

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

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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: ¹H-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.

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1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is common among children and adolescents with overweight or obesity. However, the reported prevalence varies, with estimates ranging from 1.7% to 85% depending on the ethnicity and size of the study population and the clinical setting.^{1,2} Among children and adolescents, those with overweight or obesity exhibit the highest prevalence of NAFLD, and its severity has been linked to the degree of obesity.^{3,4} NAFLD is the most prevalent chronic liver disease in children and adolescents and constitutes an independent risk factor for advanced stages of liver disease and cardiovascular disease in adulthood.⁴

NAFLD covers a spectrum of liver-related diseases in the absence of high alcohol consumption, ranging from the accumulation of fat in the liver to end-stage fibrosis.^{5,6} Recently, a new diagnostic criteria framework has been proposed defining fatty liver disease due to metabolic dysfunction, hence a change in name to metabolic dysfunction-associated fatty liver disease (MAFLD).^{7,8} This redefinition encompasses different metabolic phenotypes with either excess adiposity defined by body mass index (BMI) or increased waist circumference, prediabetes or type 2 diabetes, or evidence of metabolic dysregulation. This is in line with studies associating visceral and centrally distributed fat with cardiometabolic health and NAFLD in children and adolescents,^{9,10} emphasizing the importance of body fat distribution.

Whole-body dual-energy X-ray absorptiometry (DXA) scanning can be used to measure the relative fat distribution and body composition in children and adolescents with overweight or obesity.¹¹ It is relatively low-cost and widely accessible.¹¹ The current treatment options for paediatric NAFLD primarily consist of obesity management and monitoring of favourable changes in body composition.² Therefore, early diagnosis is important to provide effective and timely care for obesity management, reducing hepatic fat content and, thus, the risk of progression to a more severe stage of NAFLD.^{12,13}

Currently, the gold standard for diagnosing NAFLD is liver biopsy.^{2,14,15} Because NAFLD presents as a heterogeneous disease in the liver tissue, obtaining an accurate biopsy can be difficult and further challenged by its impractical, invasive nature and the risk of complications.^{16,17} Therefore, other surrogate markers are often used to diagnose NAFLD, especially in the paediatric population. Other diagnostic tools include biochemical measures of liver enzymes, proton magnetic resonance spectroscopy (¹H-MRS) liver evaluation and ultrasound of the liver.¹⁴ Compared with ultrasound, ¹H-MRS is more precise when estimating the degree of liver steatosis, but it requires specialized and expensive equipment and trained staff and is not commonly available.¹⁴ The plasma concentration of alanine transaminase (ALT) is a widely used biomarker, and our group has previously shown its ability to diagnose NAFLD in children and adolescents, although the sensitivity is low when used as a standalone. However, it should be noted that hypertransaminasemia can arise from multiple causes other than overweight and obesity, which should be accounted for in the clinical assessment.^{14,15,18}

This emphasizes the need for a NAFLD diagnosis tool that is inexpensive, fast, easy to use, and widely available while integrating clinical markers of body fat distribution. This study aimed to explore whether

anthropometric and DXA-scan-derived measures of body composition in combination with plasma ALT can be used as a diagnostic tool to identify NAFLD in children and adolescents. By comparing with ¹H-MRS, we aimed to investigate whether the estimated diagnostic ability and performance measures related to body composition and plasma ALT could identify NAFLD and estimate its prevalence in a large cohort of Danish children and adolescents with overweight or obesity.

2 | METHODS

2.1 | Study population

This study included two cohorts of children and adolescents with whole-body DXA-scan data available: (1) a population-based cohort recruited from 11 municipalities across Region Zealand, Denmark, from October 2010 to February 2015 and (2) an obesity clinic cohort recruited at The Children's Obesity Clinic, Department of Paediatrics, Copenhagen University Hospital Holbæk, Denmark, from January 2009 to May 2020.¹⁹

Informed written consent was obtained from all the participants above the age of 18 years, and legal guardians provided informed written consent for participants younger than 18 years. The study was approved by The Ethics Committee of Region Zealand (protocol no.: SJ-104) and the Danish Data Protection Agency. Trained medical staff performed all clinical evaluations, including measurements of height and weight, medical examinations, and fasting venous blood samples.

2.2 | Anthropometry

Wearing light indoor clothing and no shoes, the participants had their body weight (BC-418 Segmental Body Composition Analyser, Tanita, Tokyo, Japan) and height measured (stadiometer) to the nearest 100 g and 1 mm, respectively. From the weight and height, a BMI-standard deviation score (BMI-SDS) was calculated for each participant according to the Danish BMI charts, and overweight or obesity was defined as a BMI above the 90th percentile (corresponding to a BMI-SDS >1.28).²⁰

2.3 | Biochemical analysis

Analysis of plasma ALT has previously been described; in brief, the participants had a blood sample obtained by venipuncture of the antecubital vein between 7 and 9 am, after a fast of a minimum of 8 h.¹⁸ The plasma concentration of ALT was immediately processed and analysed at the biochemical laboratory of Copenhagen University Hospital Holbæk. All analyses were performed on a Cobas®6000 (Roche Diagnostics, Mannheim, Germany) until May 15, 2013, and on a Dimension Vista®1500 (Siemens Healthcare, Erlangen, Germany) from May 16, 2013, using the IFCC traceable enzymatic colorimetric method, with measurements performed at 37°C and an incubation

time of 5.6 minutes at 340 nm with an additional correction measurement at 700 nm.

2.4 | DXA scan

All participants had information available from DXA scans, performed on a GE Lunar iDXA (ME+200 179, GE Healthcare, Madison, Wisconsin, USA), as previously described by our group.²¹ Based on this, additional derived variable-ratios were the trunk-to-extremities-fat-ratio (as total trunk fat mass/total extremities fat mass), android-fat-ratio (as android fat mass/total fat mass), and android-to-gynoid-fat-ratio (as android fat mass/gynoid fat mass).

2.5 | ¹H-MRS to diagnose NAFLD

Liver fat content was measured by ¹H-MRS on a subset of the participants, using a 3T Achieva MR imaging system without sedation (Philips Medical Systems, Best, Netherlands), as previously described.^{18,22,23} In brief, the spectroscopy voxel (11 × 11 × 11 mm) was placed in the right liver lobe, avoiding major vessels and bile ducts. The acquired spectra were fitted to obtain their areas by an experienced senior magnetic resonance (MR) physicist using a standard postprocessing protocol with the MR imaging system. Unlike previous studies using a 5% liver fat threshold, this study defined using a threshold value of ¹H-MRS-determined liver fat content above 1.5%, which has been found to more accurately represent the upper normal limit of liver fat content in our cohort of children and adolescents with normal weight.²²

2.6 | Predictive variables

From the study data, we selected 14 variables previously associated with NAFLD in children and adolescents.^{9,24–33} The clinical and biochemical variables were sex, age, BMI-SDS, hip circumference, waist circumference and ALT. The DXA-scan variables and derived ratios were total-fat-percent, total-fat-percent-SDS, trunk-regional-fat-percent, android-regional-fat-percent, gynoid-regional-fat percent, android-to-gynoid-fat ratio, android-fat-ratio and trunk-to-extremities-fat ratio.

2.7 | Statistical analysis

Statistical analysis was performed using Stata 15.1 (StataCorp LLC, College Station; www.stata.com) and R statistical software v.3.6.3 (R Core Team [2020], Vienna, Austria; www.r-project.org). The R package ‘stepAIC’ was used to perform the stepwise variable selection, and the R package ‘pROC’ was used to calculate receiver operating characteristic (ROC) analyses and area under the curve (AUC).

The children and adolescents identified to have a complete set of observations, with ¹H-MRS and DXA scan performed within a maximum of 30 days, were randomized and split into two independent sets: a training set and a test set. This was initially done to construct logistic regression models on the training set, which afterwards was used for validation on the test set. To give sets homogeneous in outcome, division into the training and test sets was stratified by the diagnosis of NAFLD.

Before fitting the models, all variables were checked for distribution, outliers and their joint correlation using a correlation matrix. Based on existing literature, we selected the 14 most influential variables available in this cohort assumed to be associated with NAFLD. This selection process was performed a priori before any analyses. Next, logistic regression models were run with respect to the binary NAFLD indicator of liver fat content as the outcome. To reduce the number of variables and thereby simplify the model, a stepwise selection was performed (*forward*, *backwards* and *both* directions). The models found by the stepwise selection were analysed for non-linearity by adding quadratic terms and for sex interaction. The best-performing variants of each model were selected based on sensitivity, specificity, and the Akaike information criterion (AIC).

The final selected best-performing models were carried over to the test set, where their performance in detecting NAFLD was analysed and validated. The AUC was calculated for all models to evaluate prediction performance. Finally, the models were applied to estimate NAFLD prevalence in the prediction cohort comprising the children and adolescents who had not yet been included in the analyses, where a DXA scan, but no ¹H-MRS, was available. For each model, we used the sensitivity and specificity from the performance on the test set to transform the model-predicted prevalence to proper prevalence estimates for NAFLD based on the prediction cohort. In this, ALT was not included as a variable. In the subsets of the training and test sets who also had plasma ALT concentrations measured within 30 days, a mirrored analysis was performed using the same steps. Corresponding candidate models including ALT were additionally derived, tested and applied to prevalence estimation.

To evaluate the gain from adding DXA variables to simpler models when predicting NAFLD, mirroring the steps described, we constructed three additional models: first, using only basic (sex, age) and anthropometric variables (BMI-SDS, waist and hip circumferences); second, combining basic variables with ALT; third, using basic variables, anthropometrics, and ALT.

Based on the estimated outcome probabilities, an objective logistic regression prediction model was programmed to use an estimated probability cut-off of 0.5. Predictions above 0.5 then resulted in predicted NAFLD, and vice versa. Alternative lower cut-offs could be chosen to tune the performance towards higher sensitivity compensated by lower specificity and vice versa (for higher thresholds). To further evaluate the predictions, we selected the two most promising models: one with and one without the inclusion of ALT plasma concentrations. For these models, we performed an ROC analysis; as a guide, we then used the Youden index to determine the suggestive cut-off for the outcome of the logistic regression.

3 | RESULTS

3.1 | Study population

A total of 335 participants from the population-based cohort, and 2913 participants from the obesity clinic cohort, met the inclusion criterion of at least one whole-body DXA scan. In total, 767 participants (412 girls) from both cohorts had both a DXA scan and a ¹H-MRS within 30 days.

We then randomized and split these 767 children and adolescents into a training set ($n = 499$, 65%) and a test set ($n = 268$, 35%) based on stratification of liver fat defined by a threshold value of 1.5%. The training and test sets had a median age of 13.1 and 12.5 years, an NAFLD prevalence of 25.9% and 26.1%, and a prevalence of overweight (including obesity) of 87.4% and 88.4%, respectively. The prediction cohort of children and adolescents consisted of $n = 2120$ (1152 girls) with a median age of 10.8 years and a prevalence of overweight or obesity of 96.0%.

TABLE 1 Baseline characteristics of children and adolescents in the test set, training set and the prediction cohort

Children with available DXA-scan	Training set $n = 499$	Test set $n = 268$	Prediction cohort $n = 2120$	<i>p</i> -value
Girls [<i>n</i> (%)]	276 (55.3%)	136 (50.7%)	1152 (54.3%)	0.46
Age, years	13.09 (2.64)	12.74 (2.67)	10.84 (3.43)	<0.001
BMI-SDS	2.51 (1.16)	2.50 (1.14)	2.84 (0.99)	<0.001
Overweight or obesity (BMI-SDS > 1.28) [<i>n</i> (%)]	436 (87.4%)	237 (88.4%)	2035 (96.0%)	<0.001
Hip circumference, cm	101.2 (15.8)	99.7 (16.3)	94.8 (16.3)	<0.001
Waist circumference, cm	89.95 (15.20)	88.74 (16.19)	90.63 (17.02)	0.19
Total fat percent	41.26 (8.38)	41.40 (8.49)	42.84 (6.59)	<0.001
Fat percent-SDS	1.29 (1.01)	1.33 (0.99)	1.57 (0.62)	<0.001
Android-regional fat percent	44.35 (12.68)	44.55 (12.65)	46.59 (10.00)	<0.001
Gynoid-regional fat percent	42.59 (7.96)	42.71 (8.20)	45.47 (6.53)	<0.001
Trunk-regional fat percent	41.34 (10.43)	41.57 (10.46)	42.70 (8.24)	0.003
Android-to-gynoid fat ratio	0.46 (0.13)	0.47 (0.13)	0.48 (0.10)	0.003
Android-fat ratio	0.08 (0.02)	0.08 (0.02)	0.08 (0.02)	<0.001
Trunk-to-extremities fat ratio	0.97 (0.23)	0.99 (0.25)	1.00 (0.24)	0.02
ALT, U/L [median (IQR)]	26 (20, 33)	25 (20, 34)	23 (18, 31)	<0.001*
Liver fat percent [median (IQR)]	1.0 (0.5, 1.7)	0.8 (0.5, 2.0)	NA	0.59*
NAFLD ≥ 1.5% liver fat indicator [<i>n</i> (%)]	129 (25.9%)	70 (26.1%)	NA	NA
Subset of children with ALT available within 30 days of DXA-scan	$n = 386$	$n = 213$	$n = 1246$	
Girls [<i>n</i> (%)]	202 (52.3%)	105 (49.3%)	669 (53.7%)	0.48
Age, years	12.98 (2.51)	12.56 (2.57)	10.92 (3.36)	<0.001
BMI-SDS	2.77 (0.90)	2.76 (0.85)	2.91 (0.82)	0.003
Overweight or obesity (BMI-SDS > 1.28) [<i>n</i> (%)]	369 (95.6%)	206 (96.7%)	1218 (97.8%)	0.07
Hip circumference, cm	103.4 (15.2)	101.8 (15.0)	95.7 (15.9)	<0.001
Waist circumference, cm	91.9 (14.4)	90.5 (15.6)	91.1 (16.4)	0.54
Total fat percent	42.97 (6.57)	43.08 (6.77)	43.42 (6.10)	0.42
Fat percent-SDS	1.52 (0.69)	1.54 (0.71)	1.63 (0.56)	0.006
Android-regional fat percent	47.13 (9.80)	47.21 (9.74)	47.34 (9.10)	0.92
Gynoid-regional fat percent	44.10 (6.37)	44.22 (6.72)	45.77 (6.07)	<0.001
Trunk-regional fat percent	43.59 (8.11)	43.73 (8.15)	43.52 (7.59)	0.93
Android-to-gynoid fat ratio	0.49 (0.11)	0.49 (0.11)	0.49 (0.10)	0.78
Android-fat ratio	0.08 (0.01)	0.08 (0.01)	0.08 (0.01)	0.998
Trunk-to-extremities fat ratio	1.00 (0.21)	1.01 (0.24)	1.01 (0.24)	0.74
ALT, U/L [median (IQR)]	26 (20, 33)	25 (20, 34)	24 (19, 31)	0.002*
Liver fat percent [median (IQR)]	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)	NA	0.54*
NAFLD ≥ 1.5% liver fat indicator [<i>n</i> (%)]	112 (29.0%)	60 (28.2%)	NA	NA

Note: Values are in the form of mean (standard deviation), unless where otherwise is noted. *p*-values are calculated using chi-square tests for categorical variables, and either by one-way ANOVA tests (default) or Kruskal–Wallis tests (indicated by *) for continuous variables.

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; IQR, interquartile range; SDS, standard deviation score.

TABLE 2 Characteristics of models constructed to predict NAFLD

Children and adolescents with available DXA-scan	Training-set						Test-set						Prediction cohort		BMI-SDS			Android-to-gynoid-fat-ratio			Android-regional-fat-percent			Trunk-regional-fat-percent			ALT			
	n = 499						n = 268						n = 2120																	
Model	Sensitivity	Specificity	PPV	NPV	AIC	Predicted NAFLD n (%)	Sensitivity	Specificity	PPV	NPV	AUC	Predicted NAFLD n (%)	Predicted NAFLD n (%)	Estimated prevalence of NAFLD	Basic var.	Quadratic term	Sex-interaction	Basic var.	Quadratic term	Sex-interaction	Basic var.	Quadratic term	Sex-interaction	Basic var.	Quadratic term	Sex-interaction	Basic var.	Quadratic term	Sex-interaction	
A.1	47.3%	91.1%	64.9%	83.2%	422.99	94 (18.8%)	44.3%	90.9%	63.3%	82.2%	81.0%	49 (18.3%)	401 (18.9%)	27.9%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
A.2	49.6%	92.2%	68.8%	84.0%	423.54	93 (18.6%)	40.0%	91.9%	63.6%	81.2%	81.2%	44 (16.4%)	406 (19.2%)	34.6%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
A.3	46.5%	92.2%	67.4%	83.2%	420.93	89 (17.8%)	41.4%	91.9%	64.4%	81.6%	81.9%	45 (16.8%)	386 (18.2%)	30.4%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
A.4	45.7%	91.6%	65.6%	82.9%	422.12	90 (18.0%)	40.0%	91.4%	62.2%	81.2%	82.0%	45 (16.8%)	387 (18.3%)	30.7%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
B.1	40.3%	91.9%	63.4%	81.5%	426.75	82 (16.4%)	38.6%	91.4%	61.4%	80.8%	80.0%	44 (16.4%)	407 (19.2%)	35.3%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
B.2	39.5%	91.9%	61.4%	81.3%	426.71	81 (16.2%)	38.6%	91.4%	61.4%	80.8%	80.6%	44 (16.4%)	398 (18.8%)	33.9%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
Subset of children and adolescents with ALT available within 30 days of DXA-scan	n = 386						n = 213						n = 1246																	
	NAFLD prevalence, n = 112 (29.0%)						NAFLD prevalence, n = 60 (28.2%)																							
C.1	54.5%	92.1%	71.8%	83.1%	335.07	85 (22.0%)	50.0%	90.2%	66.7%	82.1%	81.0%	45 (21.1%)	270 (21.7%)	29.5%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
C.2	58.0%	91.6%	73.9%	84.2%	329.13	88 (22.8%)	50.0%	89.5%	65.2%	82.0%	82.7%	46 (21.6%)	270 (21.7%)	28.3%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
C.3	56.2%	91.2%	72.4%	83.6%	331.34	87 (22.5%)	50.0%	87.6%	61.2%	81.7%	81.6%	49 (23.0%)	268 (21.5%)	24.2%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
C.4	60.7%	90.9%	73.1%	85.0%	325.85	93 (24.1%)	51.7%	88.9%	64.6%	83.4%	83.4%	48 (22.5%)	263 (21.1%)	24.6%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
D.1	52.7%	91.6%	72.0%	82.6%	331.13	82 (21.2%)	48.3%	90.2%	65.9%	81.7%	82.2%	44 (20.7%)	275 (22.1%)	31.9%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T
D.2	56.2%	90.1%	70.0%	83.4%	329.40	90 (23.3%)	48.3%	89.5%	64.4%	81.5%	82.3%	45 (21.1%)	265 (21.3%)	28.5%	T	F	F	T	F	F	T	F	F	T	F	F	T	F	F	T

Note: The sensitivity, specificity, PPV, NPV, AIC, AUC and predictions, including performance, is shown on the training set, test set and the prediction cohort of children and adolescents for each model. Furthermore, information is included on the variables for the different models, and where quadratic terms and sex-interaction are added to each model, where 'T' = true/included and 'F' = false/not included.

Abbreviations: AIC, Akaike information criterion; ALT, alanine aminotransferase; AUC, area under the curve; BMI-SDS, body mass index - standard deviation score; DXA-scan, whole-body dual-energy X-ray absorptiometry; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value.

Subsets based on the additional criterion of available biochemical analysis of ALT within 30 days of the DXA scan resulted in $n = 386$ (202 girls) from the training set and $n = 213$ (105 girls) from the test set with a median age of 13.0 and 12.6 years, NAFLD prevalence of 29.0% and 28.2%, and overweight prevalence of 95.6% and 96.7%, respectively. Similarly, $n = 1246$ (669 girls) in the prediction cohort were eligible, with a median age of 10.9 years and overweight prevalence of 97.8%.

Detailed characteristics of the children and adolescents constituting the DXA-based training set, test set and prediction cohort and the corresponding ALT subsets, are shown in Table 1.

3.2 | Model building

When performing the stepwise selection of the variables for the training set, we ended up with two different models. One model was found by backward-selection (and by the adaptive variant working in both directions) starting with a full set of variables, A, containing BMI-SDS, android-to-gynoid fat ratio, android-regional fat percent and trunk-regional fat percent. The other model was found by forward-selection (also with the corresponding variant working in both directions) starting with an empty model, B, which contained the variables BMI-SDS and android-to-gynoid fat ratio.

Mirroring this step, but now only using individuals from the training set where ALT was available within 30 days of the DXA scan, and including ALT as an explanatory variable, we found two different models. These models, C and D, turned out exactly as for models

A and B when adding ALT to the former four and two variables, respectively.

Subsequently, all four models were first checked for non-linearity by adding quadratic terms to the variables (one at a time, and jointly when several candidates appeared); candidate models, with or without non-linearity, were selected and put forward. Next, all active models were similarly checked for sex interaction (for non-linear variables, both covariates were tested jointly). Selecting candidates in this way resulted in four variants each of models A and C and two variants each of models B and D. The specific variable combinations (including used quadratic terms and/or sex interactions) for each model can be seen in Table 2. For additional details, Table S1 shows the underlying (estimated) coefficients for each variable of all the selected models.

3.3 | Predictive model performance

To test the performance of the different variants of the models to detect NAFLD, we used the models derived from the previously described steps on the test set. Compared with the already established $^1\text{H-MRS}$ -derived measure of liver fat, in the variants of model A, sensitivity ranged from 40.0% to 44.3%, specificity was 90.9%–91.9% and the AUC was 81.0%–82.0%. Model B had a sensitivity of 38.6% and specificity of 91.4% in both variants of the model and an AUC of 80.0% and 80.6%. For model C, the sensitivity ranged from 50.0% to 51.7%, specificity was 87.6%–90.2% and the AUC was 81.0%–83.4%. In the variants of model D, sensitivity was 48.3% in both variants, specificity was 89.5%–90.2% and the AUC was 82.2%–82.3%.

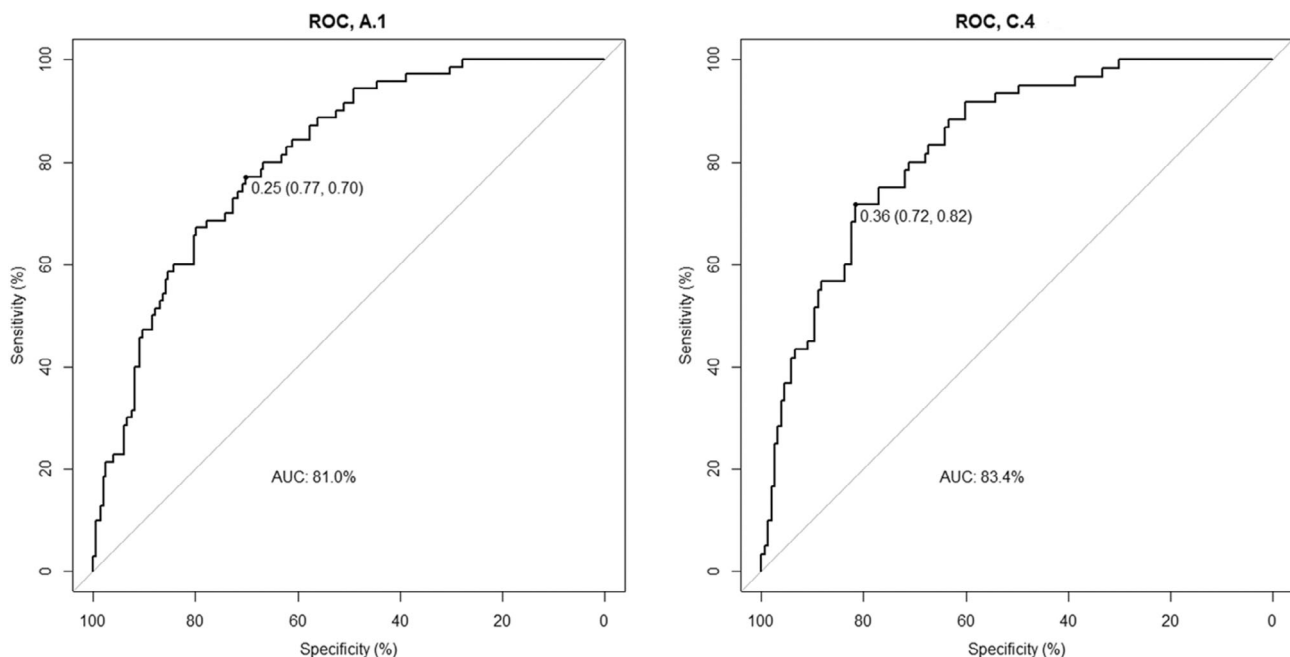


FIGURE 1 Receiver operating characteristic (ROC) curves for determining optimal cut-off, based on the Youden index optimality criterion, for predicting NAFLD in models A.1 and C.4. The area under the curve (AUC) was 81.0% for model A.1 with the probability cut-off of 0.25, which predicted NAFLD with a sensitivity of 77% and a specificity of 70%. The AUC was 83.4% for model C.4, with cut-off of 0.36, which predicted NAFLD with a sensitivity of 72% and a specificity of 82%

3.4 | Estimating NAFLD prevalence

NAFLD prevalence was estimated using the models on the prediction cohort of children and adolescents. This used the model-based predictions (the rate of indicated events) in combination with the estimated sensitivity and specificity from the corresponding test set analyses. In model A, the estimated prevalence of NAFLD ranged from 27.9% to 34.6%. Models B, C and D similarly predicted prevalence of 33.9%–35.3%, 24.2%–29.5% and 28.5%–31.9%, respectively.

3.5 | Fine-tuning predictive model performance

ROC analyses were used on two of the best-performing models subjectively selected based on a combination of sensitivity, specificity, and AUC, one from A, A.1, and one from C, C.4, to determine alternative cut-offs (Figure 1). In model A.1, the AUC was 81.0% with a suggested probability cut-off of 0.25, yielding a change in sensitivity from 44.3% to 77.1% and in specificity from 90.9% to 70.2%. Predicting the NAFLD prevalence in the prediction cohort, the estimated prevalence changed from 27.9% to 25.2%. Model C.4 displayed an AUC of 83.4% and a suggestive cut-off of 0.36, returning a sensitivity and specificity change from 51.7% to 71.7% and from 88.9% to 81.7%, respectively. The estimated NAFLD prevalence in the prediction cohort changed from 24.6% to 16.2%. The full-performance details of the fine-tuned models are shown in Table 3.

3.6 | Evaluating non-DXA variables

Constructing models using all iterations of stepwise selection on only basic and anthropometric variables yielded two variants of one model, E, containing the variables BMI-SDS, hip circumference, and waist circumference. Using the training set including ALT, two variants of one

model, F, was constructed using basic and biochemical variables: containing sex, age and ALT. Lastly, using basic, anthropometric and biochemical variables yielded a single variant of one model, G, containing BMI-SDS, waist circumference and ALT.

Model E had a sensitivity ranging from 35.7% to 37.1% and specificity from 89.4% to 89.9%, whereas the variants of Model F had a sensitivity that ranged from 21.7% to 36.7% and a specificity of 92.2%–95.4%. The single G model had a sensitivity of 45.0% and a specificity of 89.5%. Table S2 shows detailed characteristics of models E, F and G.

4 | DISCUSSION

We constructed 12 different models for predicting NAFLD as diagnosed by ¹H-MRS in children and adolescents using DXA- and non-DXA-derived measurements. Our estimates of the prevalence in the prediction cohort were 27.9%–35.3% in models A.1–4 and B.1–2, and 24.2%–31.9% in models C.1–4 and D.1–2, when taking test set sensitivity and specificity into account. These prevalence estimates displayed good similarity with both the observed NAFLD prevalence in this study, ranging from 25.9% to 29.9%, and earlier studies published by our group.^{22,23,34,35} A systematic review and meta-analysis by Anderson et al.³⁶ found a 34.2% prevalence of NAFLD in children and adolescents at obesity clinics, which agrees with the estimates found in our study. Another recent systematic review and meta-analysis by Liu et al.³⁷ found an estimated 44.9% global prevalence of paediatric MAFLD among children and adolescents from obesity clinics, regardless of the diagnostic method chosen. This might be a consequence of the MAFLD diagnosis comprising aspects of metabolic dysfunction related to both BMI and waist circumference, as well as a shift from a diagnosis of exclusion to an independent diagnosis with inclusion criteria. Furthermore, ethnicity and genetic susceptibility vary across populations, impeding the comparison of the global prevalence to the estimates of the present study, especially when differences in methodology are considered.

TABLE 3 Characteristics of the ROC-optimized models' ability to predict NAFLD

Children and adolescents with available DXA-scan	ROC-determined cut-off	Test set n = 268 NAFLD prevalence, n = 70 (26.1%)					Prediction cohort n = 2120		
		Sensitivity	Specificity	PPV	NPV	AUC	Predicted NAFLD n (%)	Predicted NAFLD n (%)	Estimated prevalence of NAFLD
A.1	0.245	77.1%	70.2%	47.8%	89.7%	81.0%	113 (42.2%)	885 (41.7%)	25.2%
Subset of children and adolescents with ALT available within 30 days of DXA scan		n = 213 NAFLD prevalence, n = 60 (28.2%)					n = 1246		
C.4	0.358	71.7%	81.7%	60.6%	88.0%	83.4%	71 (33.3%)	336 (27.0%)	16.2%

Note: The new ROC-determined cut-off, suggested by the Youden index, sensitivity, specificity, PPV, NPV, AIC, AUC and predictions, including performance, is shown for the training set, test set and the prediction cohort of children and adolescents for each model.

Abbreviations: AIC, Akaike information criterion; ALT, alanine aminotransferase; AUC, area under the curve; BMI-SDS, body mass index–standard deviation score; DXA-scan, whole-body dual-energy X-ray absorptiometry; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics.

In the initial models, excluding ALT, we investigated the predictive power of a model consisting only of non-invasive and easily accessible parameters that healthcare professionals can obtain in settings where the DXA scan is the primary modality. We later added ALT to the models to examine to what extent it would benefit them.^{14,18,38} Predominantly, the models including ALT improved sensitivity, and when analysing the coefficients for the variables, we observed that an increase in ALT was linked to an increased risk of NAFLD. This applied to all the models including ALT, emphasizing the importance of including ALT when available. Importantly, despite its sensitivity, using ALT alone to screen for NAFLD is not recommended for diagnosis, as multiple causes besides overweight and obesity can contribute to elevated ALT levels, such as viral infections, toxic damage, or autoimmune diseases. Hence, it should be used in combination with other markers linked to NAFLD.^{2,18,39–41} Additionally, analysing the results from the basic models (E, F and G), we found that excluding DXA-scan variables made them perform less well. Model F, using ALT, age and sex, performed the poorest. This further shows that these variables should not be used alone in this sense and that anthropometrics in combination with DXA-derived body composition indices can be valuable diagnostic tools to identify NAFLD. Because the models developed used ALT as an explanatory variable in logistic regression, we did not use a single upper limit normal for diagnosing NAFLD, but rather ALT as a continuous variable.

Preferably, a diagnostic test should have high sensitivity and specificity. However, in many settings, this is not achievable. The current first line of the treatment for NAFLD in children and adolescents is obesity management. Clinically, a false-positive NAFLD test for a child with overweight or obesity has no implications in terms of the treatment offered compared with those without NAFLD.¹⁹ However, the child would unnecessarily be considered to be in a more severe condition, leading to overdiagnosis, which has individual consequences and, thus, cannot be overlooked. Conversely, a false-negative result may cause NAFLD to be left untreated. This increases the risk of developing severe hepatic impairment with fibrosis in childhood or adulthood, which may advance to hepatic cirrhosis, an increasing cause of adult liver transplantation, or developing other overweight-related complications because both overweight and NAFLD are part of systemic inflammatory processes potentially affecting all organs in the body.^{5,6,17,42}

Analysing the coefficients in Table S1, we found that an increase in BMI-SDS was positively associated with NAFLD in all the models. Similarly, an increase in android-to-gynoid fat ratio showed a positive association in all the models (although this effect was seemingly attenuated for girls). This likely reflects that increased android distribution of fat, and thereby increased visceral fat, is linked to the risk of developing NAFLD in children and adolescents.³⁰ Furthermore, the two variables of android-regional-fat percent and trunk-regional fat percent were included in models A and C. Because both variables are closely correlated, it is difficult to conclude in which direction the prediction of NAFLD is driven in our models, since they appear in pairs in all the variants of models A and C and indicate opposite effect-directions (negative and positive associations with the outcome,

respectively). They both contribute to the overall predictive power of the models, and other studies have shown that they are useful alone in predicting NAFLD.^{31,32}

We used ¹H-MRS liver fat content to diagnose NAFLD because this method is increasingly accepted as the gold standard for the non-invasive quantification of liver fat content.^{43,44} Ideally, model performance would have been compared with a validation set with liver biopsy data because liver biopsy remains the gold standard for detecting histological changes in the liver, including NAFLD, especially when estimating inflammation and fibrosis is needed. However, such data were not available, and it was found unfeasible and unethical to perform liver biopsies in a large paediatric population due to the risk of complications.^{16,17} Furthermore, Martino et al. compared the ability of liver biopsy against liver ¹H-MRS to diagnose NAFLD in children and adolescents and found ¹H-MRS to be accurate.⁴⁵ Both a tissue biopsy and liver ¹H-MRS may be useful to quantify the lipid content in the liver, although both modalities come with a risk of sampling error due to the histological heterogeneity that often characterizes ectopic lipid accumulation. Compared with liver ¹H-MRS, a biopsy may not detect small differences in fat content and is prone to inter- and intraobserver variability.^{46–48} Additionally, we did not use ultrasound as a diagnostic tool for NAFLD. This is a limitation because ultrasound may be a more widespread modality at obesity clinics compared with the DXA scanner. Nevertheless, ultrasound does not reflect the fat distribution, warranting the use of DXA-scan-derived clinical parameters. Taken together, this justifies the use of ¹H-MRS to quantify liver fat content and diagnose NAFLD in this study population.

The 14 variables used to construct the predictive models were selected based on reviewing existing literature that linked variables with paediatric NAFLD. The basic variables and anthropometrics were chosen because they are all easily accessible to any clinician and describe basic body composition. The DXA-derived values were subjectively chosen to quantify both the mass and total fat percentage because these add to the risk of NAFLD. Of other variables quantifying the distribution of fat, we chose android-to-gynoid fat ratio and trunk-regional fat percent because more centrally placed fat has been shown to increase the risk of NAFLD.^{9,24–33} We chose to include ALT because several studies have shown its association with NAFLD.^{14,18,38}

This study did not include variables such as blood pressure, homeostatic model assessment for insulin resistance (HOMA-IR), or lipids in the models for predicting NAFLD in children and adolescents. In line with the new MAFLD definition, these variables are interesting in enlarged models, and not including them is a limitation. However, we chose not to include them because this study focused on paving the way for a simple assessment to predict NAFLD based on body composition indices with or without the addition of ALT. Future studies might develop more sophisticated MAFLD models, including variables covering a broader spectrum of the metabolic syndrome.

Other studies using body composition indices to predict NAFLD in children and adolescents have found similar results. Alferinik et al.³¹ found that the best predictor of NAFLD was android-to-gynoid-fat-ratio. Hsing et al.³² and Lee et al.²⁹ found that android-regional fat percent measured by DXA scan in children and adolescents was the best predictor. However,

Lee et al.²⁹ and Ramirez et al.³⁰ found visceral adipose tissue (VAT), measured by applying the 'GE COREscan' protocol to the DXA scan, to be most important. Hence, also including the variable of VAT in our analysis would have been ideal to improve predictions for the models. However, this software has not yet been validated for Danish children and adolescents and was not available at the time of writing.

A recent study by Atabaki-Pasdar et al.⁴⁹ has shown the feasibility of using surrogate markers in a model to predict NAFLD in adults. It used a different statistical approach, involving machine learning and a wider variety of data, including genetic data, proteomics and a liver fat cut-off of 5% instead of the 1.5% used in our study. The models, when validated, had an AUC of 82% or 84% depending on whether they only included the clinically accessible variables. Despite the differences in study population and methodology, the performance of the predictive models in the present study is comparable and shows the feasibility of using surrogate markers to identify and diagnose NAFLD. When assessing the models' ability to predict NAFLD in children and adolescents, notably, the models in our study are constructed and validated on cohorts that primarily consist of children and adolescents with overweight or obesity. Therefore, applying the models' prediction to individuals exhibiting overweight or obesity is important.

Clinically, our models can be used in places where advanced imaging tools are not available, preferably at the primary visit at an obesity clinic, where a NAFLD diagnosis using the presented models may lead to further diagnostic tests and more focus on obesity-related complications and early obesity management initiation. In addition, this early identification of patients, without potentially dangerous liver biopsy, is increasingly important due to the potential for treating severe consequences of NAFLD such as NASH or liver cirrhosis when future medication becomes approved and available for children and adolescents. This may avoid severe consequences such as liver transplantation, and additional non-invasive diagnostic tests may aid in selecting patients who might be eligible to participate in the clinical trials needed for approving such medication.⁵⁰

The predictive models presented provide a low-cost, readily available and uncomplicated way of identifying individuals at risk of NAFLD. In some cases, where other diagnostic tools may not be available, our diagnostic models have an obvious clinical benefit.

5 | CONCLUSION

NAFLD prediction models based on BMI-SDS and DXA-scan-derived body composition indices (android-to-gynoid fat ratio, android-regional fat percent and trunk-regional fat percent) from 767 Danish children and adolescents exhibited the ability to estimate NAFLD in children and adolescents with overweight or obesity.

The sensitivity and specificity of the models ranged from 38.6% to 44.3% and 90.9% to 91.9%, respectively. The estimates improved in the models including the biochemical marker ALT, with sensitivity and specificity ranging from 48.3% to 51.7% and 87.6% to 90.2%, respectively. Still, when ALT is not available for use, models solely using BMI-SDS and DXA-scan-derived body composition indices to

predict NAFLD in a paediatric cohort appear feasible. The estimated prevalence of NAFLD was 24.2%–35.3% when using the models on a cohort of 2120 children and adolescents with overweight and obesity.

The presented models use diagnostic equipment that is available at most obesity clinics, providing an easy and accessible method of identifying individuals at risk of NAFLD. This can aid clinicians to identify individuals who would benefit from further imaging and diagnostic procedures, which may lead to more intensive and individual obesity management and treatment in these children and adolescents.

AUTHOR CONTRIBUTIONS

Magnus Jung Johansen, Morten Asp Vonsild Lund, Cilius Esmann Fonvig and Jens-Christian Holm designed the study. Magnus Jung Johansen reviewed the literature. Morten Asp Vonsild Lund, Cilius Esmann Fonvig, Elizaveta Chabanova, Henrik S. Thomsen and Jens-Christian Holm participated in collecting the data. Magnus Jung Johansen, Morten Asp Vonsild Lund and Lars Ängquist conducted the statistical analyses. Magnus Jung Johansen, Morten Asp Vonsild Lund, Lars Ängquist, Cilius Esmann Fonvig, Louise Aas Holm and Jens-Christian Holm interpreted the results and drafted the manuscript. All authors discussed the results, revised and commented on the manuscript and approved the final submitted manuscript.

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CONFLICT OF INTEREST

All authors have nothing to disclose.

TRIAL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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