A sociodemographic, anthropometric and lifestyle-based prediction score for screening children with overweight and obesity for hepatic steatosis; the HEPAKID index

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The authors have no conflicts of interest relevant to this article to disclose.

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Abbreviations:

20mSRT: 20 m shuttle run test, ALT: alanine aminotransferase, AUC-ROC: area under the receiver-operating characteristic curve, BMI: body mass index, CI: confidence intervals, CRF: cardiorespiratory fitness, HS: hepatic steatosis, MRI: Magnetic resonance imaging, SSB: Sugar-sweetened beverage, SPSS: statistical package for social sciences, TV: television, WHO: world health organization, WHtR: the waist to height ratio, YAP: youth activity profile questionnaire.

Table of Contents Summary:

This study develops a prediction score (the HEPAKID index) using anthropometric, sociodemographic and lifestyle factors to identify children with hepatic steatosis

What's Known on This Subject

In parallel with the childhood obesity epidemic, a number of associated comorbidities, such as hepatic steatosis (HS), have become more prevalent. Non-invasive biomarkers for the early identification of children with hepatic steatosis are much needed in daily clinical practice.

What This Study Adds

The HEPAKID index is the first simple, non-invasive, sensitive and inexpensive method of screening at-risk children for hepatic steatosis in primary care clinics, allowing for their timely referral to a pediatric gastrointestinal specialist.

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CONTRIBUTORS' STATEMENT PAGE

Contributors' Statement

Maddi Oses analyzed the data, drafted the manuscript and takes full responsibility for the integrity of the data analyses, collected data, drafted the manuscript, generated the figures, participated in the interpretation of the results, and critically revised the manuscript for important intellectual content.

María Medrano and Lide Arenaza collected the data, participated in the interpretation of the results, and critically revised the manuscript for its intellectual content and approved the final version.

Arkaitz Galbete participated in the statistical analyzed, interpretation of the results and critically revised the manuscript for its intellectual content and approved the final version.

Jonatan Ruiz, Felix Sánchez-Valverde and Francisco B Ortega critically revised the manuscript for its intellectual content and approved the final version.

Idoia Labayen designed the study, coordinated and supervised data collection, drafted the manuscript, participated in the interpretation of the results, and critically revised the manuscript for important intellectual content.

ABSTRACT

Background: Hepatic steatosis (HS) is currently the most prevalent hepatic disease in pediatric population and a major risk factor for type 2 diabetes and cardiovascular diseases. The proper identification of children with HS is therefore of great public health interest.

Objective: To develop a new prediction score (the HEPAKID index) using anthropometric, sociodemographic and lifestyle factors to identify children with HS. Previously published biochemical pediatric screening tools were validated in the same cohort.

Methods: A total of 115 pre-adolescent children aged 8-12 years with overweight/obesity, recruited at hospital pediatric units were enrolled in this cross-sectional study. **HS (≥5.5% hepatic fat) was assessed by MRI.** Anthropometric, sociodemographic and lifestyle variables were collected by validated tests/questionnaires.

Results: Forty-one children had MRI-diagnosed HS (35.6%, 49% girls). These children had (p<0.01) a higher waist-height ratio, a lower cardiorespiratory fitness, a younger gestational age, and consumed more sugar-sweetened beverages than their HS-free peers. Children with HS were more likely to belong to an ethnic minority (p<0.01) and to spend longer viewing screens than recommended (p<0.05). The addition of these variables to the multivariate logistic regression model afforded a HEPAKID index with high discriminatory capacity (AUC-ROC: 0.808, 95% CI 0.715-0.901), and score of ≥25.0 was associated with high sensitivity (82%, 95% CI 68-96%). Biochemical biomarker-based pediatric tools for identifying HS showed only moderate discriminatory capacity and low sensitivity (5-41%) in this cohort.

Conclusions: The HEPAKID index is the first simple, non-invasive, sensitive, inexpensive, and easy-to-perform screening that can identify children with overweight or obesity who have HS.

INTRODUCTION

Childhood obesity is one of the 21st century's most serious public health challenges(1). In the last two decades, and in parallel with the childhood obesity epidemic, a number of associated comorbidities, such as hepatic steatosis (HS), have become more prevalent. Indeed, pediatric HS now affects some 8% of the general child population, and 34% of children with overweight or obesity(2). It is estimated that by 2025, 38 million children and adolescents will have HS(3). Depending on the diagnostic criteria and methodology used, however, prevalence rates for HS in children with overweight/obesity population can range as widely as 5-83%(2).

Unfortunately HS can progress to cirrhosis and end-stage liver disease even at a young age(4–6) and is a major risk factor for type 2 diabetes and cardiovascular diseases(7,8). In children it is may be more severe than in adults and has a poorer prognosis(9), with some 15% of patients presenting with at least stage 3 fibrosis at diagnosis(10). The proper identification of children with HS, particularly in the early stages of the disease, is therefore of great public health interest, especially since lifestyle-based treatments are effective in reducing hepatic fat and even reversing the disease before fibrosis develops(11–13).

Pediatric HS is generally a silent liver disease; it can be present but cause no symptoms and give no warning signs(6). Liver biopsy is still the gold standard for its diagnosis(5,6), although other diagnostic procedures, including magnetic resonance imaging (MRI) are available(14,15). However, these methods are invasive and/or costly. HS may be suspected when patients have high levels of alanine aminotransferase (ALT), but ALT is not a sensitive marker of this disease or its severity(16). In fact, in children, the full spectrum of histological HS may be present even though they have an entirely normal blood ALT result(16–18).

Non-invasive biomarkers or screening tools for the early identification of children with HS are much needed(19). Several scores have been developed for detecting the disease in adults(20–22), but only one exists for use with children(23). However, the accuracy and clinical usefulness of these tools remain controversial, and they are yet to be validated(24). In addition, biochemical biomarkers are required if they are to be used, and blood sampling is not routine in apparently healthy children, even if they have overweight or mild obesity. A simple and effective non-invasive screening tool is therefore needed that can be used by clinicians in the routine primary care setting. Children suspected of having HS could then be referred for a confirmatory diagnosis. The aim of the present work was to develop such a tool - the HEPAKID index - based on the recording of anthropometric, sociodemographic and lifestyle factors. Previously published pediatric screening tools were subjected to validation in the same cohort used to develop the new tool, and the results compared.

METHODS

Design, participants and data collection

This cross-sectional study made use of data collected during the EFIGRO project (ClinicalTrials.gov ID: NCT02258126), the overall aim of which was to examine the effect of exercise on percentage hepatic fat in children with overweight/obesity. In that trial, which was conducted from September 2014 to June 2017 in Vitoria-Gasteiz, Spain, all subjects participated in a 22-week family-based program involving lifestyle and psychological education. Details of sample calculation, randomization, the characteristics of the study subjects, the design of that work, its methods and the measurements taken are available elsewhere(25). For the present work, the baseline data of 115 pre-adolescent children with overweight/obesity(26), and aged between 8.5 and 12.0 years, were analyzed. Overweight and obesity status was defined according to the body mass index (BMI) international age- and sex-specific cut-off values provided by the World Obesity Federation (26). Having other hepatic disease or/and any other disease accompanied with elevated blood transaminase levels, such as viral hepatitis, toxic hepatitis or autoimmune diseases were exclusion criteria.

The Euskadi Clinical Research Ethics Committee approved the study protocol (PI2014045), which complies with the ethical guidelines of the Declaration of Helsinki (2013 revision). Subjects were recruited at the Pediatric Endocrinology Unit of the University Hospital of Araba, and at primary care clinics. The parents or legal guardians of the children provided informed consent for their charges to be enrolled in the study. The present study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines(27).

Percentage hepatic fat was assessed by MRI using a Magnetom Avanto system (Siemens Healthcare, Erlangen, Germany) as previously described(25). Thereafter,

children were divided into those with and without HS (≥5.5% or <5.5% hepatic fat respectively) (28,29).

Body mass (kg), height (m), and waist circumference (cm) were measured in duplicate following standard protocols; the body mass index (BMI) (kg/m^2) and the waist to height ratio (WHtR) were then calculated(30).

The educational level and country of origin of the children's mothers were obtained via questionnaire. Belonging to an ethnic minority was defined as having a foreign-born mother from a low or middle income country (**Supplemental table 1**) or belonging to recognized ethnic minority for Spain (i.e., Gypsies) according to the categories provided by the European Commission for Spain. Perinatal variables such as gestational age at birth (weeks), birth weight (g) and duration of breastfeeding (weeks), and any family history of obesity and diabetes were collected via a questionnaire and from clinical records.

Dietary intake was assessed by two non-consecutive 24-hour recalls within a period of seven days. Sugar-sweetened beverage (SSB) consumption was determined as the ingestion of soft drinks, sweetened juices, and energetic drinks(31) in g/day. Children were also categorized as consumers or non-consumers of SSB. Adherence to the Mediterranean dietary pattern was evaluated using the Mediterranean Diet Quality Index for children and teenagers (KIDMED) questionnaire(32).

Cardiorespiratory fitness (CRF) was estimated from the number of laps completed in the 20 m shuttle run test (20mSRT)(33), and the children classified as fit (>20th percentile) or unfit (≤20th percentile) according to the sex- and age-specific percentiles of Tomkinson et al. (34). This is a validated test used to evaluate CRF in schools(35).

Physical activity (counts per min), sedentary and sleep time (min per day) were measured by accelerometry, as reported elsewhere (36). A self-reported sedentary behavior questionnaire(37) was completed in order to determine the frequency of specified sedentary behaviors such as watching TV, playing on-screen games, and surfing the Internet; the children were then categorized as meeting (<2h/day) or not-meeting (≥2h/day) WHO recommendations regarding screen time for children(38).

A brief questionnaire to collect the required information to calculate the HEPAKID index. The calculator is available on https://bit.ly/37WXV0j. Additionally, as the CRF measurement may not be available in clinical settings, a second model was generated excluding this variable (https://bit.ly/2AQTUPa).

In addition to developing the proposed tool, three previously published ALT cut-off points and a score for diagnosing HS in pediatric populations were validated in the present study population: 1) the ALT concentrations of >22 IU/L in girls and >25 IU/L in boys, according to the criteria proposed by Schwimmer et al. (39), 2) the ALT cut-offs of ≥44 IU/L in girls and ≥52 IU/L in boys proposed by the North American Society For Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN)(40), 3) the ALT cut-off point of >35 IU/L proposed by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (41), and 4) the pediatric NAFLD (non-alcoholic fatty liver disease) score (ped-NAFLD score), determined as:

$$\text{ped-NAFLD score} = \frac{e^{[-13.83 + (0.16\,x\,WHtR) + (0.07\,x\,ALT) + (0.78\,x\,HOMA)]}}{1 + e^{[-13.83 + (0.16\,x\,WHtR) + (0.07\,x\,ALT) + (0.78\,x\,HOMA)]}}$$

for which the proposed cut-off point is 0.39(23).

The plasma concentrations of ALT and HOMA variables included in the ped-NAFLD score were measured in the present sample of children using standard protocols(25).

Statistical analysis

Differences in sociodemographic, anthropometric and lifestyle characteristics between children with or without MRI-diagnosed HS were analyzed using the independent t-test (continuous variables) or χ^2 test (categorical variables).

No missing data imputation was performed. All variables potentially associated with the presence of HS were included as candidates in a multivariate logistic regression model forming the base of the HEPAKID index. Those independent variables that showed collinearity, and those whose effect was negligible, were removed from the final model.

The probability of having HS was determined from the model, multiplying by 100 to obtain the "sociodemographic, lifestyle and anthropometric data based pediatric hepatic steatosis index (HEPAKID index)", which therefore has a 0-100 score range.

The discriminatory capacity of the HEPAKID index was examined by calculating the area under the receiver-operating characteristic curve (AUC-ROC, with 95% confidence intervals [CI]). The calibration of the model was examined using a calibration plot (plotting the expected probabilities against observed event proportions and smoothing via the Loess method) and the Hosmer-Lemeshow test. Cross validation with 150 samples was performed as an internal validation and to provide an optimism-corrected AUC-ROC.

In the external validation of the pre-existing tools, the discrimination of the ALT tests and ped-NAFLD score were assessed by AUC-ROC analysis, and the calibration of the ped-NAFLD score was evaluated using a calibration plot.

The Youden index(42) was used to identify the optimal cut-off point for the HEPAKID index, prioritizing high sensitivity (≥80%). The performance of the proposed index and the already published tools was expressed as sensitivity, specificity, positive predictive value, and negative predictive value (with their corresponding 95%CIs) for the

proposed cut-off points. All analyses were performed for the sample as a whole, and separately for boys and girls.

All calculations were performed using SPSS software v.23.0 (IBM, Armonk, NY, USA) and R statistical software v.3.6.3. Significance was set at $\alpha = 0.05$.

RESULTS

Table 1 shows the sociodemographic, anthropometric, lifestyle and biochemical characteristics of the children with (36%) and without HS (64%) as determined by MRI. Children with HS had a higher WHtR (p<0.001), higher SSB consumption (p<0.005), a lower CRF (p<0.01) and a lower gestational age at birth (p<0.01) than those without HS. Children with HS were also more likely to belong to an ethnic minority (p<0.01) and not to meet recommendations regarding screen time (p<0.05). The plasma ALT, plasma insulin and the HOMA index were also higher in children with HS (p<0.01).

Model development and validation

Table 2 shows the multivariate logistic regression analysis based on sociodemographic, anthropometric, and lifestyle variables potentially associated with having HS. The HEPAKID index was defined using the regression coefficients (β) obtained in the multivariate logistic regression model (**Table 2, I**). Only those children with valid data on maternal country of origin (non-missing data) on duration of gestation (missing data n=12), anthropometry (no missing data), screen time (no missing data), dietary habits (no missing data), and CRF level (missing data n=5) were included in the model (n=99):

$$"HEPAKID\ index" = \frac{e^{me}}{1 + e^{me}}\ x\ 100$$

me = 2.801 + 1.583 x (ethnic minority[1]) + [(-0.230) x (gestational age[2])] + 0.095 x (WHtR[3]) + 0.656 x (screen time ≥2h/day[4]) + 0.834 x (SSB[5]) + [(-0.028) x (CRF[6])]

Equation to calculate the "HEPAKID Index". Me=model equation, e=exponential function constant. [1]Ethnic minority=1 and non-ethnic minority=0, [2]Gestational age at birth in weeks, [3]WHtR: waist to height circumference ratio, [4]Screen time ≥2h/day=1 and <2h/day=0, [5]Consumer of sugar sweetened beverages=1, non-consumer=0, [6]CRF: cardiorespiratory fitness (number of laps completed in 20mSRT test).

The model included six categorical or continues variables collected in a brief questionnaire: 1) belonging to an ethnic minority (categorical, yes or no), 2) duration of

gestation in weeks (continuous), 3) the WHtR multiplied by 100 (continuous), 4) meeting or not meeting screen time recommendations (categorical, yes or no), 5) consumption of SSB (categorical, yes or no), and 6) cardiorespiratory fitness in laps (discrete variable).

The Hosmer-Lemeshow test (p=0.380) and the calibration plot (**Figure 1**) showed the HEPAKID index to be well calibrated. The AUC-ROC value of 0.808 (95%CI 0.715-0.901) showed the index to have strong discriminatory capacity for detecting HS in the study population (**Figure 1**). The optimism corrected AUC-ROC was 0.755 (Figure 1).

Supplemental Table 2 shows the diagnostic performance of the HEPAKID index at different cut-off points. A value of 25.0 was selected as the optimum cut-off for HS (sensitivity 0.82, specificity 0.62).

A second model for the index was generated excluding CRF (**Table 2, II**). In this case the AUC-ROC was 0.793 (95%CI 0.694-0.893), the Hosmer-Lemeshow test (p=0.521), and the calibration plot again demonstrated good calibration **(Supplemental Figure 1 in the Supplement)**. The optimism corrected AUC-ROC was 0.754 **(Supplemental Figure 1 in the Supplement)**. The calculator is available on https://bit.ly/2AQTUPa.

Performance of the ped-NAFLD-score and ALT tests

The AUC-ROC value for both the ped-NAFLD score and the ALT levels (AUC=0.770, 95%CI 0.679-0.861, SE: 0.046 and AUC=0.751, 95%CI 0.657-0.845, SE: 0.048, respectively) were lower than for the HEPAKID index. In addition, the ped-NAFLD score showed poor calibration and detected far fewer cases of HS than did MRI (**Supplemental Figure 2**). **Table 3** shows the diagnostic performance of the HEPAKID index (with and without CRF) compared to the ALT tests and the ped-NAFLD score using their optimum cut-offs. The HEPAKID index showed higher sensitivity (82% and 79% with and without CRF respectively) for identifying children with HS compared to the ped-NAFLD score

(33%) and the ALT tests (between 5 and 41%), but showed lower specificity (62% *vs.* 90-100%). It is remarkable that the proposed cut-offs for the NASPGHAN and ESPGHAN ALT tests identified only 4 and 2 children (all boys) respectively among the 41 children with MRI-diagnosed HS (**Table 3**).

The diagnostic accuracy of the HEPAKID index was similar in girls and boys, while the predictive capacity and accuracy of the ALT tests and the ped-NAFLD-score were lower in girls than in boys (**Table 3**).

DISCUSSION

The early, easy and rapid screening of children at increased risk of HS would allow pediatricians to identify those children who should be referred for confirmatory diagnosis. Early detection would also open the door to more effective treatment. The proposed HEPAKID index is a simple, non-invasive, sensitive, inexpensive and easy-to-perform screening method based on sociodemographic, lifestyle and anthropometric variables that can identify HS in pre-adolescent children with overweight or obesity. A HEPAKID index score of ≥25.0 shows high sensitivity and reasonable accuracy in identifying HS as detected by MRI. It could therefore be of great use in primary care clinics, allowing those children who need to be referred to pediatric gastrointestinal and hepatology specialists to be quickly identified.

The HEPAKID index includes anthropometric data (WHtR), sociodemographic factors (ethnic minority status and gestational age at birth), lifestyle variables (SSB consumption, screen time) and CRF (laps in 20mSRT test), all of which are easily measured or collected in a brief questionnaire (https://bit.ly/37WXV0j)**.**

The most important contributor to the HEPAKID index was belonging to an ethnic minority group. Previous studies have reported that ethnicity and genetics play an important role in liver fat deposition. Thus, in the United Sates, the prevalence of hepatic

steatosis was higher in Hispanic, than in non-Hispanic children(43) and adults(44). In addition, the accuracy of several predictive scores of NAFLD for adults was significantly influenced by ethnicity(45). Several genetic variants such as the *PNPLA3* polymorphism have also been associated with increased risk of developing NAFLD (28,46,47). Interestingly, this polymorphism is more prevalent in Hispanic than in non-Hispanic individuals, suggesting an ethnic predisposition for hepatic steatosis (46,47). In our study, ethnic minority was defined as belonging to a recognized ethnic minority for Spain or as having a foreign-born mother from a low- or middle-income country. Ethnic minority groups are different across countries; however, in our study this group shares social disadvantages more than a genetic or biological background. Social disadvantages such as low income and parental education, occupation, minimal social network, non-traditional family structure, migrant status or unemployment have been associated with obesogenic behaviors among children. Likewise, in high-income countries, there is an elevated prevalence of obesity and obesity-related comorbidities such as insulin resistance among racial and ethnic minority groups, as well as among individuals from disadvantaged socioeconomic backgrounds(48,49). Our results support these findings and extend to the presence of HS.

It should also be noted that a high WHtR is one of the most frequently used anthropometric measures for identifying abdominal adiposity and cardiometabolic risk in children(30), and that the lifestyle factors included in the HEPAKID index (screen time and SSB consumption) are also known to be strong determinants of pediatric obesity and/or HS(31,50,51).

In clinical practice, and particularly in primary care, the sensitivity of a screening tool is the main criterion for selecting it for use; the objective is to identify patients who warrant further, more invasive and/or expensive tests. The HEPAKID index can identify

82% (79% in the model without CFR) of children with overweight/obese who have developed HS (18% false negatives). In a sample of children and adolescents with severe obesity (N=119), a laboratory biomarker-based model (ALT, HOMA and leptin) returned a sensitivity of 77%(24). The latter authors also tested other previously published screening tools for adults (20–22) in a sample of white children with obesity (N=56) (23) and reported their sensitivity to be <70% in all cases. In the present work, the previously published ALT level tests(39–41) and the ped-NAFLD score(23) were tested in the current cohort, and their accuracy and sensitivity were found to be lower than those of the HEPAKID index. Indeed, the NASPGHAN(40) and ESPGHAN(41) ALT cut-off points failed to identify 93% of children with an MRI-diagnosed fatty liver as having HS. Indeed, even the revised ALT cut-off of Schwimmer et al. (39) failed to detect HS in 59% of MRI-diagnosed children, and the ped-NAFLD score failed to detect 67% of them. In addition, the diagnostic accuracy of these scores was particularly low in girls, while the diagnostic performance of the HEPAKID index was similar in boys and girls. These findings highlight the usefulness and likely cost-effectiveness of the HEPAKID index.

The sensitivity of the HEPAKID index could be improved, but with the loss of specificity. Specificity was only 0.62 (0.59 in the model without CRF) for the ≥25.0 cut-off point; thus, 38% of children without HS were identified as candidates for additional examination. The selected cut-point of ≥25, however, represents the best trade-off between sensitivity and specificity.

While there is agreement among scientific/medical associations on the need to develop useful screening tools and guidelines for treating HS in children, no consensus strategies have been produced. For example, the American Academy of Pediatrics recommends ALT levels be measured in all children with obesity, or with overweight *plus* any cardiometabolic risk factor(52). The recommendation of the ESPGHAN(41) is

to assess ALT levels and perform abdominal ultrasound in all children >3 years with overweight or obesity, but given the elevated prevalence of pediatric overweight and obesity this would be a large strain on public health systems. In addition, the majority of studies in children with biopsy-proven or MRI-diagnosed HS report that ALT levels and ultrasound techniques only show moderate diagnostic accuracy in terms of detecting HS in children, and that combining them leads to no improvement in sensitivity(53,54). Other authors propose blood ALT concentrations of >35 IU/L as indicative of HS. However, while this cut-off has a high specificity (between 92-94%) it has only low sensitivity (between 24-48%)(55–57). Similarly, the ALT cut-off points proposed for the pediatric population by Schwimmer et al. (39), the ESPGHAN(41) and the NASPGHAN(40), all showed high specificity (90%-100%) in the present work, but very low sensitivity (5%-41%), particularly in girls (0%-30%), making them of little use as screening tools.

The 20mSRT test is a routine test used to measure CRF in schools; the results are reported to the children and their parents. However, in clinical settings this information may not be available. For this reason, a version of the HEPAKID index that does not take CRF into account was developed. This showed slightly lower sensitivity (79% *vs.* 82%) but is still useful as a screening tool for identifying children with HS. On the other hand, the HEPAKID index should be externally validated in other multiethnic, representative, large cohorts of preadolescent children with overweight/obesity before its implementation in clinical settings. The predictive capacity of the HEPAKID index has been tested in pre-adolescent children and may not apply to adolescent population at risk of HS.

In conclusion, the HEPAKID index is the first sociodemographic, lifestyle and anthropometric data-based screening tool for identifying HS in preadolescent children with overweight or obesity aged between 8.5 and 12.0 years. Pediatricians could easily

use this index to identify children who should be referred for confirmatory diagnosis. The low cost of performing this screening, and the availability of the data required, render the HEPAKID index an ideal method for screening for HS in the pediatric primary care setting.

Bibliography

1. WHO | Childhood overweight and obesity. WHO [Internet]. 2017 [cited 2018 Sep 11]; Available from: http://www.who.int/dietphysicalactivity/childhood/en/
2. Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: A systematic review and meta-analysis. PLoS One. 2015;10(10).
3. Lobstein T, Jackson-Leach R. Planning for the worst: estimates of obesity and comorbidities in school-age children in 2025. Pediatr Obes. 2016;11(5):321–5.
4. G. Thomas Brown and David E. Kleiner. Histopathology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Metabolism. 2016;65(8):1080–6.
5. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. World J Gastroenterol. 2010;16(42):5286–96.
6. Clemente MG, Mandato C, Poeta M, Vajro P. Pediatric non-alcoholic fatty liver disease: Recent solutions, unresolved issues, and future research directions. World J Gastroenterol. 2016;22(36):8078–93.
7. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. Metabolism [Internet]. 2016;65(8):1096–108. Available from: http://dx.doi.org/10.1016/j.metabol.2016.01.001
8. Kimberly P. Newton, Jiayi Hou, Nancy A. Crimmins, Joel E. Lavine, Sarah E. Barlow, Stavra A. Xanthakos et al. Prevalence of Type 2 Diabetes and Prediabetes in Children with Nonalcoholic Fatty Liver Disease Kimberly. JAMA Pediatr. 2016;170(10):e161971.
9. Holterman AXL, Guzman G, Fantuzzi G, Wang H, Aigner K, Browne A, et al. Nonalcoholic fatty liver disease in severely obese adolescent and adult patients. Obesity. 2013;21(3):591–7.

10. Schwimmer JB, Zepeda A, Newton KP, Xanthakos SA, Behling C, Hallinan EK, et al. Longitudinal assessment of high blood pressure in children with nonalcoholic fatty liver disease. PLoS One. 2014;9(11):1–17.

11. Gallegos-Orozco J, Unzueta A. Noninvasive diagnosis of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Oncol Gastroenterol Hepatol Reports. 2013;2(2):8.

12. Luttikhuis HO, Baur L, Jansen H, Shrewsbury VA, Malley CO, Stolk P, et al. Interventions for treating obesity in children Review information Authors Background. cochrane Libr. 2008;(May).

13. Labayen I, Medrano M, Arenaza L, Maíz E, Oses M, Martínez-Vizcaíno V et al. Effects of Exercise in Addition to a Family-Based Lifestyle Intervention Program on Hepatic Fat in Children With Overweight. Diabetes Care. 2020;43(2):306–13.

14. Noureddin M, Lam J, Peterson M.R, Middleton M, Hamilton G, Thuy-Anh Le et al. Utility of Magnetic Resonance Imaging Versus Histology for Quantifying Changes in Liver Fat in Nonalcoholic Fatty Liver Disease Trials. Hepatology. 2013;58(6):1930–40.

15. Zhong X, Nickel MD, Kannengiesser SAR, Dale BM, Kiefer B, Bashir MR. Liver fat quantification using a multi-step adaptive fitting approach with multi-echo GRE imaging. Magn Reson Med. 2014;72(5):1353–65.

16. Ma X, Liu S, Zhang J, Dong M, Wang Y, Wang M, et al. Proportion of NAFLD patients with normal ALT value in overall NAFLD patients: a systematic review and meta-analysis. BMC Gastroenterol. 2020;20(1):10.

17. Park JH, Kim SH, Park S, Park MJ. Alanine aminotransferase and metabolic syndrome in adolescents: The Korean National Health and Nutrition Examination Survey Study. Pediatr Obes. 2014;9(6):411–8.

18. Kim WR, Flamm SL, Di Bisceglie AM, Bodenheimer HC. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology. 2008;47(4):1363–70.

19. Draijer L, Benninga M, Koot B. Pediatric NAFLD: an overview and recent developments in diagnostics and treatment [Internet]. Vol. 13, Expert Review of Gastroenterology and Hepatology. Taylor & Francis; 2019. 447–461 p. Available from: https://doi.org/10.1080/17474124.2019.1595589

20. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: A simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis [Internet]. 2010;42(7):503–8. Available from: http://dx.doi.org/10.1016/j.dld.2009.08.002

21. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The fatty liver index: A simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:1–7.

22. Kotronen A, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, Johansson LM, et al. Prediction of Non-Alcoholic Fatty Liver Disease and Liver Fat Using Metabolic and Genetic Factors. Gastroenterology [Internet]. 2009;137(3):865–72. Available from: http://dx.doi.org/10.1053/j.gastro.2009.06.005

23. Maffeis C, Banzato C, Rigotti F, Nobili V, Valandro S, Manfredi R, et al. Biochemical parameters and anthropometry predict NAFLD in obese children. J Pediatr Gastroenterol Nutr. 2011;53(6):590–3.

24. Koot BGP, Van Der Baan-Slootweg OH, Bohte AE, Nederveen AJ, Van Werven JR, Tamminga-Smeulders CLJ, et al. Accuracy of prediction scores and novel biomarkers for predicting nonalcoholic fatty liver disease in obese children. Obesity. 2013;21(3):583–90.

25. Medrano M, Maiz E, Maldonado-Martín S, Arenaza L, Rodríguez-Vigil B, Ortega FB, et al. The effect of a multidisciplinary intervention program on hepatic adiposity in overweight-obese children: Protocol of the EFIGRO study. Contemp Clin Trials [Internet]. 2015;45:346–55. Available from: http://dx.doi.org/10.1016/j.cct.2015.09.017

26. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012;7(4):284–94.

27. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med. 2015;162(1):W1–73.

28. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. Hepatology. 2004;40(6):1387–95.

29. Zobair M. Younossi, Rohit Loomba, Mary E. Rinella EB et al. Current and Future Therapeutic Regimens for Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Zobair. Hepatology. 2018;68(1):361–71.

30. Lo K, Wong M, Khalechelvam P, Tam W. Waist-to-height ratio, body mass index and waist circumference for screening paediatric cardio-metabolic risk factors: a meta-analysis. Obes Rev. 2016;17(12):1258–75.

31. Arenaza L, Medrano M, Oses M, Huybrechts I, Díez I, Henriksson H, et al. Dietary determinants of hepatic fat content and insulin resistance in overweight/obese children: A cross-sectional analysis of the Prevention of Diabetes in Kids (PREDIKID) study. Br J Nutr. 2019;121(10):1158–65.

32. Serra-Majem L, Ribas L, Ngo J, Ortega RM, García A, Pérez-Rodrigo C, et al.

Food, youth and the Mediterranean diet in Spain. Development of KIDMED, Mediterranean Diet Quality Index in children and adolescents. Public Health Nutr. 2004;7(7):931–5.

33. Léger LA, Mercier D, Gadoury C, Lambert J. The multistage 20 metre shuttle run test for aerobic fitness. J Sports Sci. 1988;6(2):93–101.

34. Tomkinson GR, Carver KD, Atkinson F, Daniell ND, Lewis LK, Fitzgerald JS, et al. European normative values for physical fitness in children and adolescents aged 9-17 years: Results from 2 779 165 Eurofit performances representing 30 countries. Br J Sports Med. 2018;52(22):1445–56.

35. Ruiz JR, Castro-Piñero J, España-Romero V, Artero EG, Ortega FB, Cuenca MAM, et al. Field-based fitness assessment in young people: The ALPHA health-related fitness test battery for children and adolescents. Br J Sports Med. 2011;45(6):518–24.

36. Chandler JL, Brazendale K, Beets MW, Mealing BA. Classification of physical activity intensities using a wrist-worn accelerometer in 8-12-year-old children. Pediatr Obes. 2016;11(2):120–7.

37. Moreno LA, Gottrand F, Huybrechts I, Ruiz JR, González-Gross M, DeHenauw S. Nutrition and Lifestyle in European Adolescents: The HELENA (Healthy Lifestyle in Europe by Nutrition in Adolescence) Study. Adv Nutr. 2014;5(5):615S-623S.

38. American Academy of Pediatrics. Committee on Public E. American Academy of Pediatrics: Children, adolescents, and television. Pediatrics 2001;107:423-6.

39. Jeffrey B. Schwimmer, Winston Dunn, Gregory J. Norman, Perrie E. Pardee, Michael SMiddleton, Nanda Kerkar et al. SAFETY study: Alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. Gastroenterology. 2010;138(4):1357–64.

40. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nu. J Pediatr Gastroenterol Nutr. 2017;64(2):319–34.

41. Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: Position paper of the ESPGHAN hepatology committee. J Pediatr Gastroenterol Nutr. 2012;54(5):700–13.

42. Liu X. Classification accuracy and cut point selection. Stat Med. 2012;31(23):2676–86.

43. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics. 2006;118(4):1388–93.

44. Bambha K, Belt P, Abraham M, Wilson LA, Pabst M, Ferrell L, et al. Ethnicity and nonalcoholic fatty liver disease. Hepatology. 2012;55(3):769–80.

45. Xia MF, Yki-Järvinen H, Bian H, Lin HD, Yan HM, Chang XX, et al. Influence of ethnicity on the accuracy of non-invasive scores predicting non-alcoholic fatty liver disease. PLoS One. 2016;11(8):1–12.

46. Goran MI, Walker R, Le K, Mahurkar S, Vikman S, Davis JN et al. Effects of PNPLA3 on Liver Fat and Metabolic Profile in Hispanic Children and Adolescents. Diabetes. 2010;59:3127–30.

47. Martínez LA, Larrieta E, Calva JJ, Kershenobich D TA. The Expression of PNPLA3 Polymorphism could be the Key for Severe Liver Disease in NAFLD in Hispanic Population. Ann Hepatol. 2019;16 (6):909–15.

48. Ayala-Marín AM, Iguacel I, Miguel-Etayo P De, Moreno LA. Consideration of Social Disadvantages for Understanding and Preventing Obesity in Children. Front Public Heal. 2020;8(August).

49. Iguacel I, Fernández-Alvira JM, Labayen I, Moreno LA, Samper MP, Rodríguez G. Social vulnerabilities as determinants of overweight in 2-, 4-and 6-year-old Spanish children. Eur J Public Health. 2018;28(2):289–95.

50. Rey-López JP, Bel-Serrat S, Santaliestra-Pasías A, de Moraes AC, Vicente-Rodríguez G, Ruiz JR, et al. Sedentary behaviour and clustered metabolic risk in adolescents: The HELENA study. Nutr Metab Cardiovasc Dis. 2013;23(10):1017–24.

51. Ma J, Fox CS, Jacques PF, Speliotes EK, Hoffmann U, Smith CE, et al. Sugar-sweetened beverage, diet soda, and fatty liver disease in the Framingham Heart Study cohorts. J Hepatol. 2015;63(2):462–9.

52. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120 Suppl.

53. Draijer LG, Feddouli S, Bohte AE, vd Baan Slootweg O, Pels Rijcken TH, Benninga MA, et al. Comparison of diagnostic accuracy of screening tests ALT and ultrasound for pediatric non-alcoholic fatty liver disease. Eur J Pediatr. 2019;863–70.

54. Dasarathy S, Dasarathy J, Khiyami A, Joseph R, Lopez R and AJM. Validity of real time ultrasound in the diagnosis of hepatic steatosis: A prospective study. J Hepatol. 2009;51(6):1061–7.

55. Burgert TS, Taksali SE, Dziura J, Goodman TR, Yeckel CW, Papademetris X, et al. Alanine aminotransferase levels and fatty liver in childhood obesity:

Associations with insulin resistance, adiponectin, and visceral fat. J Clin Endocrinol Metab. 2006;91(11):4287–94.

56. Vajro P, Maddaluno S, Veropalumbo C. Persistent hypertransaminasemia in asymptomatic children: A stepwise approach. World J Gastroenterol. 2013;19(18):2740–51.

57. Yu EL, Golshan S, Harlow KE, Angeles JE, Durelle J, Goyal NP, et al. Prevalence of Nonalcoholic Fatty Liver Disease in Children with Obesity. J Pediatr [Internet]. 2019;207:64–70. Available from: https://doi.org/10.1016/j.jpeds.2018.11.021

TABLES

Table 1. Sociodemographic, anthropometric, and lifestyle characteristics of overweight or obese children with and without hepatic steatosis.

	Non-hepatic steatosis		**Hepatic steatosis**		***p***
	N	**Mean (SD)**	**N**	**Mean (SD)**	
Sociodemographic characteristics					
Age (years)	74	10.6 (1.1)	41	10.5 (1.1)	0.749
Girls (N, %)	74	42, 57	41	20, 49	0.077
Ethnic minority[1] (N, %)	74	6, 8	41	11, 26	**0.007**
Maternal educational level (University N, %)	74	57, 77	40	26, 60	0.168
Family history for obesity (N, %)	74	29,39	40	20,50	0.266
Family history for T2D (N, %)	74	5,7	40	3, 8	0.882
Gestational age (weeks)	68	39.1 (2.2)	35	37.4 (3.4)	**0.009**
Birth weight (g)	72	3226 (597)	39	3072 (714)	0.256
Breastfeeding duration (weeks)	72	11.6 (10.9)	38	13.2 (14.1)	0.545
Anthropometric characteristics					
Height (cm)	74	145 (8)	41	147 (8)	0.520
Weight (kg)	74	53.4 (10.2)	41	56.7 (10.7)	0.112
Body mass index (kg/m^2)	74	25.0 (3.2)	41	26.2 (3.3)	0.059
Waist to height ratio (x100)	74	52.9 (4.5)	41	56.2 (4.3)	**<0.001**
Hepatic fat (%)	74	3.7 (1.0)	41	9.2 (4.9)	**<0.001**
Dietary, physical activity fitness, and sleep patterns					
Physical activity (counts/min)	71	3792 (676)	39	3577 (623)	0.097
Cardiorespiratory fitness (laps)	70	24 (13)	40	17 (9)	**0.002**
MVPA (min/day)	71	97 (26)	39	92 (27)	0.319
Sedentary time (min/day)	71	511 (69)	39	522 (65)	0.421
Screen hours ≥2h/day (N, %)	72	36, 50	39	31, 79.5	**0.002**
Sleep time (min/day)	71	464 (34)	40	455 (38)	0.203
SSB consumption (g/day)	74	51 (90)	41	121 (172)	**0.019**
Fruits and vegetables intake (g/day)	74	224 (159)	41	259 (182)	0.297
KIDMED index	74	5.9 (2.2)	41	6.1 (1.9)	0.694
Biochemical variables:					
ALT (IU/L)	73	18 (5)	41	25 (11)	**<0.001**
Glucose (mg/dL)	73	84.7 (4.9)	40	86.7 (6.1)	0.086
Insulin (IU/ml)	73	11.1 (4.3)	41	13.9 (5.5)	**0.006**
HOMA-IR	73	2.34 (0.95)	40	3.01 (1.28)	**0.006**

Abbreviations: T2D: type 2 diabetes mellitus, MVPA: moderate to vigorous physical activity, SSB: sugar-sweetened beverage, KIDMED: questionnaire about adherence to the Mediterranean Diet in children and young; HOMA:[1]Ethnic minority: the category of ethnic minority includes non-Spanish origin of the mother (Economic migrants: Latin America N=12, Maghreb N=3 and Eastern Europe N=5) and belonging from and Spanish ethnic minority such as Roma (N=6)).

Table 2. Multiple logistic regression analysis showing the association of sociodemographic, anthropometric and lifestyle factors with hepatic steatosis (dependent variable) with (I) and without (II) cardiorespiratory fitness among predictors.

	Hepatic steatosis	
	OR (95% CI)	β
I (n=99)		
Constant	-	1.339
Ethnic minority[1]	4.94 (1.29-18.88)	1.597
Gestational age (weeks)	0.84 (0.70-1.02)	-0.170
Waist to height ratio (x100)	1.08 (0.95-1.22)	0.073
Screen time (≥2h/day)[1]	2.06 (0.69-6.16)	0.722
SSB consumption [1]	2.77 (0.96-8.01)	1.018
Cardiorespiratory fitness (laps)	0.97 (0.93-1.02)	-0.027
II (n=100)		
Constant	-	0.417
Ethnic minority[1]	5.63 (1.51-21.09)	1.729
Gestational age (weeks)	0.82 (0.68-0.99)	-0.196
Waist to height ratio (x100)	1.01 (0.97-1.25)	0.097
Screen time (≥2h/day)[1]	2.23 (0.77-6.44)	0.801
SSB consumption [1]	2.54 (0.90-7.21)	0.933

Abbreviations: β: standardized regression coefficient; OR: Odds ratio; CI: confidence interval; SSB: sugar-sweetened beverages. Only participants with no missing data were included into the model. Missing data: gestational age (n=12), cardiorespiratory fitness (n=5). [1]: Categorical variables. The category of ethnic minority includes non-Spanish origin of the mother (economic migrants; Latin America n=12, Maghreb n=3, and Eastern Europe n=5), and belonging from and Spanish ethnic minority such as Roma (n=6).

Table 3. Diagnostic performance of the HEPAKID-index and other pediatric prediction scores.

	SN, % (95% CI)	**SP,** % (95% CI)	**PPV,** % (95% CI)	**NPV,** % (95% CI)
HEPAKID index (≥25)				
Whole sample (n=99)	82 (68-96)	62 (49-75)	53 (39-68)	86 (76-98)
Girls (n=55)	82 (61-100)	61 (54-81)	48 (28-68)	88 (74-100)
Boys (n=44)	82 (61-100)	64 (43-85)	61 (39-83)	84 (65-100)
HEPAKID index (model without CRF)				
Whole sample (n=100)	79 (64-94)	58 (45-70)	49 (35-63)	84 (73-96)
Girls (n=57)	77 (53-99)	62 (46-79)	46 (26-67)	86 (72-100)
Boys (n=43)	81 (59-100)	48 (27-69)	48 (27-69)	81 (59-100)
High ALT tests				
Schwimmer et al. (>22 IU/L girls and >25 IU/L boys)[1]				
Whole sample (n=114)	41 (25-58)	90 (83-98)	71 (51-91)	73 (64-83)
Girls (n=62)	30 (7-53)	88 (77-99)	55 (21-89)	73 (59-86)
Boys (n=52)	52 (29-76)	93 (83-100)	85 (61-100)	74 (59-89)
NASPGHAN (≥44 IU/L girls and ≥52 IU/L boys)[2]				
Whole sample (n=114)	5 (0-13)	100 (99-100)	100 (75-100)	65 (56-74)
Girls (n=62)	-	-	-	-
Boys (n=52)	9 (0-24)	100 (98-100)	100 (75-100)	62 (48-76)
ESPGHAN (>35 IU/L)[3]				
Whole sample (n=114)	7 (0-17)	99 (95-100)	75 (20-100)	65 (56-75)
Girls (n=62)	-	-	-	-
Boys (n=52)	14 (0-31)	97 (89-100)	75 (20-100)	63 (48-77)
Ped-NAFLD score (≥0.39)[4]				
Whole sample (n=113)	33 (17-48)	95 (87-100)	76 (53-99)	72 (62-81)
Girls (n=62)	30 (7-53)	95 (88-100)	75 (39-100)	74 (61-87)
Boys (n=51)	35 (12-58)	94 (83-100)	78 (45-100)	69 (54-84)

Abbreviations: SN: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; CRF: cardiorespiratory fitness.

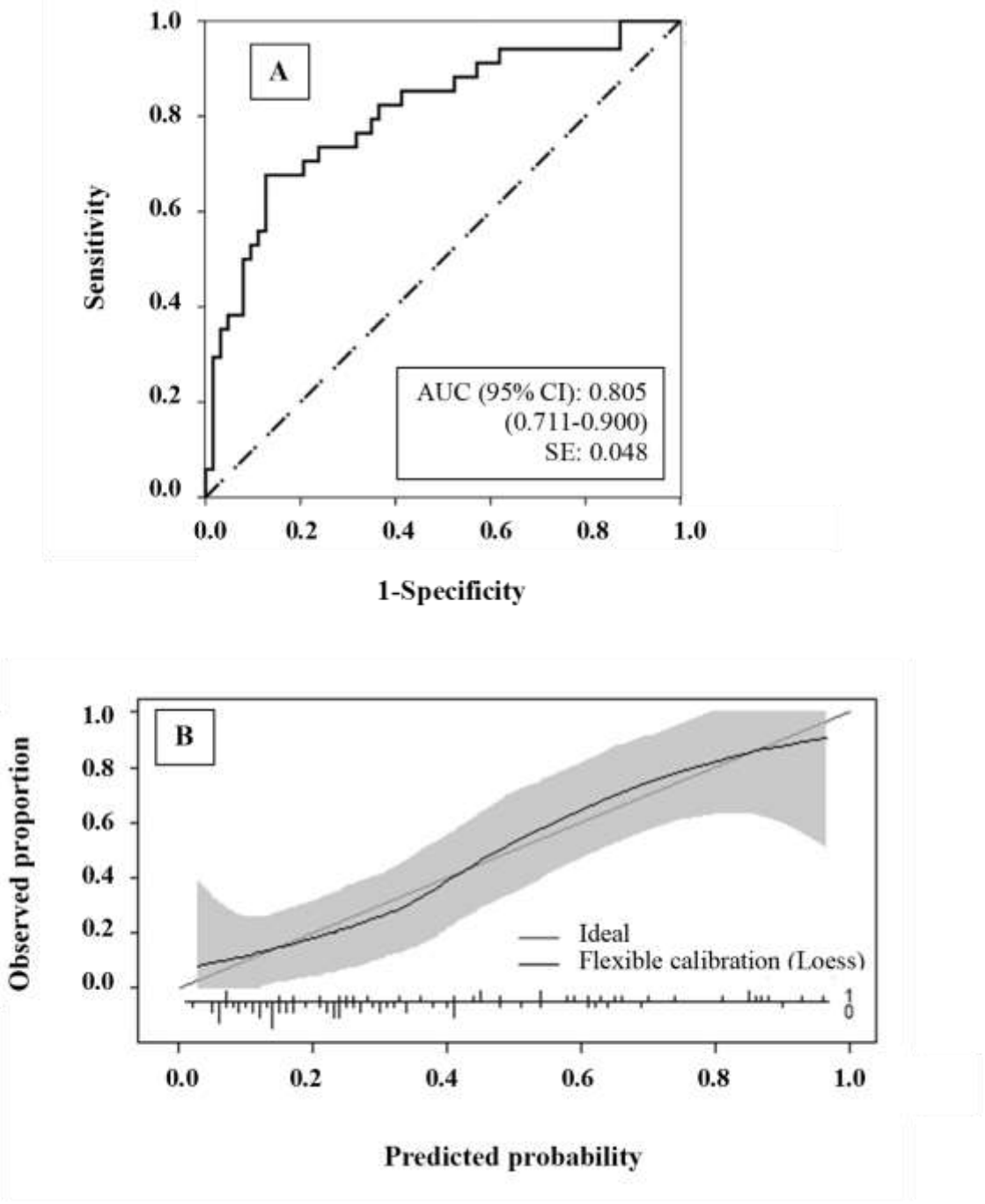


Figure 1. Receiver Operating Characteristics curve (panel A) and calibration (panel B) of the HEPAKID index (n=99). AUC-ROC: area under receiver operating characteristics curve; CI: confidence interval; SE: standard error.

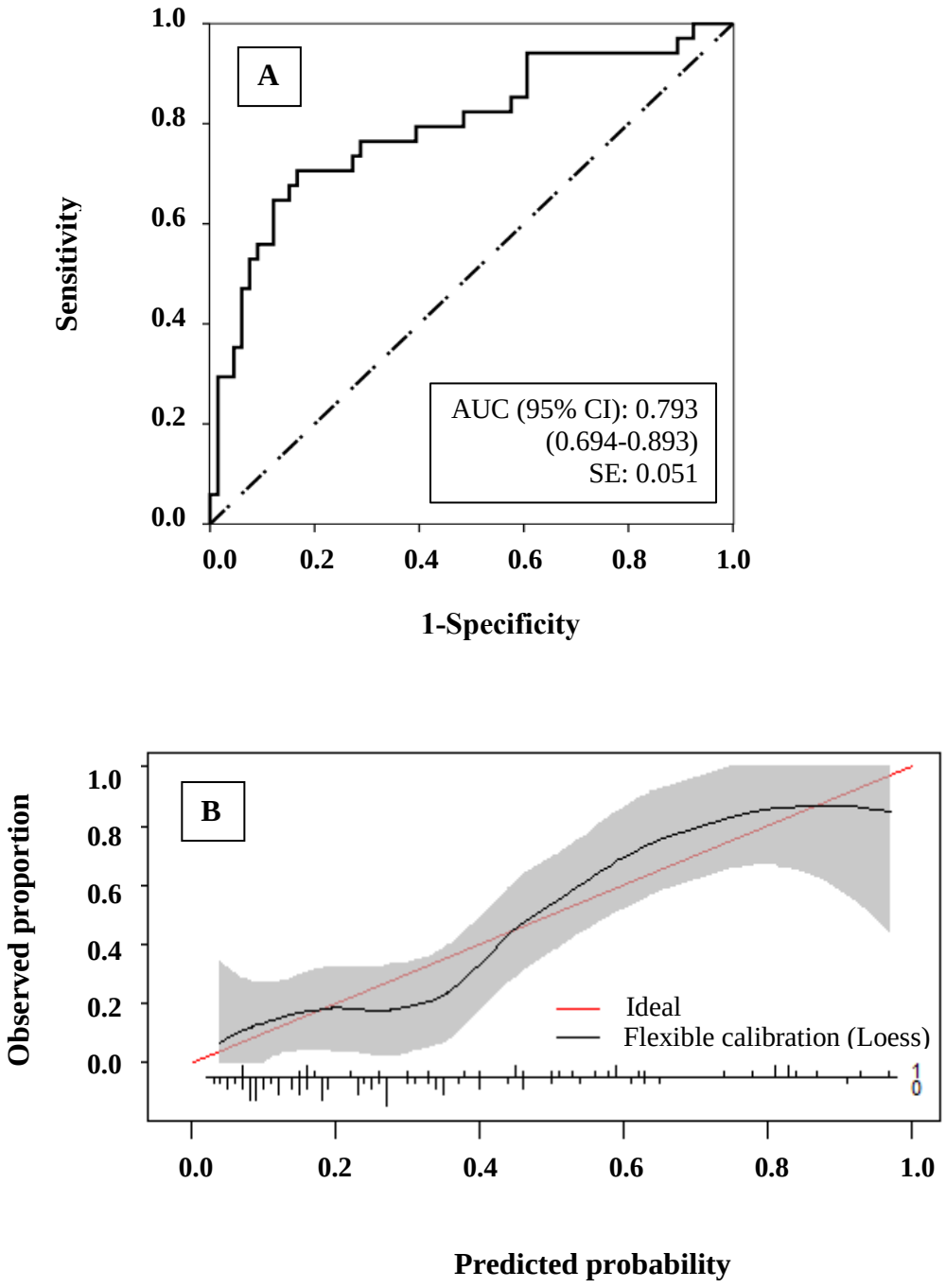
Supplemental Table 1. Spanish ethnic minority groups. (Information European Commission against Racism and Intolerance. ECRI Report on Spain (fifth monitoring cicle); 2018)

Spanish ethnic minority groups	
National ethnic minorities	Gypsies
Migrants	Latin Americans (South Americans and Central Americans) Eastern European (i.e., Romania, Bulgaria) North Africans Sub-Saharan Africans Arabian Chinese

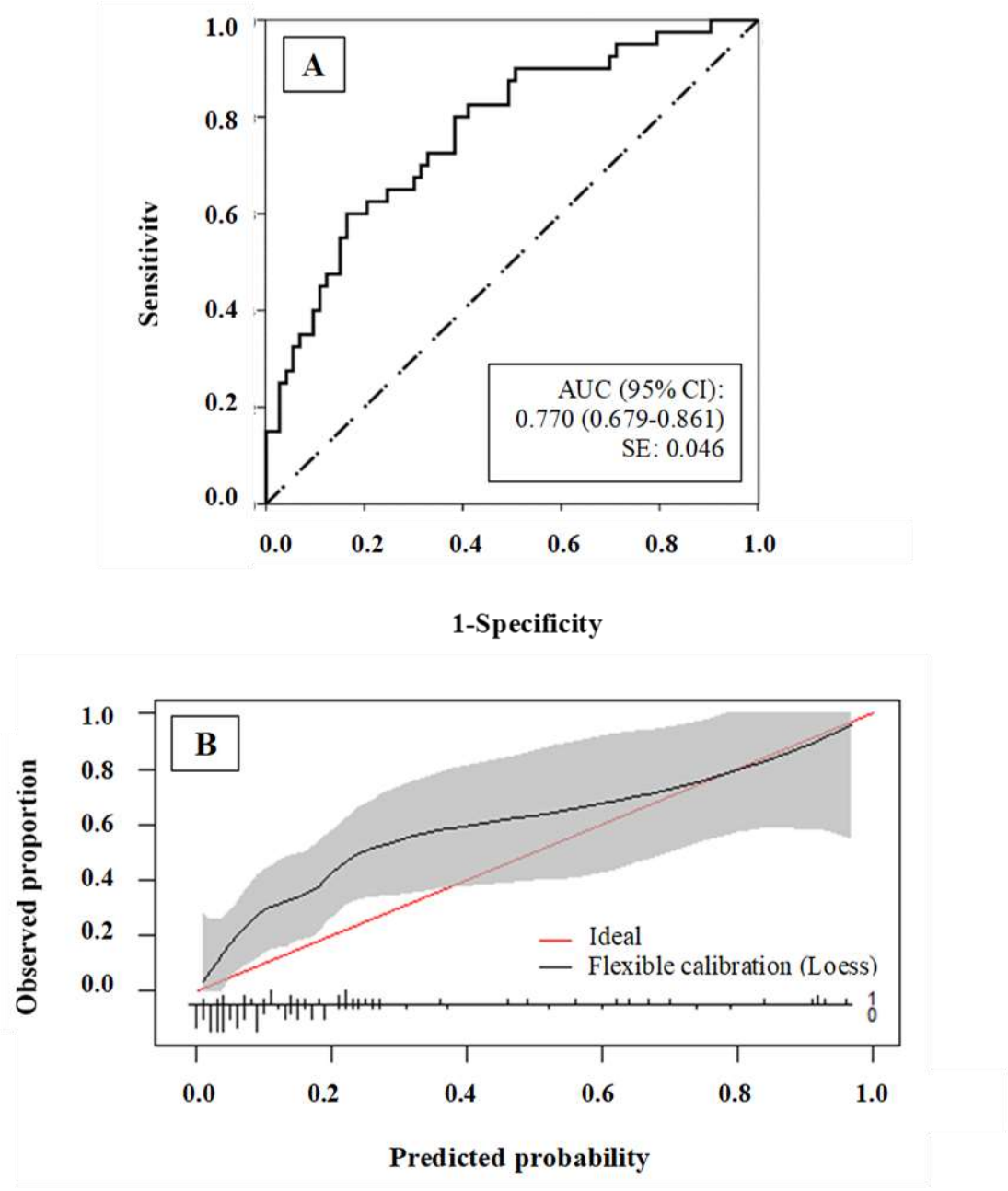
Supplemental Table 2. Prediction accuracy of the HEPAKID index.

Cut-off points	**Sensitivity (%)** (95% CI)	**Specificity (%)** (95% CI)	**PPV (%)** (95% CI)	**NPV (%)** (95% CI)	**LR+** (95% CI)	**LR-** (95% CI)
Youden index (0.55): ≥ 41.7	68 (50-85)	87 (78-96)	74 (57-91)	83 (74-93)	5.3 (2.7-10.6)	0.4 (0.2-0.6)
≥ 25	82 (68-96)	62 (49-75)	53 (39-68)	86 (76-98)	2.2 (1.5-3.1)	0.3 (0.1-0.6)
≥ 35	71 (54-87)	79 (69-90)	65 (48-81)	83 (73-94)	3.4 (2.0-5.8)	0.4 (0.2-0.6)
≥ 45	62 (44-80)	87 (78-96)	72 (54-90)	81 (71-91)	4.9 (2.4-9.8)	0.4 (0.3-0.7)
≥ 55	47 (29-65)	92 (85-99)	76 (56-97)	76 (66-86)	5.9 (2.4-14.8)	0.6 (0.4-0.8)
≥ 65	35 (18-53)	97 (92-100)	86 (64-100)	74 (63-84)	11.1 (2.6-46.8)	0.7 (0.5-0.9)
≥ 75	24 (8-39)	98 (95-100)	89 (63-100)	70 (60-81)	15.0 (2.0-113.0)	0.8 (0.6-0.9)

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio.



Supplemental Figure 1. Receiver operating characteristics curve (panel A) and calibration (panel B) of the HEPAKID index model without cardiorespiratory fitness data. AUC-ROC: area under receiver operating characteristics curve; CI: confidence interval; SE: standard error.



Supplemental Figure 2. Receiver operating characteristics curve (panel A) and calibration (panel B) of the ped-NAFLD score. AUC-ROC: area under receiver operating characteristics curve; CI: confidence interval; SE: standard error.