Received: 6 October 2023 | Accepted: 1 January 2024

DOI: 10.1002/jpn3.12124

JPGN

ORIGINAL ARTICLE

Hepatology

Pediatricians' practices and knowledge of metabolic dysfunction-associated steatotic liver disease: An international survey

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Funding information

This study received no specific grants or funding from any funding agency in the public, commercial, or not-for-profit sectors.

Abstract

Objective: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease in children. It is associated with significant intra- and extrahepatic comorbidity. Current guidelines lack consensus, potentially resulting in variation in screening, diagnosis and treatment practices, which may lead to underdiagnosing and/or insufficient treatment. The increasing prevalence of MASLD and associated long-term health risks demand adequate clinical management and consensus in guidelines. This study aims to evaluate the daily practices of pediatricians in screening, diagnosis and treatment of MASLD in children.

Methods: An online survey with 41 questions (single/multiple response options) was sent to pediatricians (with/without subspecialty) in Europe and Israel, via members of the ESPGHAN Fatty Liver Special Interest Group, between June and November 2022. The 454 pediatricians were included in this study.

Results: 51% of pediatricians indicated using any guideline for diagnosis and treatment of MASLD, with 68% reporting to follow recommendations only partially. 63% is of the opinion that guidelines need revision. The majority of pediatricians screen for MASLD with liver function tests and/or abdominal ultrasound. A large variety of treatment options is utilized, including lifestyle management, supplements and probiotics, with a notable 34% of pediatricians prescribing pharmacotherapy. When asked how often pediatricians request a liver biopsy in children with MASLD, 17% indicates they request a liver biopsy in more than 10% of cases.

Conclusions: There is limited awareness and considerable variation in screening, diagnosis and treatment practices among European pediatricians, and a clear demand for new, uniform guidelines for MASLD in children.

KEYWORDS

children, experience, NAFLD, nonalcoholic fatty liver disease

1 | INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), has become the most prevalent chronic liver disease in children.[1] MASLD is associated with significant intra- and extrahepatic comorbidities in childhood, including insulin resistance and dyslipidemia, which can track into adulthood if left untreated.[2] This indicates a serious public health issue.[3]

There is currently no consensus in guidelines on screening, diagnosis and treatment of MASLD in children.[4] Most guidelines recommend to screen children with overweight or obesity, using serum alanine aminotransferase (ALT). Use of liver ultrasonography is inconsistently recommended.[4] Other screening tools, including Fibroscan and the Pediatric NAFLD Fibrosis Score (PNFS) are already in use in clinical practice, but are not yet included in guidelines.[5] All guidelines indicate that MASLD diagnosis can be confirmed via biopsy.[1] Multidisciplinary combined lifestyle intervention is currently the primary and only treatment for MASLD.[1,6–10] Although new pharmacological options are emerging, including glucagon-like peptide-1 (GLP) receptor agonizts,[11] no recommendations have been made regarding pharmacotherapy for pediatric MASLD.[6–10,12]

The absence of consensus in guidelines may lead to variation in daily practice among pediatricians, which may potentially result in underdiagnosing and/or inadequate treatment of MASLD in children. The increasing prevalence of MASLD and associated long-term health risks demand adequate clinical management and consensus in guidelines. The aim of this study is to evaluate the daily practice of pediatricians in screening, diagnosis and treatment of MASLD in children, to aid improvement of guidelines for MASLD in children and eventually achieve consensus in clinical practice.

What is Known

- Guidelines for screening, diagnosis and treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) in children lack consensus.
- This lack of consensus may create practice variation among pediatricians and risks underdiagnosis and/or insufficient treatment of MASLD.

What is New

- This international survey is the first to evaluate the daily practices of European and Israeli pediatricians regarding MASLD.
- Limited awareness and considerable variation in screening, diagnosis and treatment practices for MASLD was observed among pediatricians.
- There is a clear demand from pediatricians for new, uniform guidelines for MASLD in children.

2 | METHODS

2.1 | Research design and participants

This cross-sectional international study was designed and conducted by the ESPGHAN Fatty Liver Special Interest Group (SIG), through an anonymous online survey in Survey Monkey (Survey Monkey Inc.). Distribution of the survey took place via members of the ESPGHAN Fatty Liver SIG. Survey and accompanying email were sent out to all members, with request to distribute the survey in their respective national professional associations. Distribution took place via multiple channels, including but not limited to email newsletters, conferences and local meetings. Multiple reminder emails were sent to members to optimize numbers of respondees. Due to utilization of different channels, it was not possible to provide a reliable response rate.

The target population were practicing pediatricians. Other medical professionals were automatically excluded through logics applied at the first survey question, covering current practice as a pediatrician. It was stated at the start of the survey, that participation implied informed consent for anonymous use of answers for scientific purposes.

2.2 | Survey

The survey included 41 questions, with single and multiple response questions concerning (1) demographics, (2) diagnosis of overweight/obesity, (3) use of guidelines for diagnosis and treatment of MASLD in children, (4) current practices in screening for MASLD and comorbidities, (5) utilized treatment options, (6) follow-up of children with MASLD, and (7) indications for liver biopsy for MASLD in children. The survey was tested multiple times within the team to ensure clarity and appropriate length. The survey can be found in appendix 1.

2.3 | Data collection and statistical analysis

Data collection was performed between 20 May 2022 and 6 December 2022. Individual results ($n = 673$) were exported from Survey Monkey. Statistical analysis was performed with IBM SPSS Statistics 28.0.

Participants were eligible for inclusion if questions on demographics were completed. A total of 454 entries were included for data analysis. Data was assumed to be normally distributed following the Central Limit Theorem. Missing data were not imputated. Data are presented as percentages or number with percentage. Post hoc analyses regarding variation in responses between the largest contributing countries was assessed in a predetermined subset of questions in this survey.

3 | RESULTS

Entries from 454 pediatricians were analyzed in this study. Forty-one percent were general pediatricians, while 59% indicated they had a subspecialty or were in training for a subspecialty. Seventeen percent of pediatricians were specialized in gastroenterology and 4% in hepatology. Fifty-one percent works in a general hospital. Other pediatricians work in out-patient clinics (18.3%), university centers (15.9%), obesity centers (2.9%) and other clinic types, including primary care clinics and private clinics (11.2%). When asked how long they had been practicing as a pediatrician, 17.8% indicated less than 5 years, 21.6% indicated 6–10 years, 17% indicated 11–15 years, 9% indicated 16–20 years and 34.6% indicated more than 20 years of experience as a pediatrician. The majority of pediatricians practiced in Ukraine (57.5%), the Netherlands (19.2%), Poland (10.6%), Israel (4.2%) and the United Kingdom (3.1%). Others practiced in Austria, Germany, Czech Republic, France, Greece, Italy, Romania, Slovenia, Turkey and USA (combined 5.4%).

3.1 | Guidelines for MASLD

This section was completed by 331 pediatricians. When asked if they used a guideline for diagnosis and treatment of pediatric MASLD, 169 pediatricians (51.1%) indicated that they did so. Fifty-two pediatricians (15.7%) indicated they were familiar with the guidelines, but do not follow them, while 110 pediatricians (33.2%) indicated they were not familiar with any guideline for MASLD.

In the group that follows guidelines, 44 pediatricians (32.4%) indicated they followed all recommendations in the guidelines, while 92 (67.6%) indicated that they followed guidelines partially. Sixty-eight pediatricians (63%) were of the opinion that the guidelines should be revised. Only 29 pediatricians (21%) indicated they were fully satisfied with the current guidelines and 21 (15%) had no opinion on this subject. The most frequently used guideline was the ESPGHAN Position Paper (34.6%).[10] Other frequently utilized guidelines were the NASPGHAN guideline (22.8%)[7] and AASLD Practice Guidance paper (14%).[9] Use of guidelines, stratified by subspecialty and country of practice is detailed in Table 1.

3.2 | Screening for MASLD

This segment of the survey was only shown to pediatricians that indicated using any guideline ($n = 169$), with 154 completing the following questions. Seventy-six pediatricians (49.4%) indicated to screen for MASLD in all children with overweight/obesity, while 33 (21.4%) only performed screening in children with overweight/obesity, if other metabolic disturbances were found. Fifty-six (36.4%) indicated they only screened children with obesity. Thirty-eight (24.6%) pediatricians also screened children with normal weight for MASLD, when metabolic disturbances were found.

When asked what tools they used for screening for MASLD, 150 out of 158 pediatricians (95.6%) indicated using liver function tests (aspartate transaminase (AST) and ALT). One hundred twenty-five pediatricians (79.1%) indicated imaging for screening, with all 125 pediatricians using abdominal ultrasound, 18 pediatricians including hepato-renal-index (HRI) measurement in the ultrasound, 25 using continuous attenuation parameter (CAP, Fibroscan©) and 15 utilizing magnetic resonance (MR) imaging. Forty pediatricians (25.3%) utilized predictive scores (including Fibrotest, enhanced liver fibrosis (ELF) test and PNFS) and 22 pediatricians (13.9%) indicated using liver biopsy to screen for MASLD. Tools utilized for screening, stratified by subspecialty and country of practice are detailed in Table 2.

One hundred ten out of 158 pediatricians (69.6%) indicated using elevated ALT levels as indication to confirm diagnosis of MASLD in children with overweight/obesity in their practice, while 101 (63.9%) used presence of liver steatosis on imaging, 28 (17.7%) indicated using CAP values suggestive for liver steatosis/fibrosis, 24 (15.2%) used predictive tests (Fibrotest, ELF test or PNFS) and 26 pediatricians (16.5%) indicated they confirmed diagnosis when liver steatosis/fibrosis was present in biopsy.

When asked if they performed additional diagnostic work-up for other causes than MASLD, 62 out of 211 pediatricians (29.4%) indicated they did not perform a diagnostic work-up for other causes (i.e. hepatitis and metabolic diseases).

3.3 | Treatment

This section was completed by 221 pediatricians. When asked about treatment options for children with MASLD, 204 pediatricians (92.3%) indicated they prescribed some form of treatment. Most pediatricians ($n = 200$, 98%) prescribed a form of lifestyle intervention. Additional indicated treatment options were pharmacotherapy,

TABLE 1 Use of guidelines for pediatric MASLD, stratified by subspecialty and country of practice.

	Specialty			Country of practice				
	General	*GE*	*Hep*	*Ukraine*	*NL*	*Poland*	*Israel*	*UK*
Do you use a guideline for diagnosis and treatment of pediatric MASLD?								
Yes	43.1% (60/139)	73.1% (49/67)	60% (12/20)	52.7% (79/150)	42.9% (36/84)	59.1% (26/44)	11.7% (2/17)	77% (10/13)
No, I am familiar with guidelines but do not use them	15.1% (21/139)	13.4% (9/67)	20% (4/20)	18.7% (28/150)	6% (5/84)	18.2% (8/44)	29.4% (5/17)	15.4% (2/13)
No, I am not familiar with guidelines	41.9% (58/139)	13.4% (9/67)	20% (4/20)	28.7% (43/150)	51.1% (43/84)	22.7% (10/44)	58.8% (10/17)	7.7%% (1/13)
Do you follow the recommendations in this guideline?								
Yes, all recommendations	30% (12/40)	20.9% (9/43)	58.3% (7/12)	39% (23/59)	23.3% (7/30)	30% (6/20)	*n* = 1	30% (3/10)
Yes, but only partially	70% (28/40)	79.1% (34/43)	41.7% (5/12)	61% (36/59)	76.7% (/30)	70% (14/20)	0%	70% (7/10)
Which guideline do you follow regarding pediatric MASLD?								
AASLD Practice Guidance (2018)	12.5% (5/40)	7% (3/43)	8.3% (1/12)	20.3% (12/59)	0%	10% (2/20)	0%	0%
BASL Guidance Document (2018)	0%	2.3% (1/43)	0%	3.4% (2/59)	0%	0%	0%	0%
BSPGHAN Guidelines (2020)	15% (6/40)	14% (6/43)	16.7% (2/12)	15.3% (9/59)	0%	0%	0%	90% (9/10)
EASL-EASD-EASO Guidelines (2016)	2.5% (1/40)	2.3% (1/43)	0%	1.7% (1/59)	0%	5% (1/20)	0%	0%
ESPGHAN Position Paper (2012)	27.5% (11/40)	41.8% (18/43)	50% (6/12)	28.8% (17/59)	33.3% (10/30)	65% (13/20)	*n* = 1	10% (1/10)
NASPGHAN Guideline (2017)	22.5% (9/40)	23.3% (10/43)	25% (3/12)	23.7% (14/59)	30% (9/30)	20% (4/20)	0%	0%
Other guidelines	20% (8/40)	9.3% (4/43)	0%	6.8% (4/59)	36.7% (11/30)	0%	0%	0%
What is your opinion on the current pediatric MASLD guidelines and should they be revised?								
Fully satisfied	22.5% (9/40)	14% (6/43)	16.7% (2/12)	37.3% (22/59)	6.7% (2/30)	15% (3/20)	0%	10% (1/10)
Partially satisfied, they should be revised	50% (20/40)	79.1% (34/43)	66.7% (8/12)	50.8% (30/59)	50% (15/30)	65% (13/20)	*n* = 1	80% (8/10)
Not satisfied, they should be revised	5% (2/40)	2.3% (1/43)	16.7% (2/12)	5.1% (3/59)	3.3% (1/30)	5% (1/20)	0%	0%
No opinion	22.5% (9/40)	4.6% (2/43)	0%	6.8% (4/59)	40% (12/30)	15% (3/20)	0%	10% (1/10)

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BASL, Belgian Association for the Study of the Liver; BSPGHAN, British Society of Pediatric Gastroenterology, Hepatology and Nutrition; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition; GE, pediatric gastroenterology; Hep, pediatric hepatology; MASLD, metabolic dysfunction-associated steatotic liver disease; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; NL, the Netherlands; UK, United Kingdom.

TABLE 2 Tools utilized for screening and follow-up of pediatric MASLD, stratified by subspecialty and country of practice.

	Specialty			Country of practice				
Utilized tools	***General***	***GE***	***Hep***	***Ukraine***	***NL***	***Poland***	***Israel***	***UK***
Liver function tests (screening)	98% (49/50)	100% (44/44)	100% (15/15)	84.1% (37/44)	100% (54/54)	100% (23/23)	100% (10/10)	100% (6/6)
Liver function tests (follow-up)	84.2% (32/38)	97.2% (35/36)	94.1% (16/17)	86.5% (32/37)	93.7% (30/32)	92.9% (13/14)	100% (3/3)	100% (11/11)
Ultrasound (screening)	58% (29/50)	86.3% (38/44)	86.7% (13/15)	47.7% (21/44)	59.2% (32/54)	95.6% (22/23)	80% (8/10)	100% (6/6)
Ultrasound (follow-up)	55.3% (21/38)	86.1% (31/36)	76.5% (13/17)	51.4% (19/37)	68.7% (22/32)	92.9% (13/14)	66.7% (2/3)	72.7% (8/11)
CAP (screening)	2% (1/50)	22.7% (10/44)	46.7% (7/15)	20.5% (9/44)	5.5% (3/54)	17.4% (4/23)	0%	16.7% (1/6)
CAP (follow-up)	7.8% (3/38)	30.5% (11/36)	52.9% (9/17)	27% (10/37)	12.5% (4/32)	35.7% (5/14)	0%	18.1% (2/11)
MR imaging (screening)	2% (1/50)	9.1% (4/44)	13.3% (2/15)	25% (11/44)	3.7% (2/54)	4.3% (1/23)	0%	0%
MR imaging (follow-up)	7.8% (3/38)	11.1% (4/36)	17.7% (3/17)	21.6% (8/37)	3.1% (1/32)	14.3% (2/14)	0%	0%
Predictive scores (screening)	18% (9/50)	22.7% (10/44)	40% (6/15)	59.1% (26/44)	5.5% (3/54)	13% (3/23)	0%	33.3% (2/6)
Predictive scores (follow-up)	21.1% (8/38)	25% (9/36)	47.1% (8/17)	54% (20/37)	15.6% (5/32)	7.1% (1/14)	33.3% (1/3)	36.3% (4/11)
Biopsy (screening)	2% (1/50)	25% (11/44)	46.7% (7/15)	11.4% (5/44)	5.5% (3/54)	21.7% (5/23)	0%	16.7% (1/6)
Biopsy (follow-up)	0%	13.9% (5/36)	11.8% (2/17)	8.1% (3/37)	0%	7.1% (1/14)	0%	9.1% (1/11)

Note: Data presented as percentages (*n*/total *n*). Liver function tests include alanine transaminase and aspartate transaminase, predictive scores include Fibrotest, Enhanced Liver Fibrosis test and Pediatric NAFLD Fibrosis Score.

Abbreviations: CAP, continuous attenuation parameter; GE, gastroenterology; Hep, hepatology; MASLD, metabolic dysfunction-associated steatotic liver disease; MR, magnetic resonance; NL, the Netherlands; UK, United Kingdom.

including metformin, pioglitazone, statins and ursodeoxycholic acid ($n = 70$, 35%), supplements, including vitamin D, vitamin E, antioxidant and omega-3 supplements ($n = 87$, 42.6%) and different probiotics, including but not limited to lactobacillus rhamnosus GG, bifid bacteria and VSL3 ($n = 39$, 19.1%). Utilized treatment options, stratified by subspecialty and country of practice can be found in Table 3.

Thirty-one pediatricians indicated they did not prescribe treatment, but immediately referred these patients to a gastroenterologist or hepatologist, while 10 pediatricians indicated that they observed patients with MASLD without prescribing treatment.

When asked what patients they prescribed pharmacotherapy, 34 out of 208 pediatricians (16.3%) indicated they utilized pharmacological treatment for patients with histologically confirmed steatohepatitis, 29 (13.9%) utilized pharmacotherapy for patients with histologically confirmed liver fibrosis and 25 (12%) utilized pharmacotherapy for patients with liver fibrosis according to liver imaging. In addition to this, 44 pediatricians (21.2%) utilized pharmacotherapy for patients with abnormal biochemistry, 50 (24%) for patients with dyslipidemia, 63 (29.8%) for patients with insulin resistance and 32 (15.4%) for patients with a BMI over 35 kg/m^2.

In contrast, 82 pediatricians (39.4%) indicated that they did not use any pharmacological treatment for children with MASLD and 26 pediatricians (12.5%) explicitly stated that pharmacological treatment for MASLD in children is currently unavailable.

3.4 | Monitoring and follow-up

This segment was completed by 221 pediatricians. When asked what they considered as monitoring proxy for treatment of MASLD in children, most pediatricians ($n = 134$, 60.6%) indicated weight reduction as a proxy. Improvement of liver anomalies was frequently specified, including improvement of liver function tests ($n = 131$, 59.3%), steatosis ($n = 124$, 56.1%), steatohepatitis ($n = 76$, 34.4%), liver fibrosis ($n = 58$, 26.2%), liver stiffness ($n = 37$, 16.7%) and/or improvement of liver fibrosis scores ($n = 39$, 17.6%). Improvement of comorbidities was also indicated, including improvement of insulin sensitivity ($n = 91$, 41.2%) and dyslipidemia ($n = 94$, 42.5%). Nine pediatricians (4.1%) explicitly stated on this question that they did not know what to use as monitoring proxy for MASLD in children.

One hundred twenty-three pediatricians (55.7%) indicated that they follow-up children with MASLD in their practice (of which 31.7% are general pediatricians, 30% pediatric gastroenterologists and 14.6% pediatric hepatologists), while 69 pediatricians (31.2%) indicated that after referral patients are followed by a gastroenterologist and 29 pediatricians (13.1%) indicated they did not follow-up these patients at all (of

TABLE 3 Treatment options for pediatric MASLD, stratified by subspecialty and country of practice.

	Specialty			Country of practice				
Treatment options for MASLD	***General***	***GE***	***Hep***	***Ukraine***	***NL***	***Poland***	***UK***	***Israel***
Lifestyle intervention	90.6% (77/85)	95.9% (47/49)	94.4% (17/18)	91.6% (76/83)	82.2% (51/62)	100% (31/31)	92.3% (12/13)	90% (9/10)
Pharmacotherapy	35% (26/85)	40.8% (20/49)	11.1% (2/18)	55.4% (46/83)	11.3% (7/62)	29% (9/31)	7.7% (1/13)	10% (1/10)
Supplements	36.5% (31/85)	40.8% (20/49)	33.3% (6/18)	63,9% (53/83)	6.5% (4/62)	64.5% (20/31)	15.4% (2/13)	10% (1/10)
Probiotics	20% (17/85)	14.3% (7/49)	16.7% (3/18)	36.1% (30/83)	0%	19.4% (6/31)	0%	10% (1/10)

Note: Data presented as percentages (*n*/total *n*).

Abbreviations: GE, gastroenterology; Hep, hepatology; MASLD, metabolic dysfunction-associated steatotic liver disease; NL, the Netherlands; UK, United Kingdom.

which 37.9% general pediatricians and 13.8% pediatric gastroenterologists).

Pediatricians that had indicated to follow-up children in their practice ($n = 123$) were asked what they used for follow-up, with 117 pediatricians completing this question. One hundred nine pediatricians (93.1%) indicated using liver function tests to follow-up MASLD in children and 93 pediatricians (79.5%) used imaging, of which 83 pediatricians (70.9%) utilized ultrasound (10 included HRI measurement in this), 29 pediatricians (24.8%) utilized CAP from Fibroscan and 14 pediatricians (12%) utilizing any MR imaging. Predictive scores (Fibrotest, ELF test or PNFS) were used by 35 pediatricians (29.9%) and 7 pediatricians (6%) used liver biopsy for follow-up. Tools utilized for follow-up, stratified by subspecialty and country of practice are detailed in Table 2.

Frequency of follow-up was diverse. Most pediatricians ($n = 62$, 53%) reported seeing children every 6 months at their (out-patient) clinic. Twenty-three pediatricians (19.7%) saw patients every 3 months while 28 pediatricians (23.9%) indicated that they followed-up children with MASLD every year.

When asked how frequently they performed monitor testing in patients with confirmed MASLD, 25 pediatricians (21.4%) reported performing tests every 3 months, 45 (38.5%) every 6 months, 31 (26.5%) every year and 5 pediatricians (4.3%) performed monitor tests every 2 years.

3.5 | Liver biopsy

Sixty-two out of 211 pediatricians (29.4%) reported performing liver biopsies in their institution. Follow-up questions regarding liver biopsy were only asked of these pediatricians, with 53 pediatricians completing this survey segment. The most frequently used indications for performing liver biopsy were “uncertainty in diagnosis” ($n = 28$, 52.8%), “noninvasively measured fibrosis” or “rapid progression of fibrosis score” (both $n = 18$, 34%) and/or hepatosplenomegaly ($n = 16$, 30.2%). “Elevated transaminase levels above two times gender-specific upper limit of normal” ($n = 14$, 26.4%) and hyperechogenicity or steatosis on ultrasound ($n = 12$, 22.6%) were also indicated.

Most pediatricians ($n = 25$, 47.2%) observed patients for 6–12 months before liver biopsy. Others observed for <6 months ($n = 12$, 22.6%) or >12 months ($n = 12$, 22.6%). One pediatrician performed liver biopsy as soon as possible.

When asked how often pediatricians performed liver biopsy in children with MASLD, the majority ($n = 40$, 75.5%) indicated that liver biopsy was performed in 10% or less than 10% of pediatric MASLD cases. Risk of complications was most often indicated ($n = 25$, 47.2%) as a concern when performing liver biopsy. Inconclusive test results were indicated as a concern by 9 pediatricians (17%), while 17 pediatricians (32.1%) indicated that they didn't have any concerns regarding liver biopsy in children with MASLD.

3.6 | Post-hoc analyses variation between countries

There was significant variation in responses between countries when asked if they used any guidelines ($p < 0.001$), which guidelines they used ($p < 0.001$), what tools they used for screening (blood tests: $p = 0.002$; predictive scores: $p < 0.001$; imaging: $p = 0.015$; biopsy: $p = 0.004$), what treatment options they utilized for MASLD in children (pharmacotherapy, supplements and probiotics: all $p < 0.001$) and if they performed liver biopsy in children with MASLD ($p < 0.001$). Only in response to the question if they prescribed any lifestyle management, no significant variation was observed between different countries ($p = 0.192$).

4 | DISCUSSION

This study is the first to evaluate daily practices of European and Israeli pediatricians in screening, diagnosis and treatment of MASLD in children. We observed considerable variation in all practices, including the use of guidelines, utilized treatment options and follow-up practices. In addition to this, our study is the first to assess how liver biopsy is utilized by pediatricians in children with MASLD.

Our findings demonstrate a striking variation in the treatment options utilized by pediatricians. Although almost all pediatricians indicated advising a form of lifestyle treatment to children with MASLD, many also resorted to additional treatment options that are outside the recommendations of current guidelines, including pharmacotherapy, supplements and probiotics.

Pharmacotherapy was prescribed by 35% of general pediatricians, 41% of pediatric gastroenterologists and 11% of hepatologists in this study. Pediatricians in Eastern Europe prescribed pharmacotherapy more often (55% of Ukrainian and 29% of Polish pediatricians), compared to Western Europe (11% of Dutch and 8% of UK pediatricians) and 10% of Israeli pediatricians. Most pediatricians prescribing pharmacotherapy indicated using guidelines for diagnosis and treatment of MASLD (ESPGHAN Position paper (29%), AASLD Practice Guidance paper (25%) and NASPGHAN guideline (25%)). However, none of these guidelines currently recommends use of pharmacotherapy in children with MASLD, as pharmacotherapy has not been proven to benefit most children with MASLD.[6] The AASLD Practice Guidance, intended for

adult patients, indicates that only pioglitazone may be used in patients with biopsy proven NASH, based on an individual risk-benefit analysis.[9] Other pharmacotherapy, including metformin and GLP-1 agonists is not recommended for treating MASLD. The ESPGHAN Position paper does not provide any treatment recommendations.[10] A plausible explanation for the discrepancy in clinical practice versus recommendations is provided in this study, as the majority (75%) of pediatricians prescribing pharmacotherapy indicated only partially following recommendations in guidelines. Nevertheless, this is an alarming observation in a medical profession that usually provides highly standardized care.

Similar results are found when evaluating use of supplements and probiotics. Supplements were prescribed by 37% of general pediatricians, 41% of pediatric gastroenterologists and 33% of hepatologists. Eastern European pediatricians prescribed supplements more often (64% of Ukrainian and 65% of Polish pediatricians), compared to Western Europe (7% of Dutch and 15% of UK pediatricians) and Israeli pediatricians (10%). Most of these pediatricians utilize the ESPGHAN Position Paper (37%), NASPGHAN guideline (24%) and the AASLD Practice Guidance (22%). Probiotics were prescribed by 20% of general pediatricians, 14% of pediatric gastroenterologists and 17% of hepatologists. Probiotics were almost solely prescribed by pediatricians in Eastern Europe (36% of Ukrainian and 19% of Polish pediatricians), compared to only one Israeli pediatrician. Western European pediatricians did not prescribe probiotics for MASLD in this study. Guidelines utilized by pediatricians prescribing probiotics were the ESPGHAN Position Paper (36%), AASLD Practice Guidance (28%) and the NASPGHAN guideline (24%). However, none of these guidelines recommends the use of supplements or probiotics for treatment of MASLD in children, as different studies present conflicting results, and most studies are small and of short duration.[6,9,10] For example, vitamin E supplementation was associated with significant improvement of liver histology in the TONIC trial with children aged 8–17 years, but other randomized controlled trials in children found that supplementation was not superior to lifestyle intervention alone.[6] Two small studies of short duration have tested the benefit of probiotics (Lactobacillus GG and VSL3), with only one study observing significant ALT improvement with supplementation compared to placebo.[6] These tentative results may explain why pediatricians do prescribe supplements and/or probiotics to children with MASLD, although it is currently not recommended to do so by guidelines. Another explanation might again be provided by the fact that majority of these pediatricians indicated that they only partially follow recommendations in guidelines.

Lifestyle treatment is consistently prescribed by general pediatricians, pediatric gastroenterologists and hepatologists and among pediatricians from the various countries in this study. However, it must be mentioned that lifestyle interventions suffer from lower compliance rates and that it is not yet elucidated which lifestyle changes benefit children with MASLD most. Future research into these variables is necessary to improve lifestyle treatment for children with MASLD.

To assess the practice variability observed in this study, awareness of guidelines for MASLD in children among pediatricians was evaluated. A remarkable number of pediatricians (33.2%) indicated they were not familiar with any guideline for diagnosis and treatment of MASLD in children. Half of these pediatricians were general pediatricians, but 12% of these pediatricians indicated a subspecialty (in training) in pediatric gastroenterology or hepatology.

The observed unfamiliarity with guidelines likely contributes significantly to the variety in clinical practice observed in this study and may lead to potential under diagnosis and/or under management. This is an alarming observation, as with the increasing prevalence of MASLD in children, more children may become exposed to preventable health risks associated with MASLD.

However, other factors presumably also contribute to the observed practice variation, as 16% of pediatricians indicated they were familiar with guidelines, but do not follow them. In addition to this, 68% of pediatricians who indicated that they did follow guidelines for diagnosis and treatment of MASLD, followed these recommendations only partially, contributing further to practice variation. Even among pediatricians indicating that they followed all recommendations in guidelines, practice variation was observed. Lack of consistency between different guidelines for MASLD is likely a key factor in this. The inconsistency in guidelines is in part due to the lack of knowledge about the natural history of MASLD in children, but is also driven by the absence of accurate and sensitive noninvasive diagnostic tools, which leads to heterogeneity between study populations in research and complicates comparison of study results. These are important factors to tackle in future research. In addition to this, results showed that 29% of the pediatricians did not perform a diagnostic work-up for other causes in patients with MASLD, which is possibly due to the lack of awareness of the diagnosis in children amongst practicing pediatricians. However, new consensus on both nomenclature of MASLD and positive diagnosis were recently published.[13,14] It is likely that this will contribute to more awareness amongst practicing pediatricians and will lead to more consensus in diagnosis of MASLD.

Another contributing factor may be that treatment and follow-up were performed by both subspecialists and general pediatricians. General pediatricians may

have received less training in the specialist area of pediatric hepatology and may rely for guidance on the inconsistent guidelines, unintentionally contributing to practice variation. Lastly, factors including but not limited to availability of specialist equipment like Fibroscan or MR spectroscopy or financial resources, were not evaluated in this study, but may also have contributed to practice variation. Additional research into these and other factors that may influence decision making by pediatricians caring for children with MASLD would be a valuable addition to the body of evidence necessary for improving care for these children.

Variation in practice was not only seen between European and Israeli pediatricians, but also when comparing with pediatric gastroenterologists in the United States (US). Shapiro et al. reported that half of US pediatric gastroenterologists utilized medication for management of MASLD in children, specifically vitamin E (31%), metformin (9%) and fish oil (8%).[15] In this study, only 16% of gastroenterologists and 11% of hepatologists prescribed vitamin E, while 27% and 5% prescribed metformin and 28% and 16% prescribed omega-3 fatty acids respectively, despite 27% of participants using the same NASGPHAN guideline as US pediatric gastroenterologists.

Part of the evaluation of daily practices in this study, was assessing how pediatricians utilize liver biopsy in children with MASLD. Although considered the gold standard for MASLD diagnosis, only 29% of pediatricians utilized liver biopsy in children with MASLD in their institution. Most of these pediatricians were specialized in gastroenterology (45%) or hepatology (29%). They requested/performed liver biopsy in 10% or less than 10% of cases of pediatric MASLD. There are no other studies performed in children that inform on how often liver biopsy is performed in this group. Fortunately, some guidance on indications for liver biopsy is available. The NASPGHAN guideline advises to consider a liver biopsy in children with an increased risk for NASH or fibrosis (presence of hepatomegaly, ALT levels above 80 U/L, or an AST/ALT ratio above 1).[6] These indications match the most frequently utilized indications by pediatricians in this study. However, when utilizing these recommendations, it is important to be aware of a possible lack of standardization and harmonization of ALT assays between different institutions and/or countries.

Risk for complications is most frequently mentioned as a barrier for performing biopsy in children with MASLD in this study. There is no literature on complications from biopsy in children with MASLD specifically, but limited data is available from children with other hepatic diseases.[16] A cohort study with 469 children undergoing liver biopsy, reported bleeding in 2.8% of cases, bile leakage in three cases (0.6%) and one case of pneumothorax (0.2%).[17] No pediatric data exists on incidence of infection, haemothorax or organ perforation after liver biopsy. In adults, pain is the most widely reported complication, but no data exists in children. However, the ESPGHAN Hepatology Committee states that pain after liver biopsy in children is "usually well tolerated and can be controlled with minor analgesia".[16] When translating these findings to the population of children with MASLD, the absence of known risk factors for complications should also be taken into account.[16] Children with MASLD usually do not present with impaired hemostasis, kidney- or acute liver failure or previous malignancy or bone marrow transplantation. Absence of these risk factors may further reduce the already small risk for complications after liver biopsy in children with MASLD. However, the choice for a liver biopsy should always be made on a personal risk-benefit analysis.

5 | STRENGTHS AND LIMITATIONS

To our knowledge, this is the first study that evaluates clinical practices in Europe regarding MASLD in children. We evaluated screening, diagnosis, treatment and follow-up practices in a large, international cohort of pediatricians. Representation of countries was skewed, with an overrepresentation of Ukraine, the Netherlands and Poland. This is most likely due to the fact that the authors of this article are residents of these countries. Post-hoc analyses were performed on key questions from the survey to assess variation in responses between countries. However, the authors felt it was important to use all responses on clinical practice to reflect the views of as many pediatricians as possible. A limitation of this study is that it provides self-reported data, rather than an objective review of medical practices. In addition to this, experience of pediatricians was only assessed through years of practice and presence of a subspecialty, while specific exposure to patients with pediatric MASLD was not determined.

6 | CONCLUSION

This study found considerable variation in screening, diagnosis and treatment practices among European and Israeli pediatricians, and a clear demand for new, uniform guidelines for MASLD in children.

To establish new guidelines, we need accurate noninvasive tools for identification of children with different stages of MASLD. By accurately identifying patients and disease progression, risk profiles can be composed and novel and current management options can be adequately tested.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts 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.

How to cite this article: Lubrecht JW, van Giesen GHJ, Jańczyk W, et al. Pediatricians' practices and knowledge of metabolic dysfunction-associated steatotic liver disease: an international survey. *J Pediatr Gastroenterol Nutr*. 2024;1-10. doi:10.1002/jpn3.12124