Holbæk-modellens effekt på fedt i leveren

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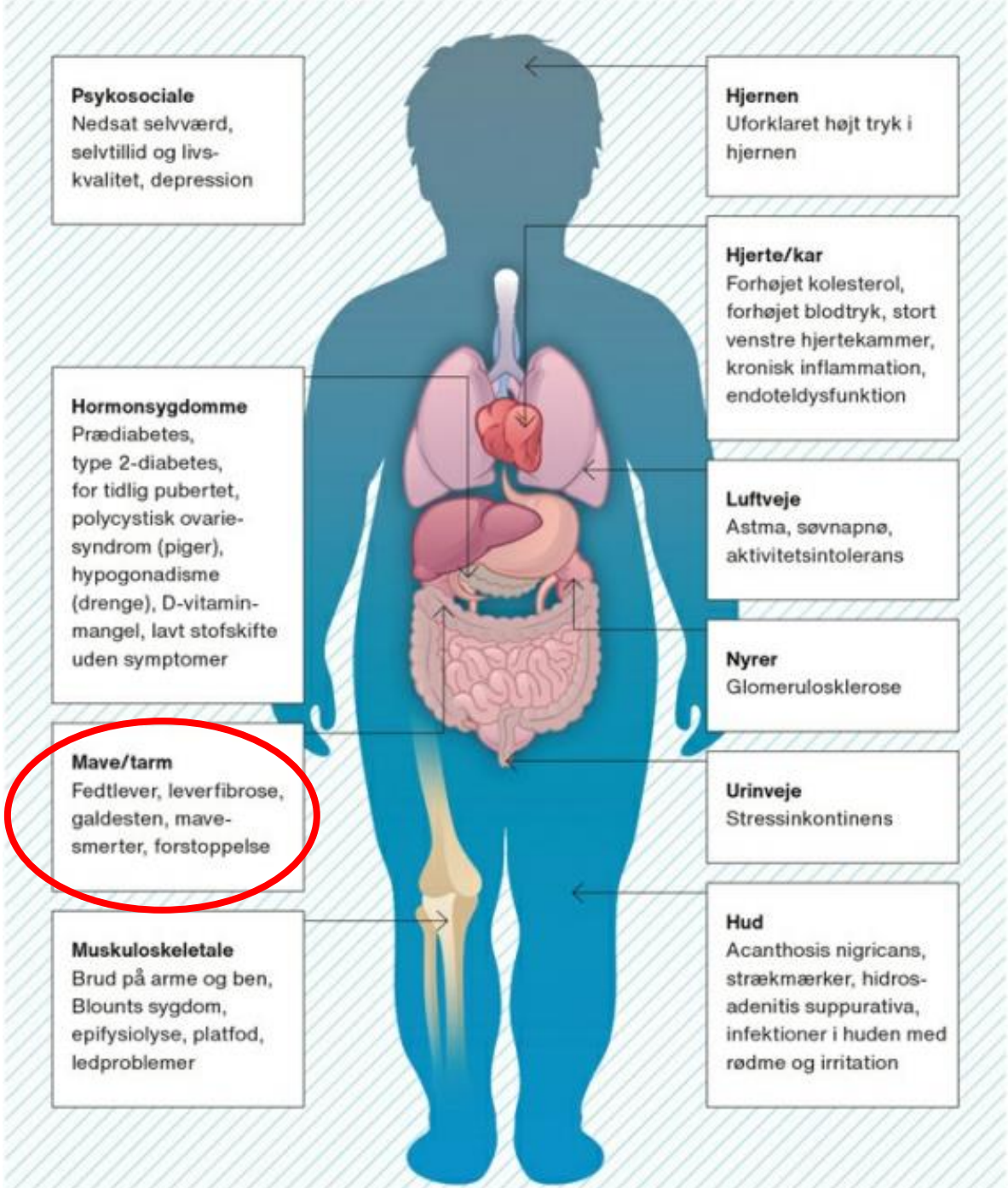
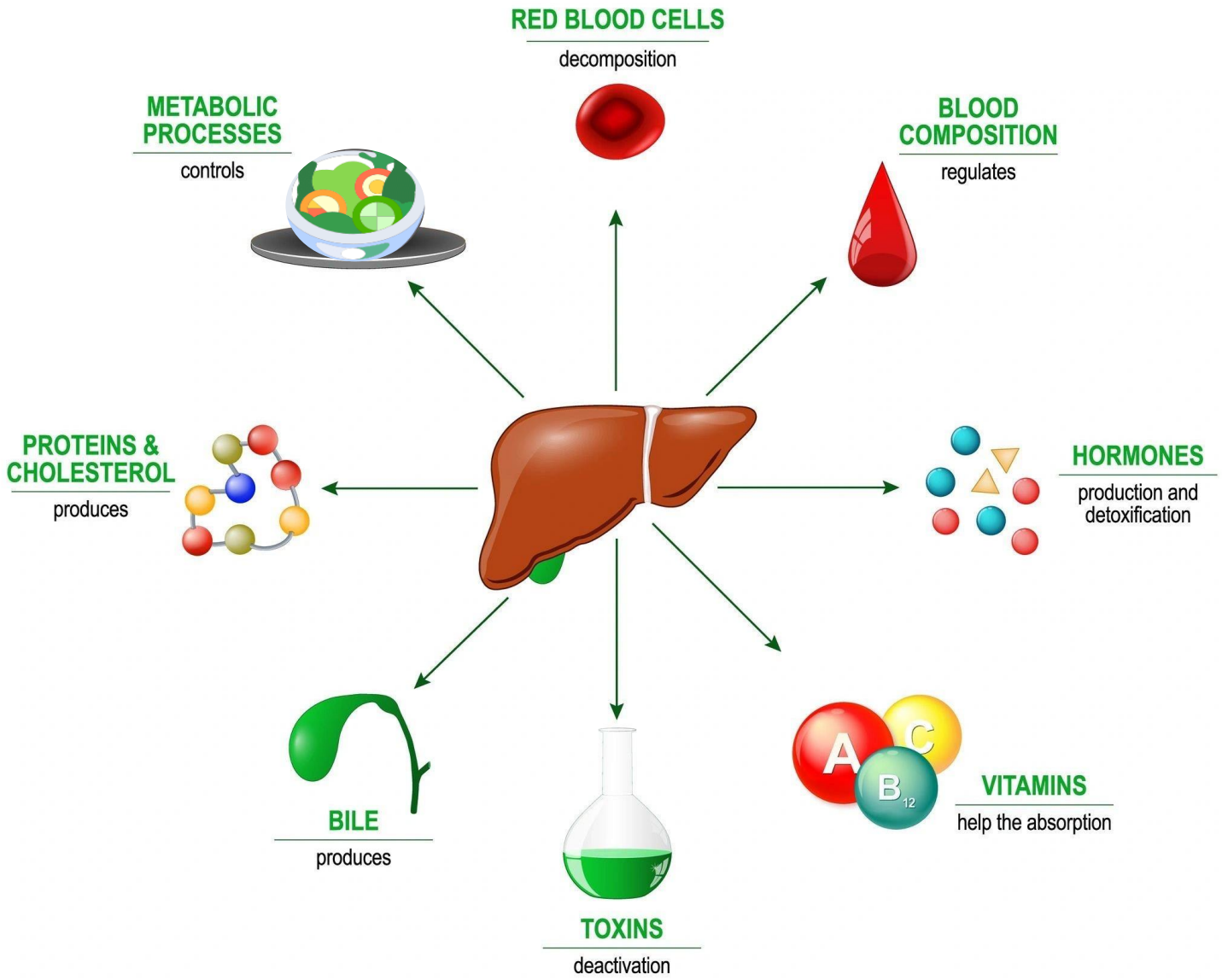
Komplikationer til adipositas hos børn/unge

- 75% med nedsat selvværd, selvtillid eller livskvalitet Fogh, *J Paediatr Child Health*. 2020; 56(4):542-549
- 82% med forstyrret spisning
  Fogh, *J Paediatr Child Health*. 2020; 56(4):542-549
- 50% med forhøjet blodtryk
  Mollerup, *J Hum Hypertens*. 2017;31(10):640-646
- 28% med forhøjet kolesterol
  Nielsen, *BMC Pediatr*. 2017 Apr 28;17(1):116
- 60% med lavt D-vitamin
  Plesner, *J Pediatr Endocrinol Metab*. 2018;26;31(1):53-61
- 14% med prædiabetes
  Kloppenborg, *Pediatr Diabetes*. 2018 May;19(3):356-365
- 45% med søvnapnø
  Andersen, *Eur Arch Otorhinolaryngol*. 2019 Mar;276(3):871-878
- 31% med fedtlever
  Fonvig, PLoS One. 2015 Aug 7;10(8):e0135018



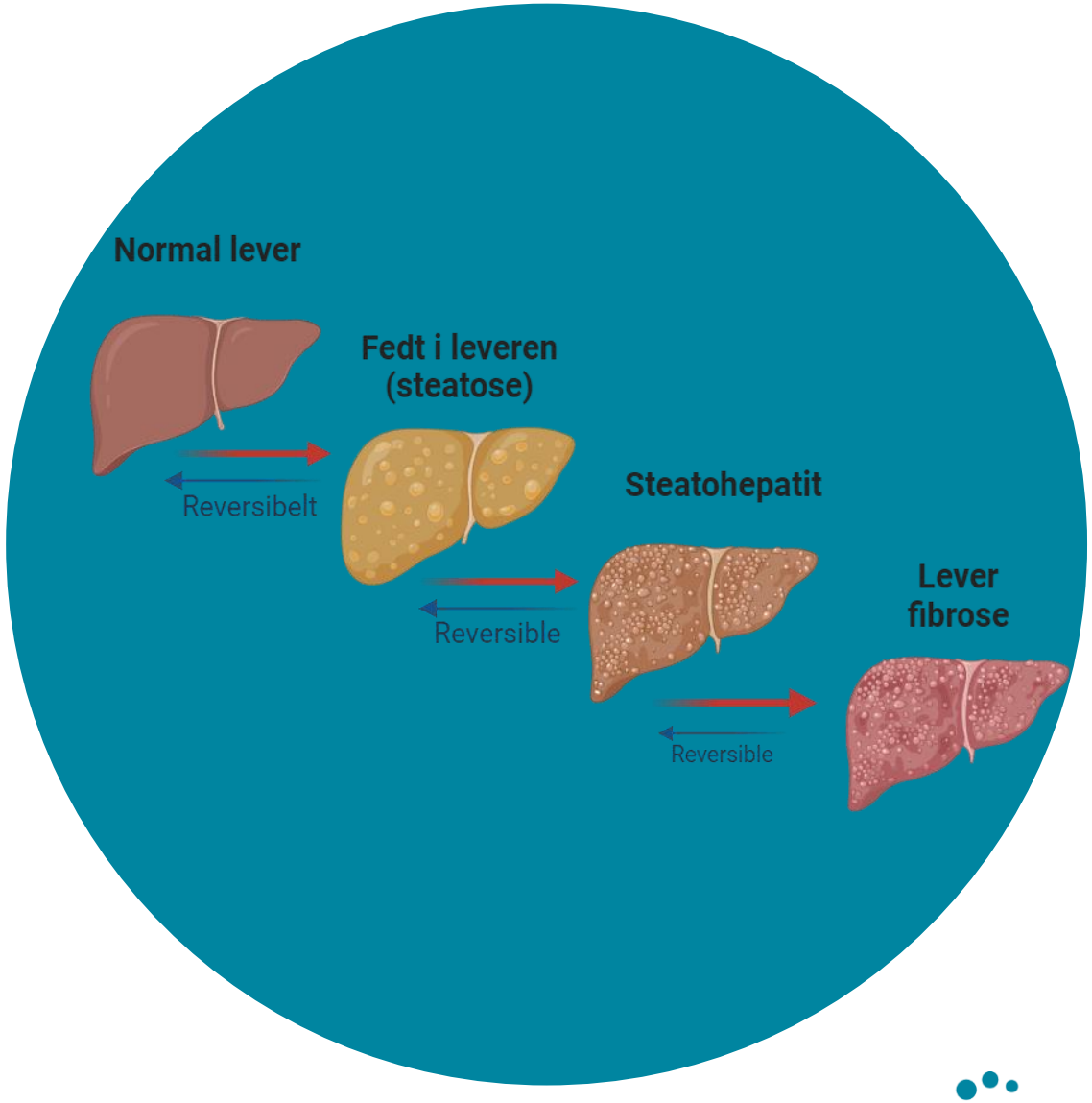
Tegning fra Det Bedste For Barnet, JC Holm, Politikens Forlag 2017


RED BLOOD CELLS
decomposition
METABOLIC PROCESSES
controls
BLOOD COMPOSITION
regulates
PROTEINS & CHOLESTEROL
produces
HORMONES
production and detoxification
BILE
produces
TOXINS
deactivation
A
C
B12
VITAMINS
help the absorption

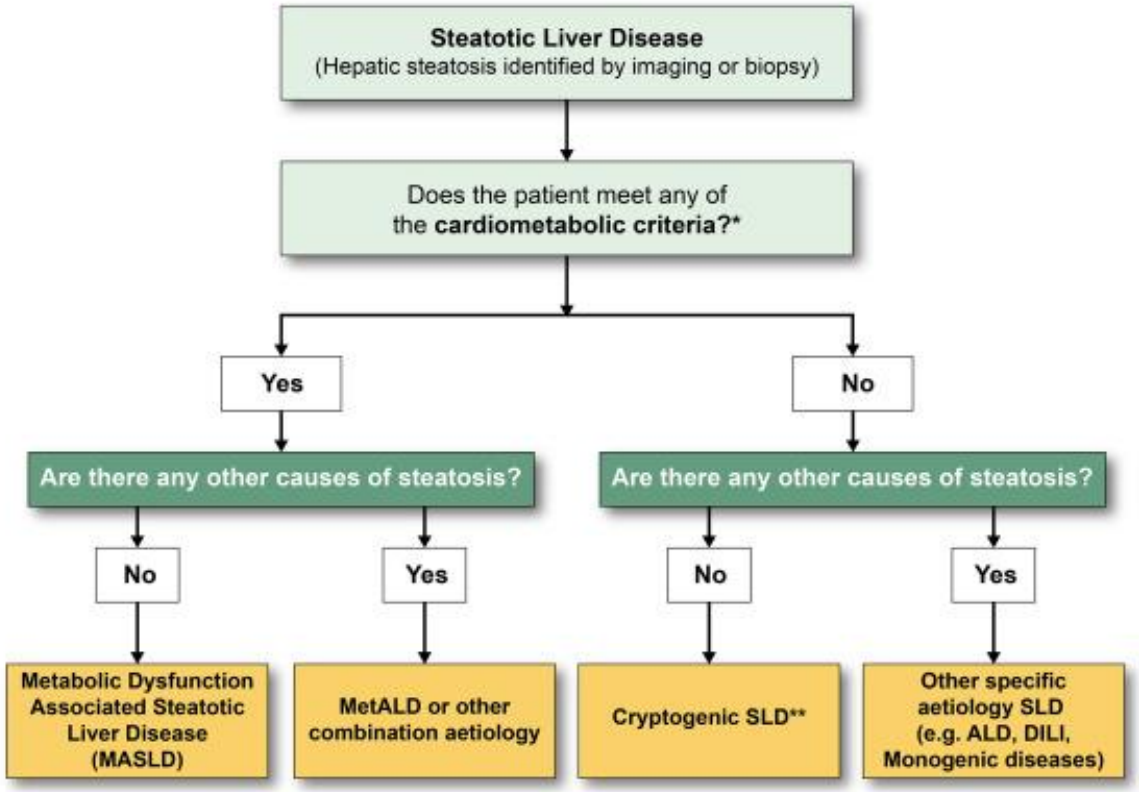
Fedt i leveren

Kendetegnet ved:

- Tilstand med *øget ophobning af fedt i leveren.*
- Kan udvikle sig med inflammation, fibrose og cirrose.
- Tæt relation til adipositas



Steatotisk leversygdom - nomenklatur



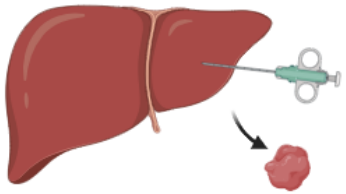
*Cardiometabolic criteria

Adult Criteria	Pediatric Criteria
At least 1 out of 5:	At least 1 out of 5:
☐ BMI ≥ 25 kg/m² [23 Asia] OR WC > 94 cm (M) 80 cm (F) OR ethnicity adjusted	☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] OR WC > 95th percentile OR ethnicity adjusted
☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR type 2 diabetes OR treatment for type 2 diabetes	☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] OR serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] OR 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] OR HbA1c ≥ 5.7% [39 mmol/L] OR already diagnosed/treated type 2 diabetes OR treatment for type 2 diabetes
☐ Blood pressure ≥ 130/85 mmHg OR specific antihypertensive drug treatment	☐ Blood pressure age < 13y, BP ≥ 95th percentile OR ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg OR specific antihypertensive drug treatment
☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] OR lipid lowering treatment	☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] OR lipid lowering treatment
☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) OR lipid lowering treatment	☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] OR lipid lowering treatment

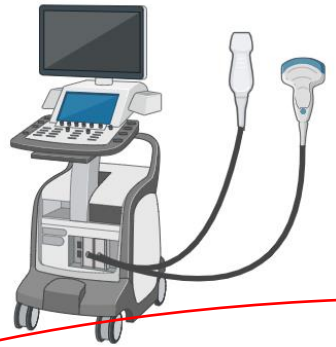
Mary E. Rinella et al.: A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Journal of Hepatology, Volume 79, Issue 6, December 2023, Pages 1542-1556

Undersøgelsesmetoder

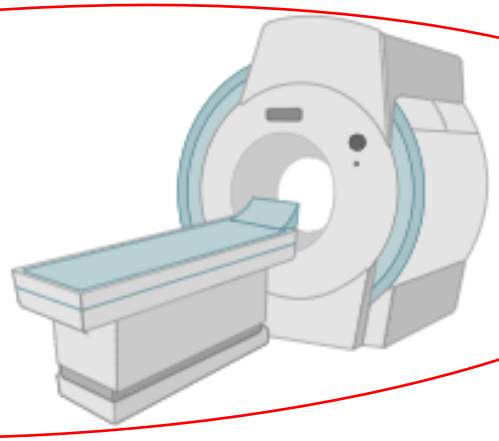
- Leverbiopsi



- Ultralyd

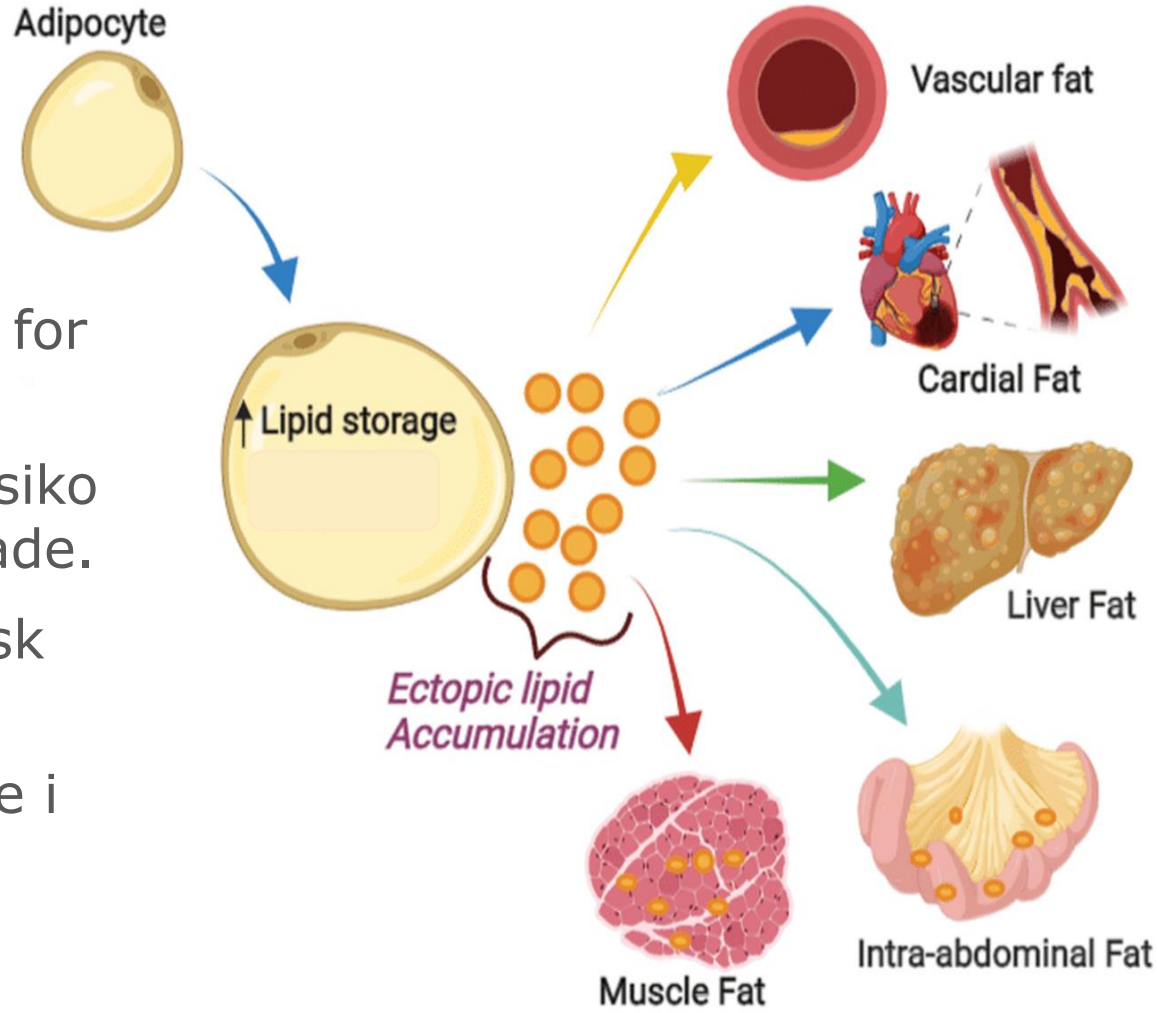


- MR-Imaging
- MR-Spektroskopi



Baggrund

- Børn/unge med adipositas har øget risiko for komplikationer
- Fedt i og omkring organerne giver øget risiko for kardiometabolisk sygdom og organskade.
- Fedt i leveren er forbundet med metabolisk dysfunktion.
- Steatotisk leversygdom kan opstå allerede i barndommen
  - Prævalensen øges med alderen, hos drenge og samtidig adipositas*.



* Cholongitas E, et al. Epidemiology of nonalcoholic fatty liver disease in Europe: a systematic review and meta-analysis. Ann Gastroenterol, 2021;
Wiegand S, et al. Obese boys at increased risk for nonalcoholic liver disease: Evaluation of 16 390 overweight or obese children and adolescents. Int J Obes. 2010

Tidligere studier

PLOS ONE

RESEARCH ARTICLE

^{1}H-MRS Measured Ectopic Fat in Liver and Muscle in Danish Lean and Obese Children and Adolescents

Cilius Esmann Fonvig[1,2]*, Elizaveta Chabanova[3], Ehm Astrup[4], Dam Ohrt[1], Oluf Pedersen[2], Torben Hansen[2,4], Henrik S. Thomsen[5], Christian Holm[1,6]

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OPEN ACCESS

Citation: Fonvig CE, Chabanova E, Andersson EA, Ohrt JD, Pedersen O, Hansen T, et al. (2015) ^{1}H-MRS Measured Ectopic Fat in Liver and Muscle in Danish Lean and Obese Children and Adolescents. PLoS ONE 10(8): e0135018. doi:10.1371/journal.pone.0135018

Editor: Marie Theare, NIH / NIDDK, UNITED STATES

Received: March 9, 2015

Accepted: July 16, 2015

Published: August 7, 2015

Data Availability Statement: Data are available from the Danish Childhood Obesity Biobank Database for researchers who meet the criteria for access to confidential data. Access may be acquired through contact to jhom@regionsjaelland.dk.

Funding: This study was funded by the Danish Innovation Foundation (grant number 0603-00484B) and by the Region Zealand Health and Medical Research Foundation (TH CEF). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Objectives

This cross sectional study aims to investigate the association mulation in liver and skeletal muscle and biochemical measur tance, anthropometry, and blood pressure in lean and overwe

Methods

Fasting plasma glucose, serum lipids, serum insulin, and exp anthropometry, blood pressure, and magnetic resonance spe fat were obtained in 327 Danish children and adolescents age

Results

In 287 overweight/obese children, the prevalences of hepatic 31% and 68%, respectively, whereas the prevalences in 40 le 10%, respectively. A multiple regression analysis adjusted for z-score (BMI SDS), and pubertal development showed that th mia was 4.2 (95%CI: [1.8; 10.2], $p = 0.0009$) when hepatic ste ing the simultaneous presence of hepatic and muscular steat steatosis, the OR of exhibiting dyslipidemia was 5.8 (95%CI: nificant associations between muscle fat and dyslipidemia, in blood pressure were observed.

Liver and muscle fat, adjusted for age, sex, BMI SDS, and ated to BMI SDS and glycosylated hemoglobin, while only live

Fonvig et al. BMC Pediatrics (2015) 15:196
DOI 10.1186/s12887-015-0513-6

BMC Pediatrics

RESEARCH ARTICLE Open Access

Multidisciplinary care of obese children and adolescents for one year reduces ectopic fat content in liver and skeletal muscle

Chabanova[3], Johanne Dam Ohrt[1], Louise Aas Nielsen[1], C
en[3,4] and Jens-Christian Holm[1,4]

on in liver and skeletal muscle tissue is related to cardiovas
in in obese children. We evaluated the hypotheses of ectop
year of multidisciplinary care specialized in childhood obesi
anges in other markers of metabolic function.

itudinal study evaluated 40 overweight children and adoles
l at the Children's Obesity Clinic, Holbæk, Denmark. The part
amples (HbA1c, glucose, insulin, lipids, and biochemical variat
assessed by magnetic resonance spectroscopy at enrollme
Univariate linear regression models adjusted for age, sex, tr
ubertal developmental stage were used for investigating
core (SDS) of baseline median body mass index (BMI) was 2.8
17). At the end of the observational period, the 40 children ar
SDS, liver fat, muscle fat, and visceral adipose tissue volum
8 to 20 % ($p = 0.26$) and the prevalence of muscular steat

were independent of changes in BMI SDS, baseline degree
developmental stage.
linary intervention program in the setting of a childhood obe
duction in liver and muscle fat; metabolic improvements that
oss.
registration number: NCT00928473, the Danish Childhood C

netic Resonance Spectroscopy, Skeletal Muscle, Non-alcoholic
isorders, Child, Adolescent

Received: 12 May 2021 | Revised: 5 May 2022 | Accepted: 9 May 2022
DOI: 10.1111/ijpo.12947

Pediatric OBESITY WILEY

ORIGINAL RESEARCH

Possible prediction of obesity-related liver disease in children and adolescents using indices of body composition

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Funding information
BRIDGE - Translational Excellence Programme, Grant/Award Number: NNF18SA0034956; Innovation Fund Denmark, Grant/Award Numbers: 0603-00484B, 603-00457B; The Novo Nordisk Foundation, Grant/Award Numbers: NNF15OC0016544, NNF15OC0016692; The Region Zealand Health Scientific Research Foundation

Summary

Background: Diagnosis of nonalcoholic fatty liver disease in children and adolescents currently requires advanced or invasive technologies.

Objectives: We aimed to develop a method to improve diagnosis, using body composition indices and liver biochemical markers.

Methods: To diagnose non-alcoholic fatty liver disease, 767 Danish children and adolescents underwent clinical examination, blood sampling, whole-body dual-energy X-ray absorptiometry scanning and proton magnetic resonance spectroscopy for liver fat quantification. Fourteen variables were selected as a starting point to construct models, narrowed by stepwise selection. Individuals were split into a training set for model construction and a validation test set. The final models were applied to 2120 Danish children and adolescents to estimate the prevalence.

Results: The final models included five variables in different combinations: body mass index–standard deviation score, android-to-gynoid-fat ratio, android-regional fat percent, trunk-regional fat percent and alanine transaminase. When validated, the sensitivity and specificity ranged from 38.6% to 51.7% and 87.6% to 91.9%, respectively. The estimated prevalence was 24.2%–35.3%. Models including alanine transaminase alongside body composition measurements displayed higher sensitivity.

Conclusions: Body composition indices and alanine transaminase can be used to estimate non-alcoholic fatty liver disease, with 38.6%–51.7% sensitivity and 87.6%–91.9%, specificity, in children and adolescents with overweight (including obesity). These estimated a 24.2%–35.3% prevalence in 2120 patients.

KEYWORDS
adolescents, body composition, children, DXA-scan, MAFLD, NAFLD

Abbreviations: ^{1}H-MRS, proton magnetic resonance spectroscopy; AIC, Akaike information criterion; ALT, alanine transaminase; AUC, area under the curve; BMI-SDS, body mass index–standard deviation score; DXA, whole-body dual-energy X-ray absorptiometry; MAFLD, metabolic dysfunction–associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics; VAT, visceral adipose tissue.

^{1}H MRS Assessment of Hepatic Fat Content: Comparison Between Normal- and Excess-weight Children and Adolescents

, Cilius Esmann Fonvig, PhD, Christine Bøjsøe, MD, hristian Holm, PhD, Henrik S. Thomsen, Dr Med Sci

purpose of the present study was to obtain a cutoff value of liver fat atic steatosis by comparing magnetic resonance (MR) spectroscopy nts with normal and excess weight.

dy included 420 children and adolescents (91 normal-weight, 99 over- ars of age. Proton magnetic resonance spectroscopy was performed t resolved spectroscopy sequence with series echo times.

ass concentration of liver fat was obtained: 0.5 ± 0.04% in normal- rmal-weight girls; 0.9 ± 0.16% in boys with overweight; 1.1 ± 0.24% 24% in boys with obesity; and 1.4 ± 0.21% in girls with obesity. mass concentration of liver fat for hepatic steatosis was found to be e, hepatic steatosis was diagnosed in 16% of boys with overweight, 2% of boys with obesity, and 27% of girls with obesity.

resonance spectroscopy was successfully applied to obtain the cutoff ration of liver fat for the diagnosis of hepatic steatosis in children and escents with obesity have higher risk of hepatic steatosis than their

ren; magnetic resonance; obesity; spectroscopy; steatosis.

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

An adult-based genetic risk score for liver fat associates with liver and plasma lipid traits in children and adolescents

Yun Huang[1] | Sara E. Stinson[1] | Helene Bæk Juel[1] | Morten A. V. Lund[2,3] | Louise Aas Holm[1,2] | Cilius E. Fonvig[1,2,4] | Trine Nielsen[1] | Niels Grarup[1] | Oluf Pedersen[1,5] | Michael Christiansen[3,6] | Elizaveta Chabanova[7] | Henrik S. Thomsen[7] | Aleksander Krag[8,9] | Stefan Stender[10] | Jens-Christian Holm[1,2] | Torben Hansen[1]

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Funding information
The Innovation Fund Denmark, Grant/Award Number: 0603-00484B; The Novo Nordisk Foundation, Grant/Award Number: NNF15OC0016544; The MicrobLiver Challenge, Grant/Award Number: NNF15OC0016692

Abstract

Background & Aims: Genome-wide association studies have identified steatogenic variants that also showed pleiotropic effects on cardiometabolic traits in adults. We investigated the effect of eight previously reported genome-wide significant steatogenic variants, individually and combined in a weighted genetic risk score (GRS), on liver and cardiometabolic traits, and the predictive ability of the GRS for hepatic steatosis in children and adolescents.

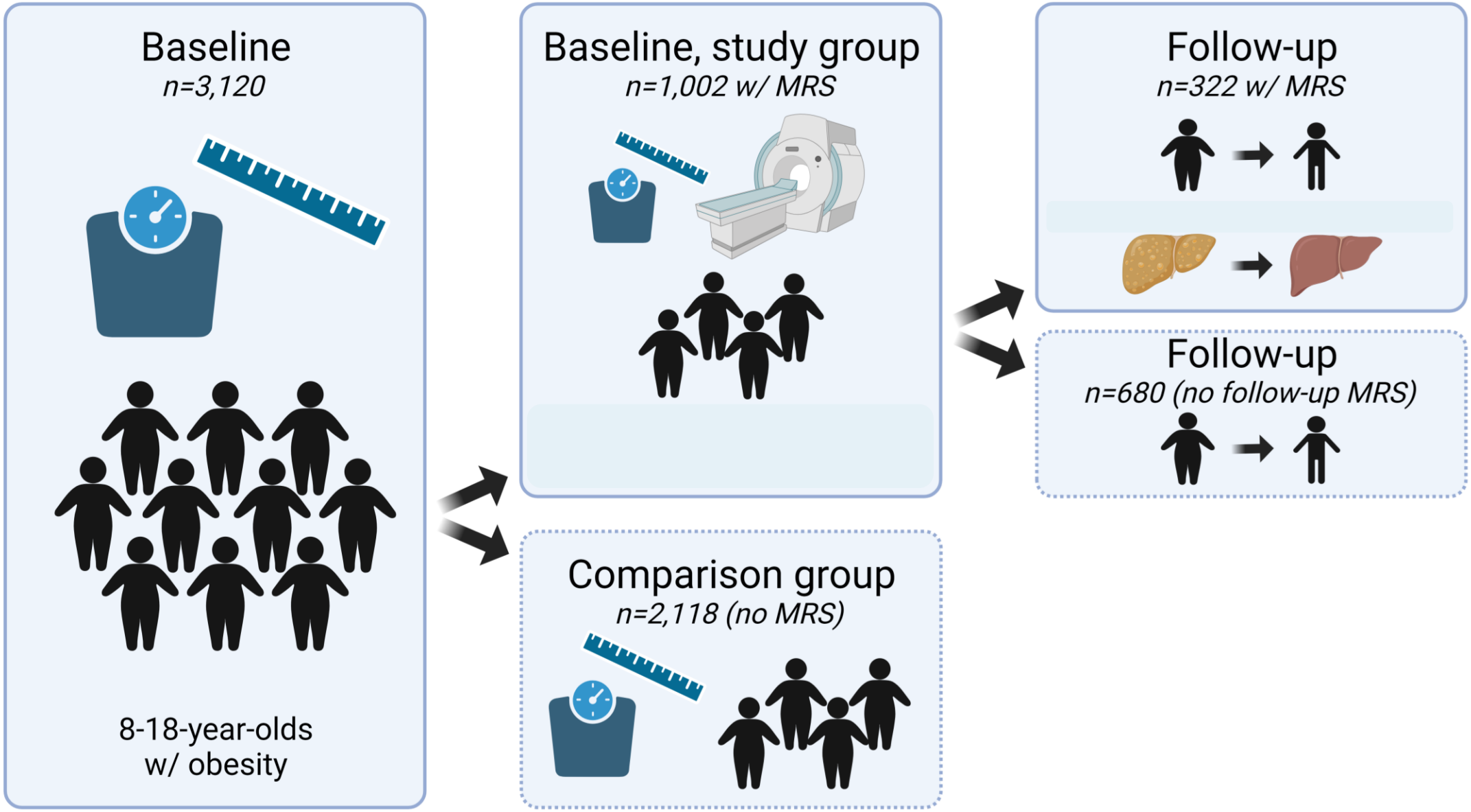
Approach & Results: Children and adolescents with overweight (including obesity) from an obesity clinic group ($n = 1768$) and a population-based group ($n = 1890$) were included. Cardiometabolic risk outcomes and genotypes were obtained. Liver fat was quantified using ^{1}H-MRS in a subset of 727 participants. Variants in *PNPLA3*, *TM6SF2*,

Abbreviations: ^{1}H-MRS, proton magnetic resonance spectroscopy; ALT, alanine aminotransferase; APOE, apolipoprotein E; AST, aspartate transaminase; AUC, area under the curve; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; DXA, dual-energy x-ray absorptiometry; GCKR, glucokinase regulator; GGT, gammaglutamyltransferase; GLP1, glucagon-like peptide-1; GPAM, glycerol-3-phosphate acyltransferase, mitochondrial; GRS, genetic risk score; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MAST4, microtubule associated serine/threonine kinase 2; MRI, magnetic resonance imaging; MTARC1, mitochondrial amidoxime reducing component 1; OR, odds ratio; PNPLA3, patatin-like phospholipase domain-containing protein 3; ROC, receiver operating curve; SBP, systolic blood pressure; SDS, standard deviation score; SHP, single nucleotide polymorphism; TC, total cholesterol; TG, triglycerides; TM6SF2, transmembrane 6 superfamily member 2; TRIB1, tribbles homologue 1; WBC, total white blood cells; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

Jens-Christian Holm and Torben Hansen are co-last authors

Herlev Gentofte, Herlev Ringvej 75, DK-2730 Herlev (E.C., H.S.T.); The Children's olbæk, Holbæk (C.E.F., C.B., J.-C.H.); The Novo Nordisk Foundation Center for hagen, Copenhagen (C.E.F., C.B., J.-C.H.); Faculty of Health Sciences, University r 23, 2016; revised February 13, 2017; accepted February 14, 2017. **Address cor-**

The HOLBAEK Study, The Children's Obesity Clinic



MASLD = Metabolic Dysfunction Associated Steatotic Liver Disease

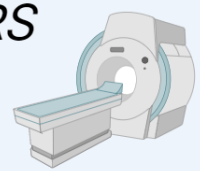
Resultater

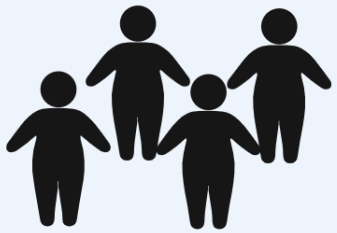
Baseline

n=3,120

Børn/unge med adipositas & MR ved opstart

n=1,002 med MRS





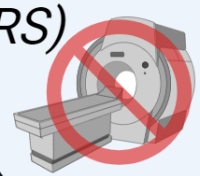
Alder: 13 år

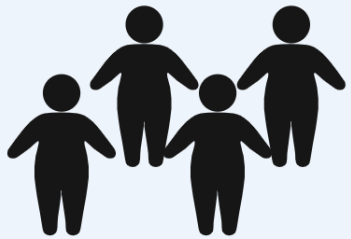
BMI SDS: 2.90

Livvidde: 2.42

Sammenligningsgruppen (Børn/unge med overvægt)

n=2,118 (ingen MRS)



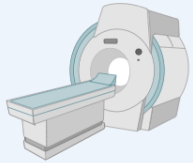


Alder: 12 år

BMI SDS: 2.93

Livvidde: 2.45

Børn/unge med adipositas
& MR ved opstart
n=1,002



Børn/unge MED fedt i leveren		Børn/unge UDEN fedt i leveren
n=378		*n=624*
Alder: 13.4 år	p = 0.02	**Alder: 12.9 år**
BMI SDS: 3.20	p < 0.001	**BMI SDS: 2.75**
Livvidde SDS: 2.62	p < 0.001	**Livvidde SDS: 2.27**

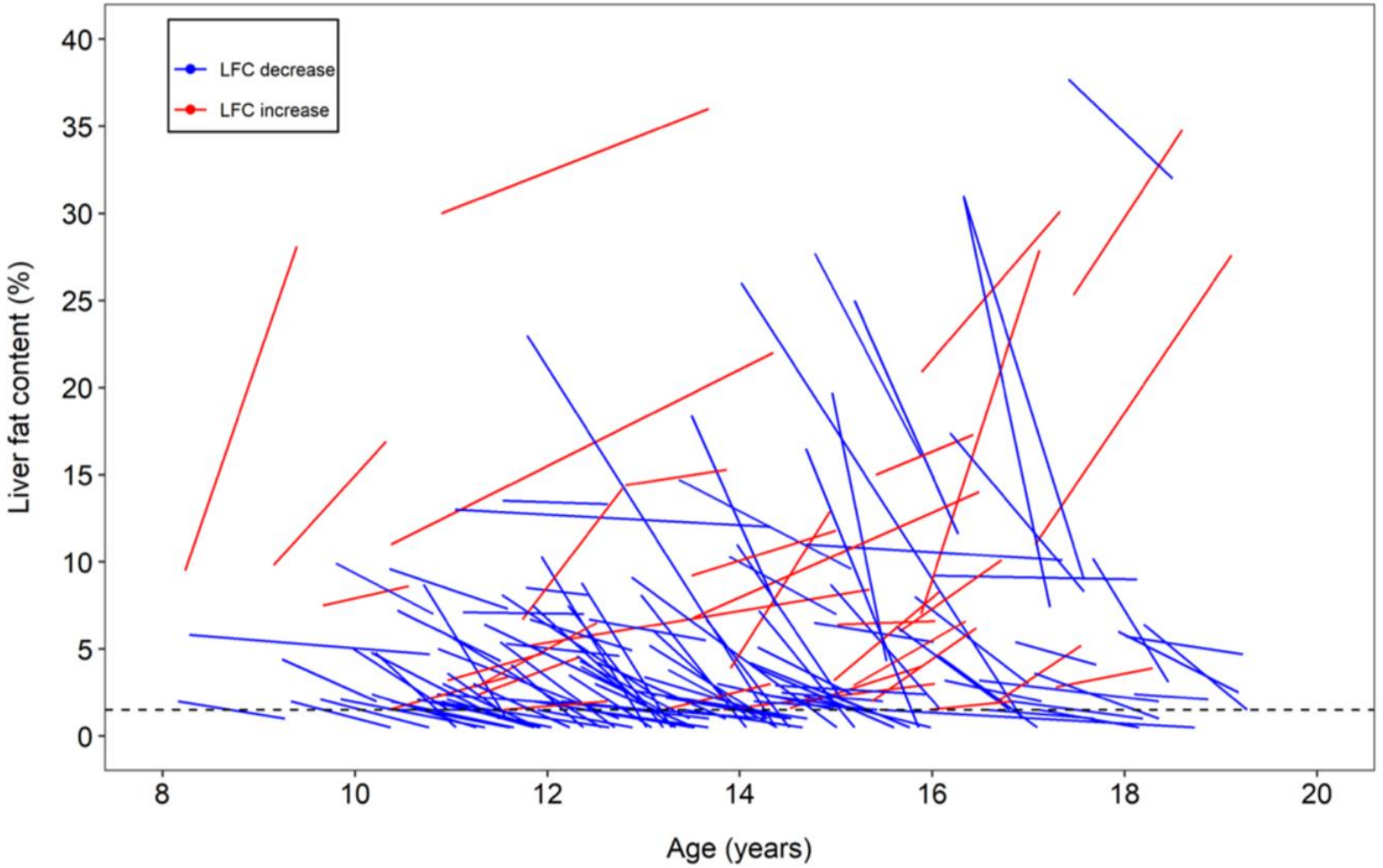
Table 1 – Study group characteristics at baseline				
	Overall	MASLD (LFC>1.5%)	No MASLD	p-value
n	1,002	378	624	
Sex – female, n (%)	525 (52.4)	172 (45.5)	353 (56.6)	0.001
Age (years), median [IQR]	13.0 [11.3, 15.0]	13.4 [11.4, 15.4]	12.9 [11.3, 14.8]	0.02
Social class[a], n (%)				0.046
High class	85 (9.7)	24 (7.5)	61 (11.0)	
Higher middle class	198 (22.6)	60 (18.7)	138 (24.9)	
Middle class	335 (38.2)	129 (40.2)	206 (37.1)	
Lower middle class	160 (18.3)	66 (20.6)	94 (16.9)	
Lower class	98 (11.2)	42 (13.1)	56 (10.1)	
Ëthicity, n (%)				0.008
Causasian	896 (89.4)	323 (85.4)	573 (91.8)	
Middle Eastern	83 (8.3)	44 (11.6)	39 (6.2)	
Asian	6 (0.6)	4 (1.1)	2 (0.3)	
African	14 (1.4)	5 (1.3)	9 (1.4)	
Hispanic	3 (0.3)	2 (0.5)	1 (0.2)	
Pubertal status[b], n (%)				0.87
Prepubertal	138 (24.7)	49 (25.4)	89 (24.4)	
Peripubertal	259 (46.4)	91 (47.2)	168 (46.0)	
Postpubertal	161 (28.9)	53 (27.5)	108 (29.6)	
BMI z-score, median [IQR]	2.90 [2.49, 3.34]	3.20 [2.78, 3.60]	2.76 [2.37, 3.15]	<0.001
Waist circumference z-score, median [IQR]	2.42 [2.02, 2.73]	2.62 [2.31, 2.88]	2.27 [1.90, 2.60]	<0.001
Waist-height ratio, median [IQR]	0.59 [0.54, 0.64]	0.62 [0.58, 0.66]	0.57 [0.53, 0.62]	<0.001
LFC, median [IQR]	1.00 [0.5, 2.80]	4.65 [2.10, 9.1]	0.50 [0.50, 1.00]	<0.001
SAT, median [IQR]	293 [222, 386]	344 [255, 456]	274 [205, 350]	<0.001
VAT, median [IQR]	70 [50, 94]	89 [68, 114]	60 [45, 80]	<0.001

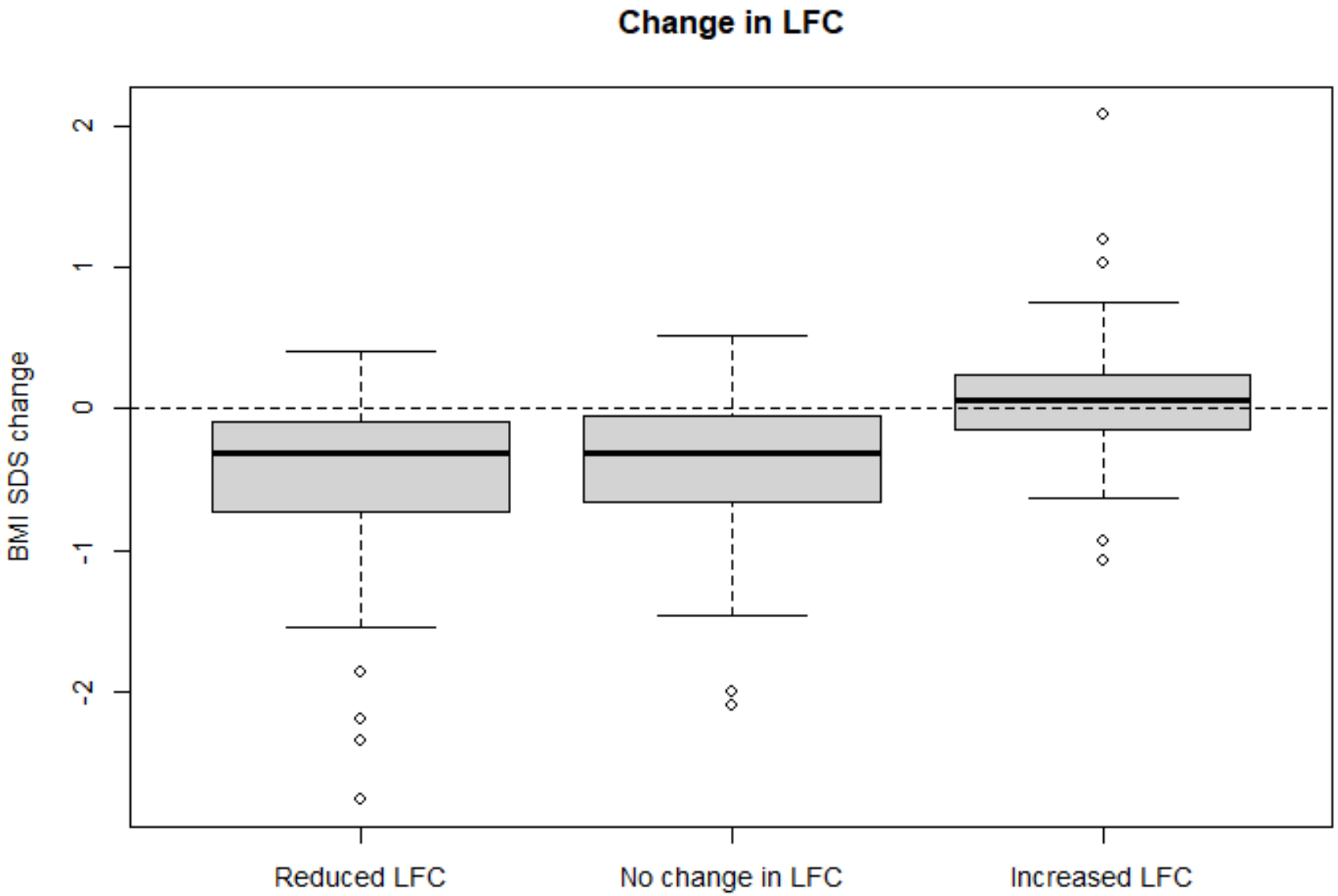
145 patients med MASLD:

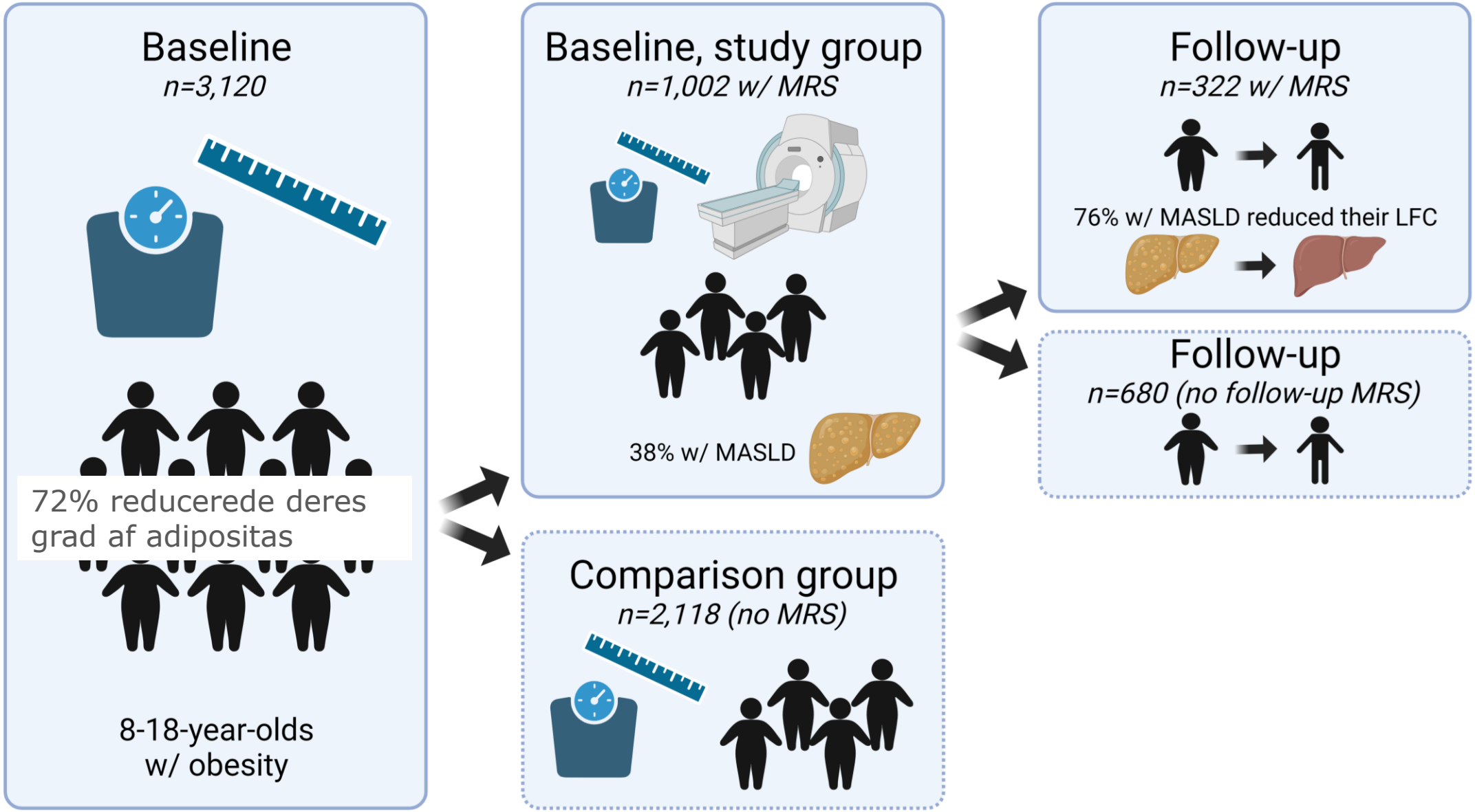
- **110 (76%)** reducerede deres leverfedt indhold
- 33 øgede LFC

- **59 (53%)** af de 110 havde ingen MASLD ved follow-up

Ændirng i leverfedt indhold (LFC) i 145 patienter MED MASLD (LFC>1.5%)




Change in LFC
BMI SDS change
2
1
0
-1
-2
Reduced LFC
No change in LFC
Increased LFC


Baseline
n=3,120
72% reducerede deres grad af adipositas
8-18-year-olds w/ obesity
Baseline, study group
n=1,002 w/ MRS
38% w/ MASLD
Comparison group
n=2,118 (no MRS)
Follow-up
n=322 w/ MRS
76% w/ MASLD reduced their LFC
Follow-up
n=680 (no follow-up MRS)

Tak til:

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- Cilius Esmann Fonvig, læge, PhD, Holbæk
- Rebecca Berg Pedersen, Stud.med., Holbæk
- Elizaveta Hansen, MR fysiker, Herlev
- Henrik Thomsen, læge, Prof., Herlev
- Enheden for Børn og Unge med Adipositas, Holbæk
- The HOLBAEK Study
- Alle deltagende børn og unge