# The impact of circadian rhythmicity in cold-induced thermogenesis in lean and obese subjects

Published: 15-10-2018
Last updated: 12-04-2024

Primary objective: To assess whether maximum cold-induced non-shivering thermogenesis (e.g. thermogenesis as a consequence of BAT activity) differs between morning and evening.Secondary objectives: a. To study whether cold-induced changes in plasma...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Glucose metabolism disorders (incl diabetes mellitus) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON50725

**Source**
ToetsingOnline

**Brief title**
Cold_rhythm

### Condition

- Glucose metabolism disorders (incl diabetes mellitus)

**Synonym**
obesity

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Interne Geneeskunde, sectie Endocrinologie
**Source(s) of monetary or material Support:** Deze studie wordt gefinancierd door persoonsgebonden beurzen van de Hartstichting;EFSD en Terpstra Award (NVDO) voor

Sander Kooijman

## Intervention

**Keyword:** Brown fat, Circadian rhythm, Thermogenesis

## Outcome measures

### Primary outcome

Cold-induced non-shivering thermogenesis/EE (as measured by indirect

calorimetry)

### Secondary outcome

Cold-induced changes in:

- supraclavicular skin temperature (as measured with iButtons and thermography)

- serum markers for lipid metabolism (TC, HDL-C, LDL-C, TG, free fatty acids)

and dynamic changes in lipoproteins.

- serum markers for sympathetic output (norepinephrine, epinephrine)

- primary and secondary endpoints between lean and obese subjects

# Study description

### Background summary

Brown adipose tissue (BAT) recently emerged as a novel player in energy expenditure (EE) in humans as it combusts fatty acids and glucose towards heat. Human BAT can be activated by sympathetic stimulation resulting from cold exposure or treatment with sympathomimetic drugs. Very interestingly, short-term acclimation to mild cold was shown to reduce fat mass in obese subjects and decrease peripheral insulin resistance of patients with T2DM by 43%. These findings have increased interest in the therapeutic potential of BAT as a target to combat obesity and diabetes. Recently, in preclinical studies we showed that BAT has a circadian rhythm. It is currently unknown whether this is also the case in humans. We postulate that BAT activity should display a circadian rhythm that adapts to changes in circadian behavior, and may

determine glucose/lipid levels throughout the day.

## Study objective

Primary objective:
To assess whether maximum cold-induced non-shivering thermogenesis (e.g. thermogenesis as a consequence of BAT activity) differs between morning and evening.

Secondary objectives:
a. To study whether cold-induced changes in plasma lipid and glucose concentrations differ between morning and evening.
b. To investigate whether rhythmicity in cold-induced non-shivering thermogenesis, glucose and lipid metabolism differ between lean, obese and obese subjects with pre-diabetes.

## Study design

The study design encompasses a single-arm randomized intervention study using cold exposure. Prior to participation, subjects will undergo a screening to exclude subjects with diabetes as well as other chronic diseases and distinguish obese subjects that are glucose tolerant from those that are prediabetic. After inclusion, the week prior to the study days, participants will be asked to report their sleep-wake pattern physical activity and dietary habits in two separate simple diaries as well as fill in a questionnaire to determine their chronotype.

In the main study, subjects will be exposed to a cooling protocol twice within a total timeframe of 72 h, once in the morning and once in the evening (for details, see protocol page 13-14). We will include male and female lean, obese glucose tolerant and obese impaired glucose tolerant men who will undergo identical measurements in the morning and evening. An intravenous catheter will be placed, a first blood sample will be drawn and wireless iButtons will be attached to the skin. Thereafter, an infrared thermal image will be made. Subjects will lie between two water-perfused mattresses and will then be exposed to 32°C (= thermoneutrality) for 15 min. Resting energy expenditure (REE) will be measured by ventilated hoods during thermoneutrality. Thereafter, a venous blood sample will be obtained. Next, the individualized cooling protocol starts. During the cooling protocol, energy expenditure will be continuously measured by ventilated hood. From the start of the cooling on, every 15 min, a blood sample will be taken. The personalized cooling protocol stops when the subject starts shivering. Then, the temperature will be slightly increased until shivering just stops and the stable cooling period starts. 60 min into the cooling procedure (approx. 60 min into stable cold exposure), REE will be measured again via ventilated hoods to assess cold-induced thermogenesis (CIT), which is an important outcome measurement of the study.

After this, the last venous blood sample will be drawn and an infrared thermal image will be made.

**Intervention**

As an intervention, a personalized cooling protocol will be used in order to activate BAT and induce non-shivering thermogenesis. During the cooling procedure, subjects will be exposed to mild cold (approx. 14°C) for 150 min. Since the onset temperature of shivering shows a high interindividual variation, we will use a personal cooling protocol to ensure maximum non-shivering EE (and thus an equal maximum activation of BAT). The right temperature will be determined via a subjective method, e.g. to ask the subject if he or she experiences shivering. The time needed to achieve the right temperature is approximately 30-45 minutes . Then, the stable cooling period of 120 min is started. During this time the subject will be asked every 15 minutes whether he is experiencing shivering. If so, temperature will be increased with 2-3°C so that shivering just stops.

**Study burden and risks**

The risks of the current study are negligible.

# Contacts

**Public**
Selecteer

Albinusdreef 2
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**Scientific**
Selecteer

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NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- Dutch white Caucasian males or females
- Age: 18-35 years
- Lean group: BMI * 18 and * 25 kg/m2
- Obese glucose tolerant group: BMI * 30 and * 42 kg/m2 and fasted plasma glucose levels < 5.5 and/or 2 h after OGTT * 7.8 mM
- Obese impaired glucose tolerant group: BMI * 30 and * 42 kg/m2 and fasted plasma glucose levels * 5.5 and/or 2 h after OGTT between 7.8 and 11.1 mM

## Exclusion criteria

- Diabetes mellitus (determined on basis of fasting glucose or OGTT defined by ADA criteria
- Any other active endocrine disease (thyroid disease, any signs of Cushing*s syndrome, adrenal disease and lipid-associated disorders such as familial hypercholesterolemia)
- Any chronic renal or hepatic disease
- Use of medication known to influence glucose and/or lipid metabolism or brown fat activity (e.g. beta blockers, antidepressants)
- Smoking
- Abuse of alcohol or other substances
- Pregnancy
- Disturbed day-night rhythm such as working night shifts or having a jet lag (participation is allowed 6 weeks after the last night shift or 6 weeks after arriving from another time zone)
- Participation in an intensive weight-loss program or vigorous exercise program during the last year before the start of the study
- Current participation in another research projects that may influence the current research project
- Clinically relevant abnormalities in clinical chemistry at screening (to be judged by the study physician)

# Study design

## Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Basic science |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 23-04-2019 |
| Enrollment: | 48 |
| Type: | Actual |

# Ethics review

Approved WMO

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|---|---|
| Date: | 15-10-2018 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

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|---|---|
| Date: | 11-06-2019 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

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|---|---|
| Date: | 18-10-2019 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

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|---|---|
| Date: | 18-02-2020 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL64299.058.17 |

# Study results

**Summary results**
Trial ended prematurely