Circadian and ultradian variations in the healthy human metabolome

You are invited to take part in a research study

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you.

Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is this study about?

You have been invited because you are a healthy male volunteer.

This is a study about human metabolism. Metabolism is the set of processes that sustain life in living cells and organisms. Many metabolic processes are rhythmic—that is they act differently at different times of the day. Disrupting these rhythms can lead to sickness and disease. For example, obesity and type 2 diabetes are strongly linked to abnormal metabolic rhythms.

The products of metabolism are called metabolites. These metabolites can be measured in human tissues like blood and saliva. By taking multiple samples over time we can build a 'profile' of the metabolism of that person. The study of metabolites in this way is called metabolomics.

We are interested in a new way of measuring metabolites by taking continuous samples of fluid from just beneath the skin. To start with we will trial this in a group of healthy men. We hope that in future we will be able to use information from this study to better understand diseases, like type 2 diabetes and obesity.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason.

Who is organising and funding the project?

This study is sponsored by the University of Bristol.

It is being done in collaboration with the University of Surrey. Funding is provided by grants obtained through the University of Bristol.

Who has reviewed this study?

This research has been reviewed and approved by the University of Bristol Faculty of Health Sciences Research Ethics Committee.

Interested?

Want to know more?

Contact us:

Dr Thomas Upton

@ thomas.upton@bristol.ac.uk

☎ 0117 331 3167

✉ Dorothy Hodgkin Building
BS1 3NY

What will happen to me if I take part? What will I have to do?

Each study involves two sessions — a screening visit and a sampling visit.
Visits will be at the Medical and Surgical Research Unit, B501, Level 5, Zone B, Bristol Royal Infirmary BS2 8HW

The screening visit will take about 30 minutes

At this visit we will check if you are eligible to take part in the study.

We will answer any questions you might have and then ask you for your informed consent. We will check your health and medication history, and will measure your height and weight.

You will be given five brief questionnaires to complete that ask about your mood, sleep habits and sleep quality. We will take a blood sample from a vein in your arm to check that

You can participate if you

- Are male aged between 18-35
- Are healthy, without active medical problems
- Take no regular medications
- Don't smoke
- Don't take illicit substances
- Meet our sleep health criteria

If we find that you are not eligible to participate for any reason, we will explain to you why not, and give you the opportunity to ask any questions.

The sampling visit involves overnight admission to our study unit

If you meet all the eligibility criteria and want to participate we will arrange a time for the sampling visit.

During the week prior to the visit we will give you a sleep diary**, wrist watch and ring that** measure your sleep and activity. **We will also place a small sensor called a continuous glucose monitor (CGM) on your arm. This measures your glucose via a tiny filament sensor that inserts just below the skin.** We will ask you not to drink alcohol or caffeine, do any vigorous exercise, or take any medications for 3 days prior to this visit. We will also give you a food diary to write down what you have eaten and drank during the 24 hours before the sampling visit starts.

On the morning of the sampling day you will be connected to our microdialysis sampling system. In this study, we will place either 1 or 2 probes just under the skin of your tummy. You can see a picture and description on the next page. This usually does not require anaesthetic. The first probe is used for measurement of metabolites. However, if you consent, a second probe will be placed for collecting additional information about your stress and sleep hormones. The second probe is optional. You can choose not to have the second probe, if you would prefer.

Fitting the probes takes about 30-60 minutes. Afterwards you have a break and then we place a cannula (plastic tube) in your vein to take blood samples during the study. Blood samples will be drawn every 20-60 minutes, either manually or using our automated blood sampling system. About 2mL of blood will be taken each time. If samples were taken every 20minutes for the full 25 hours, the total amount of blood would be slightly less than a single blood donation. We will replace this blood loss with fluid (normal physiological saline).

Once the first blood sample is taken, you will need to stay with us for another 25 hours to complete the study. We will provide all your meals and water to drink during this time. You won't be able to shower as the microdialysis system is not waterproof. A researcher will be on site at all times.

Repeating the study

At the end of the sampling visit we may ask if you would be willing to participate again.

We would like to sample each participant on up to 3 occasions so that we can see how the metabolite profile varies in the same individual over time. There would be at least 1 week between each session. There would be no obligation or any pressure to participate again if you didn't want to.

If there was a technical problem during the sampling (for example if the sampling device failed) we might ask you permission to do that study again. Again you would be under no obligation or pressure to agree. We would never ask you to do more than 3 studies in total.

The microdialysis system

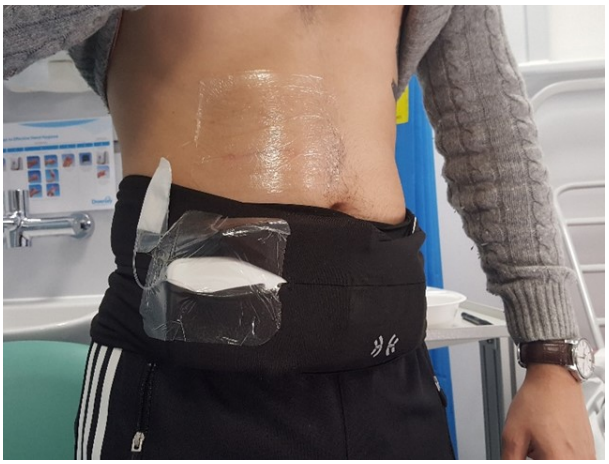
What is microdialysis?

A microdialysis probe is a very narrow tube (less than the width of a pin head) with tiny holes ("pores") through which certain molecules can pass.

In this study, the probes are placed just below the surface of your skin, around your tummy button.

Once the probe is under the skin, it is connected to a small pump and a sample collector. These are both kept in a small bag, which is worn around the waist. Together, everything weighs less than a tin of baked beans. You can see a picture of the device on this page.

The probe and pump are fully approved for use in humans (CE marked). The sample collector is a research device developed by our team. It does not have CE marking. However it has already been successfully used in several trials of healthy volunteers and patients with no problems reported. The device stores samples of fluid only – safety valves prevent any flow of liquid back toward the body.



The sample collector (top right) and pump (top left) are placed in a stretchy belt around the waist. The probe is a very small plastic tube placed just under the skin on the lower part of the abdomen (stomach).

Will I be paid to take part?

We can provide a fee as compensation for inconvenience, travel expense, and time away from work. The payment per session will be £300, or £350 if you have microdialysis 2 probes fitted.

What are the potential side effects and risks of taking part?

Blood tests and the microdialysis sampling system

The microdialysis system is safe and we do not think there will be any significant side effects or risks to you as a participant. Minor bruising at the site of the microdialysis probe insertion or around the vein where you have your blood test might occur. Very occasionally people can faint while having a blood test – we will ask you if you have ever had any problems with fainting or blood tests before we start the study.

Like any other procedure there is a small risk of discomfort during insertion or at the site of the probe. There is theoretically a small risk of infection and localized allergic reaction at the site of the probe or blood sampling. This risk is considered to be extremely low as we use an aseptic (clean) method and the probe is made from low allergy material. If infection or allergy is suspected we will immediately remove the probe and stop the study.

Glucose sensor

The continuous glucose monitoring system is a safe, reliable device that is painless when worn. We do not believe that wearing one will be of any risk to you as a participant. Occasionally, some individuals may be sensitive to the adhesive that keeps the Sensor attached to the skin. In this case, we may need to remove and or replace the Sensor.

Unexpected abnormal blood test results

If during the study your blood results reveal any abnormality we will arrange a meeting with you to explain these results. We will ask you if you wish for this information to be sent to your GP and if appropriate we may recommend an appointment with your GP.

If you have any questions regarding this you can either discuss with a researcher or take this information sheet to your GP to discuss matters of concern. If, at any time during the study, new information becomes available, the researchers will talk to you about this and discuss whether you want to continue in the study.

What support is available to me during the study?

During the week prior to the blood and microdialysis sampling visit, a study investigator will always be available to contact either via email or mobile phone. At least one study investigator will be present at all times during the sampling visit.

Are there any benefits to me if I take part?

You will not benefit directly from taking part in this research study.
However, we hope that the information we get from this study will help us to understand healthy metabolism. In the long term we hope the information will lead to further studies of metabolic diseases.

What will happen to my samples?

Screening blood tests will be analysed at the UH Bristol NHS laboratory. Microdialysis and blood samples taken during the study will first be stored in a freezer within the University of Bristol and then sent away to The University of Surrey and University Medical Centre, Groningen for analysis. All your samples will be totally anonymous and cannot be linked to you in any way.
After initial analysis any remaining samples may be stored for up to 5 years after the last person is recruited. Samples are kept in case analyses need to be repeated or if additional results are required to successfully complete the study. During this time, the residual sample could also be used for further ethically approved research studies, only with your consent. After this date anything remaining of your samples will be destroyed.

If you decide to withdraw from the study, you can ask for your samples to be destroyed even if they have not been analysed. You can also request that any information obtained from analysing your samples to be destroyed.

Will my taking part in this study be kept confidential?

Yes. All information about you will be kept strictly confidential.
Any information we collect will be made anonymous so you can't be identified personally. Your information may

What if I don't want to carry on with the study?

You can leave the study at any time.
Participation is entirely voluntary and you can withdraw at any time without having to give a reason.

What will happen to the results of the research?

The results of the study may be published in a peer reviewed journal or presented at a scientific meeting.
We can also share with you the general outcomes of the study, along with a summary of your individual results, once these have been analysed.

What happens to the data collected during the study?

We will collect information in both paper and electronic form

Information about your participation will be recorded on paper Clinical Record Forms (CRFs). These do not contain any personal identifying information. CRFs forms are stored securely in a locked office within the University of Bristol.

Results and other data collected from these forms may be transferred to password-protected electronic forms hosted on secure servers by the University of Bristol.

Data from the activity watch is stored securely within the University of Bristol

Information about your sleep and activity during the week prior to sampling is stored within the activity watch internal memory. This data will be downloaded from the watch via a USB cable and stored in anonymised form in a secure location on a password protected computer, hosted by the University of Bristol. No personal identifying information will be stored on the watch or within the data stored on the computer.

Data from the ring is stored in a secure cloud form

No personal identifying information about you is stored within the ring. Anonymised information about your heart rate, temperature and other parameters is recorded in the ring's internal memory.

This information will be downloaded from the device using software supplied by the manufacturer (OURA). OURA software is 'cloud based' - data is stored anonymously and securely on an internet server. Information is encrypted at the time of transfer from the device.

This information will only be accessed by researchers involved with the study.

For more information about how OURA protects and stores study data, visit the OURA website https://ouraring.com/privacy-policy-device-and-application/

Data from the CGMS sensor is stored securely within the University of Bristol.

Anonymous glucose measurements are automatically recorded by the device every 15 minutes while it is worn. This information is transferred wirelessly to the sensor Reader and which is then downloaded via USB cable to a Unversity of Bristol server. More information about the FreeStyle CGM system can be found here: https://www.freestylelibre.co.uk/libre/help/faqs.html

What do I do now?

If you are interested in this study please make contact. Otherwise you don't have to do anything.

You can find the contact details for our study investigators on page 1 of this information sheet. You can contact us to ask any questions about the study or to tell us that you are interested in taking part.

If you are interested we will get back to you to discuss a suitable time to come in for the screening visit.

What if I have concerns about this study?

The Research Governance team can be contacted if you wish to make a complaint or voice any concerns about this study.

Email: **research-governance@bristol.ac.uk**

Call: **+44 (0)117 928 8676**

Write to: **Research and Enterprise Development,**
3rd Floor, Senate House,
Tyndall Ave,
Bristol,
BS8 1TH