The role of gut microbiota and chronic inflammation as drivers of cardiovascular disease - Nijmegen Biomedical Study - Non Invasive markers of Atherosclerosis 3

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- To identify the causes of inflammation of adipose tissue, liver and blood leukocytes by focusing on the contribution of the gut microbiota taking into account dietary habits and genetic background.- To assess the influence of inflammation of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Myocardial disorders
Study type	Observational invasive

Summary

ID

NL-OMON38378

Source
ToetsingOnline

Brief title
NBS-NIMA3

Condition

- Myocardial disorders
- Central nervous system vascular disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis, cardiovascular disease

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: CardioVasculair Onderzoek Nederland,CardioVasculair Onderzoek Nederland

Intervention

Keyword: cardiovascular disease, inflammation, microbiota, obesity

Outcome measures

Primary outcome

Descriptive data: Questionnaires

DNA: Gene polymorphisms at DNA level

Transcriptome: RNA expression in blood and adipose tissue

Metabolome: Small molecule metabolites in blood en urine

Microbiome: Presence of groups of bacteria

Phenotype: Measures of atherosclerosis, adiposity, hepatic steatosis

Functional data: Cytokine production by adipocytes, monocytes

Follow-up data: Cardiovascular events registry

Secondary outcome

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Study description

Background summary

There is overwhelming evidence that chronic inflammation plays a critical role in both metabolic and cardiovascular diseases (CVD). Recent evidence points at a crucial role for the commensal gut microbiota. The composition of the gut microbiota is determined by dietary, environmental and host genetic factors. It

produces a vast amount of metabolites that control host inflammatory responses in the adipose tissue, liver and blood leukocytes. In turn, these organs, in combination with the gut metabolites, determine the susceptibility to developing CVD. Besides metabolic processes, leakage through the intestinal barrier can also lead to bacterial components entering into the systemic circulation and activating the
host immune system. We hypothesize that the activation of chronic inflammation is initiated and driven by a disturbed interaction between gut microbiota, the intestine, liver and adipose tissue. The resulting chronic inflammation increases the risk for atherosclerosis and cardiovascular disease.

Study objective

- To identify the causes of inflammation of adipose tissue, liver and blood leukocytes by focusing on the contribution of the gut microbiota taking into account dietary habits and genetic background.
- To assess the influence of inflammation of adipose tissue, liver and blood leukocytes on non invasive markers of atherosclerosis (NIMA) and CVD risk.

Study design

A prospective case-control study will be performed in the Radboud University Medical Centre (RUMC). The duration of the study is 5 years. This study is an extension of a large population based cohort study on the relation between non-invasive measurements of atherosclerosis and cardiovascular risk: the Nijmegen Biomedical Study - Non Invasive Measures of Atherosclerosis 2 (NBS-NIMA 2). 500 of the original 1,517 participants will be invited to participate. We will use several approaches to investigate the above described factors:

a. Baseline characteristics will be collected from all the participants using questionnaires. These questionnaires will be coded with full respect for the privacy of the individuals, will be anonymous, and will not permit the identification of the individuals.
b. Microbiome analysis will be performed on stool, oral, and skin samples.
c. The effect of gut microbiota on the metabolic profile of subjects will be investigated by conventional laboratory tests. Mass spectrometry, chromatography, and nuclear magnetic resonance (NMR) spectroscopy will be performed in collaboration with the other participants of the research consortium to assess the metabolome.
d. The function of the immune system will be analysed at several levels using circulating cells from venous blood: immunophenotyping will be done using fluorescence activated cell sorting (FACS) analysis, circulating factors will be measured in plasma or serum, in-vitro stimulations of cells and analysis of mRNA and cytokine responses.
e. In vitro studies will be performed on adipocytes acquired by biopsy of

subcutaneous abdominal and thigh adipose tissue. These will be characterized for adipocyte functionality and the type and degree of inflammation, with a focus on two crucial processes for AT inflammation: activation of the inflammasome and modulation by autophagy.
f. Fat mass and fat distribution will be assessed using anthropometric measurements, magnetic resonance imaging (MRI) of the trunk and thigh region, MR spectroscopy of the liver.
g. Subclinical atherosclerosis will be investigated by ultrasonography of the carotid arteries, pulse wave velocity (PWV), pulse wave analysis (PWA) and ankle-brachial index (ABI); furthermore subjects are followed for 3-5 years to register incident cardiovascular diseases (CVD).

Study burden and risks

Burden:
- Questionnaires
- Collection of venous blood (50 ml)
- Collection of stool, urine, oral smear, and skin smear samples
- Two adipose tissue biopsies
- Ultrasonography of the carotid arteries
- Tonography of carotid and femoral artery
- Measurement ankle-brachial index
- ECG
- MRI of trunk and thigh
- MR spectroscopy of liver
- 30 minute automated blood pressure measurement
- 2 study visits (total 4 hours)
- Follow-up: annual telephone interview and questionnaire

Risks:
Hematoma related to collection of venous blood and adipose tissue biopsies.
Small scars (0.5 cm) of adipose tissue biopsies.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- participant NIMA-NBS 2 study
- body mass index > 27 kg/m2

Exclusion criteria

- Recent cardiovascular event (myocardial infarction, transient ischemic attack, stroke < 3 months)
- History of bariatric surgery or bowel resection
- Inflammatory bowel disease
- Coagulation defects
- Thrombocytopenia (thrombocytes < 100 x 10E9)
- Liver dysfunction (INR > 1.6)
- Renal dysfunction (estimated glomerular filtration rate < 30 ml/min/1.72m2)
- Use of oral or subcutaneous anti-coagulant therapy
- Use of thrombocyte aggregation inhibitors other than acetylsalicylic acid or carbasalate calcium
- Claustrofobia
- Metallic fragments, clips or devices in brain, eyes, spinal canal
- Implantable defibrillator or pacemaker (wires)
- Mandibular magnetic implants
- Neurostimulator, bladder stimulator, non-removable insulin pump
- Metal tissue-expander in chest
- Cochlear implant

- Ossicular replacement prosthesis
- Intolerance or allergy for lidocaine

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-05-2014
Enrollment:	500
Type:	Actual

Ethics review

Approved WMO Date:	28-04-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-04-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL46846.091.13