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Does the presence or absence of the gene for PNPLA3 affect response to a change in diet in people with non-alcoholic fatty liver disease (NAFLD)?

Submission date 06/02/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 10/02/2020	**Overall study status** Completed	
Last Edited 06/12/2023	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Non-alcoholic fatty liver disease (NAFLD) affects 1 in 3 people and ranges from simple fatty liver through to steatohepatitis (liver fat and inflammation) to cirrhosis (liver fat, inflammation and cell damage). NAFLD is more likely to develop in people who are overweight or have Type 2 diabetes. The number of people with NAFLD who have advanced liver disease is rising. NAFLD also increases the risk of heart attacks and strokes.
Research is underway to help understand how the disease changes in different people over time. People with NAFLD who carry a gene called PNPLA3 are more likely to develop advanced liver disease. Currently, there are no effective drugs available and the main treatment is to lose weight and eat a healthy diet. The Mediterranean diet is a model of healthy eating that is often recommended for people with NAFLD. More research is needed on how it works in the liver to bring about its benefits. We also need to understand how the PNPLA3 gene affects an individual's response to different types of diet treatments.
The researchers hope to perform a larger randomised study in the future that will investigate if the PNPLA3 gene influences response to a Mediterranean diet in people with NAFLD. This information could help to develop diet treatments that are more tailored to the individual. This study will develop and test different methods for the future larger study to make sure they work together and are suitable for potential participants.

Who can participate?
Adults aged 18-80 years with NAFLD

What does the study involve?
Participants will be randomly allocated to one of two groups. One group will follow their usual diet and the other will follow a Mediterranean diet for 4 weeks Both groups will be asked to do their normal physical activity and keep their weight at the same level. They will provide blood and urine samples.

What are the possible benefits and risks of participating?
There may be some personal benefits from receiving the one-to-one dietary support provided in the study. The nutrition knowledge and skills gained could help making healthier food choices in the future easier. The health protective effects of following a good dietary pattern are well established both in NAFLD and other health conditions. The research team hope that the outcome of this study could help improve the care of other patients in the future.
This study involves dietary changes so there are no major risks or side effects (such as may occur with drugs). This study will have no effect on participants' future care nor will it affect any other personal arrangements such as insurance.
Participation requires time and commitment from attending 5 visits at liver outpatients clinic. The researchers hope to complete each visit within reasonable time (approximately 90 minutes) and have provided the option of undertaking the web-based diet recall programme either during visits or at home. This study involves dietary changes with the potential for additional food costs. The one-to-one dietary support provided in the study will include money-saving tips to help participants make healthier food choices.
The blood tests and investigations in this study are often taken as part of routine care, which reduces the risks of taking part. Qualified and experienced staff following hospital guidelines take these tests and investigations. The fibroscan is non-invasive, safe and does not use X-rays or any other harmful radiation.
This study involves recruiting people with NAFLD who carry the PNPLA3 gene. As the study proceeds, sufficient numbers of a given PNPLA3 genotype might be enrolled. In the unlikely event that that a participant is not taken forward into the study, they will be offered a one-to-one nutrition education and counselling session with a dietitian.
In the unlikely event that the research team become aware of a health issue that has previously not been identified, this information will be passed onto the participant's doctor. In the unlikely event, that something goes wrong and a participant suffers in any way, the arrangements are as follows. If negligence of staff led to harm, then this would be covered by the Newcastle upon Tyne Hospitals NHS Foundation Trust clinical negligence scheme. The participant may have to meet legal costs.
There is a complaints process for this study. Details will be provided to participants.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2020 to September 2021 (updated 04/11/2020, previously: February 2021)

Who is funding the study?
NIHR Newcastle Biomedical Research Centre (UK) and Newcastle University (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
268502

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
08985, IRAS 268502

Study information

Scientific Title
Personalised nutrition in non-alcoholic fatty liver disease (NAFLD): Feasibility of a nutrigenomic therapeutic approach

Study objectives
Is it feasible to conduct an RCT to investigate the impact of PNPLA3 carriage on Mediterranean diet response, lipid metabolism and hepatotoxicity in NAFLD patients?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/10/2019, East of Scotland Research Ethics Service REC 1 (Tayside Medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee DD1 9SY; +44 (0)1382 383878; eosres.tayside@nhs.net), ref: 19/ES/0112

Study design
Single-centre randomized controlled feasibility trial

Primary study design

Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Non-alcoholic fatty liver disease (NAFLD)

Interventions
Experimental: Mediterranean Diet. Participants attend one session focused on the Mediterranean diet and undertake this diet for 4 weeks, until wash-out (4 weeks). Diet education and counseling will be provided one-to-one by a dietitian. Evidence-based educational resources will be used and provided for use at home. Some intervention foods/ingredients will be supplied. Advice will be given to consume a Mediterranean diet and maintain baseline levels of physical activity and weight status (+/-3%).

Experimental: Habitual Diet. Participants attend one session focused on habitual diet and undertake this diet for 4 weeks, until wash-out (4 weeks). Diet counseling will be provided one-to-one by a dietitian. Advice will be given to consume habitual diet and maintain baseline levels of physical activity and weight status (+/-3%).

Intervention Type
Behavioural

Primary outcome measure
1. Quality of life assessed using the EQ5D, CLDQ-NASH and NASH-CHECK questionnaires at 4 and 12 weeks
2. Recruitment rate (number of participants recruited per month) assessed using the trial log between baseline and 12 months
3. Consent rate (number of eligible participants who consent divided by the total number who are eligible) assessed using the trial log between baseline and 12 months
4. Retention rate (number of participants who complete follow-up data collection divided by the total number randomised) assessed using the trial log between baseline and 12 months
5. Participant adherence to trial procedures assessed by tracking the number of completed visits and completeness of data collection assessed using the trial log between baseline and 12 months
6. Data collection burden will be measured by the time taken to administer protocol processes using the trial log between baseline and 12 months
7. Participant processing (the number of days from initial contact to enrolment) assessed using

the trial log between baseline and 12 months
8. Missing, incomplete or unreliable data recorded using a trial protocol checklist between baseline and 12 months. These data will be used to calculate data integrity and fidelity.

Secondary outcome measures
1. Body weight assessed using bioimpedance at baseline, 4, 8 and 12 weeks
2. Height assessed using a stadiometer at baseline, 4, 8 and 12 weeks
3. Waist and hip circumference assessed using a tape measure at baseline, 4, 8 and 12 weeks. These measurements will be used to calculate waist-to-hip ratio.
4. Body composition measured using a bioelectrical impedance body composition analyser
5. Hepatic steatosis assessed by measuring controlled attenuation parameter (CAP) by transient elastography (Fibroscan) at baseline
6. Hepatic fibrosis assessed by measuring liver stiffness by transient elastography (Fibroscan) at baseline
7. Levels of dietary biomarkers in urine assessed by mass spectrometry at baseline, 4, 8 and 12 weeks
8. Levels of lipid biomarkers assessed by mass spectrometry in fasted blood samples taken at baseline, 4, 8 and 12 weeks
9. Liver function assessed using liver function tests on fasted blood samples taken at baseline, 4, 8 and 12 weeks
10. Levels of ferritin measured using standard procedures by the hospital's laboratory service in fasted blood samples taken at baseline, 4, 8 and 12 weeks
11. Full blood count measured using standard procedures by the hospital's laboratory service in fasted blood samples taken at baseline, 4, 8 and 12 weeks
12. Levels of liver function biomarkers assessed by ELISA in fasted blood samples taken at baseline, 4, 8 and 12 weeks
13. Inflammation assessed using levels of C-reactive protein (CRP) measured using standard procedures by the hospital's laboratory service in fasted blood samples taken at baseline, 4, 8 and 12 weeks
14. Lipid profile measured using standard procedures by the hospital's laboratory service in fasted blood samples taken at baseline, 4, 8 and 12 weeks
15. Blood glucose level measured using standard procedures by the hospital's laboratory service in fasted blood samples taken at baseline, 4, 8 and 12 weeks
16. Glycated haemoglobin (HbA1c) level measured using standard procedures by the hospital's laboratory service in fasted blood samples taken at baseline, 4, 8 and 12 weeks
17. Mediterranean diet intake assessed using a Mediterranean diet score questionnaire at baseline, 4, 8 and 12 weeks
18. Food intake assessed using INTAKE24 (a web-based 24-h dietary recall system) at baseline, 4, 8 and 12 weeks
19. Physical activity assessed using an accelerometer worn for 7 days at baseline, 4, 8 and 12 weeks

Overall study start date
13/01/2020

Completion date
30/09/2021

Eligibility

Key inclusion criteria

1. Aged 18-80 years
2. NAFLD confirmed on liver biopsy or by clinical diagnosis with imaging evidence of steatosis
3. Weekly alcohol consumption <14 units (women) or <21 units (men) in last 24 months
4. Weight stable (+/-5%) for 3 months
5. Capacity to provide informed consent.
6. Ability to write and converse in English without assistance of an interpreter

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
60

Total final enrolment
49

Key exclusion criteria
1. Liver neoplasm/cancer within 5 years (except squamous cell carcinoma)
2. Evidence of co-existent liver disease/presence of secondary causes of NAFLD (except Gilbert's syndrome).
3. Decompensated NASH-cirrhosis (Child Pugh >5-6)
4. Uncontrolled psychiatric disorder (e.g. acute psychosis)
5. Uncontrolled medical condition (e.g. HbA1c >80mmol/l or acute coronary event or stroke within 12 months)
6. Active eating disorder
7. Active substance misuse
8. Prescribed other dietary regimens+/-food intolerances or food allergies
9. Mediterranean diet point score (MEDAS) >8 (high MD consumption)
10. Previous weight loss surgery
11. Taking anti-obesity medications+/-engaged in structured, multi-component weight management interventions (specialist, community or commercial providers)
12. Insulin use
13. Pregnancy/ lactation

Date of first enrolment
11/02/2020

Date of final enrolment
17/02/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
The Newcastle Hospitals NHS Foundation Trust
Freeman Hospital
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Newcastle Joint Research Office
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Regent Farm Road
Gosforth
Newcastle upon Tyne
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United Kingdom
NE3 3HD
+44 (0)191 282 4519
nuth.nuthsponsorship@nhs.net

Sponsor type
Hospital/treatment centre

Website
https://newcastlejro.com/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type

Government

Funder Name
NIHR Newcastle Biomedical Research Centre

Alternative Name(s)
Newcastle Biomedical Research Centre, Newcastle NIHR Biomedical Research Centre

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Funder Name
Newcastle University

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The outcomes of this trial will be published in peer-reviewed journals and presented at local, national and international meetings and conferences.

Intention to publish date
31/08/2022

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		08/04/2021	15/08/2022	Yes	No
HRA research summary			28/06/2023	No	No
Plain English results		23/11/2023	06/12/2023	No	Yes