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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Evaluation of the feasibility of screening for paediatric non-alcoholic fatty liver disease

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Abstract

Aim: To evaluate the feasibility of screening for non-alcoholic fatty liver disease (NAFLD) in clinical practice and the acceptance of a screening strategy, and to identify factors that determine compliance.

Methods: A screening protocol, based on alanine aminotransferase measurement and introduced to healthcare workers of Dutch outpatient obesity clinics in 2017, was evaluated. Medical files of children who visited the largest outpatient obesity clinic between 2017 and 2020 were evaluated. Focus group discussions (FGDs) were conducted with 14 healthcare workers who had been using the screening protocol.

Results: Screening for NAFLD was performed in 477/571 (84%) of the children. Loss of follow-up was the major reason for inadequate screening. Follow-up was performed in 81/134 children with an abnormal screening result (61%). The FGDs indicated 13 barriers for screening, regarding guideline- and knowledge-related issues.

Conclusion: Screening for NAFLD was performed in the vast majority of the children. However, adherence to the guideline after an abnormal initial screening result needs to be improved. This can be achieved by improving the loss of follow-up of patients' and physicians' awareness of the relevance of mildly elevated ALT levels.

KEYWORDS
children, guideline, non-alcoholic fatty liver disease, obesity, screening

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common and fastest growing cause of chronic liver disease in children and adults worldwide.[1] The prevalence of NAFLD in children is estimated at 7%, but with obesity being the major risk factor, this increases to 34% in those with obesity.[2] It is characterised by hepatic fat accumulation in the absence of other causes of the liver- or metabolic disease. The first stage of disease, that is, simple steatosis or non-alcoholic fatty liver (NAFL), can progress into steatohepatitis (NASH), fibrosis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FGD, focus group discussion; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; IQR, inter quartile range; LDL, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; ULN, upper limit of normal.

Laura Draijer and Maaike Voorhoeve contributed equally to this work.

See Appendix for the members of the Amsterdam Paediatric Obesity Collaboration.

or cirrhosis, which can result in end-stage liver disease and hepatocellular carcinoma.[3] Also in children cirrhosis due to NAFLD has been reported.[4,5] Morbidity and mortality are higher in adults with NAFLD due to hepatic complications, and even more frequently cardiovascular disease and malignancies.[6,7] Furthermore, NAFLD is an independent risk factor for type 2 diabetes, even at paediatric age.[8,9] Lifestyle intervention is currently the only treatment for NAFLD. It is highly effective if a 10% weight reduction is achieved, albeit this is a difficult long-term goal to achieve.[10,11]

Given the high prevalence, long-term complications and treatment options, screening for NAFLD in children with obesity is recommended in all major obesity and hepatology guidelines.[12] However, these guidelines are mostly based on experts' opinion and differ in their screening recommendations. Two important criteria of the WHO-defined prerequisites for effective screening are the feasibility and acceptance by the target population of a screening strategy. Evidence on these aspects of screening for NAFLD in children are scarce and factors that determine compliance have not been studied. Therefore, the aim of this study is to evaluate the feasibility of a NAFLD screening guideline in clinical practice by retrospectively evaluating patient compliance and physicians' adherence to the guideline, and by focus group discussions with healthcare workers to identify limitations that arise when screening.

Key Notes

- Screening for non-alcoholic fatty liver disease (NAFLD) was performed in 84% of the children with obesity.
- After screening, inadequate follow-up occurred in 39% of the children and was particularly due to physicians failing to order follow-up measurements, and loss to follow-up.
- Physicians' adherence and screening rates can be improved by implementing a screening strategy in obesity guidelines, by determining the cost-effectiveness of screening, and by increasing NAFLD awareness.

2 | PATIENTS AND METHODS

2.1 | Obesity care and NAFLD guideline

In the Netherlands, all children ≥10 years of age with obesity or overweight with additional risk factors, or <10 years with increased risk of comorbidities, are referred from primary care to outpatient obesity clinics where they are evaluated for comorbidities. Children with comorbidities are followed-up yearly and without comorbidities every 3 years. In November 2017, all paediatricians working at the outpatient obesity clinic in hospitals in Amsterdam and surroundings were introduced to a new screening protocol for NAFLD through presentations by the researchers in all hospitals. This screening strategy is based on the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guideline which is the most comprehensive screening guideline for NAFLD in children and was published in 2017.[13] The screening algorithm is presented in Figure 1. For practical reasons, the NASPGHAN guideline's sex-specific ALT thresholds were set at 30 IU/L for both boys and girls in our local screening protocol.[14,15] In accordance with the NASPGHAN guideline, screening for NAFLD is indicated in children ≥8 years of age with obesity or with overweight and additional risk factors (i.e., hyperinsulinemia, [pre-]diabetes, dyslipidemia, central adiposity, sleep apnea or a family history of NAFLD). In case of elevated ALT (≥30 IU/L), testing should be repeated after 3–6 months of lifestyle intervention. Children with persistently elevated ALT and children with ALT ≥80 IU/L at initial screening should be referred to a paediatric gastroenterologist to exclude other liver diseases and to investigate the presence of liver fibrosis. Reminders to the guideline were sent out by email to all paediatricians after 6 and 12 months and subsequently yearly.

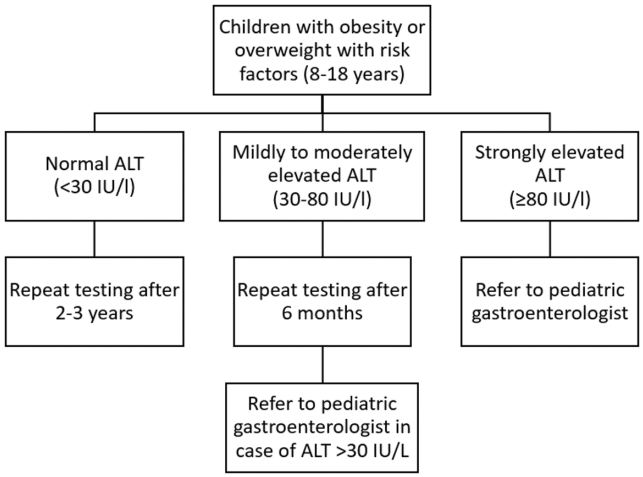

FIGURE 1 The screening algorithm used in the study is based on the NASPGHAN guideline of 2017. ALT, alanine aminotransferase; NASPGHAN, North American Society for Paediatric Gastroenterology, Hepatology and Nutrition

2.2 | Study design and patients

From May to November 2020 medical files of children who visited the largest outpatient obesity clinic in Amsterdam, the OLVG hospital, between November 2017 and March 2020 were evaluated for this study. This study was approved by the Medical Ethics Committee of the Amsterdam University Medical Centers and by the Research Board of the OLVG hospital. First, an automated search in the electronic medical record system was performed to extract a list of all children diagnosed with primary adiposity (age and sex-specific body mass index [BMI] corresponding to an adult BMI score of ≥25 kg/m^2) during the study period.[16–18] Children who did not physically visit the outpatient obesity clinic within the study period were excluded. Secondly, the electronic patient files were manually searched to assess whether the patient was screened for NAFLD according to the guideline. Data were collected from medical files at the patient's first visit to the obesity

clinic and at the moment of the first ALT measurement within the study period. Patient characteristics (sex, age and ethnicity), physical examination (BMI and BMI *z*-score) and laboratory measurements (ALT, total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, glucose and insulin levels) were recorded. Dyslipidemia was defined as either elevated LDL, total cholesterol, triglycerides or lowered HDL, according to age- and sex-specific cutoffs.[19] Hyperinsulinemia was defined as elevated fasted insulin, according to the institutional laboratory cutoff. In children with overweight, additional risk factors for NAFLD were recorded (sleep apnea, family history of NAFLD/NASH and central adiposity) to evaluate if the patient met the screening criteria. Subsequently, all follow-up ALT measurements were recorded (dates and ALT levels) in all patients, as well as referrals to the NAFLD outpatient clinic for further evaluation. For those referred, it was assessed whether patients were evaluated by a paediatric gastroenterologist.

Reasons for not measuring ALT within the study period or for not retesting ALT after an initial abnormal ALT result were extracted from the medical files. These reasons were categorised in patient- and physician-related categories.

2.3 | Focus group discussions

An explanatory mixed methods design was used in this study, wherein first quantitative and then qualitative data are collected and analysed in two consecutive phases within one study.[20] To evaluate more in depth the use of the guideline in clinical practice by healthcare workers and to understand derogations of the guideline that were found in the quantitative (retrospective) part of this study, two 60 min online focus group discussions (FGDs) were conducted in March 2021 with healthcare workers of outpatient obesity clinics who had all been introduced to the screening algorithm described above in 2017. Permission for recording was obtained at the start of the meeting. Two main questions were discussed: "What difficulties do you experience with the guideline?" and "What improvements do you envision for the guideline?". The transcripts of the FGDs were initially coded and categorised by one researcher by identifying keywords used by respondents as indicators of important themes.[21] Initial coding was conducted using ATLAS.ti version 9.0. Subsequently, the identified categories were eliminated, combined or subdivided through inductive axial coding. Lastly, the final items were inductively categorised into themes by one researcher.[22] The results were validated by the participants by sending a summary of the transcripts to all participants of the FGDs, allowing them to provide additions.

2.4 | Statistical tests

Descriptive statistics were used to calculate means with standard deviations or medians with interquartile range (IQR) for continuous variables and frequencies (percentages) for categorical variables. Differences between groups were tested using a Chi-square test for categorical variables and a student *t*-test or a Mann–Whitney *U* test for continuous variables. *p*-values lower than 0.05 were considered to be statistically significant. All statistical analyses were carried out using SPSS version 26 (IBM).

TABLE 1 Patient characteristics

	N = 571
Demographic	
New patients (first visit after November 2017), *n* (%)	316 (55)
Girls, *n* (%)	231 (41)
Age, years	9.8 (7.3–12.7)
Ethnicity, *n* (%)	
Moroccan	175 (31)
Turkish	122 (21)
Indian-Surinamese	98 (17)
Dutch	73 (13)
Other	91 (16)
Unknown	12 (2)
Clinical	
BMI *z*-score	3.64 (3.21–4.09)
ALT1, IU/L[a]	24 (18–32)
Glucose, mmol/L[b]	5.1 (4.8–5.4)
Comorbidity, *n* (%)	
Dyslipidemia[c]	151 (37)
Hyperinsulinemia[b]	128 (35)

Note: Data are presented as median with an interquartile range.
Abbreviations: ALT, alanine aminotransferase; BMI, body mass index.
[a]*n* = 477.
[b]*n* = 361.
[c]*n* = 411.

3 | RESULTS

3.1 | Patients

In total, 695 children visited the outpatient obesity clinic within the study period. Of those, 571 children met the screening criteria during the study period. Their baseline characteristics at the first visit are presented in Table 1. Most children lived in districts of Amsterdam with low or middle socioeconomic status (West, New-West and East).[23] The majority of the children were male (59%) and of Moroccan, Turkish or Indian-Surinamese descent (69%). Over one-third of the children had dyslipidemia and/or hyperinsulinemia at their first visit.

3.2 | Initial screening

Out of 571 children that were eligible for screening, ALT was measured during the study period (ALT1) in 477 children (83.5%), with a median ALT of 24 IU/L (IQR 18–32) (Figure 2). In 94/571 children (16.5%) initial screening was not performed even though they did

meet the screening criteria. Identified patient-related factors were loss to follow-up and refused blood tests (Table 2). Physician-related factors were (1) no blood test ordered for unknown reasons, (2) no blood test ordered with motivation, for example, perceived as low-risk patient due to low grade of obesity and no other comorbidities (as concluded by the physician) and (3) referred back to primary care. The reasons for not measuring ALT were equally due to patient-related factors as physician-related factors. Among these losses to follow-up was the main reason.

3.3 | Six months follow-up

Of the 477 children that were initially screened, 134 children (28%) had a mildly to moderately elevated ALT1 (30–80 IU/L) and required a second ALT measurement after 3–6 months (ALT2) (Figure 2). This ALT2 measurement was performed in 69/134 (51%) of the children. Notably, the time interval between ALT 1 and ALT2 was within 6 months in only 12 children, between 6–12 months in 41 children and more than 1 year in 16 children. In 52/134 children (39%) ALT2 measurement was erroneously not performed. This was mostly due to physician-related factors (60%) (Table 2). In the other children, no follow-up measurement was needed because they were transferred to adult care. There was no difference in ALT1 level between children that had ALT2 measurement and those that erroneously did not (both median 36 IU/L).

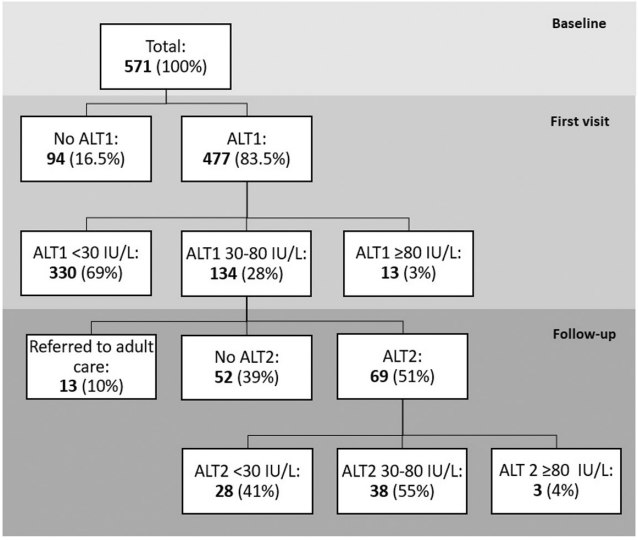

FIGURE 2 The first and second ALT measurements were performed between November 2017 and March 2020. ALT measurements are categorised into normal ALT (<30 IU/L), mildly to moderately elevated ALT (30–80 IU/L) and strongly elevated ALT (≥80 IU/L) ALT, alanine aminotransferase

3.4 | Referrals

During the study period, 54 children were eligible for referral to a paediatric gastroenterologist, having either an initial ALT of ≥80 IU/L ($n = 13$) or a persistently elevated ALT of ≥30 IU/L ($n = 41$). All except one (98%) were indeed referred, none refused referral and all were evaluated by a paediatric gastroenterologist. No other liver- or metabolic diseases, apart from NAFLD, were found in these children.

In total, 424/571 children (74%) were evaluated for NAFLD according to the guideline and 147/571 (26%) were not. The most common reason for the latter was the loss to follow-up (39%). There were no significant differences in age, BMI *z*-score, sex, ethnicity and comorbidities between both groups.

3.5 | Focus group discussions

Sixteen healthcare workers from eight hospitals in Amsterdam and surroundings were invited for the FGDs. Ten paediatricians and four specialised obesity nurses (88%) attended the FGDs. Initial coding of the transcripts resulted in 40 categories. Out of these categories emerged 13 items, comprising four main themes (Table 3). In the following paragraph, we outline the discussion that took place on the items from Table 3 focussing on the items with the largest impact on screening practice.

The 6-month period of lifestyle intervention between the first and second ALT measurement was perceived to be too short. In

TABLE 2 Patient-related and physician-related reasons for non-adherence to the guideline.

Reason	No initial ALT screening ($n = 94$)	No follow-up ALT measurement ($n = 52$)
Patient-related, *n*		
Loss to follow-up	36	21
Patient refused	14	0
Total, *n* (%)	50 (53)	21 (40)
Physician-related, *n*		
No blood test ordered for unknown reasons	18	29
No blood test ordered, with motivation	15	2
Referred back to primary care	11	0
Total, *n* (%)	44 (47)	31 (60)

Abbreviation: ALT, alanine aminotransferase.

TABLE 3 Barriers to adherence to the screening guideline are identified through focus group discussions with healthcare workers and classified by inductive thematic coding.

Guideline-related issues
Short time window between screening and follow-up ALT measurement
Conflicting recommendations in other published guidelines
Conflicting ALT cutoffs in institutional laboratories
Perceived lack of guidance on the interval of screening
NAFLD-related issues
Lack of NAFLD-specific treatment
Lack of scientific evidence on the cost-effectiveness of screening
Healthcare worker-related issues
Lack of knowledge on NAFLD
Uncertainty about the relevance of screening, particularly in children with mildly elevated ALT
Uncertainty about task division between specialist and subspecialist
Lack of time during consultation
Patient-related issues
Lack of knowledge on long-term risks in patients and parents
Patient information overload
Lack of patient information leaflets

Abbreviations: ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease.

practice, this period was frequently extended to 1 year by most physicians, to combine the ALT measurement with the yearly comorbidity screening. The healthcare workers found it confusing that other published guidelines provided different information on screening for NAFLD (e.g., national obesity guidelines advising to screen for comorbidity at a different age). In addition, some healthcare workers by habit continued to rely on the ALT cutoff set by their institutional laboratory which was in all cases higher than the cutoff in the NAFLD screening guideline. The healthcare workers suggested implementing these cutoffs in all laboratories to enhance the detection of NAFLD and correct follow-up. Working with two ALT thresholds (30 and 80 IU/L) was not perceived as a problem, as long as there is easy access to a comprehensible algorithm. Furthermore, the relevance of screening and referral was questioned, especially in children with only mildly elevated ALT levels, considering that lifestyle intervention is the only available treatment for children. The healthcare workers suggested that more information on the natural course of NAFLD and the cost-effectiveness of screening would increase their motivation for screening. All specialised nurses indicated a lack of knowledge of NAFLD, impairing their confidence in communicating about NAFLD. Patient-related issues were a lack of knowledge on the long-term risks in patients and parents and an information overload during the consultation, since patients are informed about other comorbidities as well. This could be improved by information leaflets.

4 | DISCUSSION

In this study evaluating the feasibility of screening for NAFLD in clinical practice, we found that after implementation of the screening guideline, 84% of the children at the outpatient obesity clinic of a Dutch hospital were screened for NAFLD. Identified factors that inhibited initial screening were patient-related (loss to follow-up before blood sampling and refusal), while physician-related factors were equally important, including perceived lack of relevance to test, particularly in children with mild obesity. Of the children with an abnormal screening test, 61% were adequately followed up. Inadequate follow-up was due to loss to follow-up, but even more often due to physicians failing to order follow-up ALT measurements for unknown reasons.

The screening rate for NAFLD in the current study is similar to the self-reported screening rate of 86% by Dutch paediatricians in a recent survey.[24] Only two other studies evaluated the compliance to paediatric NAFLD screening guidelines, both conducted in the United States, and using ALT measurement and repeated testing in case of an abnormal result. Ferguson et al. found a screening rate of 65% in a paediatric weight management program in a tertiary hospital in the United States with an established institutional NAFLD screening protocol that propagates screening in all children with obesity and overweight using ALT, aspartate aminotransferase or gamma-glutamyl transferase with a cutoff set at 50 IU/L for all three.[25] In another retrospective study by Sahota et al. a much lower screening rate was found by evaluating 206.117 health charts from primary care practices in California from 2009 to 2018. It showed a screening rate of 54% and 21% in the children with obesity and overweight, respectively.[26] The lower screening rate in this study could be explained by the fact that it evaluated primary care practice without prior implementation of a screening protocol and was performed in an earlier time period.[26] The latter is also reflected in the greater odds of having a further evaluation for NAFLD in the years 2012–2018 than during the years 2009–2011 found in this study.

The study by Ferguson et al.[25] showed a higher rate in repeated liver enzyme testing of 83%, compared to 60% in our study, while in the study by Sahota et al.[26] this rate was only 12%. Unsurprisingly, in both our study and in the study by Ferguson et al., loss to follow-up was the most frequent patient-related reason for the absence of repeated measurement, underscoring the relevance to motivate patients and to identify patient-related barriers for follow-up. Physician-related factors regarding inadequate screening were not reported by Ferguson et al. In the study by Sahota et al., causes of inadequate follow-up were not evaluated. However older age, female sex, higher BMI and higher ALT were the factors associated with greater odds of having further evaluation, suggesting patients' characteristics influence the interpretation of screening results, which could lead to underdiagnosing in certain patient groups.[26] In our study, there were no significantly different features identified between children that were evaluated according to the screening protocol and those that were not.

For this study, ALT was used as a screening tool since we based our protocol on the NASPGHAN guideline. We acknowledge that ALT is not the most optimal test due to its mediocre accuracy and NAFLD can also occur in patients with normal transaminases,[27] however, in clinical practice, it is the most commonly used screening tool due to low costs (€2 compared to €80 for ultrasound) and easy availability. When developing a screening strategy, it should be remarked that these factors are equally important as diagnostic accuracy in terms of the feasibility of screening. The FGDs on the healthcare workers' perception of using this guideline, showed that they did not perceive the two thresholds for ALT in the guideline as a problem. However, they suggested bringing the automated cutoff reported by laboratories in line with the threshold of the guideline to facilitate the use of this cutoff and also overcome the reported confusion due to different ALT thresholds in other published guidelines. The ALT cutoff of 30 IU/L was reported as a barrier in the FGDs as healthcare workers questioned the relevance of retesting in those with mildly elevated ALT. This is probably also reflected in the high rate of physicians not ordering follow-up ALT measurements according to the protocol. Although the optimal screening threshold that balances a high detection rate with an acceptable false positive rate has not been established, it is known that the threshold of 40 IU/L reported by many institutional laboratories, has a low detection rate for liver disease.[27–29] A high detection rate is favourable because in children with comorbidities such as NAFLD, lifestyle treatment needs to be intensified. Whether the optimal detection rate is at a threshold of 30 IU/L, or at the even lower ULN threshold for healthy children (22 IU/L for girls and 25 IU/L for boys) as propagated in the NASPGHAN guideline, remains to be established.[13,30,31]

Secondly, the short time window of 6 months between initial screening and repeated ALT measurement was experienced as a barrier and most healthcare workers preferred an extension to 1 year. Our chart review confirmed this barrier: 18% of the patients received follow-up after 6 months versus 61% after 1 year. We therefore suggest considering to extend the time window to 1 year and matching NAFLD follow-up with scheduled clinical follow-up appointments. This strategy seems safe based on the recent study of Yodoshi et al. that found another underlying disease in 2% of the children that were screened using ALT in a community setting, suggesting that the chance of missing a disease other than NAFLD is low.[32] It should be noted that in those patients with ALT >80 IU/L, alternative diagnoses are more common[28] and alertness on the presence of other disorders is important in all cases. Furthermore, paediatric NAFLD in a community setting does not seem to progress rapidly: ALT increases in 30% of the children after 2–3 years and normalises in 26%, although the progression to fibrosis in the general population is still unknown.[33] The exact cost-effectiveness of screening remains to be established, wherein the costs of screening should be balanced with the risk of missing rare diseases. Thirdly, it was perceived as a problem that the guideline does not correspond with other guidelines. This underscores the undisputed need to come to a uniform evidence-based international guideline for screening supported by both hepatology, endocrinology and obesity societies, which is likely to improve physicians' adherence and screening rates.

Other reported barriers in NAFLD screening were not related to the guideline, but to a lack of knowledge on NAFLD in both health care workers and patients and their caretakers and a lack of data on the progression of paediatric NAFLD. This highlights the urgent need for studies on the natural history of paediatric NAFLD in primary care settings. To improve NAFLD management and the confidence of physicians in communicating about NAFLD, more awareness and knowledge of NAFLD is required,[34,35] which could be achieved through educational programs and visual educational material.[36] Lastly, the emergence of drugs for NAFLD may increase the follow-up rate of patients with NAFLD in the future, but this also stresses the importance to come to a uniform and comprehensive screening strategy.

A strength of this study is the large cohort that includes all patients seen at an outpatient obesity clinic who were not selected on liver features, hence reflecting the true screening population. Since we evaluated medical files and referrals, we displayed the actual screening practice, in contrast to previous studies that relied mostly on self-reported measures of physicians. By combining a chart review with FGDs we were able to identify obstacles in the clinical use of the guideline and define possible improvements. A limitation of any study using medical files is missing data. Reasons physicians do not measure ALT were often unrecorded. Lastly, the results of this study are reflective of healthcare practices in the Netherlands and might not be translatable to other countries. We underline that this study does not evaluate the cost-effectiveness of screening, nor the efficacy of identifying cases of NAFLD. Therefore, the exact yield of screening when following the NASPGHAN guideline remains to be established. Furthermore, the present discussion on the NAFLD nomenclature and diagnostic criteria could possibly affect screening strategies in the future.[37,38]

In conclusion, screening for NAFLD by following the NASPGHAN guideline was performed in the vast majority of the children at an outpatient obesity clinic. However, adherence to the guideline after an abnormal initial screening result needs to be improved, mainly by improving the loss of follow-up of patients and physicians' awareness of the relevance of mildly elevated ALT levels. In addition, this study identifies other guidelines- and knowledge-related barriers to effective screening for NAFLD in children.

AUTHOR CONTRIBUTIONS

BK, LD and MV were involved in the design and conduction of the study. The Amsterdam Paediatric Obesity Collaboration collected the data. MV analysed the data. BK, LD and MV were involved in data interpretation. LD and BK wrote the manuscript; MV wrote the first draft. MB supervised the study. All authors significantly contributed to the improvement of the manuscript and have approved the final content of this manuscript.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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APPENDIX

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