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

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Abstract

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

Introduction

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

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

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

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

Methods

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

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

Literature Search

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

Inclusion Criteria

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

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

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

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

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

Data abstraction

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

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

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

Assessment of risk of bias in included studies

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

Statistical analysis

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

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

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

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

Exploration of small study effects

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

Results

Overview

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

Participant demographics and hypoxic exposure characteristics

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

Meta-Analysis

Individual study statistics and results for each outcome variable are summarised in 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, τ^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, τ^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, τ^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

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

[Insert Figure 2 near here]

Standardised mean difference and moderator variables for acylated ghrelin concentrations

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

[Insert Figure 3 and 4 near here]

Standardised mean difference and moderator variables for total ghrelin concentrations

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

Standardised mean difference and moderator variables for GLP-1 concentrations

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

Standardised mean difference and moderator variables for leptin concentrations

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

Standardised mean difference and moderator variables for PYY concentrations

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

Standardised mean difference and moderator variables for insulin concentrations

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

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

[Insert Figure 5 and 6 near here]

[Insert Table 1 near here]

Risk of bias

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

[Insert Figure 7 near here]

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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Conflict of Interest

The authors declare no conflicts of interest.

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

Figure 1. Forest plot of standardised mean differences (means ± 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 ± 95% CI) for the model.

Figure 2. Forest plot of standardised mean differences (means ± 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 ± 95% CI) for the model.

Figure 3. Forest plot of standardised mean differences (means ± 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 ± 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 ± 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 ± 95% CI) for the model.

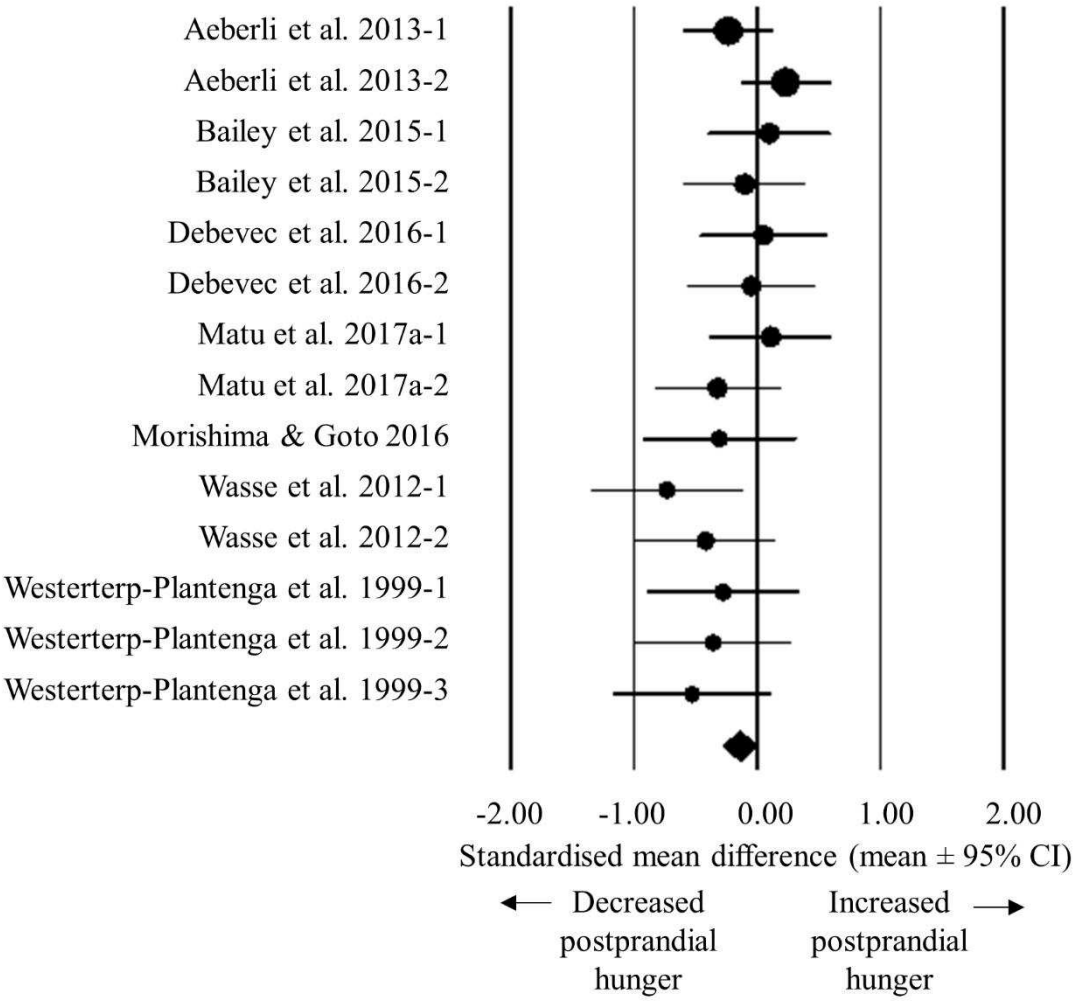
Figure 6. Univariable meta-regression for hypoxic severity versus fasted insulin concentration responses to hypoxic exposure expressed as standardised mean difference (SMD).

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	p value	Comparison
Postprandial hunger		
Acclimatisation status	0.183	Acclimatised (n = 3; SMD -0.382, 95% CI -0.749 to -0.015)
		Unacclimatised (n = 11; SMD -0.110, 95% CI -0.270 to 0.050)
Hypoxic method	0.396	Simulated hypobaric (n = 3; SMD -0.382, 95% CI -0.749 to -0.015)
		Simulated normobaric (n = 9; SMD -0.151, 95% CI -0.330 to 0.028)
		Terrestrial altitude (n = 2; SMD -0.001, 95% CI -0.457 to 0.455)
Activity status	0.049	Passive (n = 6; SMD -0.350, 95% CI -0.598 to -0.103)
		Active (n = 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 (n = 6; SMD -0.531, 95% CI -1.014 to -0.047)
		Terrestrial altitude (n = 2; SMD -0.448, 95% CI -1.045 to 0.149)
Activity status	0.970	Passive (n = 2; SMD -0.489, 95% CI -1.207 to 0.230)
		Active (n = 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 (n = 2; SMD -0.207, 95% CI -0.321 to -0.092)
		Active (n = 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 (n = 12; SMD 1.016, 95% CI 0.582 to 1.450)
		Unacclimatised (n = 22; SMD 0.121, 95% CI -0.121 to 0.363)
Hypoxic method	<0.0005	Simulated hypobaric (n = 6; SMD 1.052, 95% CI 0.638 to 1.467)
		Simulated normobaric (n = 7; SMD -0.215, 95% CI -0.913 to 0.361)
		Terrestrial altitude (n = 21; SMD 0.443, 95% CI 0.162 to 0.724)
Activity status	0.107	Passive (n = 16; SMD 0.619, 95% CI 0.184 to 1.055)
		Active (n = 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


Aeberli et al. 2013-1
Aeberli et al. 2013-2
Bailey et al. 2015-1
Bailey et al. 2015-2
Debevec et al. 2016-1
Debevec et al. 2016-2
Matu et al. 2017a-1
Matu et al. 2017a-2
Morishima & Goto 2016
Wasse et al. 2012-1
Wasse et al. 2012-2
Westerterp-Plantenga et al. 1999-1
Westerterp-Plantenga et al. 1999-2
Westerterp-Plantenga et al. 1999-3
-2.00
-1.00
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2.00
Standardised mean difference (mean ± 95% CI)
Decreased postprandial hunger
Increased postprandial hunger

Figure 2

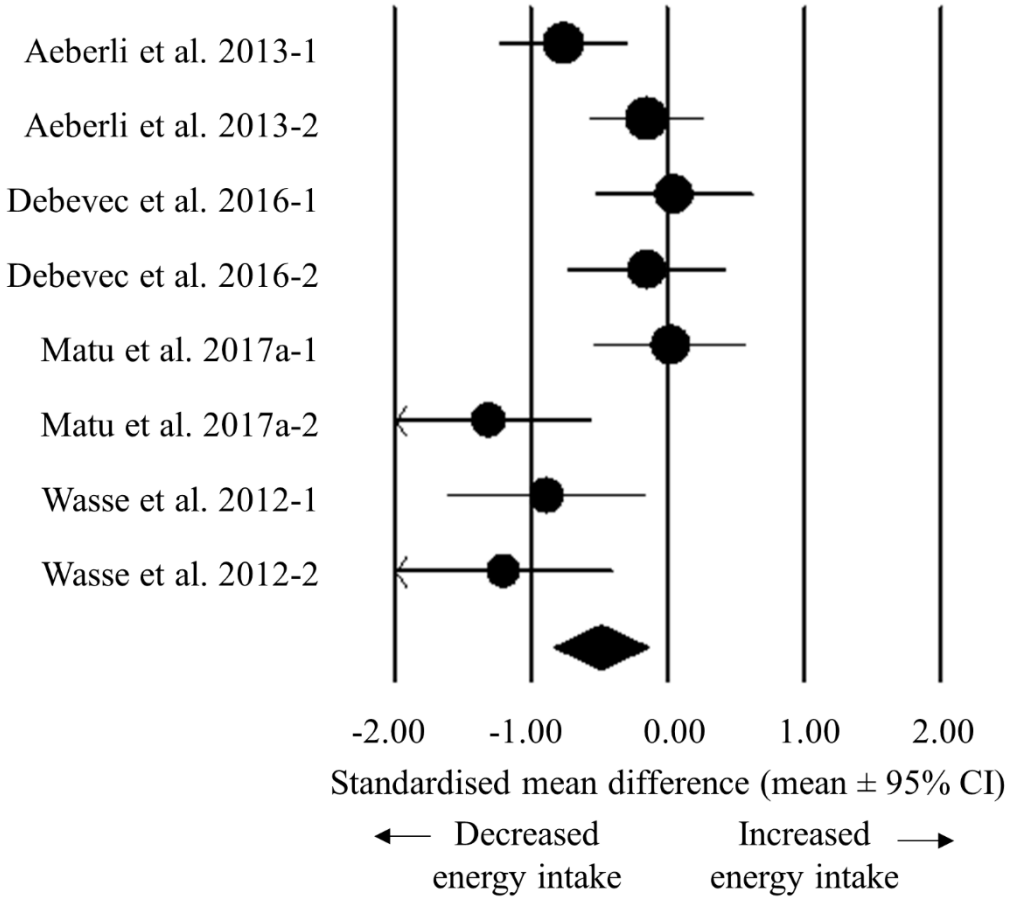

Aeberli et al. 2013-1
Aeberli et al. 2013-2
Debevec et al. 2016-1
Debevec et al. 2016-2
Matu et al. 2017a-1
Matu et al. 2017a-2
Wasse et al. 2012-1
Wasse et al. 2012-2
-2.00
-1.00
0.00
1.00
2.00
Standardised mean difference (mean ± 95% CI)
Decreased energy intake
Increased energy intake

Figure 3

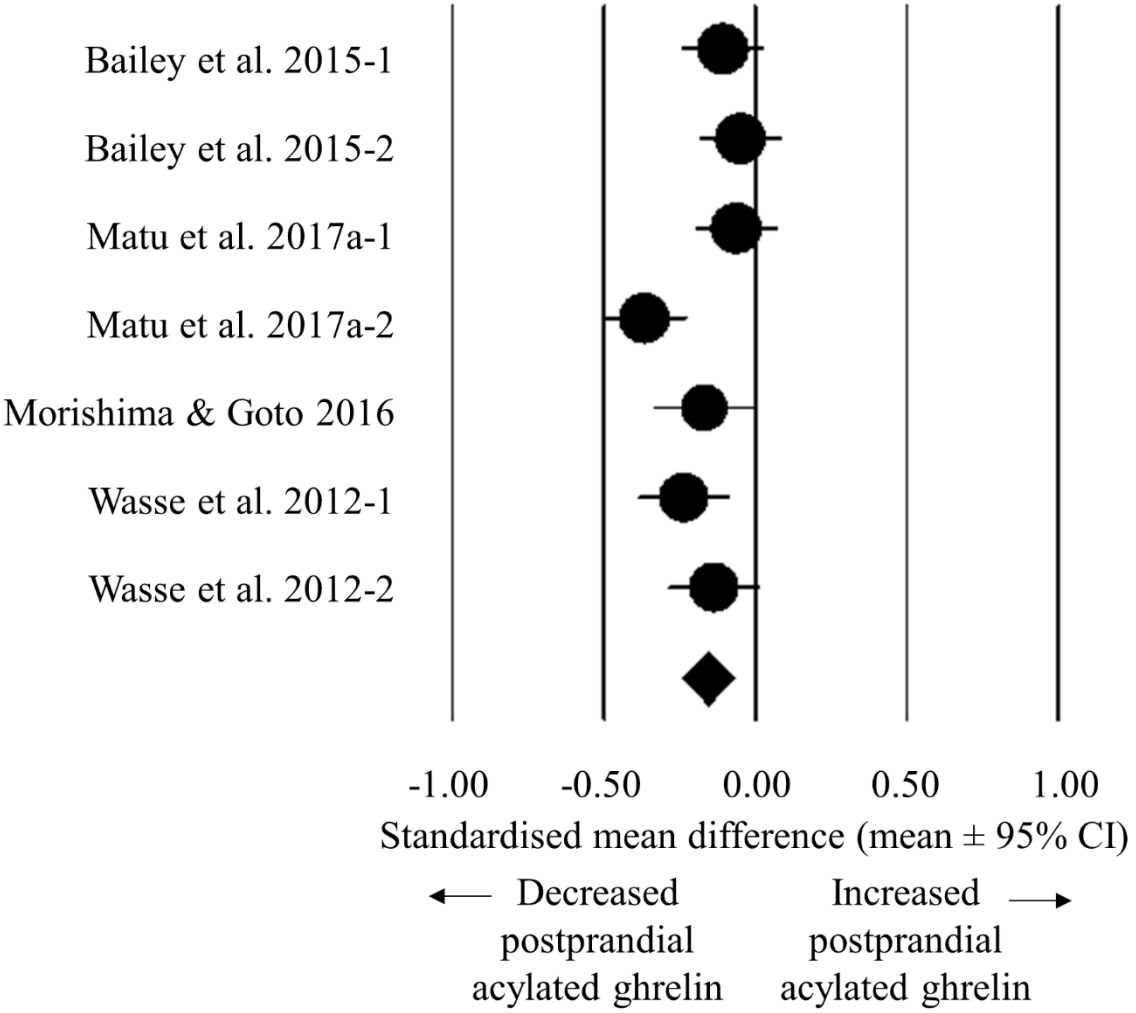

Bailey et al. 2015-1
Bailey et al. 2015-2
Matu et al. 2017a-1
Matu et al. 2017a-2
Morishima & Goto 2016
Wasse et al. 2012-1
Wasse et al. 2012-2
-1.00
-0.50
0.00
0.50
1.00
Standardised mean difference (mean ± 95% CI)
Decreased postprandial acylated ghrelin
Increased postprandial acylated ghrelin

Figure 4

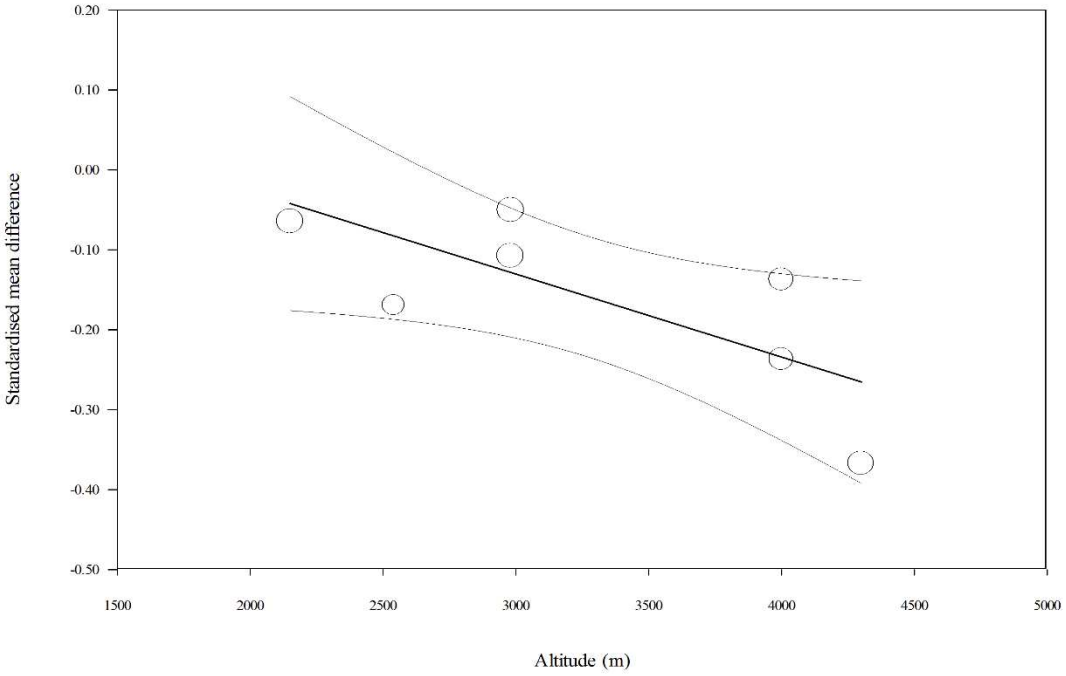

0.20
0.10
0.00
-0.10
-0.20
-0.30
-0.40
-0.50
Standardised mean difference
1500
2000
2500
3000
3500
4000
4500
5000
Altitude (m)

Figure 5

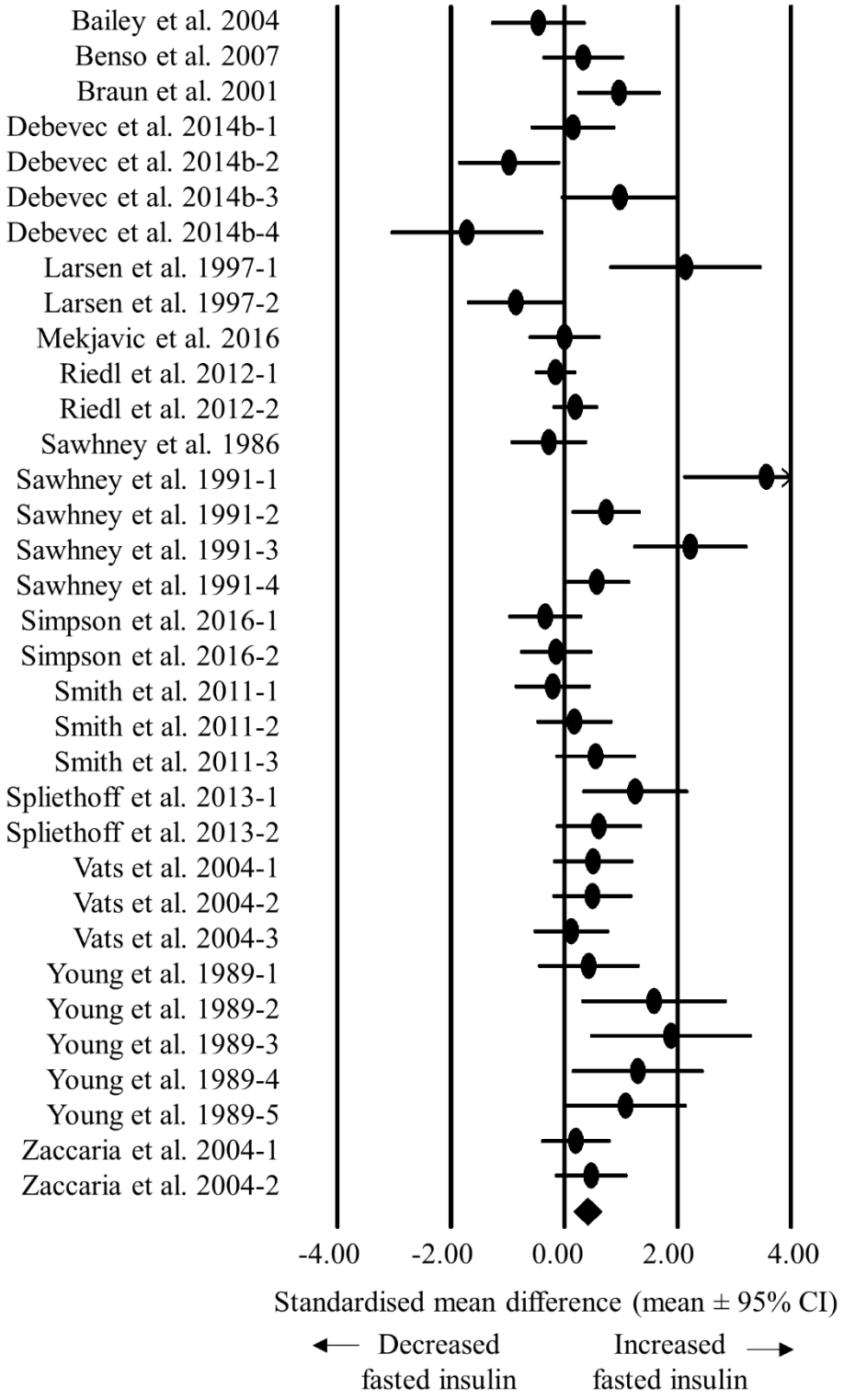

Bailey et al. 2004
Benso et al. 2007
Braun et al. 2001
Debevec et al. 2014b-1
Debevec et al. 2014b-2
Debevec et al. 2014b-3
Debevec et al. 2014b-4
Larsen et al. 1997-1
Larsen et al. 1997-2
Mekjavic et al. 2016
Riedl et al. 2012-1
Riedl et al. 2012-2
Sawhney et al. 1986
Sawhney et al. 1991-1
Sawhney et al. 1991-2
Sawhney et al. 1991-3
Sawhney et al. 1991-4
Simpson et al. 2016-1
Simpson et al. 2016-2
Smith et al. 2011-1
Smith et al. 2011-2
Smith et al. 2011-3
Spliethoff et al. 2013-1
Spliethoff et al. 2013-2
Vats et al. 2004-1
Vats et al. 2004-2
Vats et al. 2004-3
Young et al. 1989-1
Young et al. 1989-2
Young et al. 1989-3
Young et al. 1989-4
Young et al. 1989-5
Zaccaria et al. 2004-1
Zaccaria et al. 2004-2
-4.00
-2.00
0.00
2.00
4.00
Standardised mean difference (mean ± 95% CI)
Decreased fasted insulin
Increased fasted insulin

Figure 6

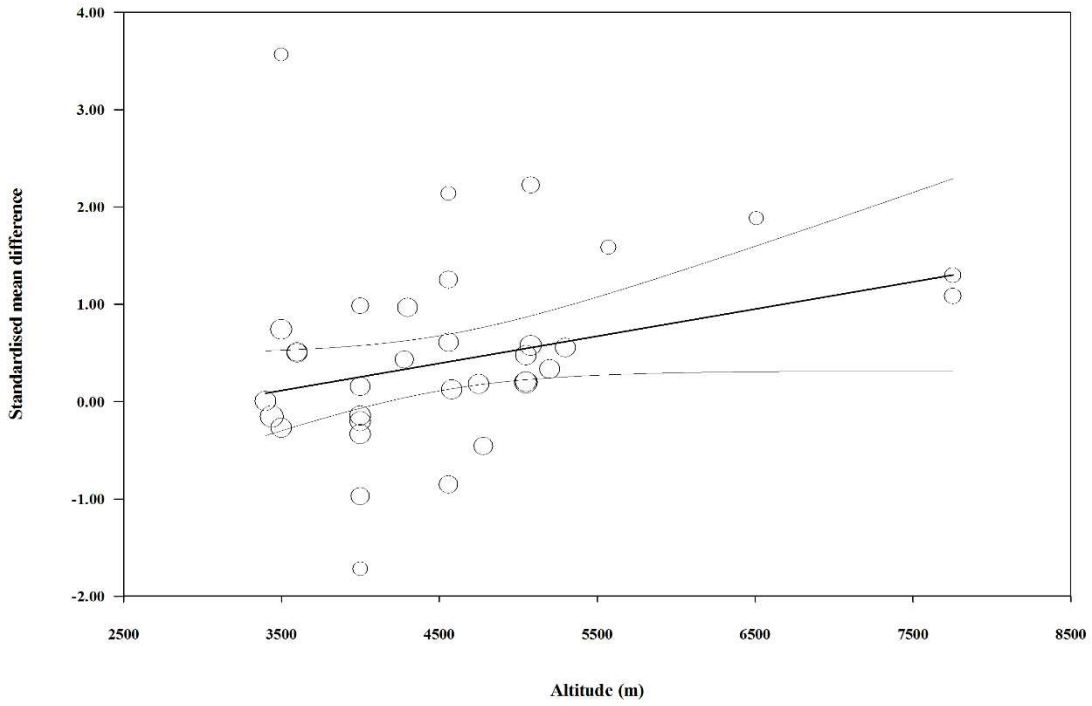
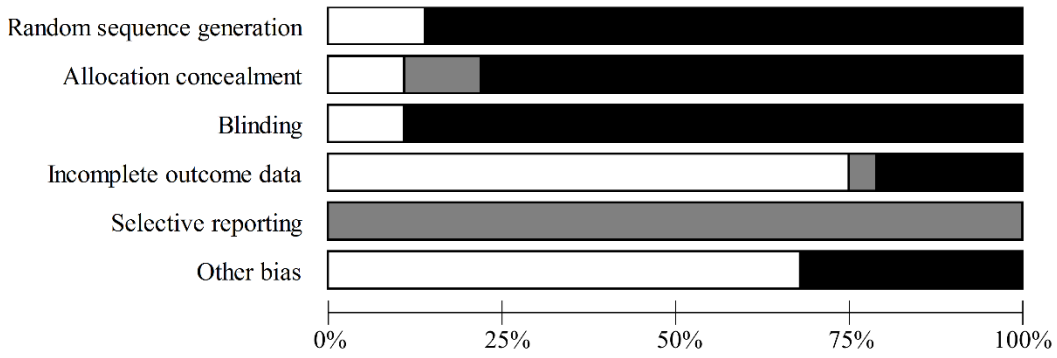
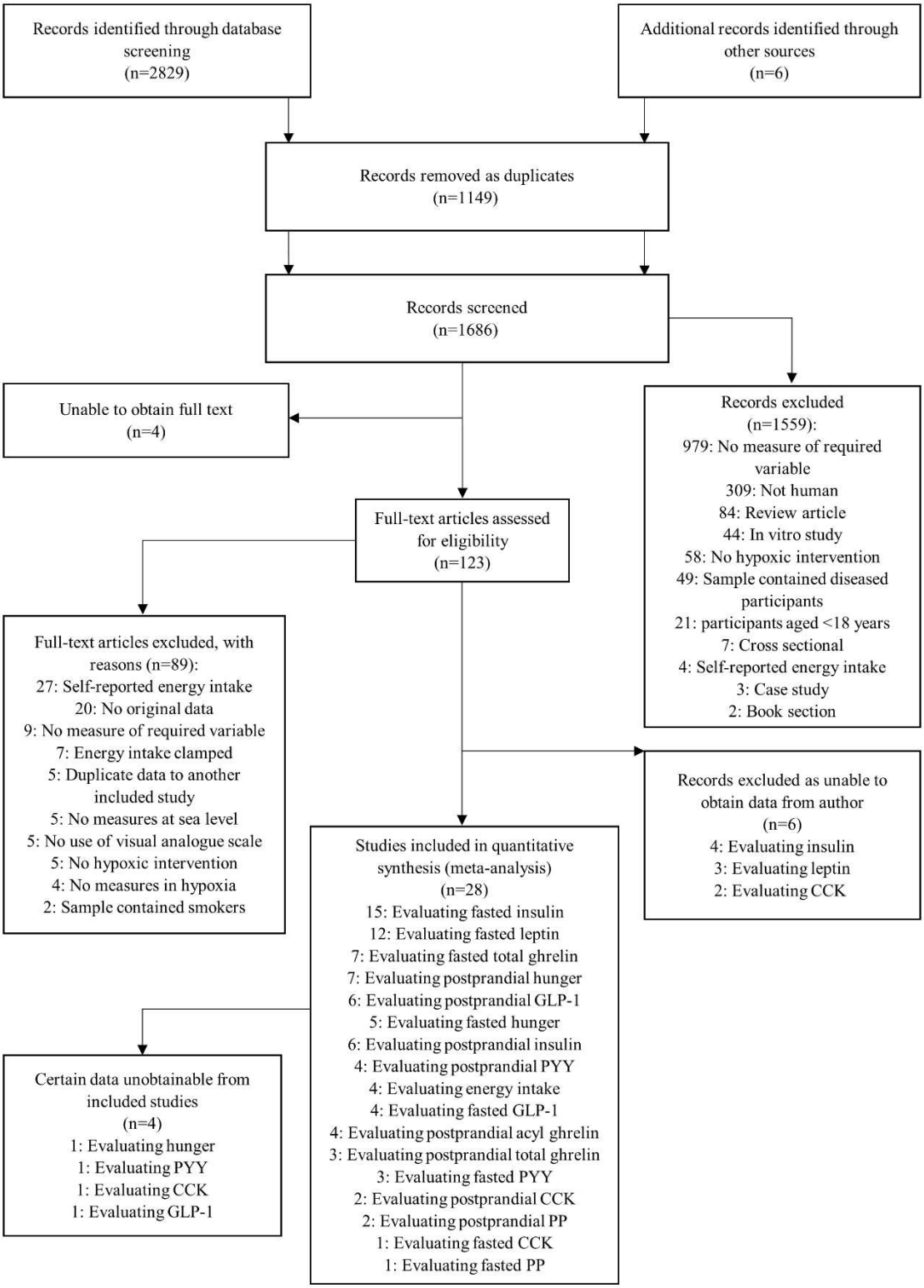

Standardised mean difference
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
2500
3500
4500
5500
6500
7500
8500
Altitude (m)

Figure 7


Random sequence generation
Allocation concealment
Blinding
Incomplete outcome data
Selective reporting
Other bias
0%
25%
50%
75%
100%

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

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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

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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}
												ALT: 135.0 (40.8)	
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)	-	-	-
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)	-	-
Spliethoff 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}
Spliethoff 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) 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) 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) 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)	-	-	-	
Spliethoff et al. 2013-1	9 men	Longitudinal	4559	2 days	Unacclimatised	Terrestrial altitude	Passive	-	-	SL: 10 (7) ALT: 9 (5)	-	-	-	-
Spliethoff 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
														ALT: 5084 (1952)
Westerterp-Plantenga et al. 1999-1	8 men	Longitudinal	5000	4 days	Acclimatised	Simulated hypobaric	Passive	SL: 44 (24) ALT: 38 (12)	-	-	-	-	-	-
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		