

## PROSPERO International prospective register of systematic reviews

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### **The effect of hypoxia on appetite, appetite regulating hormones and energy intake: a planned meta-analysis**

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#### **Citation**

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#### **Review question(s)**

How does hypoxic exposure impact subjective appetite perceptions, appetite regulatory hormone concentrations and energy intake in humans?

Does physical activity affect subjective appetite perceptions, appetite regulatory hormone concentrations and energy intake responses to hypoxia?

Is there a sex difference in the subjective appetite perceptions, appetite regulatory hormone concentrations and energy intake responses to hypoxia?

What is the severity of hypoxia needed to stimulate a change in appetite?

Does the severity of hypoxia change appetite in a linear fashion?

Are the responses of subjective appetite perceptions, appetite regulatory hormone concentrations and energy intake different when exposed to normobaric hypoxia vs. hypobaric hypoxia vs. true altitude?

#### **Searches**

We will search the following electronic bibliographic databases: PubMed and The Cochrane Library as well as searching MEDLINE, SPORTDiscus, PsycINFO, CINAHL via EBSCOhost. Reference lists of eligible studies and review articles will also be included. If only the abstract has been published the author will be contacted to obtain the full data set. The search strategy will include only terms relating to or describing the intervention. The searches will be re-run just before the final analyses and further studies will be retrieved for inclusion. No language or date of publication restrictions will be applied during the searches.

#### **Types of study to be included**

Inclusion criteria for the study design are human intervention studies that expose participants to a hypoxic environment (hypobaric and/or normobaric) with an appropriate control.

#### **Condition or domain being studied**

We are examining the effect of hypoxic exposure on subjective appetite perceptions, appetite regulatory hormones and energy intake. Subjective appetite perceptions will be measured via various visual analogue scales. Notable appetite regulatory hormones include ghrelin, leptin, glucagon-like peptide-1, peptide YY and insulin. Energy intake will be measured as the weight of food or kJ/kcal. All values will subsequently be converted to kJ by multiplying kcal values by 4.184.

#### **Participants/ population**

All studies will be evaluated using the following inclusion/exclusion criteria.

Inclusion: Human intervention studies.

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Exclusion: Studies that have included: adolescents (under 18 years of age), older adults (over 65), smokers, pregnant women and/or individuals with a history of diabetes, gastrointestinal, inflammatory, metabolic, cardiovascular, neurological or psychological disease(s).

### **Intervention(s), exposure(s)**

Hypoxic exposure interventions are 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 must be  $\geq 1000\text{m}$  in altitude (or a simulated equivalent) and be of  $\geq 30$  minutes in duration.

### **Comparator(s)/ control**

Controls with no intervention (i.e. no exposure), placebo intervention (i.e. exposure to normoxia) or appropriate before-and-after interventions will be included.

### **Context**

All studies will be included (e.g. clinical, athletic, mountaineering, geographic etc).

### **Outcome(s)**

#### **Primary outcomes**

- 1) Differences in researcher-measured (i.e. not self-reported) energy intake between normoxic and hypoxic exposure.
- 2) Differences in appetite regulatory hormones between normoxic and hypoxic exposure, measured via venous blood sampling.
- 3) Differences in subjective appetite perceptions between normoxic and hypoxic exposure, measured using visual analogue scales.
- 4) Sex, physical activity and the form of hypoxic exposure (i.e. true altitude versus simulated altitude and hypobaric versus normobaric hypoxia) will be considered as potential moderators.

#### **Secondary outcomes**

None

### **Data extraction, (selection and coding)**

At least two researchers will independently assess the title and abstracts for eligible studies. Disagreements about the eligibility of particular studies will be resolved by a third reviewer. Potential papers that cannot be excluded based on their title and/or abstract will be retrieved and reviewed against the inclusion/exclusion criteria by two independent researchers. A third researcher will be used if disagreements occur.

Data from selected papers will be extracted by at least two independent researchers and compared until consensus is reached. A third researcher will settle any disagreements. Data to be extracted include:

- 1) Study information (e.g. authors, year)
- 2) Population (sample size, participant demographics (e.g. age, sex, BMI etc.)).
- 3) Intervention (method of achieving hypoxia (simulated/true altitude and normobaric/ hypobaric hypoxia), severity and duration of hypoxia, whether exercise was included (duration, intensity and mode of exercise if included).
- 4) Outcome measures (Subjective appetite perception scores, appetite regulatory hormones including ghrelin, leptin, glucagon-like peptide-1 and peptide YY and energy intake values (kcal/kJ)). All energy intake values will be converted to kJ.
- 5) Subjective appetite perceptions assessment method, blood analytical method and energy intake assessment method.

6) Total energy expenditure measured via indirect calorimetry (e.g. Douglas bag method, breath-by-breath gas analysis etc.).

### **Risk of bias (quality) assessment**

To assess risk of bias of individual studies we will collect information using the Cochrane Collaboration tool for assessing risk of bias (Table 8.5.a in the Cochrane Handbook for Systematic Reviews of Interventions), which includes 6 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 will be made on each of the domains by two independent researchers as to whether they are 'high risk' or 'low risk'. If insufficient detail is reported of what happened in the study then the judgement will be 'unclear risk'. All judgements will be made by two independent researchers based upon the criteria for judging risk of bias (Table 8.5.c in the Cochrane Handbook for Systematic Reviews of Interventions, Higgins & Green 2008). Disagreements will be solved initially via discussion between the two independent researchers however a third researcher will be consulted for any dispute resolution. We will compute a 'risk of bias graph' which includes high, low and unclear risk for each domain. Publication bias will be examined with funnel plots and linear regression of the standardised mean difference and SEM.

### **Strategy for data synthesis**

We will provide a quantitative synthesis of the findings from the primary studies that meet the inclusion criteria and do not meet the exclusion criteria. If studies are found to have a similar design and comparator then a random-effects meta-analysis will be performed to estimate between-study variance (Tau-squared) using Review Manager (RevMan) 5.1.4 (The Cochrane Collaboration). Heterogeneity between trials will be assessed using the Chi-squared statistic with the significance level set at  $P < 0.10$  and the I-squared value; 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. Due to the nature of the intervention, we do not expect any studies to be very large in sample size ( $n > 40$ ). However, if there is substantial heterogeneity and large differences in sample size, then fixed and random-effects will both be employed and compared to assess the influence of small studies on the overall effect. This will be conducted using mean subjective appetite perception scores, mean appetite regulatory hormone concentrations, mean energy expenditure values and mean energy intake values in hypoxia vs. control. If area under the curve values are reported rather than mean values the authors of the relevant studies will be contacted in an attempt to obtain the dataset and calculate mean values.

Where values are presented in figure form, the figure will be digitized and the means and SD/SEM measured manually at the pixel level to the scale provided on the figure. Missing standard deviations were calculated from standard errors or confidence intervals. To examine whether conclusions are dependent on a single study, sensitivity analyses will be employed by repeating the analyses with each study omitted in turn.

### **Analysis of subgroups or subsets**

Subgroup analyses will be used if the necessary data are available. Possible subgroup analyses include: age, sex, mode of achieving hypoxia, severity of hypoxic exposure, whether exercise was included, pre-acclimatisation status of the subjects, hormone analytical method, training status, race and energy intake assessment method. Furthermore the duration of hypoxic exposure will be analysed using the following subgroups: <1 day, 1 - 5 days, 6 - 20 days and >20 days.

### **Dissemination plans**

We intend to publish in a peer reviewed journal and possibly present the findings at a scientific conference. An elaboration of this review will form a chapter of the named contact's PhD thesis.

### **Contact details for further information**

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There are no funding sources or sponsors for this review.

**Conflicts of interest**

None known

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England

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Subject indexing assigned by CRD

**Subject index terms**

Anoxia; Appetite; Appetite Regulation; Energy Intake; Ghrelin; Humans

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Ongoing

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**Stage of review at time of this submission**

	<b>Started</b>	<b>Completed</b>
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No

Data analysis

No

No

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