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Influence of vitamin D and a probiotic on inflammation and gut bacteria

Information Sheet for Study Participants

REC Reference number 21/SC/0403
CRF Study ID: NUT0071

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Version 3
25th March 2022

You are being invited to take part in a research study. To help you decide whether you would like to take part or not, it is important that you understand why the research is being done and what it will involve. Please read the information below carefully and ask questions if anything is not clear or if you would like more information before you decide to take part in this research. You may like to discuss it with others but it is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

As we age, our immune system becomes weaker and there is an increase in inflammation which contributes to common age-related diseases. These include heart disease, metabolic disease such as type-2 diabetes, the loss of muscle mass and strength known as sarcopenia, the weakening of bones known as osteoporosis, some cancers, and possibly dementia. A weaker immune system means older people can be more susceptible to infections and that some vaccines may not work as well as in younger adults.

The “healthy” bacteria in our intestine (called gut microbiota) have an influence on our immune system and our inflammation. Our intestinal bacteria also change with ageing and this can result in the loss of protective function and in the movement of harmful bacterial toxins and whole bacteria from the gut into the blood. Why these changes occur and how we can improve this in ageing are not understood. What we do know is that our intestinal bacteria can be altered by our diet. They can also be altered by probiotics, which are live healthy bacteria often found in yoghurts. We plan to investigate whether nutritional supplements of vitamin D and a probiotic improve measures of muscles, bone, the immune system, inflammation and intestinal bacteria. The probiotic organism, we will use is called *Lactobacillus plantarum*. Vitamin D has an important

role in maintaining healthy bones and a healthy immune system and preventing too much inflammation and has also been seen to positively affect the intestinal bacteria. *Lactobacillus plantarum* is commercially available and has been seen to positively affect the intestinal barrier but its effects on the immune system and inflammation have not been tested in older people.

We plan to compare the effects of using either vitamin D and *Lactobacillus plantarum* individually or together in combination on intestinal bacteria, the immune system and inflammation, and other measures of ageing including bones and muscles.

Why have I been asked to participate?

You have been contacted because you have expressed an interest in our research by answering our advertisement and you appear to meet the inclusion criteria. We need healthy men and women over the age of 70 years. We will be recruiting 104 subjects in total.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to sign a consent form. However, you will still be free to withdraw at any time, and without giving a reason. If you do withdraw, you will be asked whether you want us to destroy any samples you have given as part of the study.

What will happen to me if I take part?

If you decide to take part, you will be asked to attend 2 appointments at the Clinical Research Facility at Southampton General Hospital.

At both appointments (visits (V) 1 and 2), you will come in the morning before you have had your breakfast. You will be asked to fast ahead of your visit

(no food or drink apart from water from 9 pm the night before). You will receive breakfast during your visit.

At V1 we will discuss the study with you and if you are happy, you will give your written consent to participate in the study. We will measure your height, weight, waist, hip and mid-upper arm circumferences, and blood pressure as well as body composition and grip strength. We will then take some blood (~60 ml; about 3 tablespoonfuls) and you will complete three questionnaires asking you about your diet, quality of life, and physical activity. This appointment will last 1.5-2 hours. You will be provided with breakfast after we have made the body measurements and collected your blood. You will be given collection packs and instructions to collect 3 urine samples and 1 faecal sample at home within 1 week. You will be asked to return the samples in person (or have them collected from you by a researcher or a courier if this is not possible). You will complete a questionnaire about your diet over the 24 hours before collecting each urine sample. You will be allocated to one of four treatment groups. You will be provided with either 10 micrograms/day of vitamin D, 5 billion/day of *Lactobacillus plantarum*, both 10 micrograms/day of vitamin D AND 5 billion/day of *Lactobacillus plantarum*, or a daily placebo supplement for 12 weeks (3 months). This allocation will be randomised and 'blinded' so you will not know which supplement you are consuming. You will also be given collection materials and instructions to provide 3 further urine samples collected in the week before V2 and a faecal sample collected sometime during the 48 hours before V2 to bring in with you when you come for V2.

Between V1 and V2 you will be asked to record the daily ingestion of your supplement in a paper diary that we will provide you with. You will also complete

a daily questionnaire about your respiratory health. You will receive scheduled contact from the research team every 4 weeks but you will be able to contact the team yourself at any other point also.

V2 will take place about 3 months after V1. At V2 you will be required to bring along your 3 urine samples and 1 faecal sample. At V2 we will take a second set of body measurements and grip strength and collect another ~60 ml blood sample. You will then be asked to complete a final set of questionnaires; these will be the same ones as used at V1. This visit will last about 1.5-2 hours. Again you will receive breakfast during your visit.

Your blood, urine, and faeces will be treated anonymously and will not be able to be linked directly to you. Blood samples will be analysed in our own laboratories at University Hospital Southampton and University of Southampton and will also be sent to our partner at University of Birmingham for some additional analysis.

Urine samples will be analysed in our own laboratories at University of Southampton.

Faecal samples will be sent to our partner at University of Norwich for analysis of your gut bacteria.

These samples will be marked with an ID number and will not be linked to your name.

Any samples left over at the end of the study will be transferred to a research biobank for future use if you consent to this. If this happens, a record linking the ID number on the samples to you will be kept in a secure location.

If any of the measurements made in your blood are of concern, we will tell you this and provide you with a note about it to take to your GP.

What do I have to do?

You will attend Southampton General Hospital for 2 visits. Each visit will last 1.5 to 2 hours. You will be asked to answer a set of questions about your diet, quality of life, and physical activity at each visit. In between the two visits (V1 and V2) you will be asked to complete a daily paper diary to record ingestion of your supplement and complete a questionnaire every day about your respiratory health (if you are well you will not need to do this). You will attend Southampton General Hospital one week after your first visit to drop in your urine and faecal samples. You will speak with the research team every 4 weeks. The visits will take place over a period of about 3-5 months. You will be asked to provide blood, urine and faecal samples. On the days you provide urine samples you will be asked to complete a diary about your diet – this can be done as a paper diary or online.

What are the benefits of taking part?

You may benefit from positive effects to your immune system and/ or your intestinal bacteria. Knowledge gained from this study will help our research and will ultimately be of use to other researchers and consumers.

What are the possible disadvantages and risks of taking part?

You will probably be familiar with providing blood for tests or for donation. With any procedure involving blood collection with a needle, there is a very small chance of infection and a chance of bleeding and bruising at the site of insertion of the needle. This will be minimised by using sterile techniques and trained members of staff.

What data will be collected?

We will hold your contact details for the duration of the study, but these will be destroyed at the end of the study.

We will collect information about your age, sex, height, weight, general health status, and quality of life. This will be collected by research staff. We or our research partners will measure chemicals in your blood and urine, and investigate your intestinal bacteria from your faeces, that will tell us about your immune system, level of inflammation, gut health, and metabolism. We will collect information about your diet. All personal data will be kept in a locked filing cabinet and on a password protected computer. No data will be linked with your name and address, only to an anonymous study code.

Will my participation be confidential?

Your participation and the information we collect about you during the course of the research will be kept strictly confidential.

Only members of the research team and responsible members of the University of Southampton may be given access to data about you. This is for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

Do I have to take part?

No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form to show you have agreed to take part.

What happens if I change my mind?

You have the right to change your mind and withdraw at any time without giving a reason and without your participant rights (or routine care if a patient) being affected. You can withdraw by

informing the research team. If you withdraw and do not wish us to use your samples, then they will be destroyed.

What will happen to the study results?

Your personal details will remain strictly confidential. Research findings made available in any reports or publications will not include information that can directly identify you without your specific consent.

The results may be presented at scientific meetings and published in a scientific journal. You will not be identified in any of these presentations or publications. We will be happy to discuss the results with you when the study is completed and will let you know where you can obtain a copy of the published results.

Will I be reimbursed for my time?

On completion of the study reasonable travel expenses will be reimbursed.

Who is organising and funding the study?

This study is being organised by the Faculty of Medicine at The University of Southampton. The research is being funded by the UK Medical Research Council. The University of Southampton is acting as the legal sponsor of the study.

Who has reviewed the study?

The South Central Hampshire Research Ethics Committee.

What will happen if anything goes wrong?

If something goes wrong during an investigation day any procedures will be stopped and you will be seen by a doctor. Your involvement in the rest of the study may be stopped.

If you have a concern about any aspect of the study you should speak to the researcher involved who will do their best to answer your questions (telephone 077 2610 0436). If you remain unhappy and wish to complain formally you should contact the NIHR Clinical Research Facility in the first instance (telephone 023 8079 4989). Any complaint

about the way that you have been dealt with during the study or any possible harm you might suffer will be addressed.

You may also contact the University of Southampton Head of Research Integrity and Governance at rgoinfo@soton.ac.uk.

The study is covered by insurance held by the University of Southampton. This insurance covers the possibility of compensation should anything go wrong during the study.

What precautions are in place regarding Covid-19?

The Clinical Research Facility is inside Southampton General Hospital Southampton. It is a short distance from the main entrance and is only accessed by individuals and staff working in the facility or attending clinical trial appointments. As with all areas of the hospital, enhanced sanitisation is in place and face masks/coverings are currently mandatory. There are a number of hand sanitisation points along the short walk to the research facility within the hospital and social distancing is maintained by staff where possible. Appropriate PPE including gloves and aprons are routinely worn by staff for all sample collections, with the addition of face coverings during this time.

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that

relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (<https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page>).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at <http://www.southampton.ac.uk/assets/sharepoint/intranet/Is/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf>

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it. Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

The Intake24 online software used for reporting your dietary intake over the 3 days prior to urine collections, does not store any personal information about you. Dietary data collected from you is associated with an artificial user identifier that cannot be used to identify you as an individual based solely on the data stored by Intake24. Intake24 complies with general data protection regulation (GDPR) and complies with the EU-US Privacy Shield Frameworks as set forth by the U.S. Department of Commerce regarding the collection, use, and retention of personal data from the EU and Switzerland. The website may pass a "cookie" (a string of information that is sent by a website to reside on your system's hard drive and/or temporarily in your computer's memory). The purpose of a cookie is to tell the web server that you have returned to a particular page. You may set your browser to decline cookies. If you do not wish to use the online intake24 you may complete a paper version.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for one year after the study has finished. After this time any link between you and your information will be removed.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (<https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page>) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

Contact for further information

If you have any further questions then please contact Helena Fisk at The Faculty of Medicine, University of Southampton on 077 2610 0436 or e-mail H.fisk@soton.ac.uk

And finally...

Thank you for having taken the time to read this information sheet and for your interest in the study. If you do decide to take part in the study, you will be given a copy of this information sheet and a signed consent form for you to keep. You should keep this sheet for at least as long as you are participating in the study.