Screening for non-alcoholic fatty liver disease in children: do guidelines provide enough guidance?

B. G. P. Koot1 and V. Nobili2,3

1Department of Pediatric Gastroenterology and Nutrition, Emma Children’s Hospital/Academic Medical Center, Amsterdam, The Netherlands, 2Hepato-Metabolic Department, Bambino Gesù Children’s Hospital, Rome, Italy, and 3Hepato-Metabolic Disease Unit and Liver Research Unit, Bambino Gesù Children’s Hospital, Rome, Italy

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Address for correspondence: BGP Koot, Department of Pediatric Gastroenterology and Nutrition, Emma Children’s Hospital/Academic Medical Center, Amsterdam, The Netherlands. E-mail: b.g.koot@amc.nl

Summary

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the industrialized world in children. Its high prevalence and important health risks make NAFLD highly suitable for screening. In practice, screening is widely, albeit not consistently, performed.

Aim: To review the recommendations on screening for NAFLD in children.

Method: Recommendations on screening were reviewed from major paediatric obesity guidelines and NAFLD guidelines. A literature overview is provided on open questions and controversies.

Results: Screening for NAFLD is advocated in all obesity and most NAFLD guidelines. Guidelines are not uniform in whom to screen, and most guidelines do not specify how screening should be performed in practice. Screening for NAFLD remains controversial, due to lack of a highly accurate screening tool, limited knowledge to predict the natural course of NAFLD and limited data on its cost effectiveness.

Conclusions: Guidelines provide little guidance on how screening should be performed. Screening for NAFLD remains controversial because not all conditions for screening are fully met. Consensus is needed on the optimal use of currently available screening tools. Research should focus on new accurate screening tool, the natural history of NAFLD and the cost effectiveness of different screening strategies in children.

Keywords: Children, guidelines, non-alcoholic fatty liver disease, screening.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NICE, National Institute for Care and Health Excellence; ESPGHAN, European Society of Pediatric Gastroenterology Hepatology and Nutrition; AASLD, American Association for Study of Liver Disease; AGA, American Gastroenterology Association; NASPGHAN, North American Society of Pediatric Gastroenterology Hepatology and Nutrition; EASL, European Association for the Study of the Liver; EASD, European Associations for Study of Diabetes; EASO, European Associations for Study of Obesity; CASLD, Chinese Association for Study of Liver Disease; AST, aspartate aminotransferase; gGT, gamma-glutamyl transferase; ROC, receiver operating characteristic; CAP, controlled Attenuation Parameter; BSC, backscatter coefficient.
Introduction

Non-alcoholic fatty liver disease (NAFLD) is well established as one of the complications of obesity. Concomitant with the rise in obesity, NAFLD has become the most common chronic liver disease in children and adults in the industrialized world (1). At present, NAFLD is the second leading indication for liver transplantation in adults in the United States and on a trajectory to become the most common indication (2).

The spectrum of NAFLD ranges from simple steatosis, to steatohepatitis, to fibrosis and cirrhosis. In studies, the reported pooled prevalence of NAFLD in children from general population studies is 7.6% (95% CI: 5.5% to 10.3%) and 34.2% (95% CI: 27.8% to 41.2%) in studies based on child obesity clinics (3).

Most children will have simple steatosis and will not progress to more advanced stages. However, inflammation and significant fibrosis are found in a significant percentage of children (4,5). Occasionally, even cirrhosis can already develop in childhood (6). Furthermore, NAFLD is an independent additional metabolic risk factor for type 2 diabetes and, although still disputed, probably also for cardiovascular disease at adult age (7,8).

The high prevalence, long asymptomatic period and important long-term health risks make NAFLD highly suitable for screening. However, screening for NAFLD is not straightforward due to the lack of a highly accurate screening tool, limited knowledge to predict the progression of the disorder in an individual and limited data on its cost effectiveness in children. Despite these issues, screening is widely, albeit not consistently, performed in clinical practice (5,9).

The aim of this study is to provide an overview of the recommendations on screening for NAFLD from national European and USA obesity guidelines for children and from NAFLD guidelines. We identify controversies and open questions and provide an overview on the literature on these issues.

Methods

We evaluated the most recent national paediatric obesity guidelines from six major European countries and the USA (10–16) and NAFLD guidelines from the UK National Institute for Care and Health Excellence (NICE) and four major hepatology societies: the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), the American Association for Study of Liver Disease and American Gastroenterology Association (AASLD/AGA), North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) and the European Association for the Study of the Liver (EASL) (1,17–20). The EASL guideline was developed in a joint effort with the European Association for the Study of the Liver (EASL) and Obesity (EASO). The guideline from the Chinese Association for Study of Liver Disease (CASLD) was not included because it does not address NAFLD in children.

Recommendations for the following basic questions on screening were sought:

- Is screening for NAFLD recommended?
- Which screening tool should be used?
- Which screening result is considered abnormal?
- Who to screen?
- At what age screening should start?
- What is the advised frequency of screening?
- How should those identified by screening be further evaluated and/or treated?

The controversies and open questions identified in this evaluation will be discussed based on an overview of the literature.

Results

Recommendations for NAFLD screening in paediatric obesity guidelines and NAFLD guidelines are depicted in Tables 1 and 2, respectively, and are summarized below.

Is screening for non-alcoholic fatty liver disease recommended?

Obesity guidelines

All guidelines advise to screen for NAFLD.

Non-alcoholic fatty liver disease guidelines

Four guidelines advise screening (1,17,19,20). The AASLD/AGA guideline states that ‘a formal recommendation cannot be made with regards to screening for NAFLD in overweight and obese children due to a paucity of evidence’ (18). The paucity of evidence relates to uncertainties surrounding accuracy of diagnostic tests and treatment options, along with lack of knowledge related to the long-term benefits and cost effectiveness of screening.

Comment

All but one guideline recommend screening for NAFLD and in clinical practice screening is widely performed in obese children (5). The universal criteria for implying screening were defined by Wilson and Junger and are depicted in Table 3 (21). As indicated in this table, for four criteria, it is debatable whether the criteria for NAFLD screening in children are sufficiently met:

1. There should be an accepted treatment for patients with recognized disease: The treatment for obesity in general and for NAFLD is lifestyle change. This
### Table 1  Recommendations on screening for NAFLD in children as provided in national paediatric obesity guidelines

| Screen | How | Reference value | Who | Frequency | Follow-up |
|--------|-----|----------------|-----|-----------|-----------|
| UK (10) | Yes | ALT | NS | OW/Obese | NS | NS |
| France (11) | Yes | ALT | NS | OW*/Obese | NS | NS |
| Spain (12) | Yes | ALT and/or US | ALT >60 IU/L | Obese | NS | persistent >2x ULN → referral |
| Italy (13) | Yes | ALT | ALT >40 IU/L | OW*/Obese | NS | gGl, US and further evaluation |
| Germany (14) | Yes | ALT | NS | Obese | NS | Algorithm provided if persistent abnormalities |
| Netherlands (15) | Yes | ALT | NS | Obese | NS | NS |
| USA (16) | Yes | ALT | ALT >2× ULN | OW*/Obese | 1×2 years | Consultation with ped GE |

ALT, alanine aminotransferase; NS, not specified; OW, overweight; OW*, overweight with other metabolic risk factors; ped GE, paediatric gastroenterologist; ULN, upper limit of normal; US, ultrasound.

### Table 2  Recommendations on screening for NAFLD in children as provided in NAFLD guidelines

| Screen | How | Reference value | Who | Frequency | Follow-up |
|--------|-----|----------------|-----|-----------|-----------|
| ESPGHAN (1) | Yes | ALT and US | NS | OW*/Obese | NS | Algorithm |
| NASPGHAN (20) | Yes | ALT | Alt >2× ULN: Boy > 50 IU/L; Girl > 44 IU/L | OW*/Obese | NS | >80 IU/L direct further evaluation/referral*
| EASL-EASD-EASO (17) | Yes | ALT–AST–gGl and/or US | NS | OW*/Obese | 1×3–5 years | Refer to GE if elevated liver tests. In case of steatosis and normal liver tests perform noninvasive fibrosis test. If abnormal refer to GE. If normal repeat testing after 2 years |
| AASLD (18) | No | NS | NS | NS | NS | NS |
| NICE (19) | Yes | US | NS | DM type 2/Metabolic syndrome | 1×3/years | <11 years refer to paediatric GE |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; GE, gastroenterologist; gGT gamma-glutamyl transferase; NA, not applicable; NS, not specified; OW, overweight; OW*, overweight with other metabolic risk factors; RF, risk factors; US, ultrasound.

*See Fig. 1.

### Table 3  Universal criteria for implying screening defined by Wilson and Junger (21)

| Fulfilled for NAFLD | Comment |
|---------------------|---------|
| The condition sought should be an important health problem | + 2nd indication for adult liver transplantation in USA |
| There should be an accepted treatment for patients with recognized disease | +/- Lifestyle intervention. No established additional treatments. |
| Facilities for diagnosis and treatment should be available | + Can be incorporated in health checks for those with obesity. |
| There should be a recognizable latent or early symptomatic stage | + ALT and US have limited accuracy |
| There should be a suitable test or examination. | +/- |
| The test should be acceptable to the population. | + Limited knowledge who will develop liver and non-liver complications |
| The natural history of the condition, including development from latent to declared disease, should be adequately understood. | +/- |
| There should be an agreed policy on whom to treat as patients. | + Presence of NASH and/or fibrosis NAS* score ≥ 2 |
| The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. | +/- Few cost-effective studies. No studies for children. |
| Case-finding should be a continuing process and not a ‘once and for all’ project. | + Can be incorporated in health checks for those with obesity |

*NAFLD activity score (22).
treatment can be intensified if NAFLD is diagnosed. Particular focus can be given on physical exercise, which can improve NAFLD independent of its effect on body mass (22). No other specific therapies for NAFLD have been approved.

2. **There should be a suitable test or examination:** Serum alanine aminotransferase (ALT) and ultrasound (US) are imperfect markers for NAFLD limiting the effectiveness of screening, as will be discussed in the following paragraph.

3. **The natural history of the condition, including development from latent to declared disease, should be adequately understood:** At present, it is not accurately known whom and how many of those with simple steatosis, the mildest form of NAFLD, will progress to NASH and develop significant fibrosis (fibrosis stage ≥ 2 on NAFLD activity score) (23), the stage of NAFLD that in adults is associated with a lifetime increased risk for decompensated cirrhosis, liver failure, hepatocellular carcinoma and death. However, inflammation (14–16%) and significant fibrosis (56–58%) are already found in a significant percentage of children with obesity and persistent abnormal transaminases that undergo liver biopsy (4,5). In addition, several studies have shown that, sometimes rapid, progression of liver disease can occur in all stages of NAFLD in children and adults. However, the latter studies are at high risk of ascertainment and selection bias (24–26).

4. **The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole:** The 2016 NICE guideline provides a comprehensive cost-effectiveness analysis on NAFLD screening in adults. It is concluded that screening is cost-effective at a threshold of £20,000 per quality-adjusted life year. This is based on an analysis of different screening scenarios for an adult aged 45 years in a UK (publically funded) healthcare setting even if those with lower risk factors were included. No studies on cost effectiveness in children are available; however, screening in children is likely to be more cost-effective compared to adults based on a longer life expectancy (19).

It could be argued that in view of this, children with obesity should not be screened for NAFLD. However, several arguments favour screening despite the limitations: the huge and increasing health burden posed by NAFLD as it is already the second leading indication for liver transplantation and an established additional metabolic risk factor for type 2 diabetes and cardiovascular disease in adults (27); its high prevalence in well-identified risk groups allowing selective screening; the absence of symptoms until advance liver disease occurs; the easily available, albeit not perfect, screening tools that can be applied during standard health checks for those with obesity; the primary treatment, lifestyle intervention, which is widely available.

Discussion within and among the involved medical societies is needed to come to a broadly supported consensus on whether or not and how screening should be performed in children. When choosing to screen for NAFLD, a conservative approach is warranted to avoid a high false positive screening rate as we will elaborate on in the next paragraphs. In order to improve screening strategies, further research is needed into more accurate screening tools, the natural history of NAFLD and prognostic factors, additional treatment modalities and the cost effectiveness of screening in children in different healthcare settings.

**Which screening tool(s) to use? Which result is considered abnormal?**

**Obesity guidelines**

The recommended modality for screening is ALT in all guidelines. Three out of seven guidelines do not state which result of ALT should be considered abnormal. The four other guidelines all provide different threshold values for ALT (>40 IU/L, >60 IU/L and 2 times upper limit of normal). The Spanish guideline also recommends the use of liver US, without indicating which US result should be considered abnormal.

**Non-alcoholic fatty liver disease guidelines**

Two guidelines advise to use both ALT and liver US as screening tools (1,17). The NICE guideline advises to use only US and not ALT, while the NASPGHAN guideline advises the use of ALT and not US. The EASL–EASD–EASO guideline advises to also test aspartate aminotransferase (AST) and gamma-glutamyl transferase (gGT). Only the NASPGHAN guideline specifies the threshold for ALT. It is set considerably lower than in the obesity guidelines at the gender-specific 95th percentile for healthy children.

**Comment**

ALT and US are both imperfect screening tools. However, they are widely available, easy to apply and a fair amount of data on their reliability is available. No other diagnostic tool, suited for screening purposes, has been consistently proven to be superior to ALT and US. The NICE guideline discards ALT as a screening tool because no adequate studies validating ALT against liver histology were identified. Remarkably, studies that validate ALT against MR determined liver steatosis were excluded in this guideline, despite the wide acceptance of MR as a reference standard for liver steatosis. Contrary, the NASPGHAN guideline discards US as a screening tool based on a review...
study that showed a ‘low accuracy’ of US using the traditional threshold for US (28). However, the accuracy of US at a higher threshold was not evaluated in this review.

Besides lack of uniformity on what screening tool is recommended, little attention in guidelines is given on the optimal threshold of the recommended screening test and the impact of false positive and negative screening results. In the four guidelines that provide a threshold, this recommendation is not based on a comprehensive literature review but provided without evidence (12,13,16) or based on a single study not fully representative for a screening setting (20).

When screening for NAFLD a large population is targeted and missing the disorder is not directly damaging, therefore, it is paramount to limit the false positive rate in order to prevent a huge burden of unnecessary medical consumption and anxiety in patients. Therefore, the threshold of the screening test should be set high in order to obtain a high specificity. Based on available paediatric studies, an indication can be given on the accuracy of ALT and US at different thresholds. A review of these data is presented here.

Evidence on optimum threshold of alanine aminotransferase for screening

Only four small studies evaluate the accuracy of ALT as a screening tool for NAFLD in unselected cohorts of children with obesity/overweight using MR as reference standards (5,29–31). Data of these studies could not be pooled because the raw data at different ALT threshold levels were not available for these studies. Notably, the study referred to in the NASPGAN guideline to establish the ALT threshold is not among these. This study evaluates the yield of liver disorders in those with obesity and an elevated ALT referred to a tertiary hepatology clinic and thus does not represent primary screening in children with obesity.

Burgert et al. showed in a study of 72 children with obesity referred to an obesity clinic that at a threshold value for ALT > 35 IU/L, the specificity for detecting NAFLD was 94% (95% CI 83–99%), and sensitivity was 48% (95% CI 27–69%) (29). At a lower ALT threshold (>18 IU/L), sensitivity increased, but specificity dropped to 80% (95% CI 69–91%), meaning 20% of children had a false positive test result. For screening purposes, such high false positive rate would be unacceptable. Schwimmer et al. compared 50 children with obesity and NAFLD to 50 non-obese children without NAFLD (32). At the gender-specific 95th percentile of ALT for children (22 IU/L for girls and 26 IU/L for boys), sensitivity was high (92% for girls and 85% for boys); however, the specificity for detecting was only around 80% for both genders. Receiver operating characteristic (ROC) curve analyses showed, in line with the study by Burgert, that at higher ALT levels (30–40 IU/L), a specificity of 90% could be achieved at the cost of lower sensitivity of around 50%. In a study by Rehm et al., at a high threshold (65 IU/L), specificity was 100% (95% CI 97–100%), but sensitivity low at 9% (95% CI 1.4–29%), while at 24 IU/L specificity was 85% (95% CI 77–91%) and sensitivity 68% (95% CI 45–85%). Again, ROC curve analysis in this study of 77 adolescent girls with overweight showed that at ALT threshold levels above 24 IU/L, a specificity of 90% and sensitivity around 50% could be achieved. Finally, Radetti et al. observed in a small study in 44 adolescents with obesity that ALT >40 IU/L had sensitivity of 50% (95% CI 23–67%) and specificity of 97% (95% CI 83–100%), while ALT > 30 IU/L had a sensitivity of 57% (95% CI 29–82%) and specificity of 100% (95% CI 88–100) (31).

In all these studies, it is suggested that when using ALT at a threshold in the range of 30–40 IU/L, a sensitivity of 50% and specificity of 90% can be achieved. Meaning that using ALT as a screening tool, half of those with NAFLD can be detected, while 1 out of 10 would have a false positive screening result. From the presented data, it is also clear that ALT, although useful for screening, cannot be used as a single test to distinguish those with and without NAFLD. In addition, it has been shown in children with NAFLD that serum ALT correlates with steatosis and insulin resistance rather than inflammation and fibrosis (33,34). When interpreting screening results, physicians should be aware that a negative screening result does not exclude the presence of NAFLD and that no conclusion on inflammation or fibrosis can be made based on ALT levels.

Evidence on the optimum threshold of ultrasound for screening

Increased brightness and decreased US penetration of the liver parenchyma are US features indicating steatosis and are suggestive of NAFLD (35). Standardized scores to evaluate these features have been developed and are used in most studies (Table 4) (36). Three studies evaluate the

| Table 4 | Scoring of hepatic steatosis with US (36) |
|---------|------------------------------------------|
| Score   | Description                              |
| 0: No steatosis | Normal echogenicity of liver parenchyma; Normal visualization of diaphragm and intrahepatic blood vessels |
| 1: Mild steatosis | Slightly increased echogenicity of liver parenchyma; Normal visualization of diaphragm and intrahepatic blood vessels |
| 2: Moderate steatosis | Markedly increased echogenicity of liver parenchyma; Slightly impaired visualization of diaphragm and intrahepatic vessels |
| 3: Severe steatosis | Severely increased echogenicity of liver parenchyma, with poor or no visualization of diaphragm and intrahepatic vessels and posterior part of the right liver lobe |
accuracy of US for detecting NAFLD in unselected cohorts of children with obesity using MR as reference standard (37–39). Two studies evaluate the accuracy of US using liver histology as reference standard and are often referred to; however, these are performed in selected cohorts and are therefore not representative of a screening setting (35,40).

Bohte et al. in a study in 104 children with obesity showed that a US score ≥1 had a specificity of 55% (95% CI: 42–68%) and a sensitivity of 85.4 (95% CI: 75.4, 95.4) to detect any degree of steatosis. Applying a US score ≥2 as threshold value, the specificity increased to 98% (95% CI 94–100%) and sensitivity dropped to 46% (95% CI 32–60%) (41). Using US score ≥2 as threshold value, comparable accuracy rates can be calculated from the data in studies by Pozatto et al. and Pacifico et al. (38,39). Pooling these three studies (n = 224) shows that at a US threshold of ≥2, the specificity of US is 96% (95% CI 91–99%), and sensitivity is 52% (95% CI 41–64%) in children with obesity. These results indicate that using US score ≥2 as a threshold has a high specificity of over 90% for detecting any degree of steatosis, while about 50% of those affected are identified. It should be noted that the accuracy of US is highly dependent on experience of the operator and is higher when using standardized scores (42). Similar to ALT, a US result cannot be used as a single test to distinguish those with and without NAFLD. Physicians should also be aware that US has been shown to poorly correlate with presence of fibrosis and not at all with inflammation (35). Thus, similar to ALT, no statement on these features can be made.

Given the small sample size of the studies and large confidence intervals, no statement on superiority of ALT or US for screening purposes can be made. Larger studies, pooling of data and head-to-head-comparison of US and ALT are needed to accurately determine their performance and optimal cutoff. This would enable physicians to better interpret and adequately counsel on a screening results using these tools.

Who to screen?

**Obesity guidelines**

All advise to screen in all children with obesity. Four out of seven obesity guidelines also recommend screening in children with overweight. Three of these four state that this should only be done in overweight children who also have other metabolic risk factors, namely insulin resistance/type 2 diabetes or dyslipidemia (11,13,16).

**Non-alcoholic fatty liver disease guidelines**

Three guidelines advise screening all those with obesity and those with overweight plus metabolic risk factors (1,17,20). Metabolic risk factors mentioned are insulin resistance or type 2 diabetes (and the related disorders lipodystrophy and polycystic ovarian syndrome), abdominal obesity, dyslipidemia and hypertension (1,17,20). Only the EASL–AESD–EASO guideline specifies that screening is advised in those who fulfill at least three metabolic risk factors (17). The NICE guideline advises only to screen those with diabetes type two or the metabolic syndrome, thus not those with obesity *per se*. This advice is not based on prevalence or cost-effectiveness data but on the consideration that prioritization is necessary to limit the burden of diagnostics.

**Comment**

As mentioned previously, it is paramount to limit the number of false positive results in screening of NAFLD. Besides a high specificity of the screening test, targeting high-risk populations, with a high pre-test probability, lowers the absolute number of false positive test results in screening.

**Obesity as a risk factor**

In a systematic review, the pooled mean prevalence of NAFLD in children from general population studies was 7.6% (95% CI: 3.5% to 10.3%) and 34.2% (95% CI: 27.8% to 41.2%) in studies based on child obesity clinics (3). Prevalence rates of NAFLD can increase up to 50–70% in children with severe obesity or metabolic risk factors (43,44).

Table 5 depicts the accuracy data using an ALT > 35 IU/L and US score ≥2 as threshold levels for screening in a population with a prevalence of NAFLD of 32 and 38%, respectively, based on the data from the studies previously discussed (29,41). These prevalence rates are close the average prevalence among obese children of 34.2% (3). These results show that, using ALT and US for screening with a high threshold level and in a selected population, ALT and US can identify half of the affected patients (sensitivity 48 and 52%, respectively) with high probability

| Table 5 | Accuracy data for ALT and US when screening in a population with a prevalence of NAFLD of 32% (ALT) and 38% (US) (29,37–39) |
|----------------|---------------------------------------------------------------|
|               | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Positive LR | Negative LR |
| ALT > 35 IU/L | 48 (27–69)      | 94 (83–99)      | 79 (49–95)| 80 (67–89)| 7.8 (2.4–25.4)| 0.56 (0.37–0.83) |
| US score ≥2   | 52 (41–64)      | 96 (91–99)      | 89 (77–97)| 76 (69–83)| 14 (6–34)   | 0.49 (0.39–0.62) |

LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value
*Pooled data from references (37–39).
that a positive test means the screened subject is affected (PPV 79 and 89%, respectively).

**Metabolic risk factors**
The risk of NAFLD is not only dependent on BMI *per se* but also on related metabolic factors, particularly insulin resistance, abdominal fat accumulation and dyslipidemia/hypertriglyceridemia (1). No accurate prevalence data on NAFLD in children with overweight and these metabolic risk factors are available. However, it is assumed that in children with overweight together with important insulin resistance, type 2 diabetes or metabolic syndrome, the prevalence of NAFLD is at least equal to those among children with obesity. Accordingly, including children with these risk factors in screening is most consistently advised in most guidelines. However, for an evidence-based recommendation, accurate prevalence data are needed for these risk groups.

**At what age should screening start?**

**Obesity guidelines**
Age of first screening is not defined in any guideline.

**Non-alcoholic fatty liver disease guidelines**
Only the NASPGHAN guideline advises on the age to start screening, beginning between ages 9 and 11.

**Comment**
No evidence on the age to start screening is available. However, it is rational to start screening around the age of 10 as NAFLD is rare under age 10 years (1,45), and scientific data on NAFLD in children have also been almost exclusively collected in cohorts of children aged 10 years and older.

**What is the advised frequency of screening?**

**Obesity guidelines**
Only the US guideline advises on frequency of screening and proposes screening once every 2 years.

**Non-alcoholic fatty liver disease guidelines**
The EASL–EASD–AESO guideline proposes screening once every 3 to 5 years. The NICE guideline proposes screening once every 3 years.

**Comment**
As mentioned previously, the natural history of NAFLD and risk factors for progressive disease are not well established. In children, only small case series report on the histological progression of NAFLD of those who underwent repeated liver biopsies in tertiary liver centres (6,46,47). No conclusions on follow-up on population level can be made from these studies. In adults, an average progression of 1 stage fibrosis over 14.3 (95% CI, 9.1–50.0) years for patients with NAFLD and 7.1 (95% CI, 4.8–14.3) years for patients with NASH was reported in meta-analysis of six studies (26). However, progression rates can differ among individuals. The most frequent, albeit not consistently, reported risk factors in adults are higher age, increase in BMI and development of type 2 diabetes (25,26,48).

These data on the progression of NAFLD indicate that repeated screening is warranted, but its frequency cannot be established on scientific data. Screening every 3 years as advised in the NICE and EASL guideline is practical as this parallels the screening frequency for type 2 diabetes advised in the most recent USA guideline (49). This screening frequency seems on the safe side taking into account the average rate of progression of NAFLD reported in adults. Although evidence is weak, earlier repeated screening can be considered in those with a rapid increase in BMI and development of insulin resistance/type 2 diabetes (25,26,48).

**How should those identified by screening be evaluated and/or treated?**

**Obesity guidelines**
Subsequent steps in case of positive screening are not specified in three out of seven guidelines. Two guidelines advise referral to a paediatric gastroenterologist. One guideline advises additional testing using gGT and US and further evaluation for ‘causes of hepatitis’. The German guideline provides an algorithm in concordance with the hepatology guideline by ESPGHAN.

**Non-alcoholic fatty liver disease guidelines**
Both the ESPGHAN guideline and NASPGHAN guideline provide an algorithm for follow-up for those aged over 9–10 years identified by screening.

The NASPGHAN guideline is depicted in Fig. 1. Both algorithms are largely similar, although the ESPGHAN does not specify which screening results should be considered abnormal. Both algorithms include direct further evaluation or referral for those with risk factors for or signs of advanced liver disease. In all others cases, repeated testing after 6 months is advised preferably after initiating or intensifying lifestyle changes. The risk factors for advanced liver disease include an importantly elevated ALT, defined as ALT >80 IU/L in the NASPGHAN guideline. The EASL–EASD–EASO guideline and NICE guideline differ in their follow-up; both include use of serum tests for fibrosis in the selection of those with NAFLD who need referral. If normal, these tests should be repeated every 2 years (Table 2). Lifestyle modification is advocated in all NAFLD guidelines with reevaluation after 6 months.
Comment
The ESPGHAN and NASPGHAN guideline provides the most comprehensive follow-up algorithm and is specifically aimed at children. In case of persistent abnormalities after up to 6 months, other liver disorders should be excluded, and a liver biopsy should be considered. At this stage, consultation of a paediatric gastroenterologist is advised because the decision to perform a liver biopsy is an individual consideration based on the differential diagnosis and the risk of advanced liver disease. This consideration continues to shift as non-invasive markers of fibrosis become available. Some markers have proven clinically useful but need to be interpreted by a physician aware of their limitations (50–53).

Conclusion and future perspectives
Current obesity and NAFLD guidelines almost all advise screening for NAFLD in children. However, little practical guidance is provided on how screening should be performed. Moreover, the limitations and pitfalls related to screening are not addressed. Screening for NAFLD remains controversial due to the lack of highly accurate
screening tool, the limited knowledge on the natural history of NAFLD and paucity of data on its cost effectiveness in children. However, in view of its importance as a cause of liver and non-liver disease in the industrialized world, the need to come to an effective and comprehensive screening strategy is eminent.

Future perspectives

Future obesity and NAFLD guidelines that propagate screening should provide more guidance on practical issues of screening for NAFLD. Discussion within and among the involved medical societies is needed to come to a broadly supported consensus on whether or not and how screening should be performed in children.

In order to optimize screening for NAFLD, the currently advocated screening tools should be evaluated more thoroughly by performing larger studies, pooling of data and head-to-head comparison of US and ALT. A two-stage screening, combining ALT and US, merits evaluation. Such strategy could prove useful to increase the sensitivity of screening while preserving a high specificity. Ultimately, new highly accurate screening tools will be needed to come to more effective screening. New US-based modalities, like Controlled Attenuation Parameter (CAP), which is incorporated in the transient elastography system of the FibroScan® and the acoustic properties of conventional US, like the backscatter coefficient (BSC), are currently being studied and seem promising (54,55). Development of accurate markers to detect inflammation and fibrosis is even more needed than markers of steatosis, as preventing NASH and fibrosis is the final aim of screening. In addition, longitudinal follow-up studies on the natural history of NAFLD and risk factors for progressive disease and subsequent studies on the cost effectiveness of different screening strategies are needed to optimize screening strategies. Additional pharmacological therapies for NAFLD are likely to become available in the near future (56–58). This development is likely to enhance the demand for a comprehensive, effective and uniform screening strategy for NAFLD. Finally, despite their relevance as health issues, focus on NAFLD and other complications of obesity should not divert the attention of physicians from addressing the root of the problem: the prevention of obesity.

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Conflict of interest statement

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