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The RESET trial: can a novel intervention rapidly re-adjust the body clock to treat jet-lag in healthy volunteers and improve their sleep at high altitude?

Submission date
22/11/2021

Recruitment status
No longer recruiting

Registration date
24/11/2021

Overall study status
Completed

Last Edited
03/10/2025

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Biological clocks regulate how our body works, and they must synchronize to our 24-hour world. Environmental timing cues feed into a 'master clock' in the brain, which then synchronizes clocks throughout the body. Light-dark cycles, meal times, and steroid hormones form the strongest cues, tuning our internal clocks to the day-night rhythm. Genetic variation determines how our body clocks align with this rhythm, thus resulting in different 'chronotypes' (i.e. 'morning larks' and 'night owls').

Annually, millions of people stretch the limits of their body clock by rapidly crossing multiple time zones. Temporary misalignment between an individual's body clock and local time in their destination produces 'jet lag', the symptoms of which subside as the body clock adapts to the new time zone. Disruption of our body clocks—as occurs with jet lag and shift work—has far-reaching health effects, playing a role in cancer, diabetes, heart disease, and dementia. If we could rapidly reset the body clock to better accommodate our modern lifestyles, this could have enormous health benefits.

An intense challenge is faced by visitors to high altitude, since exposure to a low-oxygen environment often coincides with jet lag. A prominent feature of both jet lag and ascent to high altitude is sleep disturbance. Most studies of sleep at altitude have failed to control for individual chronotype and body clock function—factors which could substantially modify the body's adaptation to a new time zone. Research on APEX 6 addresses an important knowledge gap; the impact of individual chronotype and jet lag on how the body copes with high altitude. The RESET trial builds on this by testing whether a multi-factorial intervention can accelerate resetting of body clocks and improve sleep function in healthy volunteers exposed to jet lag and high altitude.

Who can participate?
We will recruit 35 healthy volunteers (males and females, aged 18-25 years); all participants will

be recruited from the cohort of volunteers taking part in the APEX 6 expedition to the Bolivian Andes. People who smoke or who have significant disease of their heart or their lungs will not be able to participate.

What does the study involve?
The RESET trial is an extension of research being conducted into body clocks at high altitude during the APEX 6 expedition. Taking part in the trial means that, after baseline testing, the volunteer will be randomly assigned to one of two intervention sequences, and will receive the RESET intervention on either the outbound or return leg of travel to South America. To measure body clock function throughout the expedition, volunteers will be asked to wear an activity wristband (like a 'fit bit') before, during, and after the expedition (total 25 days). Volunteers may also have the opportunity to use ingestible core body temperature monitoring 'pills' on days 1, 4 and 10 of the expedition.

The RESET intervention will last 72 hours and consists of five components, each optimally timed to promote rapid resetting of the body clock to the new time zone. Components include restrictions on the timing of (1) exposure to light, (2) food consumption, (3) physical exertion, and (4) sleep opportunity, and (5) a single, oral dose of synthetic steroid (dexamethasone) to suppress the volunteers 'stress' axis and thus reset their internal rhythm of steroid hormone. Exact timings will be determined by each volunteer's flight schedule and chronotype.

Volunteers will be asked to complete questionnaires in the lead up to, and each day during the expedition. These will document their chronotype, sleep patterns, sleep quality, mood, cognition and any symptoms of altitude sickness.

What are the possible benefits and risks of participating?
The RESET intervention may offer direct benefits to volunteers (i.e. faster resetting of the body clock, reduction in jet lag symptoms, improvements in sleep function or other parameters on exposure to high altitude). Beyond general risks associated with travel to South America and high altitude, there are risks specifically associated with taking part in the RESET trial:
Activity wristband
1.Skin irritation (allergic contact dermatitis); an extremely unlikely adverse reaction to wearing the device
Core body temperature pill
2. Worsening of pre-existing, undiagnosed gut problems.
3. Incompatibility with advanced imaging (such as MRI scans). If emergency evacuation could result in an MRI scan (extremely unlikely), the need for caution will be communicated to the clinical team.
Steroid (dexamethasone) treatment
4. There are some medical conditions for which dexamethasone would present a risk; these are listed as specific exclusion criteria for the trial. Some drugs might interact with dexamethasone; the need to use such substances would exclude a volunteer from the dexamethasone element of the intervention. The most common side effects of dexamethasone (very unlikely following a single dose) include gut problems such as a stomach ulcer. A stomach protectant (omeprazole) is included with the intervention.

Where is the study run from?
Sea-level data collection will take place in the UK (mainly the University of Edinburgh). Most data collection in Bolivia will be conducted at a high altitude field laboratory (4800m); a small amount will be conducted in La Paz. The RESET intervention will take place either during the outbound or the return leg of travel to South America.

When is the study starting and how long is it expected to run for?
September 2019 to September 2022

Who is funding the study?
The RESET trial is being organised by researchers at the University of Edinburgh, the University of Sheffield, and the MRC Laboratory of Molecular Biology, Cambridge. It is being funded from a variety of sources including the Wilderness Medical Society and the Altitude Physiology Expeditions (APEX) charity. The trial is co-sponsored by the University of Edinburgh and NHS Lothian (UK).

Who is the main contact?
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Integrated Research Application System (IRAS)
279347

Protocol serial number
Sponsor no. AC20156

Study information

Scientific Title
Rapid circadian re-Entrainment to modify Sleep parameters upon acute hypoxic Exposure after jeT lag (RESET): a randomised crossover trial

Acronym
RESET

Study objectives
Primary hypothesis
A novel, evidence-based, combinatorial intervention (the RESET intervention) will accelerate re-adjustment of body clocks in healthy volunteers flown across several time zones for the APEX 6 expedition.

Secondary hypotheses
1. Chronotype (body clock relationship with the local light/dark cycle) will be predictive of changes in sleep quality upon acute exposure to high altitude.
2. Chronotype will be predictive of changes in acute mountain sickness (AMS) score, mood, and cognitive function upon acute exposure to high altitude.
3. Chronotype will affect how quickly volunteers can ‘re-entrain’ their body clock to a new time zone (how quickly they can overcome ‘jet lag’).
4. Chronotype will be linked to genetic variation (as determined by QTL mapping) in volunteers
5. Chronotyping data will effectively control for individual body clock variation and thus clarify outcomes in parallel research elements of the APEX6 expedition (eye function, lung function, white blood cell function, and menstrual bleeding).
6. The RESET intervention will improve sleep function in APEX 6 volunteers.
7. The RESET intervention will improve (a) cognitive function and/or (b) mood in APEX 6 volunteers.
8. The RESET intervention improve altitude-related clinical outcomes (AMS score) in APEX 6 volunteers.
9. There will be a relationship between chronotype (how a person’s individual body clock aligns with the light/dark cycle) and their response to the RESET intervention.
10. Exposure to high altitude hypoxia will affect sleep and/or circadian function measures at sea level (comparing pre- and post-expedition data).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/05/2022, Edinburgh Medical School Research Ethics Committee (EMREC) (Academic and Clinical Central Office for Research and Development (ACCORD) QMRI, 47 Little France Crescent, Edinburgh, UK; no telephone number provided; emrec@ed.ac.uk), ref: 21-EMREC-044-NSA01

Primary study design
Interventional

Study design
A single centre interventional randomized crossover trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Treating jet-lag and improving sleep in healthy lowlanders flying across several time zones and ascending to high altitude

Interventions
The RESET intervention consists of five components; each will be optimally timed to promote rapid resetting of body clocks to the new time zone. These components include restrictions on timing of (1) exposure to light, (2) food consumption, (3) physical exertion, and (4) sleep opportunity, and (5) a single, oral dose of synthetic steroid (dexamethasone) to effect overnight suppression of the hypothalamic-pituitary-adrenal axis and thus reset the morning peak in endogenous steroid (cortisol). 'Restrictions' means that participants will only be permitted to expose themselves to light, eat food, exert themselves, and try to sleep at the appropriate times according to the light/dark period of the new destination. The exact timings of these restrictions will be determined by the flight schedule and individual chronotypes. The trial has a crossover design such that half of the participants receive the intervention only on the outbound journey to the Andes, and the remainder receive the intervention only on the return journey to the UK. Data will be collected at sea level (UK) before and after the expedition, and at moderate and high altitudes during the APEX 6 expedition to the Andes.

The RESET trial design considers that within-subject variation in entrainment capacity and sleep function will be less than between-subject variation, and that any carryover will be negligible with a sufficient washout period. RESET will conform to CONSORT (Dwan et al., 2019) and STAR guidelines. After one week of sea level baseline data collection, trial participants will be randomly assigned (computer generated allocation schedule), to one of two intervention sequences (see below). After a minimum 11 days washout (allowing full circadian re-adjustment) participants will crossover to the alternative intervention. Data collection will conclude one week after return to the UK.

Sequence 1 – intervention on outbound journey West, no intervention on return journey East
Sequence 2 – no intervention on outbound journey West, intervention on return journey East

The intervention will be applied for the 72 hours encompassing travel, and optimally timed according to individual chronotypes and flight schedules. To achieve light avoidance, sunglasses and eye masks will be issued and there will be temporary restrictions on the timing of use of portable electronic devices (such as mobile phones and laptops).

Updated 07/05/2022: To optimise sleep opportunity, foam ear plugs will be provided, and participants that normally consume caffeinated beverages will be asked to limit their consumption of caffeine to the period after waking and before 2 pm each day, throughout the data collection period.

The medicinal component of the intervention includes a single dose of dexamethasone (up to 4mg) taken once by mouth on the night before arrival in the new destination. The exact timing of the dose for each participant will be based on their baseline chronotype testing and flight schedule. Although the risks associated with this single dose of dexamethasone are minimal, since participants will be asked to take this medication during a period of food restriction, gastroprotection will be supplied as a precaution. This will include 10mg omeprazole taken by mouth once daily for 3 days, commencing the day before ingestion of dexamethasone.

Most participants will be randomly allocated to one of the sequences (computer-generated allocation). A subset of participants (predicted maximum 12) may need to be pseudorandomised to the second sequence in order to prevent any interference of the intervention with other research elements being conducted on the APEX 6 expedition. At the end of the laboratory period (allowing full body clock re-adjustment) participants will crossover to the alternative arm of the sequence. Actigraphy devices will be worn continuously from the day of departure until the end of the laboratory period. Participants will be asked to document bed and wake times throughout (using the event button on the ActTrust2 device). Other daily subjective assessments will include self-completed VAS for AMS symptoms, the 2018 Lake Louise AMS Score Sheet (the score includes assessment of sleep quality), PVT (cognition), and BMS (mood). To maintain a routine, and to help control for time-of-day effects, each assessment will be carried out at approximately the same time each day, and in the same order, for each volunteer. If financially feasible, core body temperature measurements will be recorded over 24 – 48 hours at three stages using ingestible FDA-approved temperature monitoring pills (CorTemp™ Core Body Temperature Sensors). The minimum temporal resolution of this data will be hourly, and readings can be taken non-invasively without disturbing a participant's sleep. CorTemp™ pills will be supplied on days 1, 4, and 8 of the expedition and recording will continue until the pill has been excreted in the stool (the sensor does not need to be collected).

Intervention Type
Mixed

Primary outcome(s)
Mean daily rate (min/day) of circadian phase (body clock) re-adjustment between the intervention and non-intervention arms over the first 5 days in the new destination. ActTrust2 device readouts for sleep and local light exposure will enable determination of the phase angle for each participant on each day of data collection (the phase angle establishes the relationship between a participant's body clock timing and that of the external light/dark cues – thus providing a measure of entrainment).

Key secondary outcome(s)
1. Chronotype measured using the Munich Chronotype Questionnaire (MCQ) and continuous monitoring of activity and light exposure by wrist-worn actigraphy. The MCQ will be conducted once, 8-10 days prior to the expedition. Actigraphy data will be collected for one week prior to the expedition, throughout the data collection period at high altitude, and from the day of return departure to the UK until 7 days after arrival in the UK.
2. Sleep quality measured using characteristics derived from actigraphy and Pittsburgh Sleep Quality Index (PSQI). Actigraphy data will be collected as described above. The PSQI score will be

obtained 8-10 days prior to the expedition and one week after returning to the UK.
3. Circadian function using the circadian function index (CFI) derived from actigraphy data, collected as described above.
4. Total Acute Mountain Sickness (AMS) score by combining the results of Visual Analogue Scale (VAS) sheets (completed pre- and post-expedition and up to four times per day during the data collection period at high altitude), and the 2018 Lake Louise AMS Score questionnaire (completed pre- and post-expedition, and once per day during the data collection period at high altitude).
5. Mood using the questionnaire-based Brunel Mood Scale (BMS), completed at pre- and post-expedition testing, and once per day during the data collection period at high altitude.
6. Cognitive function using the computer-based Psychomotor Vigilance Task (PVT) performed at pre- and post-expedition testing, and once per day during the data collection period at high altitude.
7. Genetic variation according to expression quantitative trait loci (eQTL) obtained using genomic DNA extracted from venous blood collected at baseline pre-expedition testing.

Completion date
30/09/2022

Eligibility

Key inclusion criteria
1. Accepted as members of the APEX 6 expedition (aged 18-25 years; there is no obligation to take part in the research having been accepted on the expedition).
2. Able to provide details of registration at a GP surgery.
3. In the case of volunteers who regularly attend a medical clinic, confirmation that they have informed the hospital specialist that they intend to participate in the expedition.
4. Identify themselves as being healthy.
5. Capacity to understand written and verbal information provided in English, and able to provide valid written informed consent to participate.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
25 Years

Sex
All

Total final enrolment

Key exclusion criteria

1. Previous admission to hospital with acute asthma
2. Significant cardio-respiratory disease
3. Regular cardiovascular medications
4. Advised against travel to altitude by GP, relevant hospital specialist, or APEX6 expedition doctors
5. Positive COVID-19 test within 14 days prior to departure
6. COVID-19 symptoms within 14 days prior to departure, without negative COVID-19 test
7. Pregnancy/possible pregnancy
8. Smoking

The following 'absolute research' exclusion criteria will prevent participants taking part in all research elements on the APEX 6 expedition (including the RESET trial), but will not prevent them from joining the APEX 6 expedition:
9. Subjects who have been exposed to altitude above 2500m in the two months preceding the expedition.
10. Subjects who take acetazolamide (Diamox) during the expedition
11. Subjects who consume alcohol or South American herbal-based remedies for AMS (coca-leaf tea/mate de coca) on research sampling days

The following 'specific' exclusion criteria will prevent participants taking part in the observational 'Hypoxia and body clocks' research element of APEX 6 and the RESET trial, but will not prevent them from taking part in other research elements on APEX 6:
12. Subjects who carry out night shift work in the week before the expedition, have a clinically diagnosed sleep disorder, or who do not fly to South America from Europe and back again for the expedition.

The following 'specific' exclusion criteria relate only to the RESET trial:
13. Subjects with a history of gastric ulceration, diabetes mellitus, or that take systemic steroid-based medications in the month before the expedition will be excluded from the trial in its entirety.
14. Any subject with a body weight of <80 pounds, gastrointestinal disease, history of glaucoma, gastric cancer, previous gastrointestinal surgery/obstruction, epilepsy, liver disease, heart disease, renal disease, signs/history of impaired gag reflex, previous adverse reaction to either dexamethasone or omeprazole, current infection or pre-existing immunocompromise will be excluded from the pharmaceutical aspect of the intervention and the CorTemp™ element of the trial.
15. Participants that require any prescription or non-prescription medications (with the exception of paracetamol, hormone-based contraceptives, fluoxetine, sertraline, trazodone, codeine and gabapentin; updated 07/05/2022: antihistamines, tetracycline antibiotics, isotretinoin, vitamin or
mineral supplements, locally administered steroids [including topical creams, inhalers, and nasal sprays]) during their allocated 3-day intervention period will be excluded from the medicinal aspect of the intervention only (dexamethasone and omeprazole).
16. Any subject with a body weight of <80 pounds, gastrointestinal disease, history of gastric cancer, previous gastrointestinal surgery/obstruction, signs/history of impaired gag reflex, will be excluded from the CorTemp™ component only.

Date of first enrolment

01/04/2022

Date of final enrolment
16/06/2022

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
The University of Edinburgh
The University of Edinburgh and/or Lothian Health Board
Academic and Clinical Central Office for Research and Development (ACCORD)
The Queen's Medical Research Institute
47 Little France Crescent
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Sponsor information

Organisation
University of Edinburgh

ROR
https://ror.org/01nrxwf90

Organisation
NHS Lothian

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Charity

Funder Name
Altitude Physiology Expeditions (APEX)

Funder Name
Wilderness Medical Society

Results and Publications

Individual participant data (IPD) sharing plan
Participants will not be provided with any specific results relating to them as individuals. Results from all participants will be analysed as a group, and published in publicly-accessible scientific journals and at scientific conferences. Results will also be made available on the APEX (www.altitude.org), University of Edinburgh, and Medical Research Council (MRC) Laboratory of Molecular Biology websites. All data are anonymised so it will not be possible to identify participants when results are made public.

Raw data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s). Linked-anonymised data, as well as interim and aggregate results will be shared with Drs Rzechorzek and O'Neill at the MRC Laboratory of Molecular Biology, Cambridge, and Dr Roger Thompson at the University of Sheffield, but no person-identifiable information will be shared, ensuring no breach of confidentiality across research sites. A data sharing agreement will be set up between the respective institutes for sharing the data necessary in order to complete the study. Only fully (unlinked) anonymised data sets will be made available on Open Research platforms.

Linked-anonymised data (that cannot be shared) will be stored in the University of Edinburgh DataVault, whereas shareable data will be stored long-term in the University of Edinburgh DataShare system.
https://www.ed.ac.uk/information-services/research-support/research-data-service/after/datavault
https://datashare.ed.ac.uk/

IPD sharing plan summary
Stored in publicly available repository, Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes