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RESEARCH ARTICLE

Hepatology

Alanine aminotransferase cutoffs for the pediatric fatty liver disease: Major impact of the reference population

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Abstract

Objectives and Study: The often-recommended alanine aminotransferase (ALT) cutoffs (girls 21 U/l, boys 25 U/l) are based on a NHANES cohort. A novel concept of metabolic dysfunction associated steatotic liver disease (MASLD) emphasizes the role of ALT. We tested the prevalence of increased ALT and MASLD in children with overweight or obesity applying population-based and NHANES-based cut-offs.

Methods: Six- to seventeen-year-old children underwent data collection in a prospective Physical Activity and Nutrition in Children (PANIC) study. ALT 95th percentiles were calculated from 1167 separate measurements considering various confounders. Test cohort comprised 1044 children with overweight/obesity.

Results: ALT values increased at puberty onset ($p = 0.031$) and correlated negatively with age in girls ($r = -0.222$, $p < 0.001$). Particularly overall and central obesity increased ALT, whereas underweight or metabolic abnormalities had smaller effect. After applying the tested exclusions, the age-related ALT 95th percentiles were 24–29 U/l for girls and 29–32 U/l for boys. In 6–8-year-old children with overweight/obesity, the prevalence of increased ALT and MASLD were 21.6% and 2.4% with age-specific PANIC cutoffs. In older children, when NHANES-based cutoffs were used, there was a trend for higher prevalence of increased ALT and MASLD in all age groups for both sexes, reaching significance for increased ALT in 12–16-year-old boys (NHANES 63.5%, 95% confidence interval [CI]: 56.4%–70.0% vs. PANIC 47.1%, 95% CI [40.1%–54.2%]) and 9–11-year-old girls (60.0% [49.4%–69.8%] vs. 31.8% [22.8%–42.3%]), respectively. Increased ALT/MASLD were more common in boys than in girls, and in boys these increased with age, whereas in girls these peaked at age 9–12 years.

Conclusion: A reference population impacts on the prevalence of increased ALT and MASLD. Considering this help optimizing screening while avoiding unnecessary investigations and surveillance. The prospective part of this study is registered in clinicaltrials.gov; identifier NCT01803776.

Linnea Aitokari and Siiri Lahti contributed equally to this study.

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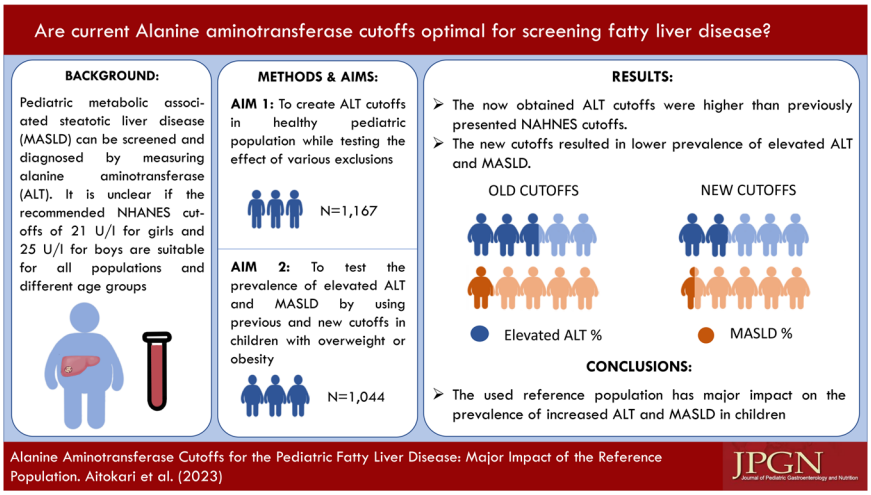

KEYWORDS
ALT, children, fatty liver, MASLD, NAFLD

1 | BACKGROUND

Obesity-related nonalcoholic fatty liver disease (NAFLD) is the most common chronic hepatic condition in children, and its noninvasive screening by serum alanine aminotransferase (ALT) is advocated.[1–4] However, establishing appropriate age- and sex-specific ALT cutoffs has been hampered by the increasing prevalence of overweight and obesity in reference populations and inconsistent exclusion of liver-affecting conditions.[4–8] Moreover, while ALT is a widely available noninvasive surrogate marker for NALFD, its diagnostic performance is only modest.[5,9,10] As a result, using too low screening cutoffs to improve the sensitivity may cause unnecessary investigations/surveillance and healthcare costs, and also anxiety to patients and their families.

ALT screening cut-offs of >25 IU/L for overweight boys and >21 IU/L for girls are currently recommended based on analysis of the National Health and Nutrition Examination Survey (NHANES) data.[4,5,11] This—although as such large and well-defined—cohort from the United States may not be the optimal reference in all circumstances as there may, for example, be significant ethnic and geographic variation in the normal ALT levels and prevalence of NAFLD.[1,2] Other limitations in NHANES as well as in other earlier studies assessing ALT normal distribution include limited age range and insufficient data on puberty.[5–7,12,13] Optimized cutoffs are becoming even more important owing to the novel concept of metabolic dysfunction associated steatotic liver disease (MASLD), which can be diagnosed in children based on overweight and sufficiently increased ALT values.[11]

What is new?

- We observed higher ALT reference values than the previous NHANES-based cutoffs in both sexes and in all pediatric age groups.
- Using the new cutoffs resulted in a trend for lower prevalence of increased ALT and MASLD in children with overweight/obesity compared to NHANES-based cutoffs, although statistical significance was observed only in the case of increased ALT levels among 12–16-year-old boys and 9–11-year-old girls.

What is known?

- Based on a National Health and Nutrition Examination Survey (NHANES) study, particularly low alanine aminotransferase (ALT) cutoffs have been recommended for screening pediatric fatty liver disease.
- Studies assessing the population-based ALT reference values are scarce and have varied in their consideration of age, puberty, and other possible confounding factors.
- A novel concept of metabolic dysfunction associated steatotic liver disease (MASLD) underlines the role of optimized ALT cutoffs.

We hypothesized that even minor differences between the reference populations used would have a major impact to the prevalence of MASLD. We investigated this by (1) establishing ALT cutoffs utilizing

a representative population sample and (2) by comparing the prevalence figures obtained when applying the new and earlier NHANES cutoffs in a large cohort overweight or obese children.

2 | METHODS

2.1 | Patients and study design

The study was conducted at Tampere University Hospital, Tampere University, and the University of Eastern Finland. It comprised a prospectively followed and population-representative Physical Activity and Nutrition in Children (PANIC) cohort and a larger sample of consecutive children and adolescents investigated due to overweight or obesity at different levels of public healthcare (cohort of children with overweight/obesity).

For PANIC (ClinicalTrials.gov NCT01803776), a random sample of children aged 6–8 years were invited from 16 separate primary schools near the city of Kuopio to participate in the prospective study, which continued up until the age of 17 years. The study involved three separate visits with a comprehensive collection of clinical data and research samples as described in detail elsewhere (Figure 1A).[14–16] The participants were comparable in terms of demographic and anthropometric data with children living in the same geographic area.[14] For the cohort of children with overweight/obesity, altogether 1044 consecutive patients aged between 2 and 16, who had received an overweight- or obesity-related International Classification of Diseases (ICD) 10 code (E65, E66.0–E66.9 and R63.5) were identified from the primary care unit of the city of Tampere and from Tampere University Hospital. Their comprehensive medical data were collected from the systematically maintained patient records. Patients with incomplete clinical data, incorrect diagnostic codes and age under 6 years, as well as those with conditions possibly affecting the liver and/or hepatotoxic medications were excluded, leaving altogether 675 children for the analyses (Figure 1B).

The study design was approved by Tampere University Hospital and the City of Tampere Healthcare Services, and by the Research Ethics Committee of the Hospital District of Northern Savo (PANIC). Written informed consent was requested from all prospectively enrolled children or their legal guardians.

2.2 | Data collection

The following clinical information recorded either during the study visit (PANIC) or at the healthcare visit (cohort of children with overweight/obesity) was collected for the present study using systematic and pretested data collection forms: demographic and anthropometric data, puberty stage, presence of chronic diseases and medications, blood pressure (reference values 1–5 years <115/75 mmHg, 6–10 years <125/85, and 11–16 years <140/90[17,18]), and use of possibly hepatotoxic supplements, herbal products, alcohol or illicit drugs. In the cohort of children with overweight/obesity, all the variables were gathered from the examinations that were

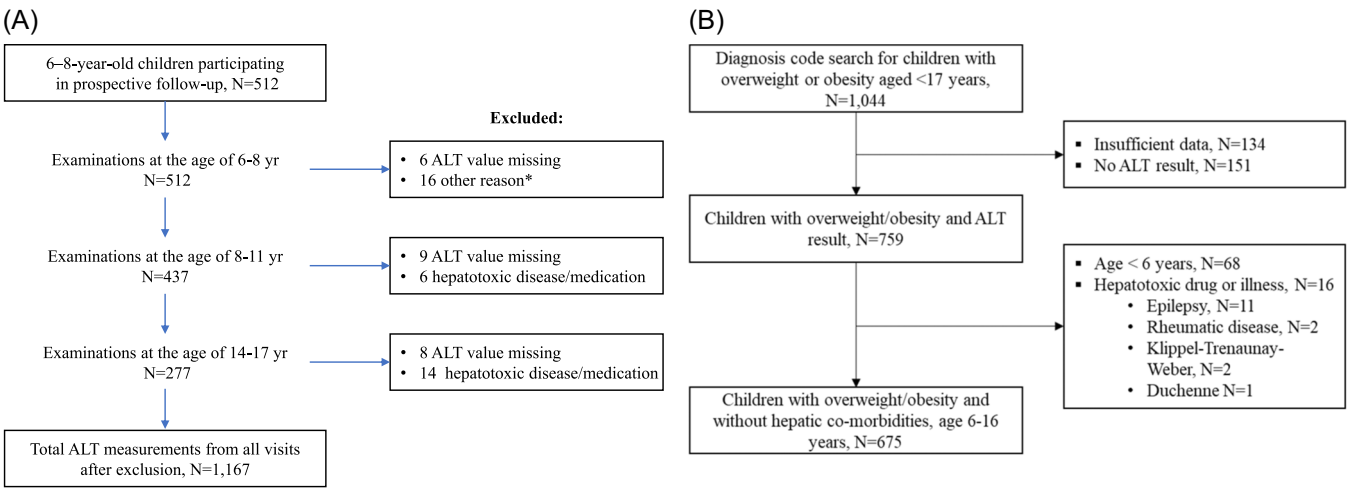

FIGURE 1 (A) Flowchart of the population-based Physical Activity and Nutrition in Children (PANIC) cohort. *Excluded due to confounding diseases/medications, including autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, inflammatory bowel disease, acne medication, epilepsy and anticonvulsants, multiple sclerosis, rheumatic diseases/their medication and testosterone treatment, or because of lack of motivation. (B) Flowchart of the cohort of children with overweight or obesity.

closest to the first obesity-related ALT measurement and within a maximum 1-year time span.

Weight status was defined based on the International Obesity Task Force (IOTF) recommended body mass index (BMI) Z-scores or, alternatively, weight-for-height percentages (WH%) if BMI Z-score was not available (altogether 48 children with overweight/obesity). Cutoff values for BMI Z-score in girls were <−1.65 (corresponding to the 5.0th percentile) for underweight, >1.16 (87.8th) for overweight, >2.11 (98.2nd) for obesity, and >2.76 (99.7th) for severe obesity, and in boys <−1.83 (3.3rd), >0.78 (78.2nd), >1.70 (95.6th), and >2.36 (99.1st) respectively. These figures correspond to BMIs of 17.0, 25.0, 30.0, and 35.0 kg/m^2 at 18 years of age.[19,20] The equivalent values for WH% were 10%–20% for overweight, 20%–40% for obesity, and >40% for severe obesity in children aged <7 years, and 20%–40%, 40%–60%, and >60% for older children respectively.[19,20] Puberty stage was classified by clinician according to the Tanner scale as prepubertal (M/G stage 1), pubertal (M/G stages 2–4), and postpubertal (M/G stage 5).[21,22] Waist-to-height ratio (WtHR) ≥ 0.5 represented central obesity.[23]

The following laboratory values were recorded: ALT, fasting glucose (reference <5.6 mmol/l), Homeostatic model assessment of insulin resistance (HOMA-IR; calculated as fasting insulin × glucose/22.5, reference <2.22 for prepubertal and <3.82 for pubertal girls and <2.67 or <5.22 for boys, respectively) total cholesterol (<6.0 mmol/l), triglycerides (<1.7 mmol/l), high-density lipoprotein (HDL) cholesterol (>1.3 mmol/l for girls and >1.0 mmol/l for boys), and low-density lipoprotein (LDL) cholesterol (<4.0 mmol/l). The reference values used were based on national evidence-based recommendations.[18,24]

2.3 | ALT normal upper limits and study outcomes

To find representative 95th percentiles, the impact of the following variables on ALT values was tested in PANIC: age, sex, puberty stage and presence of underweight or overweight, central obesity, insulin resistance, fasting hyperglycemia, dyslipidemia, and hypertension. The ALT 97.5th percentiles were calculated similarly for purposes of comparison. Prevalences of increased ALT and MASLD were assessed in the cohort of children with overweight/obesity using both the now established age-specific 95th percentiles and the former NHANES cutoffs >25 for boys and >21 for girls for children aged 9–16 years.[5] For children aged 6–8 year only the new PANIC cutoffs were utilized. MASLD was defined as ALT ≥2x upper limit of normal in children with overweight or obesity by using the fixed NHANES cutoffs or the new age-specific PANIC cutoffs.[11]

2.4 | Statistical methods

Categorical variables are reported as numbers and percentages and numerical variables as means with 95% confidence intervals (CI) or in case of skewed variables, determined through visual examination and Shapiro–Wilk test, as medians with lower and upper quartiles or as ranges. Statistical comparisons between study cohorts were made with the Mann–Whitney or Kruskal–Wallis test for continuous variables and with the Chi-square test or Fisher's exact test for binomial or nominal variables. Associations between ALT and clinical variables were analyzed with Spearman's correlation and binary logistic regression. Statistical significance was defined as $p < 0.05$. All analyses were performed using SPSS software, Version 25.0 (IBM Corp).

3 | RESULTS

3.1 | The study cohorts

The median age was 9.4 years in PANIC and 11.8 years in the cohort of children with overweight/obesity and both cohorts comprised more boys than girls (Table 1). The great majority of the children with overweight/obesity had central obesity and a laboratory diagnosis of insulin resistance, and a high percentage also had dyslipidemia and hypertension, whereas these were infrequent in PANIC (Table 1). In PANIC, however, insulin resistance (1.5% vs. 4.8% vs. 5.7%), hyperglycemia (0% vs. 1.9% vs. 15.1%), and low HDL cholesterol (0% vs. 2.1% vs. 10.8% in visits 1–3 respectively) increased with age, while other abnormalities remained uncommon at all ages (data not shown). Two individuals in the cohort of children with overweight/obesity reported irregular alcohol consumption considered nonhepatotoxic and one PANIC participant reported previously taking amphetamine. None of the children reported excessive use of possibly liver-affecting supplements or herbal products.

3.2 | ALT medians and percentiles

A total of 1167 separate ALT measurements from PANIC were available. Of the exclusion strategies tested, particularly presence of overweight or obesity and central obesity increased ALT percentiles in both sexes, while underweight, hypertension, or abnormal glucose or lipid metabolism had smaller effect (Table S1). Excluding children with these conditions left altogether 794 ALT measurements (pooled median age 9.3 years, 49.0% girls) for further analyses. The subsequent 95th percentiles for ALT were 28 U/l for all girls and 30 U/L for all boys, and 28 U/l for girls between

TABLE 1 Characteristics of the population-based Physical Activity and Nutrition in Children (PANIC) cohort and the cohort of children with overweight or obesity.

	PANIC $n = 1167$[a]			Obesity cohort $n = 675$		
	Data available	N	%	Data available	N	%
Age, median (quartiles), years	1167	9.4	7.7, 10.4	675	11.8	9.6, 14.0
BMI, Z-score, mean (95% CI)	1167	−0.1	−0.2 to −0.1	627	2.4	2.2 to 2.8
Girls	1167	556	47.6	675	279	41.3
Underweight[b]	1167	70	6.0	675	0	0
Overweight[b]	1167	175	15.0	675	675	100
Obese[b]	1167	44	3.8	675	559	88.7
Severe obesity[b]	1167	5	0.4	675	288	42.7
Central obesity[c]	1167	96	8.2	98	96	98.0
Insulin resistance[d]	1131	41	3.6	192	154	80.2
Hyperglycemia[e]	1155	46	4.0	669	186	27.8
Hypercholesterolemia[f]	1155	7	0.6	585	105	17.9
Hypertriglyseridemia[g]	1156	7	0.6	580	101	17.4
Increased LDL cholesterol[h]	1156	4	0.3	572	169	29.5
Low HDL cholesterol[i]	1156	36	3.1	577	234	40.6
Hypertension[j]	1162	8	0.7	569	101	17.8

Note: All laboratory cutoffs are based on fasting values.

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]Number of overall visits with alanine aminotransferase measurements.

[b]As defined by Cole et al.[20] and Saari et al.[19].

[c]Waist-to-height ratio >0.5.

[d]Homeostatic model assessment for insulin resistance (HOMA-IR) < 2.67 for prepubertal and <5.22 for pubertal boys and <2.22 and <3.82 for girls respectively.

[e]≥5.6 mmol/l.

[f]Total cholesterol ≥6 mmol/l.

[g]>1.69 mmol/l.

[h]≥4 mmol/l.

[i]<1.0 mmol/l in boys and <1.3 mmol/l in girls.

[j]1–5 years systolic/diastolic blood pressure >115/75 mmHg, 6–10 years >125/85 mmHg, 11–16 years >140/90 mmHg.

6 and 8 years, 29 U/l between 9 and 11 years, and 24 U/l between 14 and 17 years of age, and 29, 29, and 32 U/l for same-aged boys, respectively. The corresponding ALT 97.5th percentiles were 31–37 U/l in girls and 33–44 U/l in boys (Table S2).

Boys had higher median ALT levels in PANIC than girls in each age category with no major age-related changes, whereas in girls there was a decreasing trend ($r = -0.222$, $p < 0.001$), particularly after the age of 11 years (Figure 2). Additionally, the prepubertal (median 17 U/l) and pubertal (17 U/l) ALT values were significantly higher than the postpubertal (12 U/l) values ($p < 0.001$) in girls, whereas this was not seen in boys (medians 18, 18, and 18 U/l, $p = 1.000$ respectively). When puberty was adjusted by age, there was a significant ($p = 0.031$) increase of median ALT from stage M1/P1 (16 U/l) to M2/P2 (18 U/l) in girls and no change in boys. The ALT values correlated significantly with BMI Z-score ($r = 0.227$, $p < 0.001$), total cholesterol ($r = 0.100$, $p < 0.001$) and LDL cholesterol ($r = 0.074$, $p = 0.012$) but not with other lipid or glucose values or blood pressure (r between −0.038 and 0.049, p between 0.127 and 0.220).

3.3 | ALT and MASLD in the cohort of children with overweight or obesity

The use of NHANES-based cutoffs resulted in a trend toward higher prevalence of increased ALT and MASLD in all ages and sexes. A significant difference in the prevalence of elevated ALT was observed only for 12–16-year-old boys (NHANES 63.5% vs. PANIC 47.1%) and 9–11-year-old girls (60.0% vs. 31.8%) (Figure 3). In separate analysis, 9–16-year-old boys were significantly more likely to have increased ALT

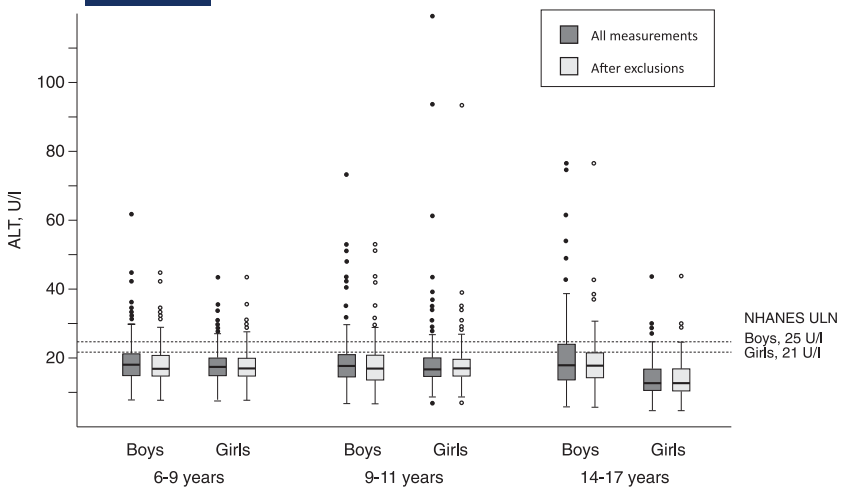

FIGURE 2 Age-categorized alanine aminotransferase (ALT) median values with lower and upper quartiles (boxplots) and range (whiskers) in girls and boys in the entire population-based Physical Activity and Nutrition in Children (PANIC) cohort, as well as after excluding children with underweight, overweight, central obesity, hypertension, and abnormal glucose or lipid metabolism. NHANES, the National Health and Nutrition Examination Survey.

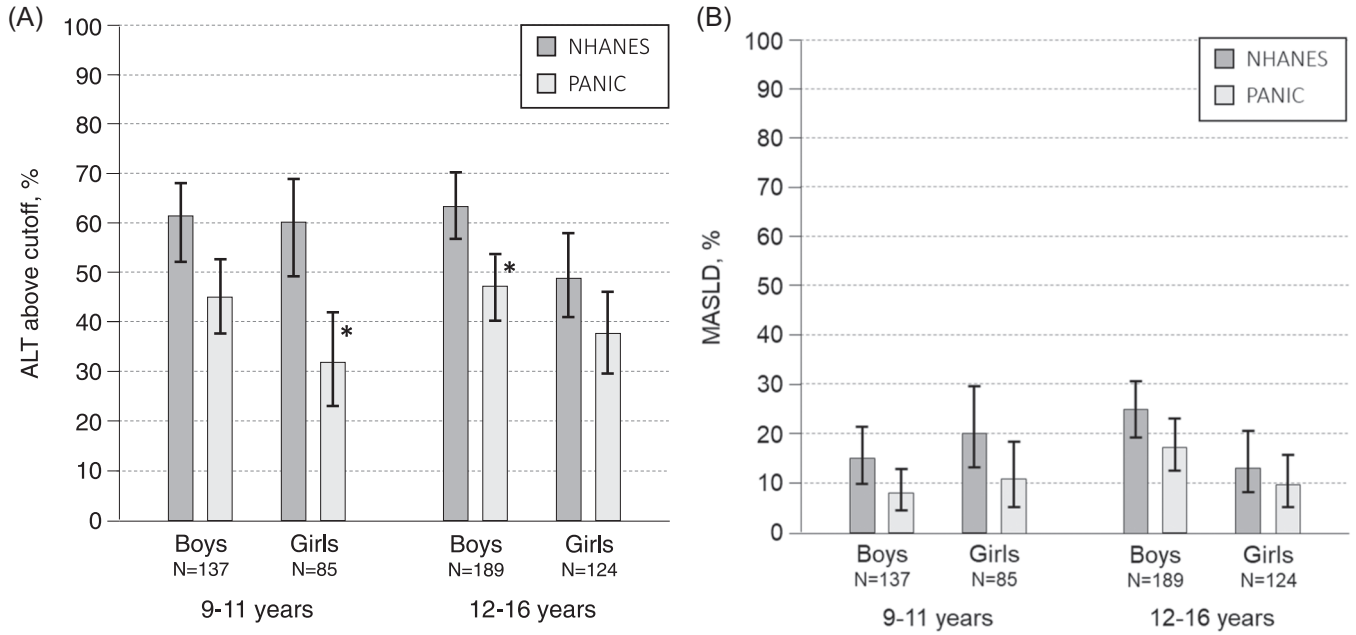

FIGURE 3 Effect of different alanine aminotransferase (ALT) cutoffs on the prevalence of increased screening value (A) and metabolic dysfunction associated steatotic liver disease (MASLD) (B) in 535 children with overweight or obesity without liver-affecting confounders. Dark gray columns represent the National Health and Nutrition Examination Survey (NHANES)-based cutoffs and light gray columns the age-specific Physical Activity and Nutrition in Children (PANIC) -based cutoffs. Whiskers represent 95% confidence intervals and *denotes statistical significance.

than girls using NHANES cutoffs (62.3% vs. 53.6%, respectively, $p = 0.046$) or PANIC cutoffs (46.3% vs. 35.4%, $p = 0.013$). The prevalence of MASLD showed a similar trend with both cutoffs (NHANES 21.8% vs. 16.3%, $p = 0.117$; PANIC 13.5% vs. 10.0%, $p = 0.233$). In boys, the prevalence of elevated ALT and MASLD increased with age, whereas in girls it peaked at the age of 9–11 years (Figure 3). Excluding obese individuals with only weight-to-height percentage available had no effect to the results (data not shown).

In 6–8-year-old children with overweight or obesity the prevalence of abnormal ALT was 21.6% (boys 20.8% vs. girls 22.3%, $p = 0.795$) and the prevalence of MASLD was 2.4% (girls 2.7% vs. boys 2.1%, $p = 1.000$) using age-specific PANIC cutoffs.

4 | DISCUSSION

By utilizing the prospective population-based PANIC cohort, we established ALT 95th percentiles between 24 and 29 U/l for Finnish girls and 29–32 U/l for boys aged 6–17 years. The values are notably higher in younger children compared to those based on 12–17-year-old adolescents participating to NHANES study. However, in comparable age groups the difference was

smaller, especially in girls.[5] Although the NHANES-based reference ranges are recommended in the widely used NASPGHAN guidelines,[4] it is notable that significantly different values have also been presented in earlier studies. For example, Park et al.[25] reported age-independent 97.5th percentile-based cutoffs of 25 and 33 U/l and Kang et al.[12] 95th percentile-based cutoffs of 17.7 and 24.1 U/l for 10–19-year-old Korean girls and boys respectively. Additionally, Bussler et al.[7] presented age-dependent 97.5th values between 24.2 and 31.7 and 29.9–38.0 U/l for 1–16-year-old German girls and boys and Southcott et al.[26] 97th values of 27–35 and 29–35 U/l for prepubertal Australian girls and boys aged 10–12 years, respectively. Earlier even higher cutoffs such as 40 U/l have been used for both sexes.[5,27,28]

Besides variable or lacking consideration for age and sex and the use of different cutoff percentiles, the above-mentioned differences between the studies may reflect genetic variation. For instance, PANIC is ethnically more homogenous than NHANES.[4,5,29] Moreover, earlier research has often involved completely unselected reference cohorts,[2,8,13,25,26,30] whereas in more recent studies the possible significance of comorbidities for ALT normal values has been conceded.[5,7,31–33] Nevertheless, the exact exclusions have rarely been reported, nor has their significance for ALT been tested as we did here. It would be especially important to consider the increasing prevalence of overweight and obesity, which may have been either inconsistently defined or even entirely ignored. For example, we and Bussler et al.[7] applied the more global IOTF recommendations,[20] whereas others may have used for example, population-based percentiles from the United States.[5,12,25,34] Of note, here metabolic disturbances had smaller effect on ALT than overweight and central obesity. This may indicate that slight disturbances in glucose or lipid metabolism in individuals without obesity have less significant role in the development of fatty liver, although it must be emphasized that the number of children affected with these conditions was small.[35]

Age affected the cutoffs particularly in girls, which concurs with earlier reports.[7,25,26,36] Earlier studies have again varied markedly in this respect. For instance, NHANES included children between 12 and 17 years,[5] whereas other cohorts may have been limited to school-aged children or included a wide age range from infancy to adolescence, nevertheless still often suggesting fixed cutoffs for all pediatric age groups.[12,13,25,26] In our study, we observed that ALT normal values increased in girls at the onset of puberty and decreased during puberty progression, whereas this pattern was not observed in boys. A similar finding at the onset of puberty was reported by Bussler et al. in both sexes, but noticeable decrease during puberty progression was observed only in girls.[7] The mechanisms remain unclear but may include physiological insulin resistance and changes in hormone levels and body composition during puberty.[7,37,38] As another contributing factor, we and Schwimmer et al.[5] applied ALT 95th percentiles, whereas other authors have used for example, 97th or 97.5th percentiles.[7,12,25,26,30] Of note, use of 97.5th percentiles resulted in 3–15 U/L higher cutoffs in our supplementary analysis. Taken together, there is a need for more standardized use of percentiles and consideration of exclusion criteria and sex, age, and puberty stage.[2]

Applying the newly obtained cutoffs to the cohort of children with overweight/obesity resulted in increased ALT in 35.4% of girls and 46.3% of boys aged 9–16 years and MASLD in 10.0% and 13.5%, respectively. The corresponding NHANES-based figures were 53.6% and 62.3% for increased ALT and 16.3% and 21.8% for MASLD. The discrepancies between the cohorts were substantial among all age groups, except for girls aged ≥12 years. Despite lacking statistical significance, likely due to limited sample size, burden to the patients and healthcare might still be considerable. Among the youngest children the difference was almost 100%, which could be partly attributed to the restricted age range of the NHANES or the smaller number of children in PANIC. It must be noted that the NHANES cutoffs are meant only for children aged ≥12 years, which is problematic as the guidelines recommend screening for NAFLD to begin at the age of 9–11 years or even earlier for those with risk factors.[4] The existing data on the significance of the cutoffs are limited.[5,10] As an indirect comparison, Welsh et al.[39] reported increased ALT to be present in 10.7%, 6.9%, and 2.7% of the population while using either the NHANES-based limits or higher cutoffs of 30 and 40 U/l. Furthermore, Park et al.[40] found elevated ALT to be 56% more frequent with NHANES instead of “local” values, and a meta-analysis reported prevalences of 6.2%–27.6% in obesity clinics with cutoffs between 20 to 50 U/l.[2] The new PANIC-based cutoffs were closer to those obtained from German children[7] and may be more applicable to the European population as well as for younger children.

A major challenge with pediatric fatty liver disease is the lack of practical diagnostic references, as liver biopsy is invasive, ultrasonography has suboptimal accuracy and better imaging methods are expensive and have limited availability.[4] MASLD is thus a welcome definition for both clinical routine and research but, at the same time, it emphasizes the role of the chosen ALT cutoffs.[11] In patient screening, sensitive thresholds would enable early lifestyle modifications and careful follow-up, which could improve prognosis.[41] At the same time, we should avoid excessive healthcare burden and patient anxiety in the midst of the growing obesity epidemic.[42] Despite its limitations, combining ultrasound with ALT might be helpful finding cases with normal ALT despite liver steatosis, but further studies are needed.[11] Altogether,

more sensitive but still practical imaging methods are called for. While MASLD can be diagnosed at any age, additional consideration for other liver conditions in younger children is advised.[11] Furthermore, the use of the MASLD definition in routine clinical practice, particularly in younger children, still requires further investigation. Eventually, only long-term prospective studies comparing the performance of the ALT cutoffs with robust diagnostic outcomes may provide optimal values for the screening and diagnosis of MASLD.

The main strengths of our study were the use of prospective and representative population sample and careful consideration of the possible confounding factors. Moreover, the cohort of children with overweight/obesity comprised a large number of patients from different levels of healthcare, including primary healthcare, the role of which in the diagnosis of MASLD will likely increase in the future. The retrospective design in the cohort was a limitation, although it was counterbalanced by the systematic collection of medical data with a pre-tested protocol. The limitation of our cohorts—in contrary to NHANES—was the lack of screening for hepatic viruses, although their prevalence in Finnish children is particularly low.[43] In addition, systematic testing to rule out liver-affecting genetic disorders was lacking. Furthermore, in a subgroup of children with obesity weight-for-height percentage was used instead of BMI-Z scores. However, excluding these cases had no effect to the results. Absence of waist circumference measurements in the cohort of children with overweight/obesity could also be considered as a limitation, as it might be more sensitive readout for diagnosing MASLD than BMI.[11] Additionally, there were no data on repeated ALT measurements or possible effect of weight loss to the ALT values. Finally, PANIC lacked study visits between the ages of 12 and 13 years.

5 | CONCLUSION

We established ALT 95th percentiles between 24 and 29 U/l for Finnish girls and 29–32 U/l for boys aged 6–17 years. Comparing these and the NHANES cutoffs showed that the exclusion criteria used, and the characteristics of the reference population may have a substantial impact on the prevalence of MASLD. We therefore recommend critical appraisal of the used cutoffs especially in children <12 years of age for screening and diagnosing MASLD, and among the youngest children more studies are eagerly called for. Altogether, the use of more tailored cutoffs based on age, gender, and puberty stage should be favored instead of fixed values. Furthermore, since the ALT levels can vary or remain normal despite MASLD, improved imaging and other noninvasive diagnostic methods are called for. Considering these issues could help to attain better research outcomes and, in clinical routine, optimized screening yield without excessive healthcare burden and patient anxiety.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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