Subject information for participation in a medical-scientific study

LACTASTIC

Official title: The effect of dietary lactose in lactase non-persistent individuals on gut microbiota

Introduction

Dear Sir/Madam,

You are being asked to take part in a medical-scientific study. Participation is voluntary. In order to participate your written consent is required. Before you decide whether you want to take part in this study, you will be given an explanation about what the study involves. Please take your time to read this information and ask the investigator if you have any questions. You can also ask the independent expert mentioned at the end of this letter for additional information. You can also discuss it with your partner, friends or family.
Further information about participating in such a study is found in the enclosed brochure ‘Medical scientific research’.

Best wishes,

Lonneke Janssen Duijghuijsen and Diederik Esser
Researchers

1. General information

This study will be conducted by researchers of Stichting Wageningen Research (Research Institute Wageningen Food & Biobased Research). This study has been initiated and is financed by FrieslandCampina (FC C.V.).
For this study, 25 subjects from various Asian origin are required. The Medical Ethics Review Committee of Utrecht has approved this study. General information about the assessment of research can be found in the brochure 'Medical research' (https://www.government.nl/topics/medical-research/documents/leaflets/2020/05/12/medical)

2. Purpose of the study

The purpose of this study is to find out whether regular intake of lactose has an effect in reducing lactose intolerance symptoms in genetically lactase-deficient individuals. We would like to know what role the gut microbiota plays in this process. If daily lactose intake would reduce symptoms, these individuals may be able to consume some dairy and dairy-based products on a daily basis without experiencing gastrointestinal discomfort. Outcomes of this study will be published.

3. Background of the study

Lactose is a type of sugar and present in most dairy and dairy-based products. Individuals that lack the enzyme lactase in their gut, so-called genetically lactase non-persistent individuals, are not able to digest and absorb lactose in the small intestine. This is very common: about 80% of the Asian population is lactase non-persistent. Lactase non-persistent persons have a genetically decreased lactase production. Lactase is an essential enzyme in the small intestine which breaks lactose down for complete digestion of dairy or dairy-based products. Lactose will then be fermented by bacteria in the colon, which may lead to some discomfort, such as bloating, cramps, and sometimes diarrhea. Earlier studies in lactase non-persistent individuals showed that regular intake of lactose may lead to colonic adaptation, via changes in its microbiota composition and function. This process can result in a reduction of lactose intolerance symptoms. Most lactase non-persistent individuals should be able to consume at least 12 grams of lactose per meal (which is comparable to 1 cup of milk). It is not exactly known which dose of lactose is needed to lower the lactose intolerance symptoms. Therefore, this study will test different doses of daily lactose intake and evaluate at which dose colonic adaptation takes place.

4. What participation involves

Information meeting

Prior to the study we organize several information meetings. The researcher explains the study aim and design and there is room for all of your questions. After the meeting, you are given a week to think about participation.

Screening

In case you decide to participate, we first have to determine whether you can participate based on a screening. You are invited to the research unit to sign the informed consent and to fill out a short questionnaire about several factors, such as your medical history, ethnicity, and lifestyle. The researcher will measure your weight and height. You will also be screened to confirm whether you are lactase non-persistent. For this, we need a cheek swap, which is painless, easy and quick. Your genetic test will only screen for the genotype (part of genetic profile) of lactase non-persistence, no other data will be collected. Based on the outcomes, we can confirm whether you are eligible to participate in the study.

You are eligible to participate when you:

- are between 18 and 50 years of age and of Asian ethnicity
- have the lactase non-persistent genotype
- are avoiding dietary lactose in habitual diet
- are apparently healthy and not using any medication (apart from an occasional pain killer)
- have a body mass index (BMI*) between 18.5 and 30 kg/m^2
- consume less than 4 glasses (men) or 2 glasses (women) of alcoholic beverages per day
- have sufficient English proficiency to understand this information sheet and the questionnaires
- have not used antibiotics in the 6 months prior to the start of the study
- do not use pre- and/or probiotics
- do not use of medication that may influence the study results, such as laxatives and lactase preparations (e.g. Kerutab). Use of medication will be judged by the medical supervisor
- do not smoke
- are not pregnant or lactating, or planning to become pregnant during the study period
- do not use illicit drugs
- do not have food allergies (food intolerances are acceptable)
- do not participate in another clinical trial at the same time
- are not employed by the Food, Health and Consumer Research group of Wageningen Food & Biobased Research, the Department of Human Nutrition of Wageningen University, or FrieslandCampina

* BMI = weight in kg/ (height in m x height in m)

The study

The study will start in September 2021 and will take place on the Campus of Wageningen University & Research. If you participate, your participation will last a total of 14 weeks. Each participant will receive different doses of lactose over a period of 12 weeks. The minimal dose consists of 6 grams of lactose per day (3 grams for breakfast, 3 grams for dinner) and the maximal dose consists of 24 grams of lactose per day (12 grams for

breakfast, 12 grams for dinner, comparable with a cup of milk with your meal). We will not inform you which dose of lactose you will receive during which week of the 12 week intervention period. We have chosen to do so to avoid a common placebo effect.

The study product

During this study you will consume twice a day a sugar blend with different ratios of lactose and dextrose. The sachets you will receive will always contain 12 grams of sugar in total. We will do this because in this way it will not be visible for you how much lactose is in there. You can dissolve the lactose/dextrose in a glass of cold water, but also for example in a cup of tea, and consume this during or directly after breakfast and dinner. During the study we ask you to stick to your normal lactose-avoiding diet and normal exercise routine.

Visits and tests

For the study, you will consume the sugar mix twice a day for 12 weeks and score your stool frequency and consistency in a daily diary. You will visit the research facility at least 9 times (See Figure 1 for a schematic overview).

- One visit to pick up a meal you have to consume before the hydrogen breath test at the start of the study (0.5 hours)
- Twice for a hydrogen breath test (Approximately 5.5 hours)
- Four times to hand-in a stool sample (two times combined with hydrogen breath test)
- Every two weeks you will pick-up your study products (0.5h, three times combined with handing over a stool sample)

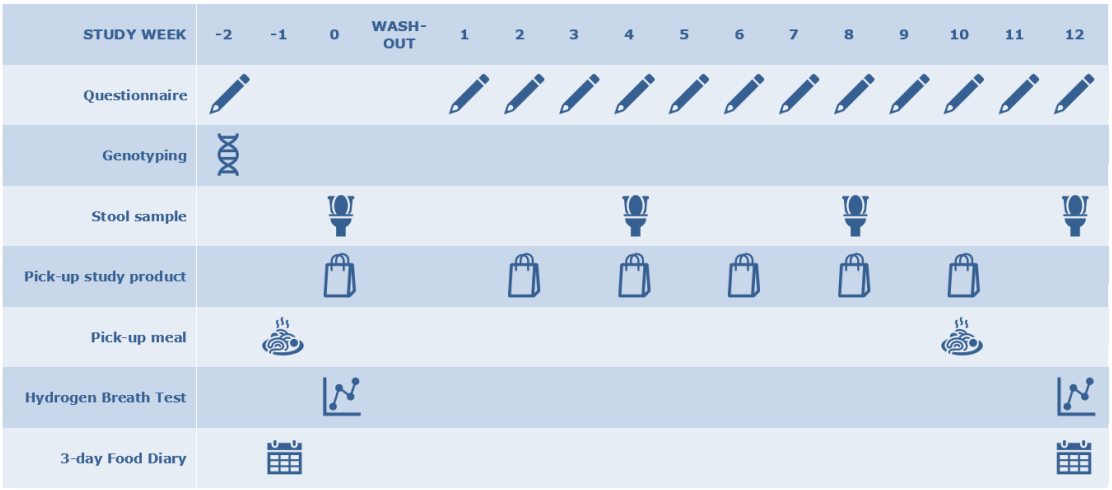

Figure 1. Study visits and measurements

Before and at the end of the 12 week intervention period, you will come to the research facility for a hydrogen breath test. The day before this test, you have to stick to some (dietary) guidelines: you have to avoid excessive exercise and the consumption of fruit and fruit juices, onions, leek, garlic, cabbage, beans, and chewing gum. You will receive a standardized dinner you can consume at home. You are not allowed to eat and drink (with the exception of water) after 20.00 hr and will arrive at the research facility without any breakfast. Brushing

your teeth is allowed. During the hydrogen breath test, a couple of your breaths will be sampled before (0) and 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, and 270min after you consume 25 grams of lactose. You will also complete a short questionnaire on gastrointestinal comfort every 30 minutes. After this test you will receive lunch and a wash-out period of 4 - 6 days will start. During this period no study activities will be performed. After the wash-out period, the intervention period will start.
During the complete intervention period you will complete a daily short questionnaire about gastrointestinal comfort and stool patterns via an app on your phone. Every other week you visit the research facility to pick up new study products and the researcher will inquire about your stool frequency and consistency and gastrointestinal comfort. At the beginning and end of the study you will fill out a three-day food diary. First you will fill out the diary yourself, after which you will be consulted by a dietician during the study visits for the hydrogen breath test, who may ask for some more details or explanations.

5. What will be expected of you

For the study to run smoothly, it is important that you stick to the following agreements.

The agreements are that you

- consume the study product as explained
- do not participate in another medical-scientific study
- follow appointments for visits
- maintain avoiding dairy in habitual diet

It is important that you contact the investigator:

- if you are hospitalised or treated in a hospital
- if you suddenly experience health symptoms
- if you no longer wish to participate in the study
- if your contact details change

6. Possible discomforts

Consumption of the study product containing lactose may result in some discomfort in your gut, such as bloating, or cramps. We do not expect severe complaints, because the maximal chosen dose of lactose has been described in scientific literature as not causing discomfort in most individuals with lactose intolerance. The dose of lactose used during the hydrogen breath test, however, is a relatively high dose, which may increase chances of experiencing some discomfort, such as bloating, cramps, flatulence, or diarrhea.
You should immediately contact the investigator if you experience severe gastrointestinal complaints.

7. Possible advantages and disadvantages

It is important that you properly consider the possible advantages and disadvantages before you decide to participate. You will not personally receive any advantage from taking part in

this study. Your participation may contribute to more knowledge about the effect of regular lactose consumption on the gut microbiota and the lowering of lactose intolerance symptoms.

Disadvantages of participation in the study may be

- Possible discomfort resulting from consumption of lactose in the study product and during the hydrogen breath test

Participation in the study also means:

- that you lose additional time;
- that you have appointments that you have to attend
- that you have dietary and exercise instructions that you have to stick to

All of these things are described above under point 4, 5 and 6.

8. If you do not want to participate, or would like to stop participating in the study

You decide for yourself whether you want to participate in the study. Participation is voluntary. If you do participate, you can always change your mind and stop, even during the study. The data obtained thus far will be used for the study. If you like, the bodily material that was collected can be destroyed.

If there is any new information about the study that is important for you, the investigator will inform you of this. You will then be asked if you wish to continue your participation.

9. End of the study

Your participation in the study ends when

- all visits and measurements according to the schedule (Figure 1) and as described under point 4 have been completed
- you personally choose to stop
- the investigator finds that it is better for you to stop
- FrieslandCampina (FC C.V.) , Wageningen FBR, the government, or the assessing Medical Ethics Review Committee, decide to stop the study.

The entire study ends when all participants are finished. After processing all the data, the investigator will inform you about the most important outcomes of the study.

10. Use and storage of your data and body material

For this study, your personal data and body material will be collected, used and stored. It involves information such as your name, address, date of birth and data about your health. For this study a cheek swap and stool samples are required. The collection, use and storage of your data and your body material is required in order to answer the questions asked in this study and to be able to publish the results. We ask your consent for the use of your data and

body material. The material collected with the cheek swap will not be stored, this will be destroyed directly after screening for lactase non-persistence.

Confidentiality of your data and body material

To protect your privacy, your data and your stool material will receive a code. Your name and other information that could directly identify you are therefore omitted. This information can only identify you with the key. The key to the code will be stored securely in the local research facility. The data and stool material that is sent to the sponsor or external laboratories only contain a code, but not your name or other data that can identify you. In reports or publications about the study, the data will also not be identifiable.

Access to your data for review

Some individuals may have full access to your data at the study site. Also to the data without a code. This is needed in order to check whether the study is performed properly and reliably. Individuals who have access to your data for review are the researchers, the sponsor (FrieslandCampina (FC C.V.)), and national regulatory authorities, for example, the Health Care Inspectorate and Youth. They will keep your data confidential. We ask your consent for this access. FrieslandCampina (FC C.V.) has access to the data, but not your personal data and therefore they cannot link any outcome to any individual.

Retention period of data and body material

Your data must be stored for 15 years at the study site. Your stool material will be stored for 5 years at the sponsors site, after which it will be destroyed. It is stored in order to perform new assessments in the course of this study, related to this study.

Information about incidental findings

During this study, there may be incidental findings that are not relevant for the study, but are for you. If this is important for your health, you will be notified by the research physician. You can then discuss with your general practitioner what needs to be done. You will also consent to this.

Withdrawal of consent

You can always withdraw your consent for the use of your personal data. This applies to this study and also for the storage and use for future research. The study data that has been collected until the time you withdraw your consent will still be used in the study. Your stool material will be destroyed after withdrawal of your consent. If measurements have already been taken with that stool material, then that data will still be used.

More information about your rights concerning the processing of data

For general information about your rights concerning the processing of your personal data, please consult the website of the Dutch Data Protection Authority. If you have any questions about your rights, please contact the person responsible for the processing of your personal

data. For this study it is: Stichting Wageningen Research. Refer to Appendix A for contact information.
If you have any questions or complaints regarding the processing of your personal information, we recommend that you contact the study site. You can also contact the Data Protection Officer for the institution (Appendix A) or the Dutch Data Protection Authority.

Registration of the study
Information about this study is also included in a summary of medical research i.e. (Nederlands Trial Register). No data that can be traced back to you is included. After the study, the website may contain a summary of the results of this study. You can find this study under 'Lactastic'.

11. Insurance for subjects

Insurance has been taken out for everyone who participates in this study. The insurance covers damage resulting from the study. Not all damage is covered. In **Appendix B** you can find more information about the insurance and the exceptions. It also states who you should report damages to.

12. Informing general practitioner

We will not inform your general practitioner that you are taking part in the study. Of course you are free to do so yourself.

13. Compensation for participation

As a compensation for your participation you will receive an expense allowance of €425,-. You will also be reimbursed for your (additional) travel expenses (€0.19 per km, with a maximum of €7.50 per visit). This is indicated to the Dutch tax administration as income. If you stop before the study ends, you will receive a proportionally lower reimbursement.

14. Do you have any questions?

If you have any questions, please contact the research team. If you would like independent advice about participation in this study, please get in touch with the independent physician. He knows a lot about the study but has nothing to do with this study. If you have any complaints about the study, you can discuss this with the researcher. If you would rather not do that, you can contact the complaints' officer of Wageningen University. All data can be found in **Appendix A**: Contact information.

15. Signing of informed consent form

When you have had a sufficient reflection period, you will be asked to decide about participation in this study. If you consent, you will be asked to confirm this on the corresponding consent form, in writing. With your written consent, you indicate that you have

understood the information and agree to participate in the study. Both you and the investigator will receive a signed version of this consent form.

Thank you for your attention.

16. Appendices with this information

A. Contact details
B. Information about the insurance
C. Consent form study participant
D. Brochure “Medical research”.

Appendix A: contact details

Investigators Wageningen FBR:

Lonneke Janssen Duijghuijsen
Phone: 0317 489390
Email: smaakonderzoek@wur.nl

Diederik Esser
Phone: 0317 484034
Email: smaakonderzoek@wur.nl

Independent physician:

Dr. N.Muhsen
Phone: 06-1696 3517
Email: nmuhsen@hotmail.com

Complaints:

Eveline Waterham
Department Human Nutrition, Wageningen University
Helix building 124
Stippeneng 4
6708 WE Wageningen
Email: Eveline.Waterham@wur.nl

Privacy:

Data Protection Office
Mr. WFEM (Frans) Pingen
Email: privacy@wur.nl

For more information about your rights: https://autoriteitpersoonsgegevens.nl/en

Appendix B: information about the insurance

The investigator has taken out insurance for everyone participating in this study. The insurance covers damage resulting from participation in the study. This applies to damage incurred during the study or within four years after the end of your participation in the study. You must have reported damage to the insurer within these four years.

The insurance does not cover all damage. The bottom of this text explains briefly what damage is not covered.
These provisions are in the Medical Research Involving Human Subjects Act. This decree can be found on www.ccmo.nl, the website of the Central Committee on Research Involving Human Subjects (see 'Library' and then 'Laws and regulations').

In case of damage, you can contact the insurance company directly.

The insurer of the study is:
Name: HDI Global SE, The Netherlands
Address: Postbus 925, 3000 AX Rotterdam
Telephone number: 020 5650654
E-mail: info@hdi-gerling.nl
Policy number: V-055-862-363-3/V0100109572
Contact person: M. Wijnsma (Amsterdam office)

The insurance offers a coverage of € 650,000 per study participant, € 5,000,000 for the entire study, and € 7,500,000 per year for all the studies of Wageningen University & Research.

The insurance will **not** cover the following damage:
- damage due to a risk about which you were informed in the written information. This does not apply if the risk is more serious than anticipated or if the risk was very unlikely;
- damage to your health that would also have occurred if you had not taken part in the study;
- damage due to not (completely) following directions or instructions;
- damage to your offspring, due to a negative effect of the study on you or your offspring;
- damage due to an existing treatment method when studying existing treatment methods.

Appendix C: consent form study participant

The effect of dietary lactose in lactase non-persistent individuals on gut microbiota

- I have read the information letter. I was also able to ask questions. My questions have been answered sufficiently. I have had enough time to decide whether or not to participate.
- I understand that participation is voluntary. I also know that I may decide at any time to not participate or to stop participating in the study. Without having to provide any reason.
- I give consent to collect and use my data and body material for answering the research question in this study.
- I know that for study monitoring purposes some individuals could have access to all my data. Those people are listed in this information letter. I consent to that access by these persons.
- I give consent to be informed of unexpected findings which are (or may be) of interest for my health.
- I give consent for the further storage of my personal data for 15 years as stated in the information letter.
- I □ give □ do not give consent for my body material to be stored after this study and for later use of this for other/more study, such as stated in the information letter.
- I want to participate in this study.

Name of study participant:……..
Signature: Date : __ / __ / __
Time : __ : __

I certify that I have fully informed this study participant about the said study.

If information becomes known during the study that could influence the consent of the study participant, I will inform him/her of this on time.

Name of investigator (or his/her representative):……
Signature: Date : __ / __ / __
Time : __ : __

The subject will receive a complete information letter, together with a signed version of the informed consent form.

Appendix D: Brochure “Medical research”

https://www.government.nl/topics/medical-research/documents/leaflets/2020/05/12/medical-research