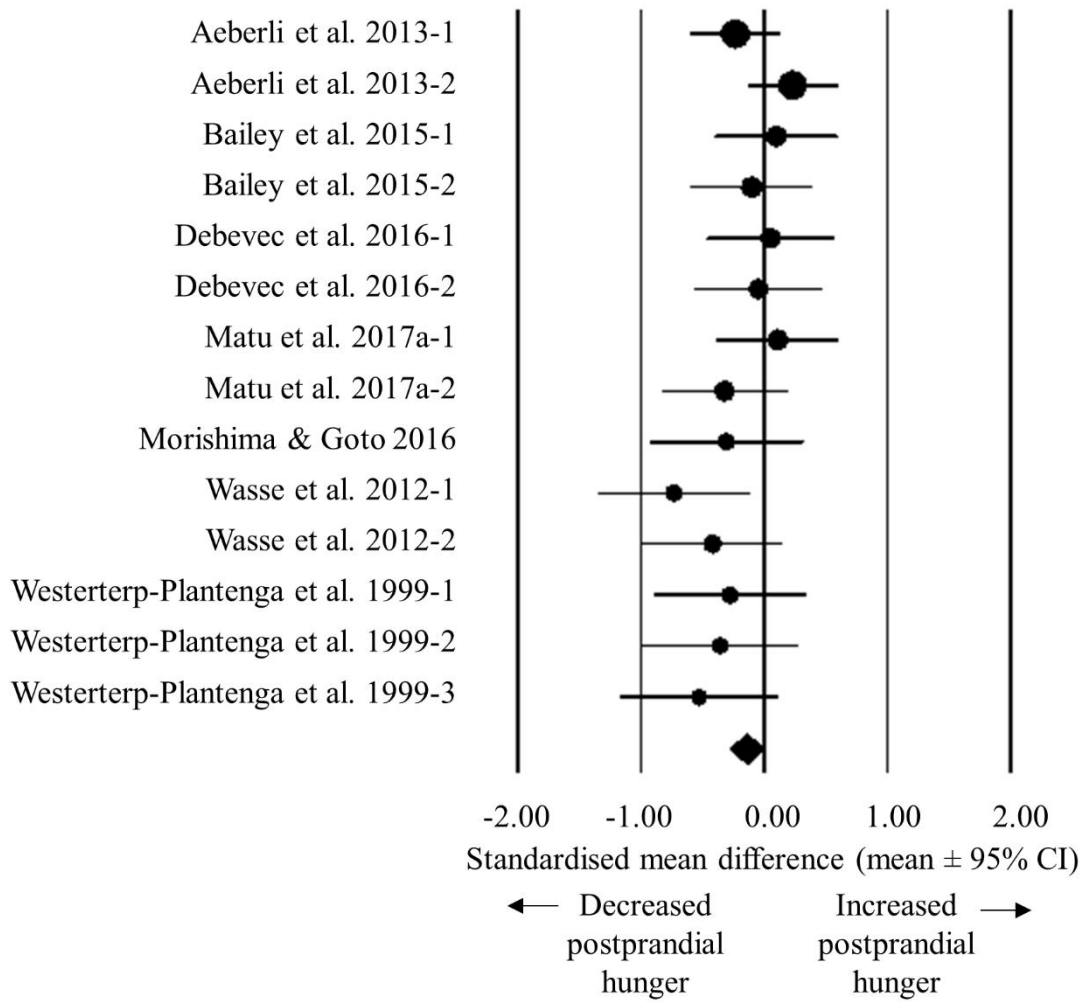


Figure 2

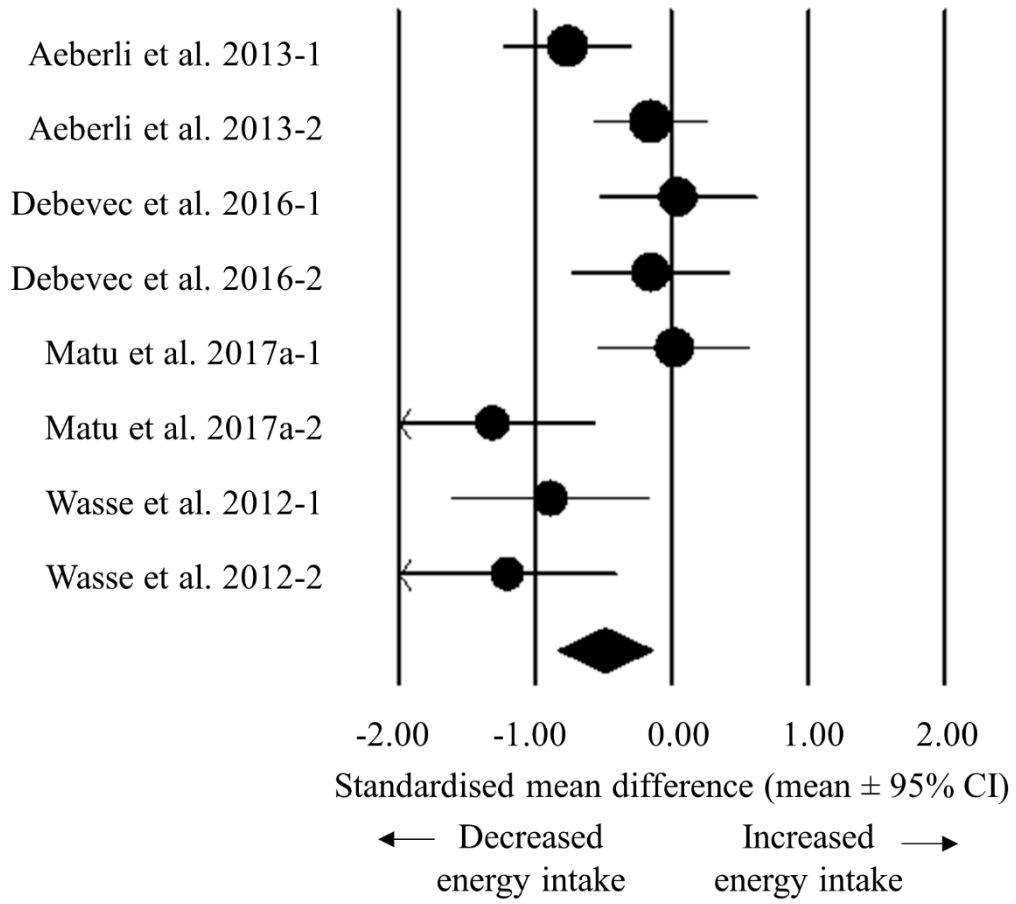


Figure 3

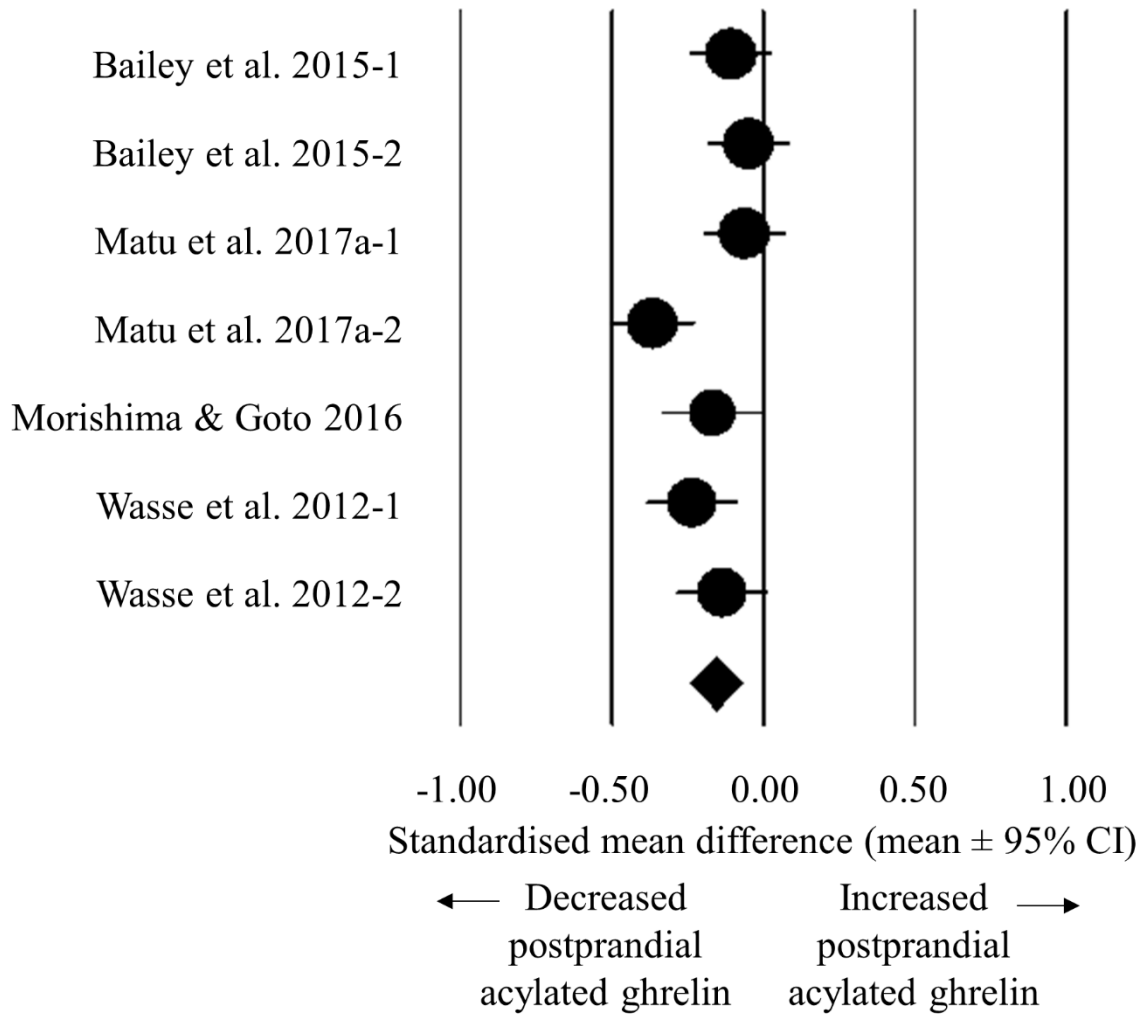


Figure 4

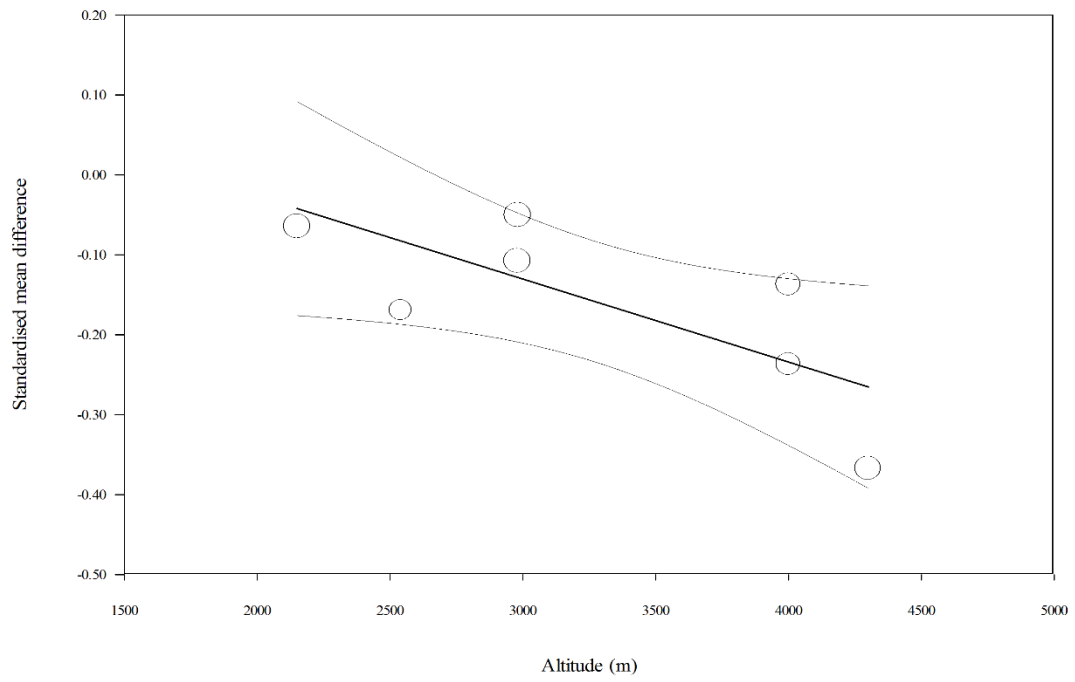


Figure 5

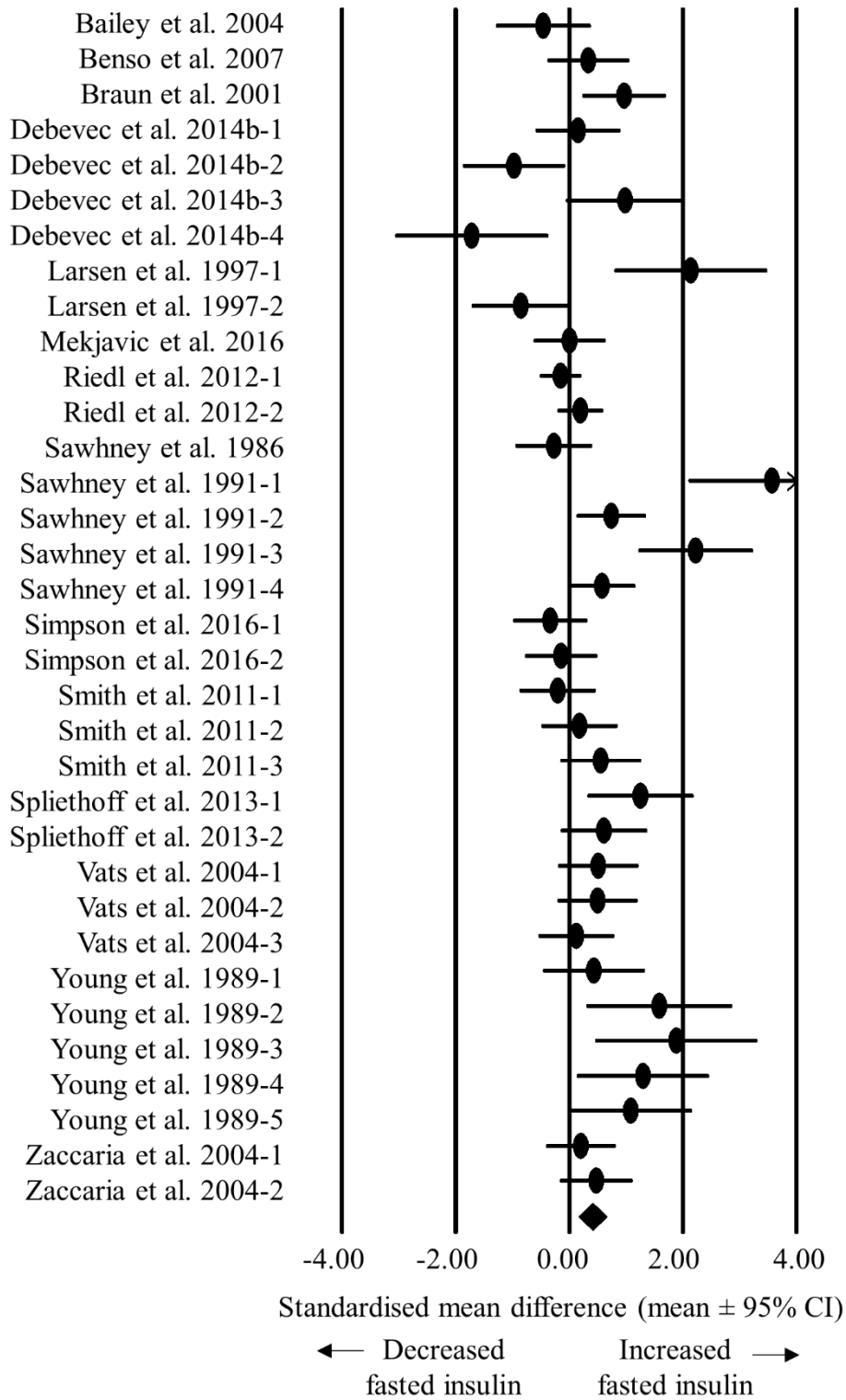


Figure 6

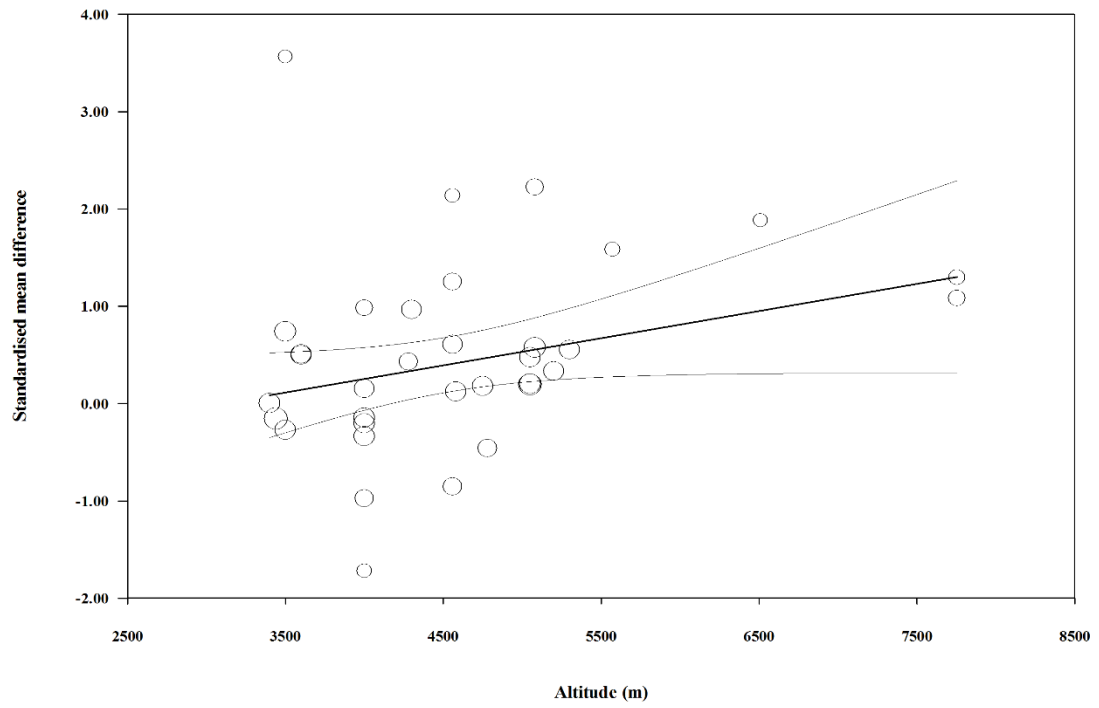
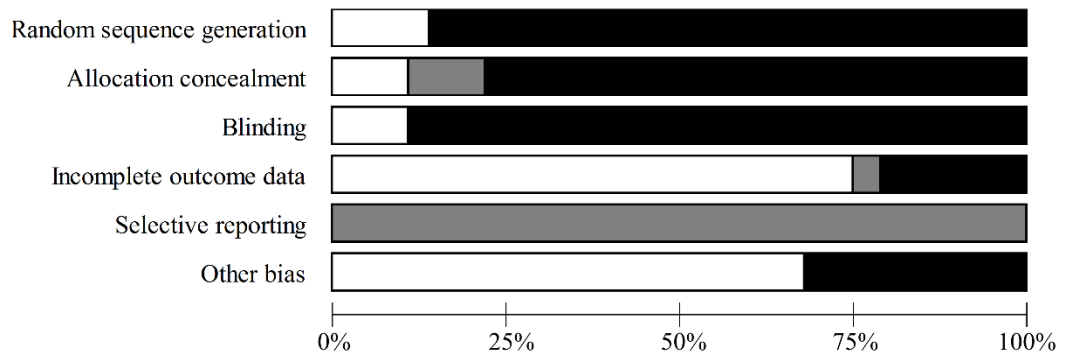
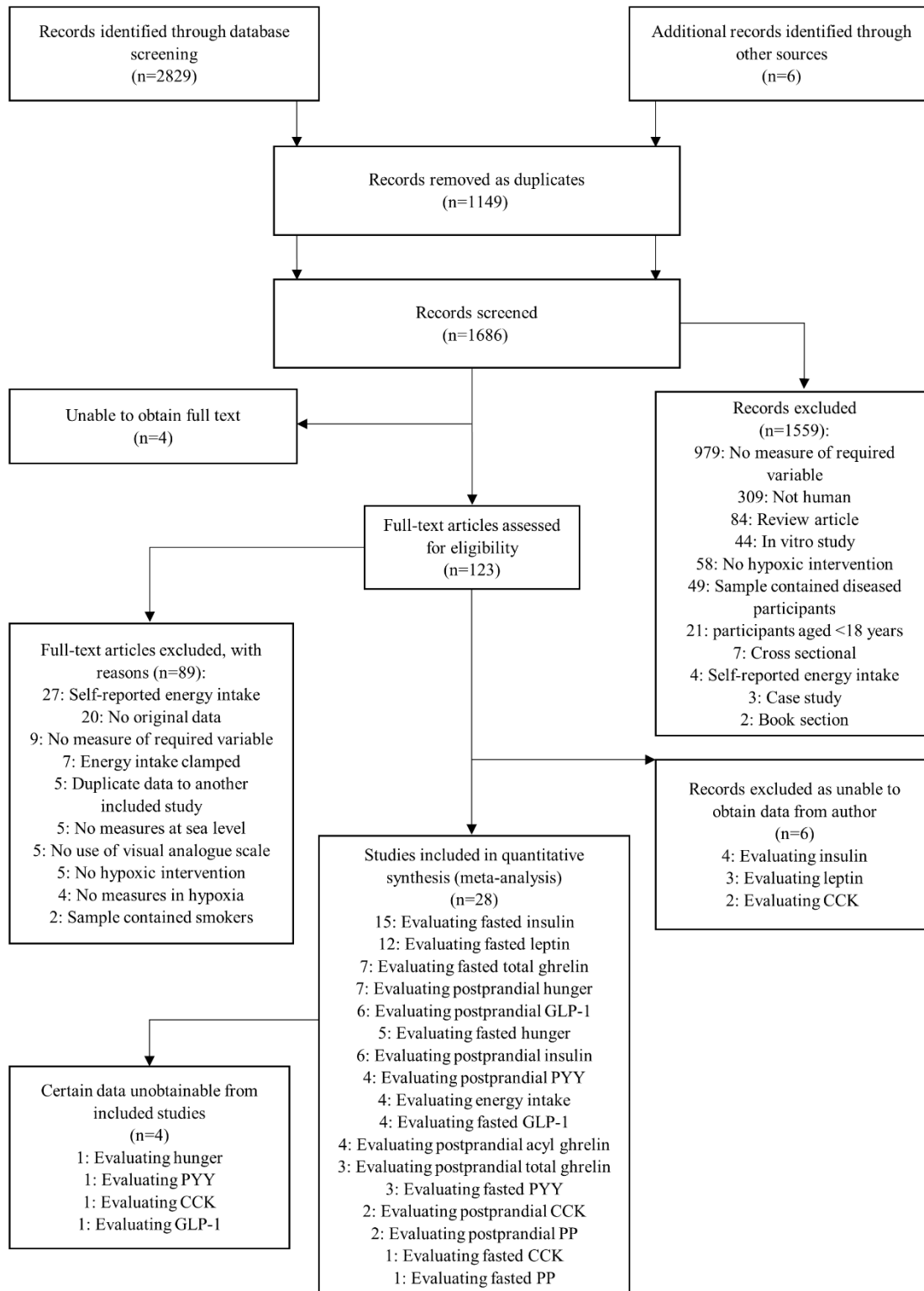


Figure 7



Supplementary figure 1



Article title: The effects of hypoxia on hunger perceptions, appetite-related hormone concentrations, and energy intake: a systematic review and meta-analysis

Journal: Appetite

Authors names: Jamie Matu, Javier T. Gonzalez, Theocharis Ispoglou, Lauren Duckworth and Kevin Deighton

Corresponding author: Dr Kevin Deighton, Institute for Sport Physical Activity & Leisure, Leeds Beckett University, Leeds, LS6 3QS, United Kingdom (email: K.Deighton@leedsbeckett.ac.uk)

Supplementary material

Search strategy: PubMed and The Cochrane Library as well as MEDLINE, SPORTDiscus, PsycINFO and CINAHL, via EBSCOhost

Search terms:

1. Altitude
2. Hypoxia
3. Hypoxic
4. Mountaineering
5. Appetite
6. Appetite hormones
7. Ghrelin
8. Acylated ghrelin
9. GLP-1
10. Glucagon like peptide-1
11. Peptide YY
12. PYY
13. Leptin
14. Pancreatic polypeptide
15. Insulin
16. CCK
17. Cholecystokinin
18. Hunger
19. Satiety
20. Energy intake
21. Food intake
22. Energy balance

Searches:

A) 1 and 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

B) 2 and 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

C) 3 and 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

D) 4 and 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

Article title: The effects of hypoxia on hunger perceptions, appetite-related hormone concentrations, and energy intake: a systematic review and meta-analysis

Journal: Appetite

Authors names: Jamie Matu, Javier T. Gonzalez, Theocharis Ispoglou, Lauren Duckworth and Kevin Deighton

Corresponding author: Dr Kevin Deighton, Institute for Sport Physical Activity & Leisure, Leeds Beckett University, Leeds, LS6 3QS, United Kingdom (email:

K.Deighton@leedsbeckett.ac.uk)

Supplementary Table 1. Effects of hypoxic exposure on fasted hunger and fasted hormone concentrations

Study	Participants	Intervention						Variables assessed					
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	Leptin /pg·ml ⁻¹	PYY /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹
Aeberli et al. 2013-1	22 men and women combined	Longitudinal	4559	2 days	Unacclimatised	Terrestrial altitude	Active	SL: 59 (8) ALT: 43 (8)	-	-	-	-	-
Aeberli et al. 2013-2	22 men and women combined	Longitudinal	4559	4 days	Unacclimatised	Terrestrial altitude	Active	SL: 59 (8) ALT: 64 (6)	-	-	-	-	-
Bailey et al. 2004	7 men and women combined	Longitudinal	4780	11 days	Unacclimatised	Terrestrial altitude	Active	-	SL: 68.2 (29.7) ALT: 89.3 (44.8)	SL: 13.3 (5.6) ALT: 10.4 (6.8)	SL: 42 (19) ALT: 34 (13) # ^a	-	-
Benso et al. 2007	9 men	Longitudinal	5200	61 days	Acclimatised	Terrestrial altitude	Active	-	-	SL: 10.1 (2.4) ALT: 10.9 (2.4)	SL: 777 (197) ALT: 606 (209)	-	SL: 147 (26) ALT: 158 (45)
Braun et al. 2001	12 females	Longitudinal	4300	16 hours	Unacclimatised	Simulated hypobaric	Passive	-	-	SL: 3.3 (1.5) ALT: 5.0 (2.0)	-	-	-
Castell et al. 2010-1	35 men	Longitudinal	2134	1 day	Unacclimatised	Terrestrial altitude	Active	-	-	-	SL: 2 (2) ALT: 2 (1)	-	-
Castell et al. 2010-2	56 men	Longitudinal	2743	14 days	Unacclimatised	Terrestrial altitude	Active	-	-	-	SL: 2 (2) ALT: 1 (1)	-	-
Castell et al. 2010-3	53 men	Longitudinal	2743	28 days	Unacclimatised	Terrestrial altitude	Active	-	-	-	SL: 2 (2) ALT: 2 (1)	-	-

Study	Participants	Intervention						Variables assessed					
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	Leptin /pg·ml ⁻¹	PYY /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹
Debevec et al. 2014a-1	11 men	Longitudinal	4000	1 day	Unacclimatised	Simulated normobaric	Active	SL: 40.2 (36.4) ALT: 45.3 (31.4)	-	-	-	-	-
Debevec et al. 2014a-2	11 men	Longitudinal	4000	21 days	Unacclimatised	Simulated normobaric	Active	SL: 40.2 (36.4) ALT: 44.3 (33.6)	-	-	-	-	-
Debevec et al. 2014a-3	11 men	Longitudinal	4000	1 day	Unacclimatised	Simulated normobaric	Passive	SL: 49.9 (29.6) ALT: 46.4 (40.0)	-	-	-	-	-
Debevec et al. 2014a-4	11 men	Longitudinal	4000	21 days	Unacclimatised	Simulated normobaric	Passive	SL: 49.9 (29.6) ALT: 47.5 (40.1)	-	-	-	-	-
Debevec et al. 2014b-1	8 men	Longitudinal	4000	1 day	Unacclimatised	Simulated normobaric	Active	SL: 45.6 (24.0) ALT: 47.0 (23.2)	SL: 12.0 (21.8) ALT: 12.4 (19.3)	SL: 10.6 (2.0) ALT: 10.9 (1.9)	SL: 4910 (3530) ALT: 6920 (4220)	SL: 97.8 (21.8) ALT: 93.8 (13.3)	SL: 911 (239) ALT: 817 (162)
Debevec et al. 2014b-2	8 men	Longitudinal	4000	10 days	Unacclimatised	Simulated normobaric	Active	SL: 45.6 (24.0) ALT: 50.5 (20.2)	SL: 12.0 (21.8) ALT: 9.1 (12.6)	SL: 10.6 (2.0) ALT: 8.7 (1.9)	SL: 4910 (3530) ALT: 3650 (2020)	SL: 97.8 (21.8) ALT: 102.2 (13.6)	SL: 911 (239) ALT: 876 (247)
Debevec et al. 2014b-3	6 men	Longitudinal	4000	1 day	Unacclimatised	Simulated normobaric	Passive	SL: 44.1 (10.9) ALT: 58.3 (19.0)	SL: 6.3 (7.0) ALT: 8.6 (7.7)	SL: 10.4 (1.5) ALT: 12.1 (1.9)	SL: 3600 (1220) ALT: 5030 (2140)	SL: 101.7 (25.6) ALT: 96.8 (31.2)	SL: 705 (160) ALT: 743 (145)
Debevec et al. 2014b-4	6 men	Longitudinal	4000	10 days	Unacclimatised	Simulated normobaric	Passive	SL: 44.1 (10.9) ALT: 33.8 (25.9)	SL: 6.3 (7.0) ALT: 5.5 (6.7)	SL: 10.4 (1.5) ALT: 8.1 (1.1)	SL: 3600 (1220) ALT: 3490 (1360)	SL: 101.7 (25.6) ALT: 93.8 (20.7)	SL: 705 (160) ALT: 782 (155)
Debevec et al. 2016-1	11 men	Longitudinal	4000	16 days	Unacclimatised	Simulated normobaric	Active	SL: 50.3 (37.5) ALT: 43.2 (36.6)	SL: 7.0 (3.8) ALT: 5.6 (1.7)	-	SL: 4487 (2977) ALT: 3449 (2891)	SL: 97.5 (34.7) ALT: 100.4 (35.4)	SL: 778 (289) ALT: 845 (296)
Debevec et al. 2016-2	11 men	Longitudinal	4000	16 days	Unacclimatised	Simulated normobaric	Passive	SL: 54.5 (26.7) ALT: 51.4 (37.5)	SL: 6.2 (5.1) ALT: 5.8 (2.5)	-	SL: 5192 (4316) ALT: 4431 (3689)	SL: 128.6 (45.9)	SL: 761 (242) ALT: 852 (254)

Study	Participants	Intervention							Variables assessed					
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	Leptin /pg·ml ⁻¹	PYY /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹	
Larsen et al. 1997-1	8 men	Longitudinal	4559	2 days	Unacclimatised	True altitude	Passive	-	-	SL: 6.8 (1.3) ALT: 10.5 (2.0)	-	-	ALT: 135.0 (40.8)	-
Larsen et al. 1997-2	8 men	Longitudinal	4559	7 days	Unacclimatised	True altitude	Passive	-	-	SL: 6.8 (1.3) ALT: 5.2 (2.2)	-	-	-	-
Mekjavic et al. 2016	11 men	Longitudinal	3400	10 days	Unacclimatised	Simulated normobaric	Passive	-	SL: 4.2 (14.0) ALT: 6.2 (18.7)	SL: 2.7 (4.4) ALT: 2.7 (5.4)	SL: 2600 (696) ALT: 3630 (862)	SL: 97.7 (90.2) ALT: 107.2 (64.3)	SL: 1030 (107) ALT: 1177 (107)	
Riedl et al. 2012-1	33 men and women combined	Longitudinal	3440	4 days	Unacclimatised	Terrestrial altitude	Active	-	-	SL: 6.2 (1.9) ALT: 5.9 (1.9)	-	-	SL: 111 (45) ALT: 119 (57)	
Riedl et al. 2012-2	28 men and women combined	Longitudinal	5050	14 days	Unacclimatised	Terrestrial altitude	Active	-	-	SL: 6.2 (1.9) ALT: 6.6 (2.4)	-	-	SL: 111 (45) ALT: 150 (70)	
Riepl et al. 2012	5 men	Longitudinal	3454	19 hours	Unacclimatised	Terrestrial altitude	Passive	-	-	-	-	-	SL: 32 (11) ALT: 27 (8)	
Sawhney et al. 1986	10 men	Longitudinal	3500	14 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 7.4 (5.4) ALT: 6.2 (2.4)	-	-	-	
Sawhney et al. 1991-1	15 men	Longitudinal	3500	3 days	Acclimatised	Terrestrial altitude	Passive	-	-	SL: 9.1 (1.2) ALT: 13.6 (1.4)	-	-	-	
Sawhney et al. 1991-2	15 men	Longitudinal	3500	21 days	Acclimatised	Terrestrial altitude	Passive	-	-	SL: 9.1 (1.2) ALT: 10.0 (1.2)	-	-	-	
Sawhney et al. 1991-3	15 men	Longitudinal	5080	30 days	Acclimatised	Terrestrial altitude	Passive	-	-	SL: 9.1 (1.2) ALT: 11.9 (1.4)	-	-	-	

Study	Participants	Intervention							Variables assessed				
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	Leptin /pg·ml ⁻¹	PYY /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹
Sawhney et al. 1991-4	15 men	Longitudinal	5080	41 days	Acclimatised	Terrestrial altitude	Passive	-	-	SL: 9.1 (1.2) ALT: 9.8 (1.4)	-	-	-
Shukla et al. 2005-1	25 men	Longitudinal	3600	2 days	Unacclimatised	Terrestrial altitude	Passive	-	-	-	SL: 3500 (2000) ALT: 3740 (1880)	-	SL: 1282 (554) ALT: 836 (564)
Shukla et al. 2005-2	25 men	Longitudinal	4300	4 days	Unacclimatised	Terrestrial altitude	Passive	-	-	-	SL: 3500 (2000) ALT: 5350 (1980)	-	SL: 1282 (554) ALT: 733 (527)
Shukla et al. 2005-3	25 men	Longitudinal	4300	11 days	Unacclimatised	Terrestrial altitude	Passive	-	-	-	SL: 3500 (2000) ALT: 5130 (1840)	-	SL: 1282 (554) ALT: 997 (653)
Simpson et al. 2016-1	11 men	Longitudinal	4000	17 days	Unacclimatised	Simulated normobaric	Active	-	-	SL: 12.1 (3.2) ALT: 10.7 (4.8)	-	-	-
Simpson et al. 2016-2	11 men	Longitudinal	4000	17 days	Unacclimatised	Simulated normobaric	Passive	-	-	SL: 12.4 (4.3) ALT: 11.9 (2.6)	-	-	-
Smith et al. 2011-1	10 men and women combined	Longitudinal	4000	3 days	Unacclimatised	Terrestrial altitude	Active	-	-	SL: 2.1 (0.3) ALT: 2.0 (0.5)	SL: 3500 (2010) ALT: 3220 (2250)	-	-
Smith et al. 2011-2	10 men and women combined	Longitudinal	4750	6 days	Unacclimatised	Terrestrial altitude	Active	-	-	SL: 2.1 (0.3) ALT: 2.2 (0.8)	SL: 3500 (2010) ALT: 3450 (1800)	-	-
Smith et al. 2011-3	10 men and women combined	Longitudinal	5300	9 days	Unacclimatised	Terrestrial altitude	Active	-	-	SL: 2.1 (0.3) ALT: 2.4 (0.7)	SL: 3500 (2010) ALT: 3640 (3000)	-	-
Snyder et al. 2008	25 men and women combined	Longitudinal	4100	17 hours	Unacclimatised	Simulated normobaric	Passive	-	-	-	SL: 5 (1) ALT: 8 (2)	-	-
Splithoff et al. 2013-1	9 men	Longitudinal	4559	2 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 5.3 (1.4) ALT: 7.0 (1.4)	-	-	-

Study	Participants	Intervention							Variables assessed				
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	Leptin /pg·ml ⁻¹	PYY /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹
Splithoff et al. 2013-2	9 men	Longitudinal	4559	4 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 5.3 (1.4) ALT: 6.2 (1.5)	-	-	-
Tschop et al. 2000	20 men	Longitudinal	4559	22 hours	Unknown	Terrestrial altitude	Active	-	-	-	SL: 1220 (850) ALT: 2060 (1521)	-	-
Vats et al. 2004-1	10 men	Longitudinal	3600	2 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 5.5 (2.9) ALT: 7.1 (3.4)	SL: 4500 (2941) ALT: 1310 (885)	-	-
Vats et al. 2004-2	10 men	Longitudinal	3600	7 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 5.5 (2.9) ALT: 9.0 (8.1)	SL: 4500 (2941) ALT: 1800 (1708)	-	-
Vats et al. 2004-3	10 men	Longitudinal	4580	9 days	Unacclimatised	Terrestrial altitude	Active	-	-	SL: 5.5 (2.9) ALT: 5.9 (3.5)	SL: 4500 (2941) ALT: 1720 (1107)	-	-
Westerterp-Plantenga et al. 1999-1	8 men	Longitudinal	5000	4 days	Acclimatised	Simulated hypobaric	Passive	SL: 75.8 (7.3) ALT: 68.0 (5.7)	-	-	-	-	-
Westerterp-Plantenga et al. 1999-2	8 men	Longitudinal	6000	11 days	Acclimatised	Simulated hypobaric	Passive	SL: 75.8 (7.3) ALT: 62.1 (4.3)	-	-	-	-	-
Westerterp-Plantenga et al. 1999-3	8 men	Longitudinal	7000	17 days	Acclimatised	Simulated hypobaric	Passive	SL: 75.8 (7.3) ALT: 53.5 (5.3)	-	-	-	-	-
Young et al. 1989-1	6 men	Longitudinal	4280	7 days	Acclimatised	Simulated hypobaric	Active	-	-	SL: 5.9 (0.7) ALT: 6.8 (2.5)	-	-	-
Young et al. 1989-2	6 men	Longitudinal	5572	16 days	Acclimatised	Simulated hypobaric	Active	-	-	SL: 5.9 (0.7) ALT: 9.7 (2.8)	-	-	-
Young et al. 1989-3	6 men	Longitudinal	6509	25 days	Acclimatised	Simulated hypobaric	Active	-	-	SL: 5.9 (0.7) ALT: 11.2 (3.3)	-	-	-

Study	Participants	Intervention							Variables assessed				
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	Leptin /pg·ml ⁻¹	PYY /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹
Young et al. 1989-4	6 men	Longitudinal	7753	32 days	Acclimatised	Simulated hypobaric	Active	-	-	SL: 5.9 (0.7) ALT: 11.4 (4.8)	-	-	-
Young et al. 1989-5	6 men	Longitudinal	7753	40 days	Acclimatised	Simulated hypobaric	Active	-	-	SL: 5.9 (0.7) ALT: 12.0 (6.3)	-	-	-
Zaccaria et al. 2004-1	12 men	Longitudinal	5050	1.6 days	Acclimatised	True altitude	Active	-	-	SL: 6.3 (1.9) ALT: 6.8 (2.7)	SL: 1880 (1120) ALT: 1210 (1040)	-	-
Zaccaria et al. 2004-2	12 men	Longitudinal	5050	14 days	Acclimatised	True altitude	Active	-	-	SL: 6.3 (1.9) ALT: 7.2 (1.4)	SL: 1880 (1120) ALT: 1060 (740)	-	-

Data are mean (SD); RCT = randomised controlled trial, SL = sea-level, ALT = altitude

Supplementary Table 2. Effects of hypoxic exposure on postprandial hunger, postprandial hormone concentration and energy intake

Study	Participants	Intervention						Variables assessed						
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	PYY /pg·ml ⁻¹	Acylated ghrelin /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹	Energy intake /kJ
Aeberli et al. 2013-1	22 men and women combined	Longitudinal	4559	2 days	Unacclimatised	Terrestrial altitude	Active	SL: 45 (34) ALT: 37 (31)	-	-	-	-	-	SL: 3983 (1916) ALT: 2690 (1289)
Aeberli et al. 2013-2	22 men and women combined	Longitudinal	4559	4 days	Unacclimatised	Terrestrial altitude	Active	SL: 45 (34) ALT: 52 (31)	-	-	-	-	-	SL: 3983 (1916) ALT: 3724 (1247)
Bailey et al. 2015-1	12 men	RCT	2980	50 minutes	Unacclimatised	Simulated normobaric	Active (moderate intensity)	SL: 39 (14) ALT: 40 (16)	SL: 164 (74) ALT: 163 (80)	SL: 12 (8) (9) ALT: 14 (9)	SL: 130 (52) ALT: 127 (5)	SL: 55 (55) ALT: 49 (53)	-	-
Bailey et al. 2015-2	12 men	RCT	2980	50 minutes	Unacclimatised	Simulated normobaric	Active (high intensity)	SL: 32 (15) ALT: 30 (14)	SL: 169 (76) ALT: 168 (76)	SL: 10 (6) (5) ALT: 10 (5)	SL: 118 (40) ALT: 138 (52)	SL: 52 (44) ALT: 48 (57)	-	-
Debevec et al. 2014b-2	8 men	Longitudinal	4000	10 days	Unacclimatised	Simulated normobaric	Active	-	SL: 19 (24) ALT: 17 (15)	SL: 52 (16) ALT: 40 (8)	SL: 121 (30) ALT: 124 (20)	-	SL: 751 (165) ALT: 734 (163)	-
Debevec et al. 2014b-4	6 men	Longitudinal	4000	10 days	Unacclimatised	Simulated normobaric	Passive	-	SL: 13 (7) ALT: 15 (8)	SL: 55 (23) ALT: 43 (11)	SL: 126 (35) ALT: 124 (29)	-	SL: 647 (94) ALT: 695 (132)	-
Debevec et al. 2016-1	11 men	Longitudinal	4000	16 days	Unacclimatised	Simulated normobaric	Active	SL: 46 (32) ALT: 48 (34)	SL: 17 (8) (7) ALT: 18 (7)	-	SL: 121 (37) ALT: 139 (76)	-	SL: 621 (237) ALT: 636 (199)	SL: 1120 (478) ALT: 1142 (478)
Debevec et al. 2016-2	11 men	Longitudinal	4000	16 days	Unacclimatised	Simulated normobaric	Passive	SL: 47 (27) ALT: 46 (34)	SL: 18 (12) ALT: 14 (7)	-	SL: 157 (48) ALT: 159 (46)	-	SL: 583 (169) ALT: 632 (160)	SL: 1075 (344) ALT: 1017 (408)
Matu et al. 2017a-1	12 men	RCT	2150	5 hours	Unacclimatised	Simulated normobaric	Active	SL: 42 (27) ALT: 45 (28)	SL: 92 (50) ALT: 96 (52)	SL: 17 (16) ALT: 16 (15)	-	SL: 97 (59) ALT: 94 (59)	-	SL: 7358 (1789) ALT: 7390 (1226)

Study	Participants	Intervention						Variables assessed						
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	PYY /pg·ml ⁻¹	Acylated ghrelin /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹	Energy intake /kJ
Matu et al. 2017a-2	12 men	RCT	4300	5 hours	Unacclimatised	Simulated normobaric	Active	SL: 42 (27) ALT: 34 (27)	SL: 92 (50) ALT: 93 (54)	SL: 17 (16) ALT: 18 (12)	-	SL: 97 (59) ALT: 56 (33)	-	SL: 7358 (1789) ALT: 3728 (3179)
Mekjavic et al. 2016	11 men	Longitudinal	3400	10 days	Unacclimatised	Simulated normobaric	Passive	-	SL: 6 (16) ALT: 8 (19)	SL: 41 (71) ALT: 62 (99)	-	-	-	-
Morishima & Goto 2016	8 men	RCT	2540	7 hours	Unacclimatised	Simulated normobaric	Passive	SL: 40 (5) ALT: 38 (7)	SL: 16 (4) ALT: 17 (5)	-	-	SL: 22 (9) ALT: 20 (9)	-	-
Riepl et al. 2012	5 men	Longitudinal	3454	19 hours	Unacclimatised	Terrestrial altitude	Passive	-	-	-	-	-	SL: 26 (7) ALT: 19 (6)	-
Simpson et al. 2016-1	11 men	Longitudinal	4000	17 days	Unacclimatised	Simulated normobaric	Active	-	-	SL: 67.1 (22.8) ALT: 58.9 (24.9)	-	-	-	-
Simpson et al. 2016-2	11 men	Longitudinal	4000	17 days	Unacclimatised	Simulated normobaric	Passive	-	-	SL: 73.0 (32.6) ALT: 77.9 (38.5)	-	-	-	-
Splithoff et al. 2013-1	9 men	Longitudinal	4559	2 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 10 (7) ALT: 9 (5)	-	-	-	-
Splithoff et al. 2013-2	9 men	Longitudinal	4559	4 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 10 (7) ALT: 12 (7)	-	-	-	-
Wasse et al. 2012-1	10 men	RCT	4000	7 hours	Unacclimatised	Simulated normobaric	Passive	SL: 50 (8) ALT: 39 (17)	-	-	SL: 125 (30) ALT: 113 (42)	SL: 109 (79) ALT: 85 (61)	-	SL: 7535 (2112) ALT: 5504 (2427)
Wasse et al. 2012-2	10 men	RCT	4000	7 hours	Unacclimatised	Simulated normobaric	Active	SL: 44 (18) ALT: 36 (19)	-	-	SL: 133 (44) ALT: 124 (40)	SL: 92 (58) ALT: 80 (71)	-	SL: 7909 (2599)

Study	Participants	Intervention					Variables assessed								
		Design	Hypoxic severity /m	Duration	Acclimatisation status	Hypoxic method	Activity status	Hunger /mm	GLP-1 /pg·ml ⁻¹	Insulin /μU·mL ⁻¹	PYY /pg·ml ⁻¹	Acylated ghrelin /pg·ml ⁻¹	Total ghrelin /pg·ml ⁻¹	Energy intake /kJ	
Westerterp-Plantenga et al. 1999-1	8 men	Longitudinal	5000	4 days	Acclimatised	Simulated hypobaric	Passive	SL: 44 (24) ALT: 38 (12)	-	-	-	-	-	-	ALT: 5084 (1952)
Westerterp-Plantenga et al. 1999-2	8 men	Longitudinal	6000	11 days	Acclimatised	Simulated hypobaric	Passive	SL: 44 (24) ALT: 36 (9)	-	-	-	-	-	-	-
Westerterp-Plantenga et al. 1999-3	8 men	Longitudinal	7000	17 days	Acclimatised	Simulated hypobaric	Passive	SL: 44 (24) ALT: 32 (8)	-	-	-	-	-	-	-

Data are mean (SD); RCT = randomised controlled trial, SL = sea-level, ALT = altitude

Supplementary Table 3. Individual study characteristics for studies evaluating fasted hunger

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Aeberli et al. 2013-1	-2.000	0.362	0.131	-2.709	-1.291	-5.528	0.000	22	5.66
Aeberli et al. 2013-2	0.692	0.233	0.054	0.236	1.148	2.976	0.003	22	6.52
Westerterp-Plantenga et al. 1999-1	-1.172	0.450	0.202	-2.054	-0.290	-2.605	0.009	8	5.04
Westerterp-Plantenga et al. 1999-2	-2.146	0.629	0.396	-3.380	-0.912	-3.409	0.001	8	3.90
Westerterp-Plantenga et al. 1999-3	-3.406	0.903	0.816	-5.177	-1.636	-3.770	0.000	8	2.61
Debevec et al. 2014a-1	0.149	0.297	0.088	-0.433	0.731	0.502	0.616	11	6.11
Debevec et al. 2014a-2	0.117	0.296	0.088	-0.464	0.698	0.394	0.693	11	6.11
Debevec et al. 2014a-3	-0.097	0.296	0.088	-0.678	0.483	-0.328	0.743	11	6.11
Debevec et al. 2014a-4	-0.067	0.296	0.087	-0.646	0.513	-0.225	0.822	11	6.11
Debevec et al. 2014b-1	0.061	0.347	0.120	-0.619	0.741	0.176	0.860	8	5.77
Debevec et al. 2014b-2	0.221	0.351	0.123	-0.466	0.908	0.631	0.528	8	5.74
Debevec et al. 2014b-3	0.859	0.468	0.219	-0.059	1.776	1.835	0.067	6	4.92
Debevec et al. 2014b-4	-0.450	0.420	0.176	-1.273	0.373	-1.072	0.284	6	5.25
Debevec et al. 2016-1	-0.191	0.298	0.089	-0.775	0.393	-0.641	0.521	11	6.10
Debevec et al. 2016-2	-0.095	0.296	0.088	-0.675	0.485	-0.321	0.748	11	6.11
Mean	-0.347	0.212	0.045	-0.763	0.069	-1.637	0.102		

Supplementary table 4. Individual study characteristics for studies evaluating postprandial hunger

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Aeberli et al. 2013-1	-0.234	0.191	0.036	0.608	0.140	1.224	0.221	22	12.96
Aeberli et al. 2013-2	0.232	0.191	0.036	-0.142	0.606	1.214	0.225	22	12.97
Westerterp-plantenga et al. 1999-1	-0.276	0.318	0.101	-0.900	0.348	-0.868	0.386	8	4.97
Westerterp-plantenga et al. 1999-2	-0.356	0.322	0.104	-0.987	0.275	-1.106	0.269	8	4.85
Westerterp-plantenga et al. 1999-3	-0.526	0.333	0.111	-1.179	0.127	-1.579	0.114	8	4.54
Bailey et al. 2015-1	0.099	0.256	0.065	-0.402	0.600	0.388	0.698	12	7.55
Bailey et al. 2015-2	-0.100	0.256	0.065	-0.601	0.401	-0.392	0.695	12	7.55
Wasse et al. 2012-1	-0.731	0.314	0.099	-1.347	-0.115	-2.324	0.020	10	5.08
Wasse et al. 2012-2	-0.416	0.291	0.085	-0.987	0.154	-1.430	0.153	10	5.89
Debevec et al. 2016-1	0.054	0.266	0.071	-0.469	0.576	0.201	0.841	11	6.97
Debevec et al. 2016-2	-0.044	0.266	0.071	-0.566	0.478	-0.165	0.869	11	6.98
Morishima & Goto 2016	-0.306	0.319	0.102	-0.932	0.320	-0.957	0.338	8	4.93
Matu et al. 2017-1	0.112	0.256	0.065	-0.390	0.613	0.436	0.663	12	7.54
Matu et al. 2017-2	-0.321	0.261	0.068	-0.834	0.191	-1.229	0.219	12	7.23
Mean	-0.146	0.072	0.005	-0.288	-0.005	-2.023	0.043		

Supplementary table 5. Individual study characteristics for studies evaluating energy intake

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Aeberli et al. 2013-1	-0.763	0.240	0.058	-1.233	-0.293	-3.181	0.001	22	14.73
Aeberli et al. 2013-2	-0.154	0.212	0.045	-0.570	0.262	-0.724	0.469	22	15.62
Wasse et al. 2012-1	-0.888	0.370	0.137	-1.613	-0.164	-2.403	0.016	10	10.78
Wasse et al. 2012-2	-1.205	0.411	0.169	-2.011	-0.399	-2.929	0.003	10	9.72
Debevec et al. 2016-1	0.046	0.299	0.089	-0.539	0.631	0.154	0.878	11	12.85
Debevec et al. 2016-2	-0.153	0.300	0.090	-0.741	0.436	-0.508	0.611	11	12.80
Matu et al. 2017a-1	0.021	0.286	0.082	-0.540	0.581	0.072	0.943	12	13.25
Matu et al. 2017a-2	-1.312	0.390	0.152	-2.076	-0.548	-3.365	0.001	12	10.26
Mean	-0.495	0.179	0.032	-0.845	-0.145	-2.770	0.006		

Supplementary table 6. Individual study characteristics for studies evaluating postprandial acylated ghrelin concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Bailey et al. 2015-1	-0.108	0.071	0.005	-0.247	0.031	-1.518	0.129	12	15.04
Bailey et al. 2015-2	-0.050	0.071	0.005	-0.189	0.089	-0.709	0.478	12	15.07
Wasse et al. 2012-1	-0.237	0.079	0.006	-0.391	-0.083	-3.015	0.003	10	13.78
Wasse et al. 2012-2	-0.137	0.078	0.006	-0.290	0.016	-1.760	0.078	10	13.90
Morishima & Goto 2016	-0.169	0.087	0.008	-0.340	0.002	-1.940	0.052	8	12.46
Matu et al. 2017a-1	-0.064	0.071	0.005	-0.203	0.074	-0.910	0.363	12	15.07
Matu et al. 2017a-2	-0.367	0.073	0.005	-0.510	-0.224	-5.026	0.000	12	14.68
Mean	-0.160	0.043	0.002	-0.245	-0.075	-3.703	0.000		

Supplementary table 7. Individual study characteristics for studies evaluating fasted total ghrelin concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Benso et al. 2007	0.295	0.373	0.139	-0.436	1.026	0.792	0.429	9	5.56
Riedl et al. 2012-1	0.154	0.192	0.037	-0.222	0.530	0.805	0.421	33	7.72
Riedl et al. 2012-2	0.644	0.227	0.052	0.198	1.090	2.830	0.005	28	7.30
Riepl et al. 2012-4	-0.478	0.517	0.267	-1.491	0.536	-0.924	0.356	5	4.11
Shukla et al. 2005-1	-0.798	0.252	0.063	-1.291	-0.305	-3.172	0.002	25	7.01
Shukla et al. 2005-2	-1.015	0.270	0.073	-1.544	-0.486	-3.764	0.000	25	6.79
Shukla et al. 2005-3	-0.469	0.231	0.053	-0.921	-0.016	-2.030	0.042	25	7.26
Debevec et al. 2014b-1	-0.450	0.406	0.165	-1.246	0.347	-1.107	0.268	8	5.19
Debevec et al. 2014b-2	-0.144	0.389	0.152	-0.907	0.619	-0.370	0.711	8	5.37
Debevec et al. 2014b-3	0.248	0.454	0.206	-0.641	1.138	0.547	0.584	6	4.70
Debevec et al. 2014b-4	0.489	0.473	0.224	-0.439	1.416	1.033	0.302	6	4.51
Mekjavic et al. 2016	1.362	0.459	0.210	0.464	2.261	2.971	0.003	11	4.65
Debevec et al. 2016-1	0.232	0.335	0.112	-0.424	0.888	0.693	0.488	11	6.00
Debevec et al. 2016-2	0.366	0.341	0.116	-0.302	1.035	1.074	0.283	11	5.92
Mean	0.003	0.170	0.029	-0.331	0.337	0.016	0.987		

Supplementary table 8. Individual study characteristics for studies evaluating postprandial total ghrelin concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Riepl et al. 2012-4	-1.098	0.549	0.301	-2.174	-0.022	-2.001	0.045	5	10.65
Debevec et al. 2014b-2	-0.106	0.344	0.118	-0.780	0.567	-0.309	0.757	8	21.35
Debevec et al. 2014b-4	0.406	0.412	0.170	-0.401	1.214	0.987	0.324	6	16.65
Debevec et al. 2016-1	0.065	0.293	0.086	-0.508	0.639	0.223	0.824	11	25.98
Debevec et al. 2016-2	0.295	0.299	0.089	-0.290	0.881	0.989	0.323	11	25.98
Mean	0.020	0.197	0.039	-0.367	0.407	0.101	0.920		

Supplementary table 9. Individual study characteristics for studies evaluating fasted GLP-1 concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Bailey et al. 2004	0.370	0.135	0.018	0.105	0.636	2.736	0.006	7	11.49
Debevec et al. 2014b-1	0.015	0.122	0.015	-0.225	0.255	0.124	0.901	8	12.48
Debevec et al. 2014b-2	-0.095	0.123	0.015	-0.336	0.146	-0.775	0.439	8	12.46
Debevec et al. 2014b-3	0.301	0.145	0.021	0.017	0.584	2.079	0.038	6	10.83
Debevec et al. 2014b-4	-0.119	0.142	0.020	-0.398	0.159	-0.842	0.400	6	11.02
Mekjavic et al. 2016	0.095	0.105	0.011	-0.110	0.300	0.910	0.363	11	13.93
Debevec 2016-1	-0.223	0.106	0.011	-0.431	-0.016	-2.112	0.035	11	13.84
Debevec 2016-2	-0.043	0.104	0.011	-0.248	0.161	-0.415	0.678	11	13.95
Mean	0.028	0.070	0.005	-0.108	0.165	0.407	0.684		

Supplementary table 10. Individual study characteristics for studies evaluating postprandial GLP-1 concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Bailey et al. 2015-1	-0.020	0.091	0.008	-0.199	0.158	-0.224	0.823	12	11.11
Bailey et al. 2015-2	-0.019	0.091	0.008	-0.198	0.160	-0.209	0.835	12	11.11
Debevec et al. 2014b-2	-0.078	0.112	0.013	-0.297	0.142	-0.694	0.488	8	8.63
Debevec et al. 2014b-4	0.299	0.132	0.017	0.040	0.557	2.265	0.024	6	6.86
Mekjavic et al. 2016	0.097	0.096	0.009	-0.090	0.284	1.014	0.310	11	10.54
Debevec et al. 2016-1	0.114	0.096	0.009	-0.073	0.302	1.197	0.231	11	10.52
Debevec et al. 2016-2	-0.227	0.097	0.009	-0.417	-0.038	-2.355	0.019	11	10.41
Morishima & Goto 2016	0.112	0.112	0.013	-0.108	0.332	0.996	0.319	8	8.62
Matu et al. 2017a-1	0.075	0.091	0.008	-0.105	0.254	0.816	0.414	12	11.09
Matu et al. 2017a-2	0.027	0.091	0.008	-0.152	0.206	0.297	0.767	12	11.11
Mean	0.029	0.040	0.002	-0.050	0.108	0.716	0.474		

Supplementary table 11. Individual study characteristics for studies evaluating fasted leptin concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Zaccaria et al. 2004-1	-0.620	0.368	0.135	-1.340	0.101	-1.686	0.092	12	4.04
Zaccaria et al. 2004-2	-0.848	0.393	0.154	-1.617	-0.079	-2.160	0.031	12	3.92
Bailey et al. 2004	-0.482	0.466	0.217	-1.394	0.431	-1.034	0.301	7	3.58
Benso et al. 2007	-0.842	0.452	0.205	-1.729	0.045	-1.861	0.063	9	3.64
Castell et al. 2010-1	-0.533	0.211	0.044	-0.946	-0.121	-2.532	0.011	35	4.73
Castell et al. 2010-2	-1.035	0.193	0.037	-1.414	-0.657	-5.361	0.000	56	4.79
Castell et al. 2010-3	-0.510	0.170	0.029	-0.844	-0.176	-2.996	0.003	53	4.86
Shukla et al. 2005-1	0.124	0.214	0.046	-0.295	0.542	0.578	0.563	30	4.71
Shukla et al. 2005-2	0.930	0.255	0.065	0.430	1.429	3.648	0.000	30	4.55
Shukla et al. 2005-3	0.848	0.248	0.062	0.361	1.334	3.414	0.001	30	4.58
Smith et al. 2011-1	-0.131	0.370	0.137	-0.857	0.595	-0.354	0.723	10	4.03
Smith et al. 2011-2	-0.026	0.369	0.136	-0.749	0.697	-0.071	0.943	10	4.04
Smith et al. 2011-3	0.054	0.369	0.136	-0.669	0.777	0.146	0.884	10	4.04
Tschop et al. 2000	0.659	0.288	0.083	0.095	1.223	2.292	0.022	20	4.41
Vats et al. 2004-1	-1.335	0.507	0.257	-2.329	-0.341	-2.632	0.008	10	3.39
Vats et al. 2004-2	-1.090	0.466	0.217	-2.002	-0.177	-2.340	0.019	10	3.58
Vats et al. 2004-3	-1.162	0.477	0.228	-2.097	-0.226	-2.434	0.015	10	3.52
Debevec et al. 2014b-1	0.515	0.439	0.193	-0.345	1.375	1.173	0.241	8	3.70
Debevec et al. 2014b-2	-0.425	0.430	0.185	-1.268	0.419	-0.986	0.324	8	3.74
Debevec et al. 2014b-3	0.795	0.546	0.298	-0.275	1.866	1.456	0.145	6	3.21
Debevec et al. 2014b-4	-0.085	0.477	0.227	-1.020	0.850	-0.178	0.859	6	3.53
Snyder et al. 2008	2.242	0.437	0.191	1.385	3.098	5.128	0.000	25	3.71
Mekjavic et al. 2016	1.307	0.479	0.229	0.369	2.246	2.730	0.006	11	3.52
Debevec et al. 2016-1	-0.354	0.362	0.131	-1.064	0.356	-0.977	0.329	11	4.07
Debevec et al. 2016-2	-0.189	0.355	0.126	-0.884	0.506	-0.532	0.595	11	4.10
Mean	-0.086	0.159	0.025	-0.399	0.226	-0.542	0.588		

Supplementary table 12. Individual study characteristics for studies evaluating fasted PYY concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Debevec et al. 2014b-1	-0.197	0.277	0.076	-0.739	0.345	-0.714	0.475	8	13.07
Debevec et al. 2014b-2	0.218	0.277	0.077	-0.325	0.761	0.786	0.432	8	13.02
Debevec et al. 2014b-3	-0.168	0.318	0.101	-0.792	0.456	-0.527	0.598	6	9.85
Debevec et al. 2014b-4	-0.331	0.325	0.105	-0.967	0.306	-1.019	0.308	6	9.47
Mekjavic et al. 2016	0.114	0.234	0.055	-0.345	0.573	0.487	0.626	11	18.20
Debevec et al. 2016-1	0.083	0.234	0.055	-0.375	0.542	0.357	0.721	11	18.26
Debevec et al. 2016-2	0.145	0.235	0.055	-0.315	0.606	0.620	0.535	11	18.13
Mean	0.017	0.100	0.010	-0.179	0.213	0.170	0.865		

Supplementary table 13. Individual study characteristics for studies evaluating postprandial PYY concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Bailey et al. 2015-1	-0.055	0.153	0.023	-0.354	0.245	-0.357	0.721	12	14.06
Bailey et al. 2015-2	0.398	0.159	0.025	0.087	0.709	2.507	0.012	12	13.53
Debevec et al. 2014b-2	0.103	0.188	0.035	-0.265	0.471	0.549	0.583	8	11.20
Debevec et al. 2014b-4	-0.041	0.216	0.047	-0.465	0.383	-0.190	0.850	6	9.34
Wasse et al. 2012-1	-0.285	0.171	0.029	-0.620	0.049	-1.670	0.095	10	12.50
Wasse et al. 2012-2	-0.220	0.169	0.029	-0.552	0.112	-1.297	0.195	10	12.61
Debevec et al. 2016-1	0.195	0.161	0.026	-0.121	0.510	1.208	0.227	11	13.32
Debevec et al. 2016-2	0.022	0.160	0.025	-0.291	0.335	0.138	0.890	11	13.45
Mean	0.019	0.081	0.006	-0.139	0.177	0.241	0.810		

Supplementary table 14. Individual study characteristics for studies evaluating fasted insulin concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Zaccaria et al. 2004-1	0.204	0.311	0.097	-0.406	0.814	0.655	0.513	12	3.48
Zaccaria et al. 2004-2	0.475	0.325	0.106	-0.162	1.113	1.462	0.144	12	3.40
Bailey et al. 2004	-0.459	0.424	0.180	-1.290	0.373	-1.081	0.280	7	2.90
Benso et al. 2007	0.333	0.366	0.134	-0.383	1.050	0.912	0.362	9	3.20
Riedl et al. 2012-1	-0.154	0.187	0.035	-0.520	0.213	-0.823	0.411	33	4.08
Riedl et al. 2012-2	0.196	0.204	0.041	-0.204	0.595	0.961	0.337	28	4.01
Smith et al. 2011-1	-0.203	0.341	0.116	-0.871	0.466	-0.595	0.552	10	3.32
Smith et al. 2011-2	0.180	0.340	0.116	-0.487	0.847	0.529	0.597	10	3.33
Smith et al. 2011-3	0.553	0.363	0.131	-0.157	1.264	1.526	0.127	10	3.21
Spliethoff et al. 2013-1	1.252	0.475	0.226	0.320	2.183	2.634	0.008	9	2.66
Spliethoff et al. 2013-2	0.609	0.387	0.150	-0.151	1.368	1.571	0.116	9	3.09
Vats et al. 2004-1	0.510	0.359	0.129	-0.193	1.214	1.421	0.155	10	3.23
Vats et al. 2004-2	0.499	0.358	0.128	-0.203	1.201	1.393	0.164	10	3.24
Vats et al. 2004-3	0.124	0.339	0.115	-0.541	0.788	0.365	0.715	10	3.33
Young et al. 1989-1	0.431	0.456	0.208	-0.462	1.324	0.946	0.344	6	2.75
Young et al. 1989-2	1.584	0.655	0.428	0.301	2.867	2.420	0.016	6	1.94
Young et al. 1989-3	1.884	0.726	0.527	0.461	3.307	2.595	0.009	6	1.72
Young et al. 1989-4	1.297	0.591	0.350	0.138	2.456	2.193	0.028	6	2.17
Young et al. 1989-5	1.083	0.549	0.301	0.007	2.159	1.973	0.049	6	2.34
Sawhney et al. 1991-1	3.565	0.748	0.559	2.099	5.030	4.768	0.000	15	1.65
Sawhney et al. 1991-2	0.740	0.311	0.097	0.130	1.350	2.379	0.017	15	3.48
Sawhney et al. 1991-3	2.224	0.514	0.264	1.217	3.231	4.329	0.000	15	2.49
Sawhney et al. 1991-4	0.576	0.298	0.089	-0.008	1.159	1.934	0.053	15	3.55
Sawhney et al. 1986	-0.270	0.344	0.118	-0.944	0.403	-0.787	0.431	10	3.31
Larsen et al. 1997-1	2.138	0.684	0.468	0.797	3.479	3.124	0.002	8	1.84
Larsen et al. 1997-2	-0.852	0.441	0.194	-1.716	0.012	-1.934	0.053	8	2.82
Braun et al. 2001	0.965	0.373	0.139	0.234	1.697	2.587	0.010	12	3.16
Debevec et al. 2014b-1	0.154	0.380	0.144	-0.591	0.898	0.405	0.686	8	3.12
Debevec et al. 2014b-2	-0.974	0.458	0.210	-1.872	-0.075	-2.124	0.034	8	2.74
Debevec et al. 2014b-3	0.983	0.531	0.282	-0.057	2.024	1.852	0.064	6	2.41
Debevec et al. 2014b-4	-1.719	0.686	0.471	-3.064	-0.374	-2.505	0.012	6	1.84
Mekjavic et al. 2016	0.004	0.322	0.104	-0.627	0.635	0.013	0.990	11	3.42
Simpson et al. 2016-1	-0.336	0.331	0.109	-0.985	0.312	-1.016	0.310	11	3.38

Simpson et al. 2016-2	-0.145	0.324	0.105	-0.780	0.489	-0.449	0.653	11	3.41
Mean	0.408	0.121	0.015	0.171	0.645	3.377	0.001		

Supplementary table 15. Individual study characteristics for studies evaluating postprandial insulin concentrations

Study	Standardised mean difference	Standard error	Variance	Lower 95% confidence interval	Upper 95% confidence interval	z-value	p-value	Sample size	Weight
Spliethoff et al. 2013-1	-0.104	0.324	0.105	-0.739	0.531	-0.321	0.748	9	8.25
Spliethoff et al. 2013-2	0.223	0.327	0.107	-0.418	0.864	0.682	0.495	9	8.10
Bailey et al. 2015-1	0.156	0.282	0.079	-0.396	0.708	0.555	0.579	12	10.93
Bailey et al. 2015-2	0.049	0.280	0.078	-0.500	0.598	0.175	0.861	12	11.05
Debevec et al. 2014b-2	-0.845	0.399	0.159	-1.627	-0.062	-2.116	0.034	8	5.44
Debevec et al. 2014b-4	-0.609	0.431	0.186	-1.454	0.236	-1.413	0.158	6	4.67
Mekjavic et al. 2016	0.240	0.297	0.088	-0.341	0.821	0.810	0.418	11	9.86
Matu et al. 2017a-1	-0.056	0.280	0.078	-0.605	0.493	-0.201	0.841	12	11.05
Matu et al. 2017a-2	0.082	0.280	0.079	-0.467	0.632	0.294	0.769	12	11.03
Simpson et al. 2016-1	-0.343	0.301	0.090	-0.932	0.247	-1.139	0.255	11	9.58
Simpson et al. 2016-2	0.136	0.294	0.086	-0.439	0.712	0.464	0.643	11	10.05
Mean	-0.035	0.093	0.009	-0.217	0.147	-0.376	0.707		