Identification and characterization of non-alcoholic fatty liver disease in primary care.

Published: 29-06-2020
Last updated: 07-06-2025

The primary objective of this cohort study is to determine the prevalence of simple and progressed NAFLD in subjects at risk followed by the general practitioner The secondary objectives are:1. To study the factors linked to the development of NAFLD…

Ethical review	Approved WMO
Status	Recruitment started
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON54037

Source
ToetsingOnline

Brief title
NAFLD primary care

Condition

- Hepatic and hepatobiliary disorders

Synonym
fatty liver Non-alcoholic fatty liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Owlstone Medical (VK),Eerste geldstroom (geld van Ministerie van OC&W aan universiteiten)

Intervention

- No intervention

Keyword: Characterisation, Identification, Non-alcoholic fatty liver disease

Explanation

N.a.

Outcome measures

Primary outcome

The primary outcome of this cohort is the diagnosis of NAFLD with fibrosis.

Secondary outcome

• The degree of hepatic steatosis and/or fibrosis (using FibroScan® and
non-invasive score calculation)
• The presence of hepatic inflammation (e.g. using biochemical parameters)
• Association between lifestyle, metabolic and inflammatory parameters by
collecting filled in questionnaires, anthropometric data, blood, urine, and
exhaled air.
• Receiver operating characteristic curves (ROC), sensitivity, specificity, and
accuracy of a limonene breath levels before and after food additives
administration, obtained by comparing breath benzylalcohol, 2-pentanol,
2-butanol, nonanal and limonene levels of patients with progressed NALFD
(FibroScan >=7.5 kPa) to patients with earlier NAFLD (FibroScan <= 7 kPa and CAP
score <= S1)
• Multiple correlation analysis of breath benzylalcohol, 2-pentanol, 2-butanol,
nonanal and imonene levels and early or progressed NAFLD
classification/staging parameters and co-morbidities. A value of r >= |0.7| will
be considered as threshold for the presence of a correlation between breath
benzylalcohol, 2-pentanol, 2-butanol, nonanal and limonene levels and:
1) FibroScan kPa, expected positive
2) Body parameters (i.e., height, weight, BMI), no correlation
3) Biomarkers of liver function (i.e., Bilirubin, albumin, PT-INR), Negative
for albumin, positive for the others(57)
4) Biomarker of liver damage (ALT, ALP, AST), no correlation(57)
5) Fib-4, positive correlation
6) MELD and UKELD, positive correlation
7) Comorbidities and complications (i.e., diabetes, portal hypertension)

Study description

Background summary

Non-alcoholic fatty liver disease (NAFLD) is with 25% the most prevalent liver disorder in Western society and is associated with overweight, obesity, metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD) and increased risk of cancer development. NAFLD is defined by a hepatic fat accumulation of more than 5% in the absence of classical causes of steatogenesis (e.g. alcohol and steatogenic drugs). It represents a broad spectrum of clinical entities from non-alcoholic fatty liver (NAFL) to advanced liver disease with hepatic failure. Most of the patients have simple steatosis, however in about 15-30% non-alcoholic steatohepatitis (NASH) develops, which leads to an overall increase in morbidity and mortality due to the progression to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Patients with NAFLD have no or few, mainly a specific symptoms; and generally there is a silent progression of simple steatosis to NASH and in the end liver-related morbidity and mortality.
Despite the clinical importance and the potential impact on healthcare resources, there is a striking lack of awareness on all levels of NAFLD. Furthermore, little to no data are available concerning the quality of life of NAFLD patients. Additionally, the majority of NAFLD patients are currently not detected due to the lack of non-invasive methods to diagnose NAFLD. Most of these patients, as a first contact in the healthcare system, will be found in the outpatient clinic of the general practitioner (GP). To date, it is not clear what the burden is of NAFLD and related diseases in at risk subjects in primary care. Therefore, identification of NAFLD patients in this cohort will give information on the prevalence in the group of uncomplicated overweight and obesity and those with concomitant cardiometabolic diseases. By early detecting these patients at risk to develop progressive liver diseases and extrahepatic manifestations, it will be possible to intervene and improve health.

Study objective

The primary objective of this cohort study is to determine the prevalence of simple and progressed NAFLD in subjects at risk followed by the general practitioner
The secondary objectives are:
1. To study the factors linked to the development of NAFLD (e.g. overweight, obesity, metabolic syndrome, T2DM and CVD) in a population of at risk primary care subjects.
2. To investigate non-invasive tools, both blood sample derived scores and FibroScan® with Controlled Attenuation Parameter (CAP)TM, to identify patients with more progressed NAFLD e.g. liver fibrosis.
3. To assess the quality of life and social-economic consequences of NAFLD patients with validated questionnaires.

4. To compare the clinical characteristics of a matched control group of the Maastricht Study with the cohort of NAFLD patients found in primary care.
5. Assess the performance of a benzylalcohol, 2-pentanol, 2-butanol, nonanal and limonene breath levels (after administration of a standard dose) in discriminating patients with progressed NALFD (FibroScan >=7.5 kPa) from patients with early NAFLD (FibroScan <= 7 kPa and CAP score <= S1).
6. Explore correlations between hepatic metabolism of benzylalcohol, 2-pentanol, 2-butanol, nonanal and limonene and NAFLD co-morbidities.
7. Investigate correlations between breath benzylalcohol, 2-pentanol, 2-butanol, nonanal end limonene and blood biomarkers of liver performance/damage or fibrosis.

Study design

A multicentre cohort study in primary care.
Eligible subjects will be included by the GP practices. Subjects will undergo a FibroScan® with CAPTM measurement to diagnose the stage of NAFLD. All participants will be asked to complete several questionnaires (i.e. demographics, clinical data, SF-36, GAD-7 and PHQ-9, Baecke, WPAI-SHP, MDS and sleep questionnaire) and to undergo anthropometric measurements. Furthermore, blood samples and exhaled air will be collected. The urine of the patients will be tested for proteinuria and glycemia. After analysis the blood, urine and exhaled air samples are destroyed. Additionally, patients are asked to test their hand grip strength with a hand dynamometer. This will be the standard to be collected data set.
The subjects identified with NAFLD in primary care will be compared to a healthy, matched control group from the Maastricht Study.
Subjects that will be recruited from the NAFLD primary care cohort will be allocated to the sample or control group based on their FibroScan result.
The sample group (also referred to as progressed NAFLD) will be represented by subjects with FibroScan >=7.5 kPa. The control group (also referred to as early NAFLD), will be represented by subjects with FibroScan <= 7 kPa and CAP score <= S1. (Fig. 2.1) The FibroScan test is performed on the day of the GP visit. Ideally, on that day the subject will be invited to participate to the food additives and limonene part of the study. Subjects for which the FibroScan fails will not be considered for breath testing.
The metabolism of benzylalcohol, 2-pentanol, 2-butanol, nonanal and limonene will be evaluated by collecting breath samples using the ReCIVA breath collector, developed by Owlstone Medical and classified as research use only device, before and after administration of food additives and limonene(Fig. 1.1 and Table 1.1). Information about diet, smoking status, alcohol intake and utilization of medication will be collected by a questionnaire.

Study burden and risks

The measurements, data and sample collections will be planned with the

participant. Anthropometric data collection, hand grip strength, blood collection, urine dipstick, exhaled air (VOC), and FibroScan® with CAPTM will be performed during study visit 1 after signing the informed consent. The participant can fill out the questionnaires at home and bring the forms when visiting the research physician or fill out the questionnaires via an online survey.
No side effects of the investigations are expected, apart from a small bruise of taking the blood samples. Three tubes (21 ml) will be collected for research purposes; if possible this will be combined with regular blood sampling. If participants are not regular patients at the outpatient clinic, a maximum of 4 extra tubes (max.17,5 ml in total) will be collected to determine (part of) the standard clinical laboratory investigations (e.g. liver function tests, cholesterol) for research purposes only.
The time burden associated with participating in the research is: 45 minutes to fill out the questionnaires, 30 min for the study visit to collect samples, anthropometry data and perform a FibroScan®.
In case of unexpected findings, awareness of normally unknown pathology may affect a person*s perception of his own health condition negatively. On the other hand, early detection is likely to have favourable effects on disease progression and enable early intervention.

Contacts

Scientific
Universiteit Maastricht
GH Koek
P. Debeyelaan 25
Maastricht 6202 AZ
Netherlands
043 3875021
Public
Universiteit Maastricht
GH Koek
P. Debeyelaan 25
Maastricht 6202 AZ
Netherlands
043 3875021

Trial sites

Trial sites in the Netherlands

Gezondheidscentrum Heer
Target size: 210

Huisartsenpraktijk Geulle
Target size: 210

Huisartsenpraktijk Cadier en Keer
Target size: 210

Dokters van Hier
Target size: 210

Huisartsenpraktijk Dorine Verschure
Target size: 210

Maastricht Universitair Medisch Centrum +
Target size: 72

Huisartsenpraktijk Bandkeramiek
Target size: 210

Huisartsenpraktijk Daalhof
Target size: 210

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Able to understand and sign the informed consent
Able to speak Dutch
Between 18-80 years
BMI >25 kg/m²
Having one of the following conditions: 1)overweight, 2) obesity, 3) type 2 diabetes mellitus, 4) cardiovascular diseases (hypertension, atherosclerosis, angina pectoris, ischaemic heart condition, cerebrovascular condition)

Additional inclusion criteria valid only for the other food additives and limonene breath test

• All those listed in the main protocol +
• NAFLD F2-F3-F4 fibrosis stage (FibroScan >= 7.5 kPa)
• Capability to complete an overnight fasting (>=10h)
• Willingness to share data with Owlstone Medical LTD.

Exclusion criteria

Excessive alcohol use
o more than 20 g/day for women and 30g/day for men
o >2 glasses alcohol/day for women and >3 glasses for men
Other liver diseases: Hepatitis B virus, Hepatitis C virus, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson*s disease, Alpha 1 antitrypsin deficiency
Secondary causes for steatosis: disorders of lipid metabolism, HCV Genotype 3, total parental nutrition, severe surgical weight loss, medications (amiodarone, tamoxifen, methotrexate, corticosteroids and HAART), lean steatosis, Celiac disease, environmental toxicity
Pregnancy and breastfeeding.
A history of bariatric surgery.
Diagnosis of liver cirrhosis and/or hepatocellular carcinoma.
Current diagnosis of extrahepatic malignancy(s) or prior diagnosis within last 5 years.
Individuals about to undergo a surgery or otherwise medical procedure that will interfere with data collection and analyses planned within the current cohort, will initially be excluded from participation, but are offered the opportunity to participate at a later moment in time (e.g., after 3 months are myocardial infarction patients are eligible for participation).

Additional inclusion criteria valid only for the other food additives and limonene breath test
• All those listed in the main protocol +
• Inability to complete the breath sampling procedure
• Known carrier of α-1 Antitrypsin deficiency

Study design

Design

Study phase:	N/A
Study type:	Observational invasive
Intervention model:	Single

Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment started
Start date (anticipated):	12-05-2021
Enrollment:	1450
Duration:	1 months (per patient)
Type:	Actual

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Undecided

Plan description
N.a.

Ethics review

Approved WMO

Date:	15-01-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	17-12-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	10-03-2022
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-11-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Notification accepted Date:	30-05-2025
Application type:	Amendment
Review commission:	METC AZM/UM

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
ClinicalTrials.gov	NCT04918732
CCMO	NL73265.068.20
Research portal	NL-006386