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Research Article

JOURNAL OF PEDIATRICS, PERINATOLOGY AND CHILD HEALTH

ISSN: 2641-7405

Normative Values for Liver Ultrasound Shear Wave Elastography, Shear Wave Dispersion and Attenuation Imaging in a Pediatric Cohort during Free Breathing

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Abstract

Ultrasound markers for liver characterization show promise to improve diagnostics but normative data in children are scarce. The purpose was to report normative values of liver ultrasound Shear Wave Elastography (SWE), Shear Wave Dispersion (SWD) and Attenuation Imaging (ATI), reflecting hepatic elasticity, viscosity, and steatosis respectively, in children. Seventy-one children, without liver disease, referred for ultrasound-guided kidney biopsy were consecutively enrolled. Individuals with BMI>25 were excluded. SWE, SWD and ATI were measured during free breathing, fasting >4h and under general anesthesia (n=60) and/or while awake (n=42) and correlation to anesthesia, sex, age, and BMI were investigated. The mean age and BMI were 10.8 years (range 2.3-17.8), and 18.4 (range 12.8-25.0) respectively, 49% were boys. Averages and standard deviations were SWE 4.9±1.1kPa, SWD 11.9±1.5m/s/kHz, and ATI 0.56±0.09dB/cm/MHz. There was no difference between sexes ($p>0.15$), effect of anesthesia ($p>0.32$), or between age groups (0-5, 5-12, 12-18 years; $p>0.15$). A moderate correlation was found between BMI and SWD ($R=-0.43$, $p=0.006$), while no other significant correlations were identified ($R<0.31$, $p>0.08$). Normative pediatric values for SWE, SWD and ATI, during both free breathing and fasting, are reported. Other than a weak negative correlation between BMI and SWD, the lack of significant associations implies that these normative values can be applied across ages and sexes.

Keywords: Elastography; Liver; Shear wave elastography; Shear wave dispersion; Attenuation imaging; Pediatric radiology

Introduction

Chronic liver disease is rising in children, driven primarily by metabolic dysfunction-associated steatotic liver disease [1]. As more treatment options are available, there is an increasing need to evaluate the liver for diagnosis and surveillance of disease. Liver biopsy is considered the gold standard [2,3], however, this is an expensive and invasive procedure that additionally requires anesthesia in the majority of pediatric patients.

Non-invasive imaging methods to evaluate the liver have emerged in recent years [3-23]. Ultrasound-based liver stiffness measurement with shear wave elastography (SWE) has been shown to be a valid method for liver fibrosis detection and staging in chronic liver diseases in adults. However, reference values for infants and young children are still lacking and SWE needs validation in large cohort pediatric studies before being implemented

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Citation: Sarovic Darko, Cetinic Ivan, Ekvall Nils, Lagerstrand Kerstin, de Lange Charlotte, Hebelka, Hanna. Normative Values for Liver Ultrasound Shear Wave Elastography, Shear Wave Dispersion and Attenuation Imaging in a Pediatric Cohort during Free Breathing. Journal of Pediatrics, Perinatology and Child Health. 8 (2024): 53-61.

Received: March 27, 2024
Accepted: April 12, 2024
Published: April 22, 2024

Darko S, et al., J Pediatr Perinatol Child Health 2024
DOI:10.26502/jppch.74050181

in clinical routine. Recent advancements in ultrasound techniques have provided additional, promising, ultrasound-based liver markers: shear wave dispersion (SWD) and attenuation imaging coefficient (ATI). These show promise to provide a more detailed assessment of liver characteristics non-invasively. SWD is based on the elastography technique and provides information on the frequency-dependent variation in velocity of the shear wave [3,24], which is related to tissue viscosity [25]. Since the liver is an organ with viscoelastic properties, SWD thus has potential to provide biomechanical information concerning the state of the liver. For example, as a potential marker of liver inflammation [26]. ATI, on the other hand, quantifies the attenuation of the ultrasound beams as it moves through the tissue, and has been shown to reflect steatosis of the liver in adults [27].

Although publications in the area have increased over the past 2-3 years, there are only approximately 20 studies reporting on SWD in clinical adult patients with various underlying diseases [3,4,7-10,12,13,15-17,25,28,29]. About half of these have used histology as a reference method and only half studied cohorts of over 100 individuals. Within the pediatric population, SWD studies are very scarce. To our knowledge, only a few studies exists [4,5,22,23] of which only two use histology as the reference method [4,5]. Likewise, studies regarding ATI in children are also scarce, especially with histological correlation [23,30,31]. Only small feasibility studies have been published regarding ATI with biopsy correlate in children [5]. To use these image-based liver markers clinically in differentiation between normal and pathological conditions, it is important to establish how the markers appear in a pediatric population without liver disease. Establishing normative values for these ultrasound biomarkers in children has seen some efforts [22,23,31], but data is very limited and diverse, and results are contradictory regarding the influence of age and sex.

The aim of the present study was to define normative values of SWE, SWD and ATI, during free breathing and fasting, in a cohort of children without a known history of liver disease.

Methods

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the regional ethical review board of the University of Gothenburg (DNR: 634-18) and all included participants, depending on their age, either provided their informed consent or assent (in which case their guardians consented).

Sample

We consecutively recruited 71 children undergoing ultrasound guided kidney biopsy between May 2021 and October 2023 that were included as controls in an ongoing large scale study investigating SWE, SWD and ATI in children with liver disease in correlation to biopsy, both during awake and sedated state. Therefore, a control cohort examined under similar examinations conditions was demanded. We excluded individuals with known liver disease or hepatotoxic medication. In individuals for whom their established or suspected kidney disease may secondarily affect liver function, liver enzymes were obtained and those with abnormal liver enzymes were excluded. Overweight individuals, i.e., BMI > 25 were excluded (six individuals). The final sample included 65 individuals.

The age range was 2.3–17.8 years (mean 10.8), the BMI ranged from 12.8 to 24.9 (mean 18.4), and 49.2% were boys (n = 32). We were not able to record SWD and ATI in all participants, the reason was that the software was lacking in one out of three used ultrasound machines. In total 65 patients, 61 were scanned during sleep (n for SWE, SWD, and ATI were 61, 41 and 33 respectively). In addition, 40 patients were scanned when awake (n for SWE, SWD, and ATI were 40, 34 and 32 respectively). Fifteen of the included participants have previously been presented in a feasibility study, where they constituted a control cohort to 35 children with liver disease [5].

Scanning

Intercostal ultrasound scans of the right liver lobe were performed using Canon Medical, Aplio i800 with a curved transducer iC8× MHz and according to guidelines from the Society of Radiologists in Ultrasound Liver Elastography Consensus Statement [32]. Scans were performed by one out of four pediatric radiologists with at least 5 years' experience within the field, in the supine position with slight elevation of the right side of the body and the right arm above the head, avoiding transducer pressure. The participants were fasting (at least 4 hours) and scanned with multimodal sampling during free breathing when awake (in cooperating individuals) and immediately after, during general anesthesia ("sleep"). The SWE/SWD estimates were based on ten measurements 1.5-3 cm below the liver capsule. The ATI estimates were based on five measurements. We recorded the median, standard deviation (SD), inter-quartile range (IQR), and IQR/median for the following ultrasound biomarkers: SWE (kPa), SWD (m/s KHz), and ATI (db/cm/MHz). SWE and SWD estimates where the corresponding SWE had an IQR/median above 0.30, and ATI estimates with a median R^2 <0.8 were excluded.

Clinical variables

For each participant, we recorded sex, age, height, weight, and BMI, as well as the reason for performing the kidney biopsy. Indications for biopsy are presented in Table 1.

Statistical analyses

The normality of each biomarker was assessed using one-sample Kolmogorov-Smirnov (KS) test and skewed variables

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DOI:10.26502/jppch.74050181

were log-transformed prior to comparisons to improve linearity and homoscadasticity. Since all three biomarkers departed from normality, non-parametric tests were used.

To simultaneously assess group-wise differences in mean, variance, and skewness of our non-normally distributed data, we used the two-sample KS test to assess the effect of anesthesia (sleep vs. awake) and sex (male vs. female). Since there were no effect of sex or anesthesia, we included both sexes in all further analyses, and computed the intra-individual sleep-awake average (SAμ) for each biomarker between sleep and awake (to reduce random error between scans). The SAμ for each biomarker was compared with age and BMI using Spearman correlations. Finally, we separated the dataset into three age brackets (0-5 years, >5-12 years, >12-18 years) and compared the SAμ for each biomarker using Kruskal-Wallis test.

Holm-Bonferroni correction for three observations (SWE, SWD, ATI) was applied to a baseline alpha of $p = 0.05$ within each family of observations (p-thresholds of 0.017, 0.025 and 0.05). Interobserver reliability of SWE measurements, and indirectly SWD measurements, for the physicians participating in the current study have previously reported as excellent, as was intraobserver reliability measurements on previously obtained multimode cine-loops SWE sampling [33].

Table 1: Reasons for kidney biopsies.

Indication	Number
Persistent macroscopic or microscopic hematuria	13
Relapse from nephrotic syndrome	11
Persistent hematuria and albuminuria	10
Suspicion of IgA-nephropathy	7
Rising creatinine levels in patient with kidney transplant	7
Persistent albuminuria	4
Unknown kidney failure	4
Treatment evaluation for IgA neohropathy	3
Suspicion of Lupus Nephritis	2
Pain in left flank and macroscopic hematuria	1
Increasing creatinine levels in patient with nephrotic syndrome	1
Increasing creatinine levels in patient with granulomatosis polyangiitis	1
Evaluation of treatment in C3-Glomerulonephropathy	1
Total	**65**

Results

Outcomes for liver ultrasound biomarkers are presented in Table 2. There was no significant difference between sleep and awake (all $p \geq 0.32$; see Table 3) or between males and females for any of the biomarkers (all $p \geq 0.15$; see Table 3). Because there were no differences, the average between awake and sedated (SAμ) were used and both sexes were included in the following analyses.

There were no significant correlations between age and any of the ultrasound biomarkers ($p \geq 0.13$; see Figure 1). For BMI there was a significant correlation with SWD ($r = -.43$, $p = 0.006$), but not for the other biomarkers ($p \geq 0.11$; see Figure 1). After stratification of age into three age brackets, there were no significant differences between the groups for any of the ultrasound biomarkers (SWE: $p = 0.57$; SWD: $p = 0.29$; ATI: $p = 0.29$; see Figure 2).

Discussion

This study defines normative values for SWE, SWD and ATI during free breathing and fasting in children without known liver disease. Other than a weak negative correlation between BMI and SWD, the lack of significant associations implies that the normative values presented in this paper can be applied across ages and sexes.

To the best of our knowledge, only a handful of studies exist that report on SWD in children [4,5,22,23,34] and even fewer on normative values [32]. The mean SWD of 11.9 (m/s)/kHz in the current study is congruous with the mean SWD 11.4 (m/s)/kHz reported in 128 children without liver disease by Trout et al. [22]. Higher SWD, mean 12.96 (m/s)/kHz, was reported in 112 children without liver disease by Cetiner et al. [23]. Normative values in children appear higher comparted to adults [22], possibly attributed to age-related differences in viscoelastic properties [35]. Differences in tissue characteristics between the liver of children and adults exists, with increased collagen content in the adult liver. Thus, it seems reasonable that there may be differences in viscous liver properties, reflected by differences in normal SWD values [35]. However, the cohort in the current study was

Table 2: Liver ultrasound biomarkers.

	Sleep Mean ± SD (n)	Awake Mean ± SD (n)	SAμ Mean ± SD (n)
Elasticity (kPa)	4.7 ± 1.0 (61)	5.1 ± 1.3 (40)	4.9 ± 1.1 (62)
Dispersion (m/s/kHz)	11.6± 1.8 (41)	12.3± 1.7 (34)	11.9 ± 1.5 (43)
Attenuation (dB/cm/MHz)	0.5 ± 0.1 (33)	0.6 ± 0.1 (32)	0.6 ± 0.1 (39)
SAμ = average of sleep and awake, SD = Standard deviation.			

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DOI:10.26502/jppch.74050181

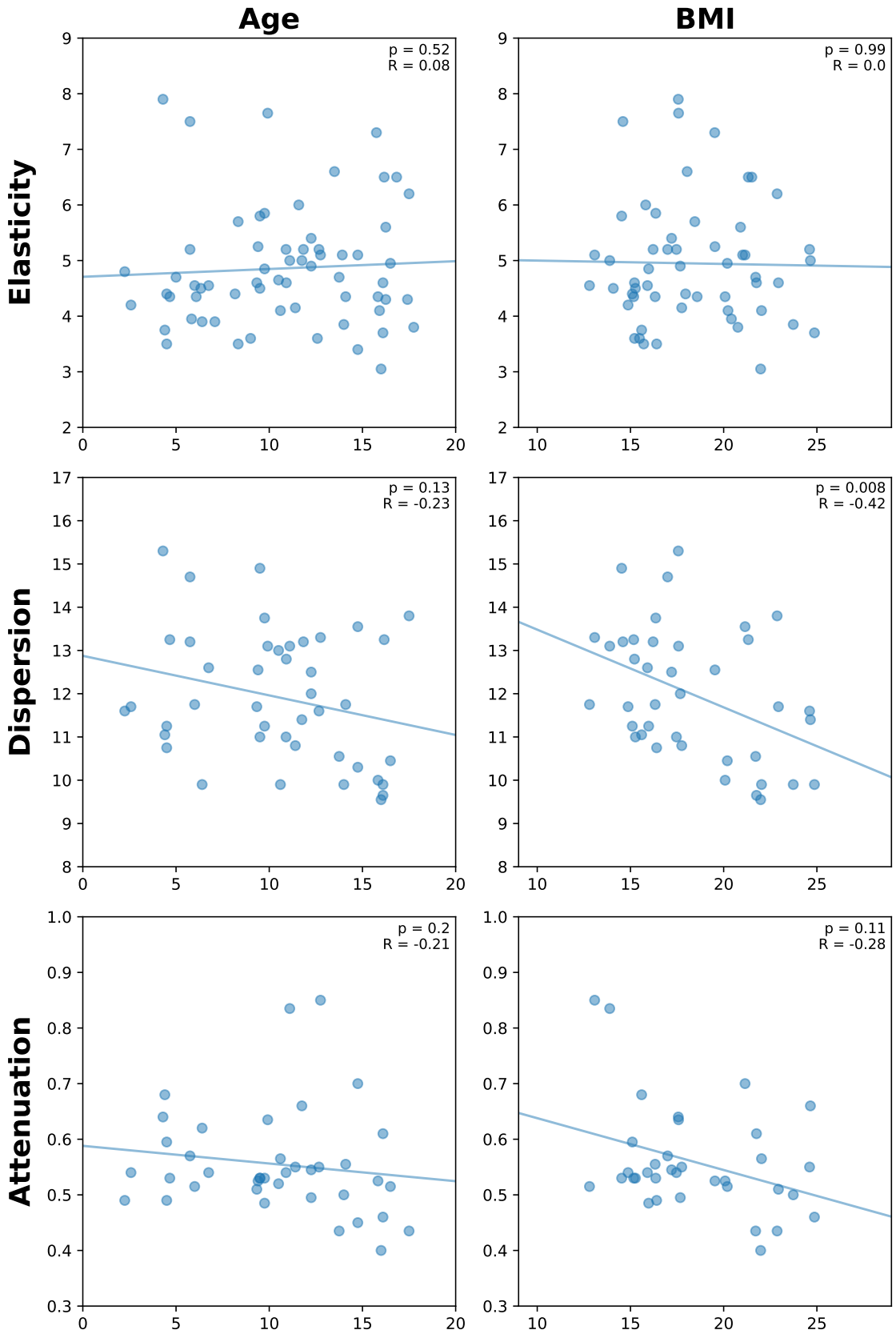

Figure 1: Correlations of liver ultrasound biomarkers with age and BMI. BMI = Body Mass Index.

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Table 3: Comparisons between ultrasound markers and clinical variables.

	Sex*	Anesthesia*
Elasticity (kPa)	p = 0.15	p = 0.48
Dispersion (m/s/kHz)	p = 0.81	p = 0.49
Attenuation (dB/cm/MHz)	p = 0.60	p = 0.32
*Tested with two-sample Kolmogorov-Smirnov test.		

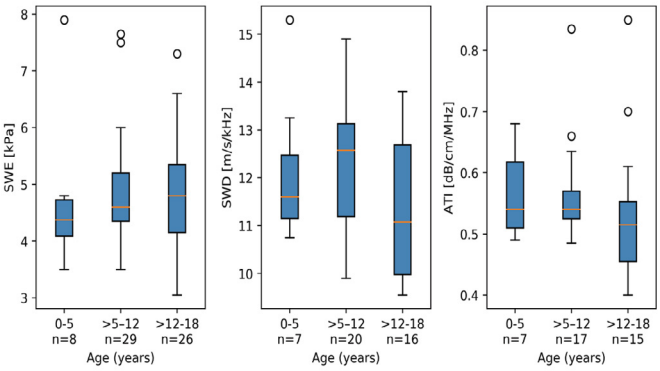

Figure 2: Comparison between different age brackets and the ultrasound biomarkers. SWE = Shear Wave Elastography, SWD = Shear Wave Dispersion, ATI = Attenuation Imaging, n = number of participants.

not entirely healthy, neither were the two previous pediatric studies, which is why it cannot be excluded that, even though they were not affected by "liver disease", other factors could have influenced the liver viscosity and therefore the SWD. Future studies are encouraged to determine normative values in a healthy pediatric cohort without any disease.

SWD has been proposed as a promising marker for inflammation [5,14,17,21,26]. In a feasibility study of 32 children with various types of liver diseases, a mean SWD of 14.4 (m/s)/kHz was found [5]. When excluding patients with biopsy verified inflammation the SWD remained high (13.1 m/s/kHz). This shows that also other factors seem to affect SWD. Since other conditions are known to affect the dispersion slope, such as such as cell necrosis, edema and cholestasis [36], it is expected that inflammation is not the only determinant for increased viscosity, and therefore increased SWD. Congruous with this, in a study on pediatric liver transplants, in which 46 children were investigated with ultrasound SWD and biopsy, a mean SWD of 13.6 (m/s)/kHz was reported [4]. All of the included patients were referred for an elective examination, i.e., none were acute, however, various components of liver affection, such as fibrosis, inflammation, and vascular affection, existed in the cohort, likely explaining high SWD.

The ATI value of 0.54 dB/cm/MHz from our study aligns with previous research on children without liver steatosis [5,23,30,34]. Cetinic et al. [5] found a similar mean ATI in children with suspected liver disease but histology verified absence of steatosis [5]. Hwang et al. [30] studied ATI in 49 obese and 40 normal weighted children and reported higher ATI in the former group and mean ATI of 0.50 dB/cm/MHz in the normal weighted children [30]. They suggested ATI as a more effective tool for diagnosing hepatic steatosis in children than other non-invasive methods. Contrary to our study they found that BMI was a significant factor for increased ATI values, which also Song et al. did in their study on approximately 100 children with suspected liver steatosis [34]. One potential explanation for why we failed to find this association is the lack of a sufficiently wide range of BMI and ATI values respectively in our normal weighted cohort. For instance, Song et al. [34] reported higher ATI values in obese children with moderate to severe steatosis. Most studies indicate the normal mean ATI value in children without steatosis is approximately 0.50-0.56 dB/cm/MHz. One exception is the study by Callioce et al. [31], reporting median ATI of 0.65 dB/cm/MHz in 88 children without suspected liver disease [31]. This value surpasses reported adult normative values (0.52 dB/cm/MHz) [22], reaching a level indicative of mild steatosis (0.63-0.70 dB/cm/MHz) in adults [27]. Therefore, one might suspect confounding factors in their cohort, referred for ultrasound for various reasons other than suspected liver disease. Further, they obtained a minimum of two ATI measures while we obtained five, thus potential measurement errors are more likely to be reduced in the current study. Callioce et al. [31] hypothesized that a thickened hepatocyte layer pattern in younger children (<5 years) could explain the increased ATI, however they did not perform age-associated analysis. They did not find age, sex, weight, or BMI to significantly affect ATI or SWE [31], a conclusion supported by other research as well [37].

Interestingly, we found a significant negative correlation between BMI and SWD which was also found by Cetiner et al. [23]. The relationship between body composition, reflected by BMI, and SWD is likely to be complex and may vary on several factors such as specific populations and ethnicities studied, comorbidities and elastography techniques used. This association may also be physiological, related to age since viscosity in the pediatric liver seems to be higher in general as compared to adults [38]. It is difficult to find any obvious explanation for this negative correlation, as factors that may affect SWD values have not been mapped. Future studies are encouraged to investigate the association, preferably using BMI z-score/BMI Standard Deviation Score which are more appropriate in children [39].

Our mean SWE of 4.9 kPa is within the same range as the majority of the few previously reported pediatric normative values [5,22,31,40]. Callioce et al. [31], using the same ultrasound manufacturer [31], reported a median SWE 4.6 kPa in their healthy children and Cetinic et al. [5] found a median SWE value of 4.9 kPa in pediatric patients with biopsy verified absence of fibrosis [5]. Hebelka et al. [6]

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DOI:10.26502/jppch.74050181

studied 90 children with suspected/confirmed liver disease using a Toshiba Aplio i700 and correlated SWE to histology [6]. They suggested a cutoff value of <4.7 kPa to exclude significant fibrosis, in parallel with normal values reported by others using the same manufacturer [22]. Although there are several reports of normal values within the same range [40-42], ultrasound elastography values are dependent on manufacturer/machine used, why normative values need to be adopted for each manufacturer.

Results are conflicting regarding SWE and the impact of age [22,40-42]; like our study some have reported no influence by age while others reported slightly increased SWE with increasing age. Thus, larger studies are needed to determine if, and how, SWE is influenced by age, but until those large-scale studies are in place this study strengthens the argument that age does not seem to influence SWE significantly, nor SWD or ATI. Also, this study adds to the literature that there were no gender-based differences in the assessed liver ultrasound markers.

No significant difference was found between markers obtained awake or during anaesthesia. There were slightly higher values and variability during awake state, likely due to values from some less cooperative patients and sometimes forceful breathing, impacting measurements. In a larger sample this may approach significance, but the effect size is likely small and therefore not clinically relevant. The lack of a significant difference implies we can treat them as equivalent and the use of the average between the conditions decreases random measurement error. Multiple data collectors increase random noise but increases generalizability for normative values, which is a strength with the current study.

Fasting may impact liver stiffness measurements, as food intake can affect blood flow and liver perfusion, potentially influencing elastography results. Conflicting results regarding the impact of fasting have been reported. Postprandial state has been reported to have a significant effect on SWE measurements in several studies [43,44]. Petzgold et al. [44] reported an 11% risk of misclassifying non-fasting, healthy patients as having significant fibrosis when not accounting for postprandial state [44]. However, others state that there is no difference between fasting and non-fasting in terms of increased liver stiffness or viscosity [45]. Irrespectively, the 4 h fasting standardization in the current study is a strength.

Free breathing increases variability and it might be considered a limitation that we did not measure and control for depth and frequency of breathing during examination. However, since infants and small children cannot hold their breath, there is considerable variability in breath-hold performance, we opted to determine normal values with a method that is clinically applicable in all children.

One major limitation is that the investigated cohort is not "healthy" children, rather a cohort without known or suspected liver disease, why liver affection cannot be entirely excluded. Since none of the investigated individuals had any known or suspected liver disease, laboratory tests for viral hepatitis or other liver diseases were not sampled in all patients. However, some renal conditions can potentially affect the liver without affecting liver function tests. One such condition is SLE nephritis, which was confirmed at renal biopsy in two patients. Hence, it cannot be entirely excluded, in these individuals and in those in which such liver function tests were not sampled, that the liver was unaffected. However, it is unlikely that this would have affected the results on a group level, although it could have affected the measures on an individual level.

Apparent limitations are also a quite low sample size for SWD and ATI and the use of clinical sampling rather than population-based sampling. However, due to the scarcity in pediatric normal SWD and ATI values we believe that, until large scale studies are performed, this study adds to the literature of what can be considered normative-range values, and will be of great clinical utility.

Knowledge of diagnostic thresholds for ultrasound biomarkers and how they diverge in the healthy population is important. To conclude, this study adds to the existing literature within what range normative values for SWE, SWD and ATI can be expected during both free-breathing and fasting in children. Other than a weak negative correlation between BMI and SWD, the lack of significant associations implies that the normative values presented in this paper can be applied across ages and sexes. Future studies are strongly encouraged to determine normative values for these ultrasound biomarkers in large-scale population-based cohort with healthy children.

Acknowledgments

This work was presented as a poster presentation at the European Congress of Radiology in 2024.

Funding statement

DS was supported by Fredrik och Ingrid Thurings stiftelse (2020-00581, 2022-00704), Märta Lundqvists Stiftelse, Göteborgs Läkaresällskap and Kristina Stenborgs Stiftelse (GLS-960453), and the Department of Radiology, Sahlgrenska University Hospital. HH and IC were supported by ALF-grant Swedish Government (ALFGBG-965176), Jerringfonden and Åke Wibergs Stiftelse. This study was also supported by Grant from the Swedish Research Council dnr 2023-01951. Other than financial support, there was no involvement in the study.

Ethical approval statement

The study was conducted according to the guidelines of

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the Declaration of Helsinki and approved by the regional ethical review board of the University of Gothenburg (DNR: 634-18).

Informed consent statement

All included participants, depending on their age, either provided their informed consent or assent (in which case their guardians consented).

Conflicts of interest statement

The authors declare no conflict of interest.

Data availability statement

The data is available upon reasonable request.

Author Contributions statement

Conceptualization, Darko Sarovic, Kerstin Lagerstrand, Charlotte de Lange and Hanna Hebelka; Data curation, Darko Sarovic and Ivan Cetinic; Formal analysis, Darko Sarovic; Funding acquisition, Darko Sarovic and Hanna Hebelka; Investigation, Ivan Cetinic, Nils Ekvall, Charlotte de Lange and Hanna Hebelka; Methodology, Nils Ekvall, Kerstin Lagerstrand, Charlotte de Lange and Hanna Hebelka; Project administration, Kerstin Lagerstrand, Charlotte de Lange and Hanna Hebelka; Resources, Darko Sarovic, Ivan Cetinic, Nils Ekvall, Charlotte de Lange and Hanna Hebelka; Software, Darko Sarovic; Supervision, Hanna Hebelka; Validation, Darko Sarovic and Ivan Cetinic; Visualization, Darko Sarovic; Writing – original draft, Darko Sarovic, Ivan Cetinic and Hanna Hebelka; Writing – review & editing, Darko Sarovic, Ivan Cetinic, Nils Ekvall, Kerstin Lagerstrand, Charlotte de Lange and Hanna Hebelka.

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Citation: Sarovic Darko, Cetinic Ivan, Ekvall Nils, Lagerstrand Kerstin, de Lange Charlotte, Hebelka, Hanna. Normative Values for Liver Ultrasound Shear Wave Elastography, Shear Wave Dispersion and Attenuation Imaging in a Pediatric Cohort during Free Breathing. Journal of Pediatrics, Perinatology and Child Health. 8 (2024): 53-61.