REFErence Repository for healthy livers

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To determine differences in omics data sets of several biological layers between men and women withand without NAFLD and investigate to what extent these signatures contribute to NAFLD development.Therefore, we will establish a reference repository...

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

Summary

ID

NL-OMON49481

Source
ToetsingOnline

Brief title
REFER

Condition

- Other condition

Synonym
Fatty Liver Disease, Non-Alcoholic Fatty liver Disease

Health condition

Galsteenlijden

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: VIDI Max Nieuwdorp

Intervention

Keyword: adipose tissue, gut microbiome, healthy controls, Liver, Non-Alcoholic Fatty Liver Disease

Outcome measures

Primary outcome

To determine differences in omics data sets of several biological layers

between men and women with

and without NAFLD and investigate to what extent these signatures contribute to

NAFLD development.

Therefore, we will establish a reference repository of healthy liver biopsies

to establish an integrative

signature of healthy and diseased (NAFLD) liver metabolism in men and women. To

this end we will

collect on the day of surgery the following parameters.

1. Presence of NAFLD/NASH parameters in liver biopsy using histology (NASH-CRN

/ Steatosis Activity and Fibrosis Score)8 and liver RNA sequencing

Secondary outcome

1. Presence of bacterial DNA, histology and inflammatory genes (RNA seq) liver

and abdominal adipose tissue depots as well as metabolites in plasma, feces and

urine

2. Fecal and oral microbiota composition

3. Dietary, psychology and satiety lists and excreted metabolites

4. Clinical data (body weight and composition), waist circumference and blood

pressure

5. Genomic DNA (buffy coat)

6. 7. Gallbladder tissue and bile acid collection after cholecystectomy surgery

Study description

Background summary

The current estimated global prevalence of non-alcoholic fatty liver disease (NAFLD) is 25 - 30% and
is diagnosed in up to 80% of individuals with obesity and type 2 diabetes (T2D) 1,2. The rapidly growing
prevalence of NAFLD and lack of effective treatment options to tackle this potentially debilitating
disease, will further increase obesity-related burden on public health and economies.
In order to develop appropriate, non-invasive diagnostic methods and treatment options, it is critical to
deeply investigate the complex pathophysiology of NAFLD. Genome-wide analysis of large cohorts
(containing hundreds of patients to insure the robustness of results), is required to obtain insight in
hepatic metabolism in NAFLD. A number of such genome-wide transcriptomic studies have indeed
characterized alterations in hepatic gene expression in individuals with NAFLD and its more severe,
progressive form non-alcoholic steatohepatitis (NASH). Nevertheless, these studies have thus far
not been able to define a predictive transcriptome signature for NAFLD. Multiple confounding factors
such as differences in genetic origin, sex and unappreciated environmental factors, including the gut
microbiota, might have contributed to this.
Our unpublished liver and adipose tissue transcriptomics, fecal metagenomics and plasma metabolomics
data show striking differences in gene expression and metabolite profiles in female vs male NAFLD
patients (BARIA study METC 2015_357). This implies that there are strong sex differences in
hepatocellular and systemic processes in the pathophysiology of this disease. In addition, this
emphasizes the uprising awareness in the field to develop tailored (men vs

women) treatment and
prevention regimes for NAFLD.
Our transcriptomics, fecal metagenomics and metabolomics data were derived from obese NAFLD
patients. Because all participants were (morbidly) obese, and hence metabolically challenged, it is
difficult to interpret if the strong transcriptomic/metabolic sex differences are driven by a male- or
female-specific metabolic response to obesity or whether it is a *true* sex difference. Obtaining liver
transcriptomic, fecal metagenomic and plasma metabolic data from non-obese, otherwise healthy
individuals will be critical to 1) better understand the basis of NAFLD development and 2) develop
tailored (men vs women) preventive or treatment strategies for this disease.
Our research question therefore is how omics data of several biological layers are different between men
and women with and without NAFLD and to what extent these signatures contribute to NAFLD
development.
To answer this question, we will establish liver transcriptomic, fecal metagenomic and plasma
metabolomics profiles of otherwise healthy men and women. Therefore, we will set up a cross-sectional
cohort and include non-obese, otherwise healthy individuals scheduled for cholecystectomy. Using
state-of-the-art sequencing and systems biology approaches, we can integrate plasma/urinary
metabolomics, liver and adipose transcriptomic and fecal metagenomics data to create a unique much
needed signature of healthy individuals (men and women). This database will be integrated in our large
cohort of obese men and women with and without NAFLD (BARIA study METC 2015_357).

Study objective

To determine differences in omics data sets of several biological layers between men and women with
and without NAFLD and investigate to what extent these signatures contribute to NAFLD development.
Therefore, we will establish a reference repository of healthy liver biopsies to establish an integrative
signature of healthy and diseased (NAFLD) liver metabolism in men and women.

Study design

Cross-sectional cohort study.

Study burden and risks

Participants scheduled for laparoscopic cholecystectomy will be recruited from the outpatient clinics of Surgery and Internal Medicine at Spaarne Gasthuis hospital. After provision of informed consent, biological samples (blood, urine and feces) will be collected on the day of surgery and will be asked to fill in a psychological questionnaire. During cholecystectomy, a liver and mesenteric, omental and subcutaneous adipose tissue biopsy will be obtained. The risk of bleeding from the biopsy sites during the surgery procedure is very low because the biopsy sites are completely visible to the surgeon and local haemostasis will be checked. Moreover, bleeding disorders are an exclusion criterion. Total amount of blood taken is 40 ml (once for screening 20 ml and once on day of surgery 20 ml). This study will function as a much-needed reference database for all ongoing human trials investigating human liver disease including NAFLD. We therefore believe that the scientific insight of our findings will outweigh the minimal risks for the participating individuals in this study.

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

- 18-65 years of age
- BMI < 30 kg/m2
- Individual should be able to give informed consent

Exclusion criteria

- Type 2 diabetes mellitus
- Prior bariatric surgery
- Inflammatory bowel disease
- Primary lipid disorder
- Known genetic basis for insulin resistance or glucose intolerance
- Ethanol intake > 2 U/week
- Pregnancy, females who are breastfeeding
- Hepatitis B and/or C
- Liver cirrhosis
- Auto-immune hepatitis
- Wilson disease3/ alpha 1-antitripsine deficiency
- Hemochromatosis

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):	12-11-2020
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	02-09-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL74348.018.20