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Study to explain the reason for the variation in blood cholesterol responses to saturated fat

Submission date
01/08/2019

Recruitment status
No longer recruiting

Registration date
13/08/2019

Overall study status
Completed

Last Edited
10/07/2024

Condition category
Circulatory System

[X] 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
The type of fat that we eat plays an important role in the development of heart disease. Diets high in saturated fats (found mostly in animal products such as meat and dairy foods) are related to higher levels of blood cholesterol (also known as Low Density Lipoprotein (LDL) cholesterol), which increase the risk of developing heart disease compared with diets high in unsaturated fats (found in vegetable oils). As a result, reducing intake of saturated fat to lower blood cholesterol levels has been a key dietary guideline to prevent heart disease for over 30 years. Studies have shown that there is significant variability between individuals in the extent to which blood cholesterol levels can be lowered by reducing the intake of saturated fat. However, very little is known about the factors that determine this variability in blood cholesterol levels between individuals, and the different ways in which people process saturated fat and regulate their blood cholesterol. The main aim of this study is to determine the factors that explain the individual variation in blood cholesterol response to saturated fat. In part 1 of this two-part study, the main aim was to measure the amount of variation in blood LDL-cholesterol in up to 150 healthy men in response to a high saturated fat diet consumed for 4 weeks, followed by a low saturated fat diet for a further 4 weeks. The latter diet was designed to meet the intake of saturated fat recommended by the UK government for the prevention of heart disease. These dietary interventions made it possible to identify and retain two groups of men who showed either a high or low blood LDL-cholesterol response to the reduction in dietary saturated intake, as defined by the top and bottom 10% of hyper-responders/or low-responders. In part 2 of this study, the aim is to study the metabolic characteristics of these two groups of men retained from part 1 in more depth, to investigate the possible underlying causes for the variation in their blood LDL-cholesterol response.

Who can participate?
Men aged 30-65 who participated in part 1 of the study (RISSCI-1) (responders and non-responders)

What does the study involve?
Participants are asked to repeat the same two dietary interventions as in part 1 (high and low

saturated fat diet) for 4 weeks each, but undergo a more detailed investigation of their metabolism at the end of each diet, to help understand why some people's blood LDL-cholesterol is more sensitive to changes in dietary saturated fat intake than others.

What are the possible benefits and risks of participating?
The knowledge gained from this study will help to show how and why dietary fats influence some peoples blood cholesterol level (a risk factor for developing heart disease) and not others. It will also help participants to understand how they personally respond to dietary fat. Potential risks (albeit small) include slight bruising/pain due to cannulation for blood sampling.

Where is the study run from?
1. University of Surrey (UK)
2. University of Reading (UK)
3. Imperial College London (UK)

When is the study starting and how long is it expected to run for?
August 2019 to August 2021

Who is funding the study?
Biotechnology and Biological Sciences Research Council (UK)

Who is the main contact?
1. Prof. Bruce Griffin
b.griffin@surrey.ac.uk
2. Prof. Julie Lovegrove
j.a.lovegrove@reading.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Bruce Griffin

Contact details
Leggett Building
University of Surre
Guildford
United Kingdom
GU2 &WG
+44 (0)1483 689724
b.griffin@surrey.ac.uk

Type(s)
Scientific

Contact name
Prof Julie Lovegrove

Contact details

Hugh Sinclair Unit of Human Nutrition
University of Reading
Reading
United Kingdom
RG6 6AP
+44 (0)118 378 6418
j.a.lovegrove@reading.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
BBSRC BB/P010245/1

Study information

Scientific Title
Reading Imperial Surrey Saturated fat and Cholesterol Intervention (RISSCI): a metabolic phenotyping study (RISSCI-2)

Acronym
RISSCI-2

Study objectives
1. It is predicted that men who show a greater reduction in blood LDL-cholesterol response ('hyper-responders') when changing from a high to a low SFA diet, will show a greater reduction in the absorption of dietary fat in their gut than low or 'hypo-responders'.
2. It is believed that this effect may be explained, in part, by changes in the permeability of the gut lining, which may be increased by eating SFA.
3. Responders may also have a greater number of receptors on the surface of cells that remove LDL cholesterol from the blood ('LDL-receptors'), most notably in the liver, when changing from a high to a low SFA diet.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 25/07/2019, University of Reading Ethics Committee (Whiteknights House, Whiteknights, PO Box 217, Reading, RG6 6AH; Tel: +44 (0)118 378 7119; Email: m.j.proven@reading.ac.uk), ref: UREC 19/29
2. Approved 12/08/2019, University of Surrey Ethics Committee (Research and Innovation Services, Senate House, University of Surrey, GU2 7XH; Tel: +44(0) 1483 689103; Email: s.bird@surrey.ac.uk), ref: UEC 2019 051 FHMS

Study design
Multi-centre sequential dietary intervention study

Primary study design

Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Heart disease risk

Interventions
Participants will undergo, sequentially, a high (18%) SFA diet (Diet 1) followed by a low (10%) SFA diet (Diet 2) for 4 weeks each. Metabolic assessments will be conducted at the end of Diets 1 and 2. To comply with current UK dietary recommendations, Diets 1 and 2 will both contain ~35% energy from total fat. These diets will be consumed within the homes of free-living participants, by the substitution of ~40g of habitual fat, with either SFA-rich or mono/poly-unsaturated fatty acid-rich (MUFA/PUFA) cooking oils, spreads and snack foods, while maintaining their habitual diet (consistent intake of protein and carbohydrates, including dietary fibre). This will be achieved using a dietary exchange model developed for the 'DIVAS' study (Vafeiadou K et al (2015) Am J Clin Nut 102, 40-8). The diet is identical to the diet used in Part 1 of this two-part intervention study.

Intervention Type
Behavioural

Primary outcome(s)
1. Lipid profile (Total Cholesterol (TC), LDL-C, HDL-C and triacylglycerol (TAG)) measured via direct quantification and/or auto-analyser at baseline, the end of diet 1 and at the end of diet 2
2. Dietary fat absorption, measured by feeding a manufactured fat that has been labelled with safe stable isotope tracer that can be traced in the body and can be used to measure how much is excreted in the stool, at the end of diet 1 and at the end of diet 2

Key secondary outcome(s))
1. Gut permeability measured using the urinary recovery of ingested carbohydrates provided as part of a drink, at baseline, the end of diet 1 and at the end of diet 2
2. LDL-receptor expression measured in peripheral blood mononuclear cells (PBMC) via PCR at baseline, the end of diet 1 and at the end of diet 2
3. Gut microbiota composition measured in stool samples using NGS/FISH at baseline, the end of diet 1 and at the end of diet 2
4. Endogenous cholesterol synthesis measured by measuring serum phytosterols, a biomarker of this process, using GCMS at baseline, the end of diet 1 and at the end of diet 2
5. Serum deconjugated bile acids measured using targeted UPLC-MS at baseline, the end of diet 1 and at the end of diet 2
7. Metabolomic signatures in urine, plasma and stool measured using 1H-NMR & UPLC-MS metabonomics at baseline, the end of diet 1 and at the end of diet 2
8. Markers of inflammation and endothelial function measured using commercially available kits (e.g. ELISA) at baseline, the end of diet 1 and at the end of diet 2
9. HDL composition/function measured via cell-based cholesterol efflux capacity assay at baseline, the end of diet 1 and at the end of diet 2

Completion date
14/08/2021

Eligibility

Key inclusion criteria
1. Hyper- and hypo-responsive males, defined as the participants (derived from the first stage of the project, RISSCI-1: https://clinicaltrials.gov/ct2/show/NCT03270527) exhibiting changes in serum LDL-cholesterol in response to a lowering of SFA intake in the top and bottom 10% of a larger cohort (n=150)
2. Middle-aged men (30-65 years)
3. BMI 19-32 kg/m2
4. Fasting serum total cholesterol < 7.5 mmol/l and TAG < 2.3 mmol/l

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
30 years

Upper age limit
65 years

Sex
Male

Total final enrolment
36

Key exclusion criteria
1. Smokers
2. Medical history of MI or stroke in the past 12 months
3. Diabetes (defined as fasting glucose > 7.0 mmol/l) or other endocrine disorders
4. Medication for hyperlipidaemia (e.g. statins) or prescribed antibiotics within the last three months
5. Drinking in excess of 14 units of alcohol per week, anaemia (<130 g/L haemoglobin)
6. Planning a weight-reducing regime or taking any dietary supplements known to influence lipids/gut microbiota (e.g. plant stanols, fish oil, phytochemicals, natural laxatives, probiotics and prebiotics)
7. Unwilling to regularly consume study intervention products (butter/spreads, oils, dairy, snacks)
8. Any other unusual medical history or diet and lifestyle habits or practices that would preclude participants from participating in a dietary intervention metabolic study

Date of first enrolment
13/08/2019

Date of final enrolment

30/08/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Surrey
Nutritional Sciences
Stag Hill Campus
Guildford
United Kingdom
GU2 7XH

Study participating centre
University of Reading
High Sinclair Unit of Human Nutrition (HSUHN)
Harry Nursten Building
Reading
United Kingdom
RG6 6AP

Study participating centre
Imperial College London
Faculty of Medicine, Department of Surgery & Cancer
South Kensington Campus
London
United Kingdom
SW7 2AZ

Sponsor information

Organisation
University of Surrey

Organisation

University of Reading

Organisation
Imperial College London

Funder(s)

Funder type
Research council

Funder Name
Biotechnology and Biological Sciences Research Council

Alternative Name(s)
UKRI - Biotechnology And Biological Sciences Research Council, Agricultural and Food Research Council, Biotechnology & Biological Sciences Research Council, BBSRC, BBSRC UK, AFRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 5	25/11/2019	11/09/2023	No	No