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Do adults born small show specific traits that allow them to save energy and hence have increased risk for obesity, diabetes, and heart disease?

Submission date
05/11/2018

Recruitment status
No longer recruiting

Registration date
04/12/2018

Overall study status
Completed

Last Edited
09/02/2024

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Obesity has reached epidemic proportions worldwide and is the driving force behind an equally alarming explosion of type 2 diabetes and cardiovascular (heart) disease. While our 'obesogenic' environment - with abundant energy-dense foods and sedentary (inactive) lifestyle – plays a central role in the development of obesity and cardiometabolic diseases, it is also recognized that factors operating during fetal life (before birth) - and resulting in low birth weight - may program the individual for greater susceptibility towards the development of excess fat and type 2 diabetes and cardiovascular diseases later in life. There is indeed compelling evidence - from large population and clinical studies - that adults who had low birth weight (which reflects limitations in optimal growth as a fetus) have higher susceptibility for obesity, type 2 diabetes or cardiovascular diseases, particularly when catch-up growth occurs early after birth. This work forms the basis of the Barker Hypothesis, which states that growth retardation in the uterus, low birth weight, and premature birth are all linked to greater risk of high blood pressure, heart disease and diabetes in middle age. These risks for cardiometabolic disease have been shown across various populations worldwide and within different ethnic groups. The mechanisms by which such early growth patterns (relatively slow growth followed by catch-up growth) predispose to obesity and insulin-related diseases remain unclear, but have been proposed to be due to fetal or neonatal programming for a thrifty (energy-saving) state. According to the Thrifty Phenotype Hypothesis, early growth constraint (due to inadequate nutrition, small womb size, maternal smoking or other factors) can lead to adaptations that reduce the detrimental effects of growth retardation on vital tissues/organ development and functions. If these adaptations take place during critical windows of development, they may become permanent, and may continue even during improved nutrition later in life, thereby predisposing the individual to diseases such as diabetes and cardiovascular disease. This study seeks to find out to what extent young and healthy adults with low birth weight have energy saving characteristics. These adaptations could favor the development of obesity due to a reduction in the ability to burn calories, as well as a lower body temperature. This study aims to answer the following main questions: Do young adults born with a low birth weight have reduced energy expenditure? In

response to food (sugar, protein) or physical activities of daily life, are these young adults different than those born with normal birth weight in terms of their energy expenditure? Is central body temperature lower in young adults with low birth weight than in those born with normal birth weight?

Who can participate?
Healthy volunteers aged 18-35 whose birth weight was in the range of 1.5 – 4 kg

What does the study involve?
Participants are instructed to refrain from heavy exercise and from drinking caffeinated drinks and alcohol on the day before each experiment, and to eat a normal meal on the evening before the experiment. Women are only tested during the follicular phase of their menstrual cycle. In addition to the days scheduled for test experiments, participants come to the laboratory for two short preliminary visits. On the 1st visit (20-30 min), the participant receives all information about the study, is able to ask questions and visits the lab to become familiar with devices used during testing. On the 2nd visit (about 40 min), participants give their written consent for the study (after appropriate reflection time and before any procedure or collection of data relating to the study), complete questionnaires and undergo initial body measurements. On test days, upon arrival at the laboratory in the morning, participants are asked to empty their bladders if necessary, and to relax in a comfortable armchair. The monitoring equipment is then connected, and energy expenditure is measured in all three protocols below:
I. Participants undergo an oral glucose tolerance test, which involves drinking glucose dissolved in water and providing blood samples.
II. Energy expenditure is measured before and after eating a moderately-high protein test meals (two slices of toast and a milk-based drink to which protein powder, butter, and jam are added to adjust the protein content as necessary).
III. On the day before the experiment, participants swallow a capsule sensor and energy expenditure measurements are undertaken the following morning (after an overnight fast of about 12 hours) to measure the energy cost of low-level physical activity. After about a 15 minute period of rest, the participant is connected to the equipment for resting energy expenditure monitoring for 30 minutes before and 60-90 minutes after a glass of cold water is drank over a 10-minute period. Finger skin temperature is measured by an infra-red camera before the cold water drink, and then every 15 minutes during 60-90 minutes afterward.

What are the possible benefits and risks of participating?
This study will help to find out why people born with low birth weight are more likely to develop obesity and cardiovascular diseases, and help to find accurate ways to identify those most at risk. Although this study is of no potential personal benefit to the participants, they will be provided with information on their body composition. In terms of risk, this study involves non-invasive techniques except for blood taking which may cause a small amount of pain, but which will be reduced by using well-trained staff (a medical doctor or a registered nurse) to collect the samples.

Where is the study run from?
University of Fribourg (Switzerland)

When is the study starting and how long is it expected to run for?
April 2017 to April 2020

Who is funding the study?
Swiss National Science Foundation (Switzerland)

Who is the main contact?
Prof. Abdul Dulloo

Contact information

Type(s)
Scientific

Contact name
Prof Abdul Dulloo

ORCID ID
https://orcid.org/0000-0003-3877-6149

Contact details
University of Fribourg
Chemin du Musée 5
Fribourg
Switzerland
1700

Additional identifiers

Study information

Scientific Title
Phenotyping for thrifty metabolic traits in young adults born small: a risk factor for obesity and cardiometabolic diseases

Study objectives
In young adults with low birth weight, thrifty metabolic traits may be expressed through one or more compartments of energy expenditure (EE) namely (i) in diminished glucose-induced thermogenesis, (ii) diminished dietary protein-induced thermogenesis, (iii) diminished energy cost of performing low-intensity physical activity, (iv) in a lower core body temperature.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Commission cantonale (VD) d'éthique de la recherché sur l'être humain (CER-VD), 29/12/2017, ref: 2017-02087

Study design
Observational monocentric study

Primary study design
Observational

Study type(s)

Other

Health condition(s) or problem(s) studied
Obesity, diabetes, and heart disease

Interventions
Current interventions as of 09/02/2024:

Study centered on energy expenditure measurements to be conducted according to three protocols:

I. Oral glucose tolerance test (OGTT) will be performed according to the guidelines provided by the American Diabetes Association (75 g glucose dissolved in 300 ml water; ingested within 5 minutes).

II. Moderately high (24-25%) protein test meals will be provided. The test meal will consist of a simple breakfast meal base (two slices of toast and a milk-based drink to which protein powder, butter, and jam are added to adjust the protein content as necessary).

III: In the afternoon of the day preceeding the experiment involving core temperature measurements, a capsule telemetric sensor will be ingested by the subject. Standardized energy expenditure measurements will be undertaken the following morning (after an overnight fast of ~12 h) using indirect calorimetry to measure energy cost of low-level physical activity. After about a 15 min period of rest, the subject is connected to the calorimetry system for resting energy expenditure monitoring for 30 min before and 60-90 min after a glass of cold water is ingested over a 10 min period. Finger skin temperature will be measured by an infra-red thermography camera prior to the cold water drink, and then every 15 min during 60-90 min post-drink period.

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Previous interventions:

Oral glucose tolerance test (OGTT) will be performed according to the guidelines provided by the American Diabetes Association (75 g glucose dissolved in 300 ml water; ingested within 5 minutes).

Low (11-12%) and high (24-25%) protein test meals will be provided. The test meal will consist of a simple breakfast meal base (two slices of toast and a milk-based drink to which protein powder, butter, and jam are added to adjust the protein content as necessary).

In the afternoon of the day preceding the experiment involving core temperature measurements, a capsule telemetric sensor will be ingested by the subject. Standardized energy expenditure measurements will be undertaken the following morning (after an overnight fast of ~12 h) using indirect calorimetry to measure energy cost of low-level physical activity. After about a 15 min period of rest, the subject is connected to the calorimetry system for resting energy expenditure monitoring for 30 min before and 60-90 min after a glass of cold water is ingested over a 10 min period. Finger skin temperature will be measured by an infra-red thermography camera prior to the cold water drink, and then every 15 min during 60-90 min post-drink period.

Intervention Type

Other

Primary outcome(s)

Current primary outcome measure as of 09/02/2024:

The following measurements will be taken only once as this is an acute response study and does not involve any follow-up:
1. Energy expenditure (EE) in the pre- and post-prandial states, assessed at rest in a comfortably seated position by gas exchange (using indirect calorimetry) – measurements will be performed 30 min before and for 2 and 3 hours after glucose drink and the meal, respectively.
2. EE in response to standardized low-intensity exercises measured by indirect calorimetry after 30 min of cycling on a bicycle ergometer and intermittent leg press over 40 min
3. Core body temperature measured by telemetry using ingested pill-sized sensors over 24 hours after sensor ingestion
4. Blood glucose and insulin measured during the oral glucose tolerance test after 30 min baseline and at 30, 60, 90, 120 min post-glucose drink (75 g glucose dissolved in 300 ml water); blood insulin will be measured by using an ELISA assay kit, whilst glucose will be measured by the reference method with hexokinase Glucose HK Gen 3

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Previous primary outcome measure:

The following measurements will be taken only once as this is an acute response study and does not involve any follow-up:
1. Energy expenditure (EE) in the pre- and post-prandial states, assessed at rest in a comfortably seated position by gas exchange (using indirect calorimetry) – measurements will be performed 30 min before and for 3 hours after the meal
2. EE in response to standardized low-intensity exercises measured by indirect calorimetry after 30 min of cycling on a bicycle ergometer and intermittent leg press over 40 min
3. Core body temperature measured by telemetry using ingested pill-sized sensors over 24 hours after sensor ingestion
4. Blood glucose and insulin measured during the oral glucose tolerance test after 30 min baseline and at 30, 60, 90, 120 min post-glucose drink (75 g glucose dissolved in 300 ml water); blood insulin will be measured by using an ELISA assay kit, whilst glucose will be measured by the reference method with hexokinase Glucose HK Gen 3

Key secondary outcome(s))

Current secondary outcome measures as of 09/02/2024:

The following measurements will be taken only once as this is an acute response study and does not involve any follow-up:
1. Respiratory quotient, measured using indirect calorimetry as per EE above
2. Anthropometry and body composition
3. Cardiovascular health and function
4. Potential sex-related differences

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Previous secondary outcome measures:

The following measurements will be taken only once as this is an acute response study and does not involve any follow-up:
1. Respiratory quotient, measured using indirect calorimetry as per EE above

Completion date
30/01/2020

Eligibility

Key inclusion criteria
Current inclusion criteria as of 09/02/2024:

1. Young men and women (18-35 years old)
2. Healthy (as determined from medical history)
3. Non-obese, body mass index (BMI) < 30kg/m2
4. Non-smokers
5. Birth weight in the range of 1.5 – 4 kg

Previous inclusion criteria:

1. Young men and women (18-35 years old)
2. Healthy (as determined from medical history)
3. Non-obese, body mass index (BMI) < 30kg/m2
4. Non-smokers
5. Birth weight in the range of 1.5 – 3.5 kg

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
35 years

Sex
All

Total final enrolment
90

Key exclusion criteria

1. Subjects born very premature defined as less than 28 weeks of gestation
2. Subjects who were treated for short stature (e.g. with growth hormone therapy)
3. Subjects taking medications that may alter body temperature, and any other condition that might impair the subject's ability to participate in the study
4. Competition athletes, smokers, or overtly sedentary, or have eating disorders
5. Subjects who fear or have adverse reactions to cannulation
6. Subjects with a history of alcohol or any other drug abuse
7. Weight loss > 5% during 6 weeks prior to inclusion in the study
8. Pregnant and lactating women or females who desire to become pregnant over the study period (a pregnancy test is performed prior to each experimental protocol)
9. Subjects with gastro-intestinal complications, and fulfilling the official contraindications for the ingestion of the telemetry pill such as those diagnosed for diverticulitis, inflammatory bowel disease, gag reflex disorders or impairments, previous gastrointestinal surgery, hypo-motility of the gastrointestinal tract
10. Any person who might undergo magnetic resonance imaging (MRI) scanning while the telemetry pill is within the body, or having a cardiac pacemaker or another implanted electro-medical device

Date of first enrolment
01/06/2018

Date of final enrolment
31/12/2019

Locations

Countries of recruitment
Switzerland

Study participating centre
Department of Endocrinology, Metabolism and Cardiovascular System
University of Fribourg
Chemin du Musée 5
Fribourg
Switzerland
1700

Sponsor information

Organisation
Swiss National Science Foundation (SNSF)

ROR
https://ror.org/00yjd3n13

Funder(s)

Funder type
Research council

Funder Name
Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung

Alternative Name(s)
Schweizerischer Nationalfonds, Swiss National Science Foundation, Fonds National Suisse de la Recherche Scientifique, Fondo Nazionale Svizzero per la Ricerca Scientifica, Fonds National Suisse, Fondo Nazionale Svizzero, Schweizerische Nationalfonds, The Swiss National Science Foundation (SNSF), SNF, SNSF, FNS

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The dataset generated during and/or analysed during the current study may be available upon reasonable request to Prof. Abdul Dulloo (abdul.dulloo@alumni.unifr.ch).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		20/12/2017	09/02/2024	No	No