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Nonpharmacological Childhood Obesity Management in Denmark Reduces Steatotic Liver Disease and Obesity

Rebecca Berg Pedersen, MD,[1] Maria Martens Fraulund, MD,[1] Elizaveta Chabanova, PhD,[2] Louise Aas Holm, MD,[1,3] Torben Hansen, MD, PhD,[3] Henrik S. Thomsen, MD, PhD,[2,4] Jens-Christian Holm, MD, PhD,[1,3,4] and Cilius Esmann Fonvig, MD, PhD[1,3,4]

Abstract

Background: Steatotic liver disease (SLD) represents a multisystem disease and is a common complication of childhood obesity. We studied fat content at the abdominal level (liver, subcutaneous, and visceral) and the response to childhood obesity management.

Methods: In this retrospective longitudinal study, 8–18-year-olds with a body mass index (BMI) z-score above 1.28 (corresponding to a BMI above the 90th percentile), as a proxy for obesity, were offered person-centered, family-oriented obesity management in a hospital setting and in a magnetic resonance (MR) scan. Liver fat content (LFC) was assessed by MR spectroscopy, whereas subcutaneous adipose tissue and visceral adipose tissue (VAT) were assessed by MR imaging. We conducted nonparametric tests to evaluate baseline-to-follow-up changes and comparisons between participants with and without an MR assessment. Additionally, a logistic regression model examined the association between changes in LFC and BMI z-score.

Results: The study group comprised 1002 children and adolescents (52% females) with an MR assessment at baseline. The median age was 13.0 years, the median BMI was 28.4, and the BMI z-score was 2.90. At baseline, 378 (38%) exhibited SLD defined by an LFC above 1.5%. Among the 322 with a follow-up MR scan, 76% of the patients with SLD reduced their LFC. BMI z-score and VAT (both $p < 0.001$) were reduced during intervention.

Conclusions: SLD is highly prevalent (38%) in children and adolescents with obesity. A chronic care obesity management model reduced the fat content in the liver, the visceral fat, and the degree of obesity.

Keywords: fatty liver; magnetic resonance imaging; magnetic resonance spectroscopy; obesity management; pediatric obesity; steatotic liver disease

Introduction

Childhood obesity (including overweight), defined by excessive fat deposits that can impair health,[1] is a major global health concern with high prevalence.[2] Childhood obesity is associated with multiple complications,[3–7] which can track into adulthood.[8,9] Ectopic fat deposition in the liver is associated with metabolic dysfunction, increased risk of cardiometabolic diseases, and organ damage.[3,5,10]

[1]Department of Pediactrics, The Children's Obesity Clinic, Accredited European Centre for Obesity Management, Copenhagen University Hospital Holbæk, Holbæk, Denmark.
[2]Department of Radiology, Herlev and Gentofte Hospital, Herlev, Denmark.
[3]Faculty of Health and Medical Sciences, Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark.
[4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

In this study, we use the 2023 consensus nomenclature, where steatotic liver disease (SLD) is defined as hepatic steatosis identified by imaging, and the further presence of cardiometabolic features, such as obesity, is called metabolic dysfunction-associated steatotic liver disease (MASLD).[11] The spectrum of MASLD is one of multiple obesity-related complications arising already in childhood.[9]

Emerging evidence suggests that accumulation of fat in the liver can progress into more advanced disease stages with inflammation (steatohepatitis) and fibrosis and carries a significantly higher mortality risk later in life.[3,10,12] The estimated prevalence of MASLD in children and adolescents with obesity varies greatly in the literature from 12% to 53%, although increasing with age and male sex.[3–7] Liver fat accumulation is known to be a highly important factor in metabolic health,[13–15] where increased visceral fat can be an indicator of liver fat accumulation.[16–18] Early onset (i.e., during childhood) of ectopic fat deposition in the liver, and the related insulin resistance, may reflect a more metabolically deranged obesity phenotype compared with later onset.[14,19]

Historically, the gold standard for quantifying SLD has been liver biopsy,[20] which, in children and adolescents, is challenging due to risks of pain, bleeding, and infection. Liver biopsy is useful in the histological identification of infiltration, inflammation, scarring, and other conditions, although it is not suitable as screening procedures.[7,21–23] Noninvasive diagnostic tools in SLD are available. Proton magnetic resonance spectroscopy (MRS) and imaging (MRI) are used for assessments of quantification of liver fat content (LFC).[19,24–26] The MR technique is a precise, feasible, and safe procedure. MRS quantification of LFC can be measured simultaneously with MRI assessments of subcutaneous and visceral fat.[23]

Intensive nonpharmacological obesity management is recommended as a first-line treatment of MASLD in children and adolescents with obesity.[27] Such intensive obesity management has, in smaller studies, shown reductions in LFC and hepatic fibrosis.[28] Likewise, The HOLBAEK Model has previously proven effective in reducing MASLD among children and adolescents.[29]

This study investigates the MRS-assessed LFC and MRI-assessed subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) in children and adolescents with obesity during nonpharmacological, nonsurgical childhood obesity management.

Materials and Methods

Study Population

In this retrospective longitudinal cohort study, we extracted data from The HOLBAEK Study (formerly known as The Danish Childhood Obesity Data- and Biobank). The patients were 8–18 years of age, had a body mass index (BMI) z-score above 1.28 (corresponding to a BMI above the 90th percentile) (as a proxy for obesity), and were enrolled in obesity management at The Children's Obesity Clinic, an accredited European Center for Obesity Management at Copenhagen University Hospital Holbæk, Denmark.[30] The recruiting obesity management clinic has no exclusion criteria.

Anthropometry

All children and adolescents had anthropometric measures performed at enrollment, including height, weight, and waist circumference. The same measurements were performed at yearly visits. The height was measured to the nearest millimeter with a stadiometer. The weight was measured to the nearest 0.1 kg on an electronic scale with regular certified calibration. Waist circumference was measured in a standing position at the umbilical level to the nearest 0.5 cm. We calculated the BMI z-score with the LMS method from Danish references.[31,32] We calculated the waist circumference z-score with the GAMLSS method[33] from a Danish reference population of 2541 children and adolescents.[34]

MR Scans

Since May 2015, The Children's Obesity Clinic has been offering MR scans for abdominal fat content and distribution analysis and evaluation to children and adolescents with obesity who were 8 years or older at enrollment. We used the MR scans of the liver and abdomen to evaluate the LFC, SAT, and VAT and investigate the prevalence of MASLD.[29,35]

Since all study participants exhibited obesity (per eligibility criteria), any occurrence of SLD in the present study was labeled as MASLD, according to definition.[11]

The measurements of LFC were done with ^{1}H-MRS, using a 3T Achieva MR imaging system (Philips Medical Systems, Best, Netherlands) without sedation. The method has been described in our previous studies.[21,22,36] The procedure was performed with a standard postprocessing protocol for the MR imaging system by an experienced senior MR physicist. The spectroscopy was placed in the right liver lobe corresponding to the level of the third lumbar vertebra (L3) as described by Chabanova et al.[21] For this study, SLD was defined as LFC >1.5% since children and adolescents with normal weight have shown to have an LFC <1.5% with this type of ^{1}H-MRS scan.[21]

Puberty Stage

Pubertal development stage was classified according to sexual maturity rating[37,38] by breast development in girls and gonad development in boys, evaluated by a pediatrician. Puberty stage was categorized as prepubertal (sexual maturity rating 1), peripubertal (sexual maturity rating 2–4), or postpubertal (sexual maturity rating 5).

Socioeconomic Status

Socioeconomic status (SES) was categorized into five groups depending on parental education and occupation

based on the official Danish national classification (DISCO-08)[39] adapted from the International Standard Classification of Occupations (ISCO-08). The five categories are high SES (general directors and higher educational level), high middle SES (office and customer service and medium educational level), middle SES (functionaries and skilled workers), lower middle SES (workers, manual labor, and students), and lower SES (unemployed).

The Intervention

The children and adolescents with obesity followed the person-centered, family-oriented, multifaceted, chronic care treatment approach, The HOLBAEK Model, at The Children's Obesity Clinic.[40,41] The intervention strategy is based on the understanding of obesity as a chronic disease, the neuroendocrinological regulation of fat mass, and its homeostatic ability to counteract weight loss and preserve fat mass.[40,42] The HOLBAEK Model represents a paradigm shift, challenging existing strategies such as caloric restriction, motivational thinking, and the incremental step approach. For example, instead of caloric restriction, patients are encouraged to achieve reasonable satiety at each main meal, featuring diverse and nutritious food options, with compassionate guidance. The treatment protocol is hospital based and uses a behavioral modifying technique, targeting all food and beverage intake, physical activity, inactivity, sleep, allowances, means of transport, sugar dependency, picky eating, and more. The family receives an individually tailored plan of advice addressing all the relevant aspects for the family. The family consults a pediatrician yearly and on a per-need basis and other health care professionals such as dieticians, nurses, psychologists, and social workers in between if relevant. The average intensity was 5 (interquartile range [IQR]: 3–7) visits, amounting to 4–5 hours of health care professional time per patient the first year. All patients undergo a thorough examination at the start of treatment, screening for other concomitant conditions and obesity-related complications.

Statistical Analysis

Statistical analyses were performed using "R" statistical software version v. 4.1.2.[43] The level of significance was set at $p < 0.05$. The normality of data was assessed with histograms, qq-plots, and the Shapiro–Wilk test. As the data were non-normally distributed, nonparametric analyses were performed. Differences between the groups were tested using the Wilcoxon rank-sum or chi-squared test. The Wilcoxon signed rank test was used to analyze differences from baseline to follow-up. The differences in paired categorical data of fractions of MASLD and pubertal developmental stage were analyzed by McNemar's test and Kruskal–Wallis rank sum test, respectively. Associations with categorical variables were investigated by a logistic regression model of the binomial family. SES was categorized into five groups depending on parental occupation using a national classification.[39]

Ethical Aspects

This study has been approved by the Ethics Committee of Region Zealand, Denmark (ID: SJ-104) and the Danish Data Protection Agency (ID: REG-043-2013). The study is registered at ClinicalTrials.gov (NCT00928473). Informed assent was provided from all study participants. Written consent was obtained from the study participants 18 years of age and older and from the parents of the study participants younger than 18 years.

Results

Until March 2022, 3751 children and adolescents were enrolled in obesity treatment at The Children's Obesity Clinic. Around 3135 were of age 8–18 years, whereas 15 were excluded from this study due to a BMI z-score of 1.28 or lower. None exhibited other known liver disease or had known use of antiobesity medication. The 3120 eligible participants were divided into the study group, $n = 1002$ (with MR assessment at baseline), and the comparison group, $n = 2118$ (without MR assessment at baseline; Fig. 1, Table 1).

Baseline

At baseline, the study group and the comparison group were comparable regarding sex, ethnicity, and BMI z-score (2.90 vs. 2.93, $p = 0.94$), whereas the study group was older (13.0 years vs. 12.0 years, $p < 0.001$) and more advanced in pubertal development (see Supplementary Table S1). The study group had a median age of 13.0 years and a median BMI of 28.4 and a BMI z-score of 2.90. About 378 (38%) exhibited MASLD (LFC >1.5%). Further, 183 (18%) exhibited an LFC >5.0%. In the children and adolescents with MASLD, the BMI z-score was significantly higher than among the children and adolescents without MASLD (3.20 vs. 2.76, $p < 0.001$; Table 1). Likewise, the waist–height ratio, waist circumference z-score, SAT, and VAT were significantly higher (all $p < 0.001$) among the children and adolescents with MASLD compared with those without. Middle Eastern ethnicity was overrepresented (12% vs. 6%) among the children and adolescents with MASLD compared with those without. Among the children and adolescents with MASLD, baseline LFC ranged from 1.5% to 43%.

In a logistic regression model, the presence of MASLD at baseline was positively correlated with SAT ($p = 0.01$), VAT ($p < 0.001$), and older age ($p < 0.001$) but not with BMI z-score ($p = 0.20$) nor sex ($p = 0.32$).

Follow-up

In the study group, follow-up data were collected after a median treatment period of 12.7 months (IQR: 11.2–14.5) after baseline. Among those with a follow-up MR scan, the median change in BMI z-score was −0.17 (IQR: −0.51–0.06; see Supplementary Table S2). A total of 69% decreased their BMI z-score.

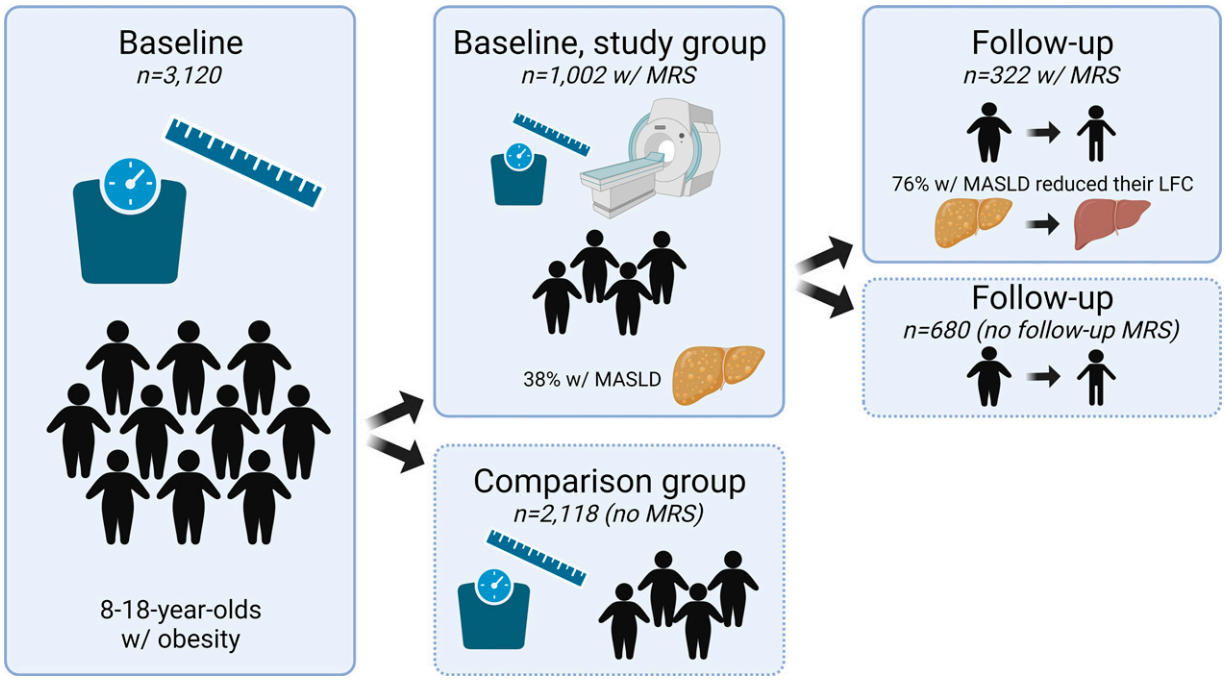

Figure 1. Visual abstract. LFC, liver fat content; MRS, magnetic resonance spectroscopy; MASLD, metabolic dysfunction-associated steatotic liver disease.

In the group without a follow-up MR scan, a total of 74% decreased their BMI z-score after a median follow-up time of 12.4 months. The median change in BMI z-score was −0.18 (IQR: −0.47–0.01). No group difference in BMI z-score change was observed (p = 0.42; Supplementary Table S2).

Overall, 72% reduced their BMI z-score with a median follow-up time of 12.5 months.

Follow-Up MR Scan

Among the 322 children and adolescents (161 females) with a follow-up MR scan, 145 (45%) exhibited MASLD at baseline (Table 2). At follow-up, LFC was reduced from a median of 5.0% (IQR: 2.4–8.8) to a median of 2.0% (IQR: 0.5–7.0) among the 145 patients with MASLD at baseline (p < 0.001). Looking at the 110 (76%) who reduced their LFC, of these 145 patients, the LFC was reduced from a median of 4.9% (IQR: 2.4–8.4) to a median of 1.0% (IQR: 0.5–3.1; p < 0.001), data not shown. Furthermore, of these 110 children and adolescents, 59 (53%) had a complete remission of MASLD at follow-up. The LFC changes for each of the 145 patients with MASLD are shown in Figure 2.

The fraction of patients with MASLD was reduced from 45% to 36% (p = 0.004), and the fraction exhibiting LFC of 5.0% or above was reduced from 23% to 16% (p = 0.001). Among the 177 children and adolescents without MASLD at baseline, 29 (16%) presented with MASLD at follow-up.

For the 322 children and adolescents with a follow-up MR scan, the median BMI z-score was reduced (from 2.88 to 2.61, p < 0.001) alongside reductions in waist circumference z-score (from 2.42 to 2.12, p < 0.001), waist-height ratio (from 0.59 to 0.55, p < 0.001), and VAT (from 73 to 63 cm^3, p < 0.001). SAT did not change significantly (from 279 to 287 cm^3, p = 0.08).

BMI z-score change is positively associated with change in LFC.

Among the patients with follow-up MR scans, a logistic regression model shows that the categorical change in LFC (increase, stable, or decrease) was independent of baseline LFC, age, sex, and treatment duration (all p > 0.10), whereas a higher reduction in BMI z-score was associated with increased odds of reducing LFC (p < 0.001; see Fig. 3).

Among the patients with follow-up MR scans, a predictive logistic regression model shows that the categorical change in LFC (increase, stable, or decrease) was independent of baseline LFC, age, sex, and treatment duration (all p > 0.10), whereas a higher baseline BMI z-score was associated with increased odds of reducing LFC (p = 0.004).

Discussion

This study investigated MRS-assessed LFC in children and adolescents with obesity who received treatment with The HOBAEK Model. Reductions of the LFC were achieved in 76% of patients with MASLD during intervention. The literature is generally sparse regarding the fraction of children and adolescents with MASLD reducing MR-assessed LFC.

Our group has previously shown LFC reductions among 91% of 11 pediatric patients with MASLD.[29] Schwimmer et al. found a prevalence of 25% (n = 20) with MASLD, among whom 20%–40% reduced their LFC after 8 weeks of dietary intervention.[44] Other

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
SES[a], *n (%)*				0.046
High SES	85 (9.7)	24 (7.5)	61 (11.0)	
High middle SES	198 (22.6)	60 (18.7)	138 (24.9)	
Middle SES	335 (38.2)	129 (40.2)	206 (37.1)	
Lower middle SES	160 (18.3)	66 (20.6)	94 (16.9)	
Lower SES	98 (11.2)	42 (13.1)	56 (10.1)	
Ethnicity, *n (%)*				0.008
Caucasian	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, *median [IQR]*	28.4 [25.2, 31.7]	29.9 [27.0, 34.5]	27.6 [24.7, 30.5]	<0.001
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 (cm), *median [IQR]*	95.0 [86.0, 104.5]	100.0 [91.0, 111.0]	91.0 [84.0, 100.0]	<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

[a]SES, socioeconomic status: high SES (general directors and higher educational level), high middle SES (office and customer service and medium educational level), middle SES (functionaries and skilled workers), lower middle SES (workers, manual labor, and students), and lower SES (unemployed).

[b]Pubertal status is grouped according to sexual maturity rating: prepubertal (sexual maturity rating stage 1), peripubertal (sexual maturity rating stage 2–4), and postpubertal (sexual maturity rating stage 5).

BMI, body mass index; LFC, liver fat content; MASLD, metabolic dysfunction-associated steatotic liver disease; MR, magnetic resonance; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

intervention studies ($n = 27–102$), also nonpharmacological, have shown reductions in MR-assessed LFC among children and adolescents with obesity after 1 year of treatment, although without reporting the fractions of patients reducing their LFC.[45,46]

In the present study, 53% of patients with MASLD at baseline showed complete remission, which is higher than Chan et al. ($n = 52$), who reported complete remission of MASLD among 31% after 68 weeks of intervention.[47] The differences of higher fractions with LFC reduction and a higher complete MASLD remission fraction in the present study could be due to a higher treatment intensity, including a more person-centered and multifaceted approach.

Table 2. Study Group Characteristics at Baseline and Follow-Up Stratified by Follow-Up MR Scan

	Overall	With follow-up MR scan	No follow-up MR scan	*p* value
n (%)	1,002 (100)	322 (32)	680 (68)	
Sex: female, *n (%)*	525 (52.4)	161 (50.0)	364 (53.5)	0.31
Age (years) at baseline, *median [IQR]*	13.0 [11.3, 15.0]	12.5 [11.0, 14.4]	13.3 [11.5, 15.2]	0.001
Follow-up time (months), *median [IQR]*	13.2 [10.8, 14.4]	13.2 [12.0, 15.6]	12.0 [9.6, 14.4]	<0.001
BMI at baseline, *median [IQR]*	28.4 [25.2, 31.7]	27.9 [24.9, 31.1]	28.6 [25.6, 32.2]	0.008
BMI z-score at baseline, *median [IQR]*	2.90 [2.49, 3.34]	2.88 [2.47, 3.32]	2.93 [2.49, 3.35]	0.48
BMI at follow-up, *median [IQR]*	27.5 [24.3, 31.7]	27.4 [24.0, 31.5]	27.6 [24.5, 31.9]	0.68
BMI z-score at follow-up, *median [IQR]*	2.61 [2.10, 3.20]	2.61 [2.04, 3.20]	2.62 [2.13, 3.21]	0.79
Waist circumference at baseline *(cm)*, *median [IQR]*	95.0 [86.0, 104.5]	94.5 [84.5, 103.0]	95.0 [86.4, 105.0]	0.23
Waist circumference z-score at baseline, *median [IQR]*	2.42 [2.02, 2.73]	2.42 [2.05, 2.73]	2.42 [2.00, 2.72]	0.59
Waist circumference at follow-up *(cm)*, *median [IQR]*	92.0 [82.5, 102.0]	90.5 [82.0, 101.5]	93.0 [84.0, 103.0]	0.12
Waist circumference z-score at follow-up, *median [IQR]*	2.18 [1.62, 2.57]	2.12 [1.60, 2.56]	2.27 [1.64, 2.61]	0.06
Waist–height ratio at baseline, *median [IQR]*	0.59 [0.54, 0.64]	0.59 [0.54, 0.64]	0.59 [0.54, 0.63]	0.91
Waist–height ratio at follow-up, *median [IQR]*	0.56 [0.51, 0.61]	0.55 [0.50, 0.60]	0.57 [0.52, 0.62]	0.051
LFC at baseline, *median [IQR]*	1.0 [0.5, 2.8]	1.0 [0.5, 4.2]	1.0 [0.5, 2.0]	0.003
LFC at follow-up, *median [IQR]*		1.0 [0.5, 2.3]	NA	
SAT (cm^3) at baseline, *median [IQR]*	293 [222, 386]	279 [219, 369]	298 [224, 392]	0.046
SAT (cm^3) at follow-up, *median [IQR]*		287 [210, 381]	NA	
VAT (cm^3) at baseline, *median [IQR]*	70 [50, 94]	73 [52, 95]	68 [50, 94]	0.30
VAT (cm^3) at follow-up, *median [IQR]*		63 [42, 87]	NA	

Data are presented as medians [with interquartile ranges] unless stated otherwise.

BMI, body mass index; LFC, liver fat content; MASLD, metabolic dysfunction-associated steatotic liver disease; MR, magnetic resonance; SAD, sagittal abdominal diameter; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

The present study showed changes in LFC from a median of 5% to 2% among the 145 patients with MASLD and an MR follow-up scan. This magnitude of LFC reduction seems comparable to other successful MRS-based studies of pediatric patients with obesity and MASLD: one study ($n = 15$) from a mean of 9% to 6% LFC during a 12-week period[48] and another study ($n = 52$) from 13% to ~10% LFC during a 68-week intervention.[47]

The present study showed a high prevalence of MASLD (38%) among children and adolescents with obesity, comparable to findings in other studies assessing LFC by MR.[6,15,35] The comparison between studies has traditionally been made by using the cut-off at LFC >5%, which was based on a different MR method and liver biopsy-derived cut-offs.[3,21,49] In the present study, we define SLD as LFC >1.5%, as suggested by Chabanova et al.,[21] which is relevant to the applied MRS method to assess LFC. The threshold of LFC >1.5% was established based on measurements in children and adolescents with normal weight to serve as a diagnostic criterion for differentiating SLD from normal LFC,[21] with the goal of improving diagnostic accuracy. Despite methodological differences, the MASLD prevalence observed in the present study appears consistent with findings from other studies.[3,6]

Despite the notable disparity in BMI z-score between the groups with and without MASLD at baseline, the logistic regression model did not reveal a significant association between MASLD and BMI z-score. This suggests that the variables positively correlated with MASLD—SAT, VAT, and age—hold more significance than BMI z-score and sex in the development of MASLD in this cohort. This finding contrasts with our prior observations in 287 children and adolescents with obesity.[35] The difference may stem from the enhanced statistical power in the present study, enabling a nuanced detection of associations, implying that body composition and fat distribution yield more importance in identifying metabolic dysfunction than BMI z-score alone.

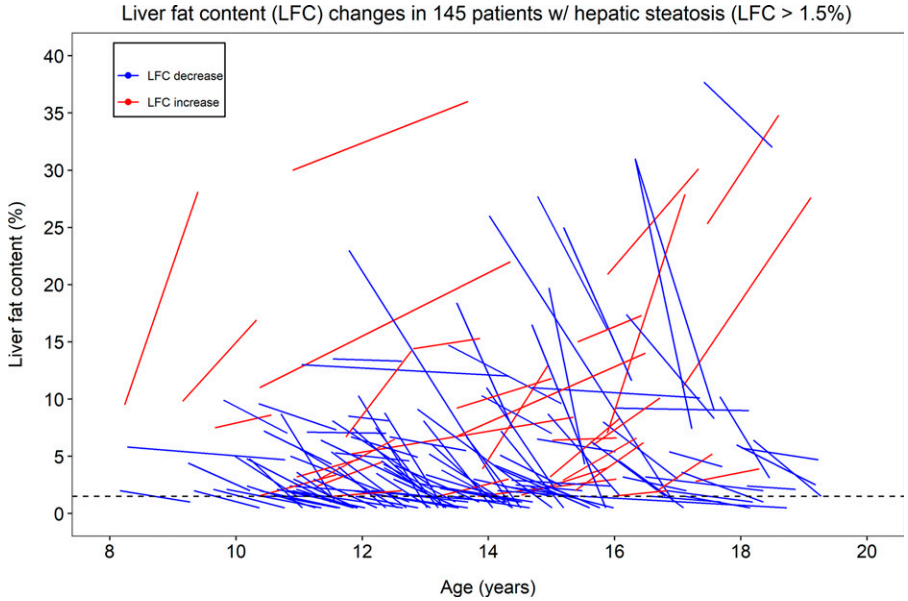

Figure 2. LFC changes in each of 145 patients without MASLD (LFC > 1.5%). Dashed line shows the 1.5% LFC cut-off defining MASLD. LFC, liver fat content; MASLD, metabolic dysfunction-associated steatotic liver disease.

The number of patients who reduced their BMI z-score during treatment was lower in the study group than in the comparison group. This could be due to a younger age and lower pubertal stage in the comparison group, since obesity treatment is often seen more effective in younger children.

The study group and the comparison group were comparable regarding the distribution of sex, ethnicity, degree of obesity, and fraction reducing BMI z-score, but not regarding age. This age difference may be attributed to many younger children not being able to undergo MR scans, since it required them to lay still for 40 minutes. Despite the age and pubertal stage differences between the groups, we found no difference in pubertal stages between those with and without MASLD.

Although Middle Eastern ethnicity applies to <10% of our cohort, the results indicate that Middle Eastern ethnicity is associated with a higher risk of developing MASLD.

A few limitations to the study must be taken into consideration. The study was in a clinical setting with real-life variability and challenges. Not all patients were offered an MR scan due to low availability. Some patients may have discontinued treatment (dropped out) due to a variety of factors such as moving away, becoming older, and experiencing treatment success or failure. This can lead to missing data and potentially bias the result of the study. Some patients may not return for the follow-up visit including those delayed due to lockdowns during the COVID-19 pandemic. This may result in less complete follow-up data compared with the baseline data, reducing

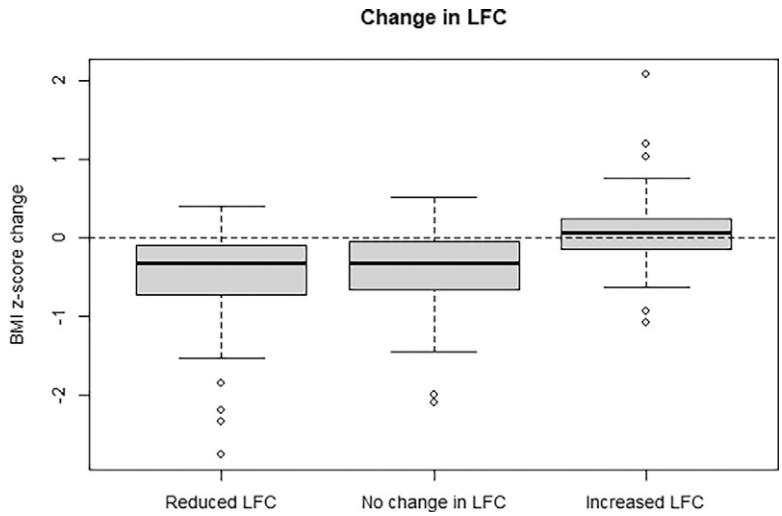

Figure 3. BMI z-score change relative to categorical changes in LFC. BMI, body mass index; LFC, liver fat content.

the sample size, which could be a potential selection bias that limits the generalizability of the findings. A follow-up MR scan was completed by 32% of the study group. Nonetheless, between those with and without a follow-up MR scan, baseline BMI z-score and change in BMI z-score were comparable (both $p > 0.40$), potentially mirroring concomitant improvements in LFC as well.

Despite these limitations, the study remains a tool for understanding the effectiveness of the intervention with the big sample size that this study contains.

This study did not include analyses of liver enzymes or other biomarkers. In other studies from our clinic, we have shown improvements in lipids[50] and blood pressure[51] during obesity treatment. In future studies, we would like to investigate the association between liver enzymes and LFC during obesity management.

Conclusions

The present study revealed a high prevalence (38%) of MASLD in children and adolescents with obesity. Nevertheless, we observed that the evidence-based, nonpharmacological, nonsurgical obesity management was successful in reducing LFC in 76% and obtaining a normal LFC in 53% of patients with MASLD. Additionally, the degree of obesity was reduced in 72% of the children and adolescents with obesity.

Impact Statement

Magnetic resonance spectroscopy-confirmed steatotic liver disease (SLD) is strongly linked to obesity and is highly prevalent already in childhood. Childhood obesity, nonpharmacological management with chronic care, effectively decreases both the degree of obesity and SLD in the majority of children and adolescents with obesity.

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Authors' Contributions

R.B.P.: investigation, writing—original draft, writing—review and editing, and visualization. M.M.F.: investigation, writing—review and editing, and visualization. E.C.: validation, investigation, and writing—review and editing. L.A.H.: writing—review and editing and funding acquisition. T.H.: conceptualization, methodology, writing—review and editing, and funding acquisition. H.S.T.: conceptualization, validation, resources, and writing—review and editing. J.-C.H.: conceptualization, methodology, investigation, resources, writing—review and editing, project administration, and funding acquisition. C.E.F.: conceptualization, methodology, formal analysis, investigation, writing—review and editing, visualization, and funding acquisition. All authors have read and agreed to the published version of the article.

Author Disclosure Statement

The authors declare no conflict of interest.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

References

1. World Health Organization. Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Accessed November 14, 2024].
2. Lister NB, Baur LA, Felix JF, et al. Child and adolescent obesity. Nat Rev Dis Primers 2023;9(1):24; doi: 10.1038/s41572-023-00435-4
3. Cariou B, Byrne CD, Loomba R, et al. Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review. Diabetes Obes Metab Blackwell Publishing Ltd 2021;23(5): 1069–1083; doi: 10.1111/dom.14322
4. Wiegand S, Keller KM, Röbl M, et al. APV-Study Group and the German Competence Network Adipositas. Obese boys at increased risk for nonalcoholic liver disease: Evaluation of 16 390 overweight or obese children and adolescents. Int J Obes (Lond) 2010; 34(10):1468–1474; doi: 10.1038/ijo.2010.106
5. Putri RR, Casswall T, Hagman E. Risk and protective factors of non-alcoholic fatty liver disease in paediatric obesity: A nationwide nested case–control study. Clin Obes 2022;12(2):e12502; doi: 10 .1111/cob.12502
6. Cholongitas E, Pavlopoulou I, Papatheodoridi M, et al. Epidemiology of nonalcoholic fatty liver disease in europe: A systematic review and meta-analysis. Ann Gastroenterol 2021;34(3):404–414; doi: 10.20524/aog.2021.0604

7. Bille DS, Chabanova E, Gamborg M, et al. Liver fat content investigated by magnetic resonance spectroscopy in obese children and youths included in multidisciplinary treatment. Clin Obes 2012; 2(1–2):41–49; doi: 10.1111/j.1758-8111.2012.00038.x
8. Li J, Ha A, Rui F, et al. Meta-analysis: Global prevalence, trend and forecasting of non-alcoholic fatty liver disease in children and adolescents, 2000–2021. Aliment Pharmacol Ther 2022;56(3): 396–406; doi: 10.1111/apt.17096
9. Caprio S, Santoro N, Weiss R. Childhood obesity and the associated rise in cardiometabolic complications. Nat Metab 2020;2(3): 223–232; doi: 10.1038/s42255-020-0183-z
10. Eslam M, Alkhouri N, Vajro P, et al. Defining paediatric metabolic (dysfunction)-associated fatty liver disease - an international expert consensus statement. Lancet Gastroenterol Hepatol 2021;6(10): 864–873; doi: 10.1016/S2468-1253(21)00183-7
11. Rinella ME, Lazarus JV, Ratziu V, et al. NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6): 1542–1556; doi: 10.1016/j.jhep.2023.06.003
12. Simon TG, Roelstraete B, Hartjes K, et al. Non-alcoholic fatty liver disease in children and young adults is associated with increased long-term mortality. J Hepatol 2021;75(5):1034–1041; doi: 10 .1016/j.jhep.2021.06.034
13. Gyllenhammer LE, Alderete TL, Toledo-Corral CM, et al. Saturation of subcutaneous adipose tissue expansion and accumulation of ectopic fat associated with metabolic dysfunction during late and post-pubertal growth. Int J Obes (Lond) 2016;40(4):601–606; doi: 10.1038/ijo.2015.207
14. Cohen CC, Perng W, Sundaram SS, et al. Hepatic Fat in Early Childhood Is Independently Associated with Estimated Insulin Resistance: The Healthy Start Study. J Clin Endocrinol Metab 2021;106(11):3140–3150; doi: 10.1210/clinem/dgab541
15. Wicklow BA, Wittmeier KDM, MacIntosh AC, et al. Metabolic consequences of hepatic steatosis in overweight and obese adolescents. Diabetes Care 2012;35(4):905–910; doi: 10.2337/dc11-1754
16. Wu AJ, Rifas-Shiman SL, Taveras EM, et al. Associations of DXA-measured abdominal adiposity with cardio-metabolic risk and related markers in early adolescence in Project Viva. Pediatr Obes 2021;16(2):e12704; doi: 10.1111/ijpo.12704
17. Silveira LS, Monteiro PA, de Moura Mello Antunes B, et al. Intra-abdominal fat is related to metabolic syndrome and non-alcoholic fat liver disease in obese youth. BMC Pediatr 2013;13(1):115; doi: 10.1186/1471-2431-13-115
18. van der Poorten D, Milner KL, Hui J, et al. Visceral fat: A key mediator of steatohepatitis in metabolic liver disease. Hepatology 2008;48(2):449–457; doi: 10.1002/hep.22350
19. Demir M, Bornstein SR, Mantzoros CS, et al. Liver fat as risk factor of hepatic and cardiometabolic diseases. Obes Rev 2023; 24(10):e13612; doi: 10.1111/obr.13612
20. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328–357; doi: 10.1002/hep.29367
21. Chabanova E, Fonvig CE, Bøjsøe C, et al. 1H MRS assessment of hepatic fat content: Comparison Between normal- and excess-weight children and adolescents. Acad Radiol 2017;24(8):982–987; doi: 10.1016/j.acra.2017.02.010
22. Chabanova E, Bille DS, Thisted E, et al. MR spectroscopy of liver in overweight children and adolescents: Investigation of 1H T 2 relaxation times at 3 T. Eur J Radiol 2012;81(5):811–814; doi: 10 .1016/j.ejrad.2011.02.017
23. Chabanova E, Bille DS, Thisted E, et al. 1H MRS assessment of hepatic steatosis in overweight children and adolescents: Comparison between 3T and open 1T MR-systems. Abdom Imaging 2013;38(2):315–319; doi: 10.1007/s00261-012-9930-2
24. Middleton MS, Natta ML V, Heba ER, et al. NASH Clinical Research Network. Diagnostic accuracy of magnetic resonance imaging hepatic proton density fat fraction in pediatric nonalcoholic fatty liver disease. Hepatology 2018;67(3):858–872; doi: 10 .1002/hep.29596
25. Martino MD, Pacifico L, Bezzi M, et al. Comparison of magnetic resonance spectroscopy, proton density fat fraction and histological analysis in the quantification of liver steatosis in children and adolescents. World J Gastroenterol 2016;22(39):8812–8819; doi: 10 .3748/wjg.v22.i39.8812
26. Netaji A, Jain V, Gupta AK, et al. Utility of MR proton density fat fraction and its correlation with ultrasonography and biochemical markers in nonalcoholic fatty liver disease in overweight adolescents. J Pediatr Endocrinol Metab 2020;33(4):473–479; doi: 10 .1515/jpem-2019-0463
27. Hegarty R, Kyrana E, Fitzpatrick E, et al. Fatty liver disease in children (MAFLD/PeFLD Type 2): Unique classification considerations and challenges. Ther Adv Endocrinol Metab 2023;14: 20420188231160388; doi: 10.1177/20420188231160388
28. Lefere S, Dupont E, Guchtenaere AD, et al. Intensive lifestyle management improves steatosis and fibrosis in pediatric nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2022;20(10): 2317–2326.e4; doi: 10.1016/j.cgh.2021.11.039
29. Fonvig CE, Chabanova E, Ohrt JD, et al. Multidisciplinary care of obese children and adolescents for one year reduces ectopic fat content in liver and skeletal muscle. BMC Pediatr 2015;15(1):196; doi: 10.1186/s12887-015-0513-6
30. THE CHILDREN'S OBESITY CLINIC, HOLBAEK UNIVERSITY HOSPITAL. n.d. Available from: https://easo.org/com/the-childrens-obesity-clinic-holbaek-university-hospital/ [Last accessed 11 14, 2024].
31. Cole TJ, Green PJ. Smoothing reference centile curves: The LMS method and penalized likelihood. Stat Med 1992;11(10): 1305–1319; doi: 10.1002/sim.4780111005
32. Nysom K, Mølgaard C, Hutchings B, et al. Body mass index of 0 to 45-y-old Danes: Reference values and comparison with published European reference values. Int J Obes Relat Metab Disord 2001;25(2):177–184; doi: 10.1038/sj.ijo.0801515
33. Rigby RA, Stasinopoulos DM. Generalized Additive Models for Location, Scale and Shape. J R Stat Soc Ser C Appl Stat 2005; 54(3):507–554; doi: 10.1111/j.1467-9876.2005.00510.x
34. Frithioff-Bøjsøe C, Lund MAV, Kloppenborg JT, et al. Glucose metabolism in children and adolescents: Population-based reference values and comparisons to children and adolescents enrolled in obesity treatment. Pediatr Diabetes 2019;20(5):538–548; doi: 10 .1111/pedi.12859
35. Fonvig CE, Chabanova E, Andersson EA, et al. 1H-MRS Measured Ectopic Fat in Liver and Muscle in Danish Lean and Obese Children and Adolescents. Thearle M. ed. PLoS One 2015;10(8): e0135018; doi: 10.1371/journal.pone.0135018
36. Johansen MJ, Lund MAV, Ängquist L, et al. Possible prediction of obesity-related liver disease in children and adolescents using indices of body composition. Pediatr Obes 2022;17(10):e12947; doi: 10.1111/ijpo.12947
37. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44(235):291–303; doi: 10 .1136/adc.44.235.291
38. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45(239):13–23; doi: 10 .1136/adc.45.239.13

39. Statistik D. Danmarks Statistiks Fagklassifikation (DISCO-08), v1:2010. 2010.

40. Holm JC, Gamborg M, Bille DS, et al. Chronic care treatment of obese children and adolescents. Int J Pediatr Obes 2011;6(3–4): 188–196; doi: 10.3109/17477166.2011.575157

41. Fogh M, Lund MAVV, Mollerup PM, et al. Disturbed eating behaviours do not impact treatment response in a paediatric obesity chronic care treatment programme. J Paediatr Child Health 2020; 56(4):542–549; doi: 10.1111/jpc.14678

42. Dâmaso AR, Piano AD, Campos RMDS, et al. Multidisciplinary approach to the treatment of obese adolescents: Effects on cardiovascular risk factors, inflammatory profile, and Neuroendocrine Regulation of Energy Balance. Int J Endocrinol 2013;2013: 541032; doi: 10.1155/2013/541032

43. R Core Team. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing 2024. Available from: https://www.R-project.org

44. Schwimmer JB, Ugalde-Nicalo P, Welsh JA, et al. Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys. JAMA 2019;321(3):256–265; doi: 10.1001/jama.2018.20579

45. Medrano M, Arenaza L, Ramírez-Vélez R, et al. Prevalence of responders for hepatic fat, adiposity and liver enzyme levels in response to a lifestyle intervention in children with overweight/obesity: EFIGRO randomized controlled trial. Pediatr Diabetes 2020;21(2):215–223; doi: 10.1111/pedi.12949

46. Koh H, Kim S, Kim MJ, et al. Hepatic fat quantification magnetic resonance for monitoring treatment response in pediatric nonalcoholic steatohepatitis. World J Gastroenterol 2015;21(33):9741–9748; doi: 10.3748/wjg.v21.i33.9741

47. Chan DFYY, So HK, Hui SCNN, et al. Dietitian-led lifestyle modification programme for obese Chinese adolescents with non-alcoholic fatty liver disease: A randomized controlled study. Int J Obes (Lond) 2018;42(9):1680–1690; doi: 10.1038/s41366-018-0010-8

48. van der Heijden G-J, Wang ZJ, Chu ZD, et al. A 12-Week Aerobic Exercise Program Reduces Hepatic Fat Accumulation and Insulin Resistance in Obese, Hispanic Adolescents. Obesity (Silver Spring) 2010;18(2):384–390; doi: 10.1038/oby.2009.274

49. Schwimmer JB, Deutsch R, Kahen T, et al. Prevalence of fatty liver in children and adolescents. Pediatrics 2006;118(4):1388–1393; doi: 10.1542/peds.2006-1212

50. Nielsen TRH, Gamborg M, Fonvig CE, et al. Changes in lipidemia during chronic care treatment of childhood obesity. Child Obes 2012;8(6):533–541; doi: 10.1089/chi.2011.0098

51. Hvidt KN, Olsen MH, Ibsen H, et al. Effect of changes in BMI and waist circumference on ambulatory blood pressure in obese children and adolescents. J Hypertens 2014;32(7):1470–1477; doi: 10.1097/HJH.0000000000000188

Address correspondence to:
Cilius Esmann Fonvig, MD, PhD
Department of Pediactrics
The Children's Obesity Clinic
Accredited European Centre for Obesity Management
Copenhagen University Hospital Holbæk
Holbæk
Denmark

E-mail: crfo@regionsjaelland.dk