

Survey on screening for paediatric non-alcoholic fatty liver disease in clinical practice in Dutch hospitals

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Abstract

Aim: Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent liver disease that affects 34% of children with obesity. Besides the liver-related morbidity, NAFLD also increases the risk of cardiometabolic diseases at adult age. Diverse screening recommendations exist on paediatric NAFLD. The aim of this study was to assess screening practices among paediatricians managing children with obesity in the Netherlands.

Methods: Between 2016 and 2017, an Internet-based survey was sent to all 167 members of the endocrinology section of the Dutch Paediatricians Society, that includes all paediatricians involved in obesity care. Descriptive statistics (frequencies) were used to analyse responses.

Results: In total, 42/167 (25%) of the invited paediatricians responded. Thirty-six of 42 respondents (86%) screen for NAFLD. One-third of those do not follow any guideline. Most respondents use ALT as screening tool, with thresholds varying between 21-80 IU/L. The majority (29/36) indicate they lack guidance on screening and follow-up.

Conclusion: In this study sample of Dutch paediatricians, screening for paediatric NAFLD is widely, albeit not universally, performed and in a highly variable way. This underlines the need come to a uniform and comprehensive screening strategy and raise awareness about NAFLD among physicians treating children with obesity.

KEYWORDS

children, non-alcoholic fatty liver disease, obesity, screening, survey

1 | INTRODUCTION

Due to the epidemic of obesity, non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in adults and children in western countries. The spectrum of NAFLD encompasses simple steatosis ('NAFL'), non-alcoholic steatohepatitis

(NASH), fibrosis and cirrhosis.¹ The pooled prevalence of NAFLD in children in the general population is 7.6% (95% CI: 5.5% to 10.3%) and 34.2% (95% CI: 27.8% to 41.2%) in children with obesity.²

Hepatic complications due to NAFLD include decompensated cirrhosis, liver failure and hepatocellular carcinoma. All of which mostly occur at adult age.^{3,4} In addition, children with NAFLD have a higher

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM2, diabetes mellitus type 2; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; γ GT, gamma-glutamyltransferase.

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prevalence of cardiovascular risk factors and therefore may be at higher risk for cardiovascular disease than children without NAFLD.⁵ Also, prediabetes and type 2 diabetes are more common in children with NAFLD, which are associated with severe NASH.⁵⁻⁷ Although this has not been established, children with NAFLD might be at higher risk of these long-term complications compared to adults, given their longer life expectancy. Besides the health burden, the economic burden of NAFLD is also high, not least due to the high number of those affected by NAFLD. The annual economic burden of NAFLD in 4 European countries (Germany, France, Italy, United Kingdom) is estimated at €35 billion, which is in line with the economic costs of diabetes and cardiovascular diseases.⁸ The burden is significantly higher when societal costs are included, and it is expected to increase if the incidence of NAFLD continues to rise parallel to that of obesity.

The high prevalence and costs, risk of long-term complications and lack of symptoms in the initial stages of the disease make NAFLD highly suitable for screening. Indeed, most NAFLD and obesity guidelines for adults and children advocate screening. However, they lack uniformity and clarity in their recommendations on who to screen, when to screen, which screening tool to use and what screening result to consider abnormal.⁹

The aim of this study is to determine how screening for NAFLD in children is performed and perceived by paediatricians in the Netherlands.

2 | MATERIALS AND METHODS

2.1 | Survey

An Internet-based questionnaire was developed by the study investigators using the survey administration application Google Forms (Google LLC).

The survey included 6 multiple choice and 8 open-ended questions (Appendix S1) mainly focused on whether and how screening and follow-up after an abnormal screening result are performed.

2.2 | Survey distribution

In the Netherlands, general physicians and youth healthcare physicians at Child Health Clinics check growth and development in all children. Those with overweight or obesity are referred to a paediatrician at obesity outpatient clinics, to screen for comorbidity and referral to appropriate lifestyle intervention programs based on their risk assessment. Other paediatric subgroups that frequently see children with obesity will always refer them to a paediatrician that specializes in obesity. The targeted physicians in this study were general paediatricians and paediatric endocrinologists working in obesity outpatient clinics. For this purpose, the survey was sent to the members of the endocrinology section of the Dutch Paediatricians Society since virtually all paediatricians involved in obesity care are member of this section. This group

Key notes

- Screening practices for non-alcoholic fatty liver disease (NAFLD) in children were highly variable in a sample of paediatricians surveyed in the Netherlands.
- The majority of the surveyed paediatricians in this study, that are involved in the management of children with obesity, indicate they lack guidance on screening for NAFLD.
- There is a need to come to a uniform and comprehensive screening guideline for NAFLD in children with obesity.

includes paediatricians from secondary and tertiary care hospitals. Between September 2016 and June 2017, the survey questionnaire was sent via email, which included a link to the survey. Responders filled in the questionnaire anonymously. Seven weeks after the initial email, a reminder was sent. In total, 167 paediatricians were invited for participation.

2.3 | Analysis

Descriptive statistics (frequencies) were used to analyse responses. No comparative statistics were used.

3 | RESULTS

3.1 | Respondents

In total, 42/167 (25%) of the invited paediatricians participated to the study. Of those, 35 (83%) were working in a non-university hospital and 6 (14%) in a university hospital. One respondent was working in an independent obesity clinic. Thirty-one per cent of the participants had been practicing for more than 20 years. Fourteen per cent had been practicing for 0-5 years. The majority (60%) was treating children with obesity and type 2 diabetes. Demographics of the responding paediatricians are presented in Table 1.

3.2 | The use of guidelines for NAFLD

In total, 36/42 (86%) of the respondents screen for NAFLD. Screening practice as reported by the respondents is summarised in Table 2. The majority of the respondents (60%) bases their practice at the guideline of the Dutch Institute for Healthcare Improvement: 'Diagnostics and treatment in adults and children with obesity', 2008-2011.¹⁰ Almost a third of the respondents (29%) does not follow any guideline on screening for NAFLD. Only a minority (5/36) follows a local guideline for obesity in children. None of the respondents uses an international guideline.^{11,12}

3.3 | Whom to screen

Screening is mostly performed in children with obesity (32/36, 89%). Two out of four remaining respondents screen in children with overweight who have metabolic risk factors or metabolic syndrome. The other two respondents screen in children with overweight/obesity plus a family history of NAFLD. Other additional indications for screening, besides obesity, as reported by the respondents are presented in Figure 1.

Frequently reported additional metabolic risk factors include elevated transaminases, familial hypercholesterolaemia, hyperlipidaemia, acanthosis nigricans, hypertension and insulin resistance.

Twenty-two per cent (8/36) of the respondents screen at all ages, 7/36 (19%) respondents screen children aged 10 years or older. All other reported age thresholds ranged from 3 to 12 years.

3.4 | How to screen

All respondents use alanine aminotransferase (ALT) as primary screening tool. Seventy-eight per cent additionally use aspartate aminotransferase (AST), 47% also use gamma-glutamyltransferase (yGT). Twenty-two per cent (8/36) also use ultrasound to screen for NAFLD and consider steatosis as defined by the radiologist as an abnormal screening result. Laboratory results that were considered abnormal differed among the respondents. Most respondents (11/36, 31%) use the upper limit of normal, as defined by their hospital laboratory, as cut-off. Two times the upper limit of normal was another frequently used cut-off (7/36, 19%). Overall, the thresholds used for ALT ranged from 21 to 80 IU/L.

Most respondents (15/36, 42%) screen in a frequency of once a year. A smaller proportion (7/36) screen once every two to three

TABLE 1 Demographics of respondents

Hospital setting	N (%)
Academical hospital	6 (14)
Non-academical hospital	35 (83)
Other	1 (2)
Patient populations	
Obesity and DM2	25 (60)
Obesity	12 (29)
DM2	3 (7)
General paediatric population	2 (5)
Years of work experience	
0-5 y	6 (14)
5-10 y	9 (21)
10-15 y	7 (17)
15-20 y	7 (17)
More than 20 y	13 (31)

Note: Demographics of the respondents (n = 42).
Abbreviation: DM2, diabetes mellitus type 2.

years, while 8/36 of the respondents only screen once. Six respondents did not fill out this question.

3.5 | Follow-up after screening

Half of the respondents (18/36) perform abdominal ultrasound for further evaluation. Nineteen per cent (7/36) intensifies lifestyle interventions. One-third (12/36) repeat testing after 6-12 months. Only two respondents perform additional laboratory tests to exclude other liver diseases. Four respondents consult or refer to a paediatric gastroenterologist in case of an abnormal first screening result. Twenty-seven per cent (10/36) of the respondents report that a standardised management plan for patient with an abnormal screening test is lacking.

The vast majority of the respondents (29/42) indicate that in their opinion, there is not enough guidance on screening and follow-up after screening for NAFLD in children with overweight/obesity and type 2 diabetes.

4 | DISCUSSION

Screening for NAFLD is advised by almost all national and international Obesity and Hepatology societies. This study showed that

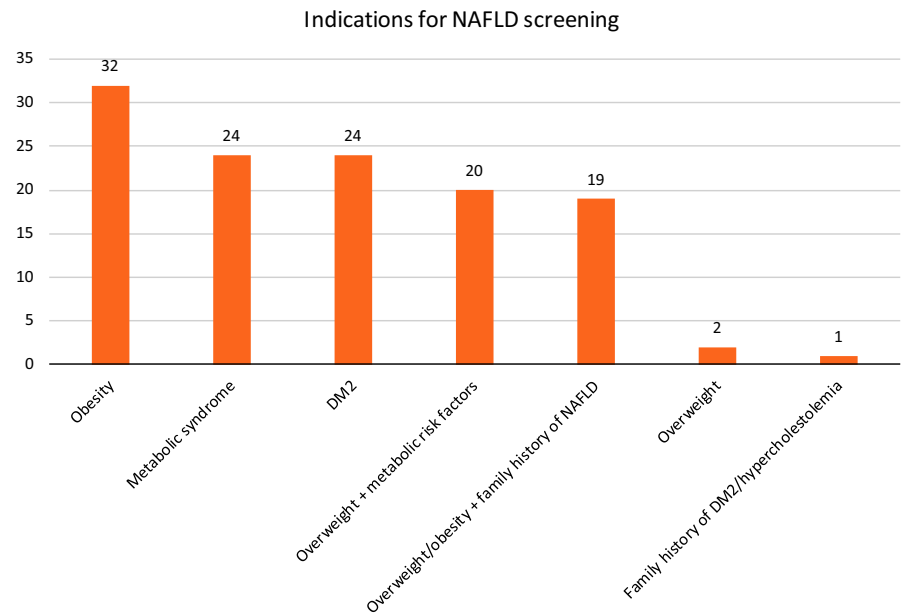
TABLE 2 Screening practice for paediatric NAFLD

Screening based on which guideline?	N (%)
Dutch Institute for Healthcare Improvement	21 (60)
Local guideline for obesity in children	5 (19)
International guideline	0 (0)
None	10 (29)
Screening at what age?	
10 years and older	7 (19)
All ages	8 (22)
Other; varying between 3-12 y	21 (58)
Screening tools	
ALT	36 (100)
> ULN as defined by hospital laboratory	11 (31)
> 2x ULN	7 (19)
Other thresholds, ranging from 21-80 IU/L	18 (50)
ALT + yGY	17 (47)
ALT + US	8 (22)
Frequency of screening	
1 × per year	15 (42)
1 × per 2-3 y	7 (19)
Once	8 (22)

Note: Values are presented as n (%) of a total of 36 respondents that screen for NAFLD.

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal; US, ultrasonography; yGT, gamma-glutamyltransferase.

FIGURE 1 Indications for screening. Indications for NAFLD screening as reported by the respondents ($n = 36$). Abbreviations: DM2, diabetes mellitus type 2



the majority of Dutch paediatricians surveyed in this study screen for NAFLD in children with obesity, overweight or type II diabetes. However, the way screening is performed differed greatly and 69% of the survey respondents indicate that they lack guidance on how to screen for this disorder.

The majority (60%) of the respondents that screen for NAFLD bases their screening on the Dutch guideline for obesity in adults and children.¹⁰ This guideline advises to measure 'liver functions' at the first consultation in children with obesity and additional risk factors. However, what result to consider abnormal and how patients with abnormal screening results should be further evaluated are not specified. This is reflected in a wide variety in both liver tests used, threshold to consider the screening test abnormal and the subsequent steps after initial screening. In addition, almost one-third of the respondents that screen for NAFLD does not use any guideline and none uses an international guideline.

Several paediatric, endocrine and hepatology societies have published screening recommendations for paediatric NAFLD. A review in 2017 provides an overview of recommendations of guidelines in 6 European countries and the USA.⁹ All but one guideline advise to screen in children with obesity and in those with overweight with cardiometabolic risk factors; however which risk factors differ among guidelines. The majority of guidelines advises to use ALT as screening tool, and some advocate ultrasonography. The definition on which screening result is considered abnormal, the frequency of screening and the further evaluation of those with an abnormal screening result is in most guidelines not specified. Furthermore, one guideline (AASLD) opposes screening, as they state 'there is a paucity of evidence that 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'.¹³ Arguments favouring and opposing screening are presented in Table 3.

The challenges of screening in daily clinical practice have been previously described in the study of Ferguson et al that retrospectively evaluated the NAFLD screening process in children admitted to a weight management programme in an obesity centre in the US.¹⁴ Even while a local screening protocol was available, screening was performed in only 65% of the children and additional testing to exclude other causes of hepatitis was performed in only 67% of the cases where this was indicated. This study showed that even when protocols are available, there remains a barrier to perform screening. A nationwide survey of Mouzaki et al among Canadian paediatric hepatologists also showed important discrepancies in the additional testing and follow-up of children suspected of NAFLD and the use of guidelines.¹⁵ The lack of NAFLD screening strategies is also underlined by the recent study of Lazarus et al that evaluated the public health response to NAFLD in 29 European countries. None of the countries had a national or regional government strategy addressing NAFLD in adults.¹⁶ The clinical guidelines addressing NAFLD that are used in some countries do not universally recommend screening for NAFLD. They suggest this might be due to an undervaluation of the clinical and economic burden of NAFLD on society.

The strength of our study is that the survey was distributed through the section of the Dutch National Society of Paediatricians, which includes all paediatricians involved in care of children with obesity. Since in the Netherlands paediatricians are those who screen children with obesity for comorbidities, the invited physicians do reflect the screening practice in the Netherlands. A limitation is the low response rate of 25% that could possibly bias the results. Paediatricians with more knowledge on NAFLD might have been more likely to have responded in this survey, which could potentially bias the results on the proportion that screen for NAFLD and used screening methods. We cannot establish whether the problems in screening identified in this national survey are similar in other countries. However, as previously established national guidelines on screening for NAFLD in children in other European countries and

Pros	Cons
High prevalence	Limitations of screening tools
Higher prevalence in risk groups, allowing selective screening	Limited knowledge to predict disease progression
Long asymptomatic period	Lack of longitudinal data on natural history
Important long-term health risks	No pharmacotherapeutical options
Huge economic and health burden of NAFLD	No data on cost effectiveness of screening
Widely available screening tools that can be applied during routine health checks	Lack of knowledge on long-term benefit
Primary treatment, that is lifestyle intervention, is widely available	

TABLE 3 Pros and cons of screening for paediatric NAFLD

the US also lack a comprehensive approach.⁹ It is therefore likely that variability in the screening practices is also a problem in other countries.

These findings from our study and the above-mentioned studies suggest that a lack of comprehensive guidelines, familiarity with guidelines and the complexity of integrating these guidelines as part of clinical care for children with obesity are factors that play a role in the wide variability in how and whether screening for NAFLD is performed. These results underscore the need to come to uniform guidelines on an international and national level that are both comprehensive and easy to perform. Advocating implication of NAFLD screening guidelines into clinical practice of those caring for children with obesity needs to improve. At the same time, the limitations of screening for NAFLD based on the current available evidence need to be acknowledged. Further studies into the optimal use of currently used screening tools and new screening tools, cost effectiveness of different strategies and the natural history of paediatric NAFLD are needed to come to better evidenced-based screening guidelines. These steps are needed since effective early identification of children with NAFLD is important in order to intensify lifestyle interventions which, if effective, can prevent extrahepatic complications and progression of NASH and fibrosis and thus lower the future economic burden of this disease on society.¹⁷⁻¹⁹

In conclusion, the results of this study suggest screening for NAFLD in children with obesity in the Netherlands is widely performed but in highly variable way. This emphasises the need to come to one comprehensive and easy to apply screening strategy on international and national level. If well implemented, this could result in better early identification and treatment of children with NAFLD with the potential to reduce the risk of long-term complications of this highly prevalent disorder.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

COMPLIANCE WITH ETHICAL STATEMENTS

This manuscript describes original work and is not under consideration by any other journal.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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