# Name of Journal: World Journal of Hepatology

**Manuscript NO:** 72515

**Manuscript Type:** MINIREVIEWS

**Metabolic-associated fatty liver disease from childhood to adulthood: State of art and future directions**

Lanzaro F *et al.* Metabolic fatty liver in children

Francesca Lanzaro, Stefano Guarino, Elisabetta D'Addio, Alessandra Salvatori, Josè Alberto D'Anna, Pierluigi Marzuillo, Emanuele Miraglia del Giudice, Anna Di Sessa

**Francesca Lanzaro, Stefano Guarino, Elisabetta D'Addio, Alessandra Salvatori, Josè Alberto D'Anna, Pierluigi Marzuillo, Emanuele Miraglia del Giudice, Anna Di Sessa,** Department of Woman, Child, and General and Specialized Surgery, University of Campania “Luigi Vanvitelli”, Naples 80138, Italy

**Author contributions:** Lanzaro F wrote the first draft of the manuscript; Miraglia del Giudice E, Di Sessa A, and Marzuillo P conceived the manuscript; Di Sessa A, Miraglia del Giudice E, and Marzuillo P supervised the manuscript drafting; D'Addio E, Salvatori A, Guarino S, and D'Anna JA reviewed the literature data; Guarino S and Lanzaro F prepared the tables; all author contributed important intellectual content during manuscript drafting or revision.

**Corresponding author: Pierluigi Marzuillo, MD, PhD, Assistant Professor,** Department of Woman, Child, and General and Specialized Surgery, University of Campania “Luigi Vanvitelli”, Via de Crecchio, 2, Naples 80138, Italy. pierluigi.marzuillo@gmail.com

**Received:** October 18, 2021

**Revised:** December 26, 2021

**Accepted:** April 25, 2022

**Published online:** June 27, 2022

**ABSTRACT**

In 2020, an international group of experts proposed to replace the term of nonalcoholic fatty liver disease with metabolic-associated fatty liver disease (MAFLD). This recent proposal reflects the close association of fatty liver with metabolic derangements, as demonstrated by previous robust data. Several factors [including genetics, inflammation, metabolic abnormalities, insulin resistance (IR), obesity, prenatal determinants, and gut–liver axis] have been found to be involved in MAFLD pathophysiology, but this tangled puzzle remains to be clearly understood. In particular, IR has been recognized as a key player in metabolic impairments development in children with fatty liver. On this ground, MAFLD definition focuses on the pathophysiological basis of the disease, by emphasizing the crucial role of metabolic impairments in this condition. Although primarily developed for adults, MAFLD diagnostic criteria have been recently updated with an age-appropriate definition for sex and age percentiles, because of the increasing attention to cardiometabolic risk in childhood. To date, accumulating evidence is available on the feasibility of MAFLD definition in clinical practice, but some data are still conflicting in highly selected populations. Considering the growing prevalence worldwide of fatty liver and its close relationship with metabolic dysfunction both in children and adults with subsequent increased cardiovascular risk, early strategies for MAFLD identification, treatment and prevention are needed. Novel therapeutic insights for MAFLD based on promising innovative biological techniques are also emerging. We aimed to summarize the most recent evidence in this intriguing research area both in children and adults.

**Key Words:** Metabolic; dysfunction; Fatty; Liver; Pathophysiology; Cardiovascular; Risk; Adults; Children

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Lanzaro F, Guarino S, D'Addio E, Salvatori A, D'anna JA, Marzuillo P, Miraglia del Giudice E, Di Sessa A. Metabolic-associated fatty liver disease from childhood to adulthood: State of art and future directions. *World J Hepatol* 2022; 14(6): 1087-1098

**URL**: <https://www.wjgnet.com/1948-5182/full/v14/i6/1087.htm>

**DOI**: https://dx.doi.org/10.4254/wjh.v14.i6.1087

**Core tip:** Recently, experts have proposed to rename nonalcoholic fatty liver disease as metabolic-associated fatty liver disease (MAFLD), by emphasizing the close association of fatty liver with the metabolic milieu. Given that, a growing number of studies have tested the effectiveness of the new definition in adults and children, although evidence in this latter population is still limited. However, expanding knowledge about MAFLD and its pathophysiology is crucial for a better identification of subjects at greater metabolic risk.

**INTRODUCTION**

As proposed by an international consensus in 2020[1], the nomenclature of nonalcoholic fatty liver disease (NAFLD) has been updated to metabolic-associated fatty liver disease (MAFLD). MAFLD diagnosis is based on histological (biopsy), imaging or blood biomarker evidence of hepatic steatosis, and on the presence of any condition among: (1) overweight/obesity; (2) diabetes mellitus; or (3) evidence of metabolic dysregulation[1], commonly defined as ≥ 2 of these characteristics: (1) waist circumference ≥ 102 cm in Caucasian male subjects and 88 cm in women (or ≥ 90/80 cm in Asian individuals); (2) blood pressure ≥ 130/85 mmHg or specific drug treatment; (3) triglyceride level ≥ 1.70 mmol/L or specific drug treatment; (4) high-density lipoprotein (HDL)-cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women; (5) prediabetes (*i.e.,* fasting glucose levels 5.6–6.9 mmol/L, or 2-h post-load glucose levels 7.8–11.0 mmol/L or hemoglobin A1c 5.7%–6.4%; (6) homeostasis model assessment-insulin resistance (HOMA-IR) score ≥ 2.5; and (7) high-sensitive C-reactive protein (hs-CRP) level > 2 mg/L.

Numerous different factors such as inflammation, sex, age, ethnicity, diet, microbiota, hormones, and genetics have been pathogenically linked to NAFLD[2-4], but current knowledge about MAFLD pathophysiology is still limited[5-6].

During the past decades, research focused on the strong association between insulin resistance (IR) and NAFLD[7]. In particular, previous data have largely supported the role of NAFLD as a hepatic manifestation of systemic metabolic disorders[2,3]. Based on these premises, the new nomenclature aims to strengthened the close association of fatty liver with metabolic dysfunction[2,8-12] to identify early subjects at higher risk of long-term metabolic consequences.

As noted for obesity and its related consequences [*e.g.,* metabolic syndrome (MetS) and Type 2 diabetes (T2D)[13-15]], a key pathogenic role has been described for the low-grade systemic inflammation in modulating fibrosis development and the overall course of the hepatic disease. As a result, an inflammatory biomarker such as hs-CRP, has been considered as a MAFLD diagnostic criterion. However, it should be kept in mind that further specific diagnostic criteria for MetS define this peculiar cluster of metabolic abnormalities, according to age group[16,18]. In fact, the MetS definition provided for adults and children aged ≥ 10 years by the International Diabetes Federation (IDF)[16,17] was further integrated for subjects aged 2–11 years (Table 1). The comparison between MetS and MAFLD criteria (Tables 2 and 3) allows identification of MetS subjects with fatty liver as MAFLD patients. Although both conditions allow identification of subjects at higher cardiometabolic risk, the inclusion of fatty liver as a MAFLD criterion enhances the multifactorial pathophysiology of the disease and its close relationship with metabolic derangements[16-20]. Given the overall emphasis of this latter association in MAFLD definition (from normal weight to obesity), the new term includes a wide phenotypical range from metabolically unhealthy normal weight to metabolically unhealthy. Nevertheless, an accurate definition of metabolic health is still lacking, especially in patients with obesity[21].

An increasing number of studies have explored metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO) in adult and pediatric cohorts[22-24]. MUO individuals have a higher cardiovascular risk than their metabolically healthy counterparts. However, MHO also might predispose over time to an increased risk of cardiometabolic derangements[25-27]. In light of this, a detailed clinical assessment of the cardiometabolic risk in children (including evaluation of anthropometric measures such as weight, height, waist, and hip circumferences according to age- and gender-specific percentiles and acanthosis nigricans detection as a clinical marker of IR) represents a crucial first step for the evaluation of these patients.

Adipose distribution pattern is considered to have a critical influence on MAFLD development, as demonstrated by the positive correlation of amount of visceral adipose tissue with liver inflammation and fibrosis[4].

To date, the clinical feasibility of MAFLD definition has been mostly studied in adults, but a similar growing interest is also emerging in children. Therefore, we aimed to provide a comprehensive overview by summarizing the most recent evidence on the tangled puzzle of MAFLD in adults and children.

**PATHOPHYSIOLOGY**

Fatty liver pathophysiology includes a well-known spectrum of determinants such as inflammation, IR, genetics and environment[4,28,29]. Genetic determinants commonly implied in NAFLD susceptibility (such as *PNPLA3*[30-32], *TM6SF2*[33], *MBOAT7*[34-36] and *HSD17B13*[37-42] genes) have been also linked to MAFLD pathogenesis[43-45] (Table 2). In particular, the effect of the *PNPLA3* I148M polymorphism as a key genetic factor for NAFLD susceptibility across different ethnicities has been largely recognized both in adults and children[45]. Similarly, robust data have also supported the role of the *TM6SF2* gene in hepatic steatosis development both in adults and children[46-48]. Noteworthy, a pleiotropic effect has been described for both genes because of their extrahepatic role in affecting also kidney function in children with obesity[49,50] and adult with T2D and fatty liver[51]. In addition, robust evidence showed that the downregulation of the *MBOAT7* gene predisposed to fatty liver development both in children and adults[34,52,53]. In contrast, the *HSD17B13* variant has been recognized as a protective factor against liver injury and its progression[38,54,55]. As described for other well-known single nucleotide polymorphisms related to fatty liver, this variant has been found also to influence kidney function[56].

Minor genetic variants affecting IR, oxidative stress and inflammation pathways have been found to be related to fatty liver development [45,57]. In particular, a significant association between the rs17618244 G>A variant in the *KLB* gene and hepatic fibrosis has been described, and this gene is a central player in obesity and lipid and glucose metabolism, as demonstrated by its association with lobular inflammation and cirrhosis in patients clustered according to obesity degree[57].

MAFLD genetic susceptibility is still poorly explored[58,59]. Liu *et al*[59] confirmed the role of the *HSD17B13* region in a cohort of 427 Han Chinese adults as a genetic factor predisposing to MAFLD-related fibrosis and of modulated *PNPLA3* rs738409 polymorphism on fatty liver development[58]. Recent evidence supports an inverse allelic effect of the association of *HSD17B13* variants on liver damage: in particular, hepatic fibrosis risk has been found to be increased by the minor allele TA of the rs72613567 variant, while a protective role against liver damage for the minor A allele of thers6531975 variant has been demonstrated [59].

**EVIDENCE ON MAFLD: FROM ADULTHOOD TO CHILDHOOD**

As the renaming of the liver condition, the clinical usefulness of MAFLD definition has been tested in several studies [60-64] (Table 2). Lin *et al*[60] first compared MAFLD and NAFLD criteria in a large cohort of 13 083 subjects grouped as MAFLD (31.24%), NAFLD (33.23%) and non-metabolic-dysfunction-associated NAFLD (non-MD-NAFLD) (4.74%) (*e.g.,* subjects with NAFLD but not covered by MAFLD criteria)[61-62]. Authors found that patients with fatty liver were older, more likely to be male, and have worse cardiometabolic and hepatic profile independently of the used criteria[60].

Compared to NAFLD, MAFLD subjects were older (48.39 ± 15.20 years) and presented with higher body mass index (BMI), liver enzymes, and noninvasive liver fibrosis scores. In addition, an increased percentage of metabolic comorbidities (including diabetes, IR and hypertension) was reported in these patients[60]. Patients in the non-MD-NAFLD group were the youngest and presented with a better metabolic profile than those belonging to the MAFLD and NAFLD groups. In this framework, a more accurate identification of patients at higher risk of negative metabolic consequences seemed to be achieved by MAFLD criteria[60].

Conversely, no significant differences for the main clinical and biochemical variables between NAFLD and MAFLD were found in a large cohort of 780 adult patients with biopsy-proven fatty liver diagnosis [55]. Taking into account the alcohol consumption in MAFLD definition, patients with MAFLD with significant alcohol intake showed a worse hepatic profile (characterized by higher steatosis degree and transaminase levels) compared to those with MAFLD only[55].

The usefulness of MAFLD definition has been also examined by Sun *et al*[65] in a highly selected population such as patients with chronic kidney disease (CKD). Authors demonstrated a better performance of MAFLD diagnostic criteria than NAFLD in identifying patients with CKD[65], as previously found[64]. Of note, a strong and independent relationship of MAFLD and MAFLD with increased liver fibrosis scores with CKD and abnormal albuminuria was described[65].

Recently, differences between NAFLD and MAFLD criteria were tested in a 2-year follow-up Italian study conducted in 221 patients receiving a new diagnosis of celiac disease (CD) as a high-risk condition for fatty liver[66]. Compared to NAFLD, MAFLD definition allowed a better identification of CD patients at risk of disease progression and the coexistence of fibrosis seemed to enhance the occurrence of adverse outcomes in these patients[66].

Yamamura *et al*[67] compared the diagnostic accuracy of MAFLD and NAFLD in identifying individuals with significant hepatic fibrosis and clarified the influence of mild alcohol consumption (< 20 g/d) on the degree of the hepatic disease in a large cohort of 765 subjects clustered in two groups as NAFLD and MAFLD. Compared to NAFLD, MAFLD criteria provided careful detection of hepatic fibrosis, as reflected by the strong relationship between certain hepatic fibrosis markers and liver stiffness in patients diagnosed with MAFLD[67]. Given that, dysmetabolic patients at high risk of adverse hepatic outcomes were better identified through MAFLD than NAFLD criteria[12,21].

As the well-known relevance of alcohol intake on hepatic fibrosis risk development was not included in MAFLD definition, the authors also examined its influence on fatty liver severity[67]. Patients with MAFLD and alcohol intake of 1–59 g/d were more likely to be male and to have higher fasting blood glucose, serum liver enzymes, creatinine, and uric acid levels than those with MAFLD and no alcohol consumption[67]. Of note, there is no evidence on the potential negative effect of alcohol intake on renal damage risk in MAFLD individuals[67]. Authors concluded that MAFLD presence was an independent risk factor for significant fibrosis (defined by FIB-4 index ≥ 1.3 and liver stiffness ≥ 6.6 kPa using Shear wave elastography), and both MAFLD and mild alcohol intake were associated with increased prevalence of significant fibrosis (25.0% *vs* 15.5%)[67].

Further data examining the role of alcohol intake in this context[60] demonstrated a better metabolic profile but increased transaminase levels in subjects with MAFLD having a greater alcohol intake compared to those with no alcohol consumption. However, no consensus has been reached on the effect of alcohol in MAFLD, but some noninvasive fibrosis scores have been positively associated with MAFLD and alcohol intake[60].

Despite accumulating data on the impact of MAFLD on liver disease severity[60,65,67], its influence on the potential malignant transformation into hepatocellular cancer has been not evaluated.

Unlike adults, pediatric MAFLD data are limited. Because of the widespread distribution of this hepatic condition in childhood, recent epidemiological data reported a worrying increase of pediatric MAFLD prevalence[68-70].

MAFLD definition has been tested first in adult subjects; therefore, its clinical utility in a pediatric setting is still under investigation, since the fatty liver etiology at this stage[71-73] and the obesity status[21]. A recent Italian study investigated the usefulness of MAFLD criteria in 954 children with obesity[21]. The authors grouped their cohort as subjects with (1) obesity only; (2) obesity and NAFLD; and (3) obesity, NAFLD and metabolic dysregulation. The latter group was significantly older and showed higher BMI, systolic blood pressure, diastolic blood pressure, waist/hip ratio, HOMA-IR, triglyceride levels, baseline and 2-h oral glucose tolerance test glycemia, and transaminase levels. A higher prevalence of carriers of the *PNPLA3* rare allele was reported in this group compared with others. Taken together, these findings suggest a worse cardiometabolic profile in subjects with obesity, fatty liver, and metabolic dysregulation than in those belonging to other groups. As a preliminary study, MAFLD diagnosis based on metabolic dysregulation in children with obesity seemed more accurate for cardiometabolic risk stratification in a high-risk population such as children with obesity[21]. *PNPLA3* gene seems to play a role in a wider metabolic milieu beyond NAFLD[21], as previously found in a similar pediatric cohort[50,74].

More recently, an international panel[75] has proposed an age-appropriate MAFLD definition based on sex and age percentiles. Diagnostic criteria for pediatric MAFLD are based on the presence of hepatic steatosis (detected either by liver histology, imaging, blood biomarkers or blood scores) in addition to one of the following conditions: excess adiposity, T2D or prediabetes, or evidence of metabolic dysregulation (defined by the presence of at least two metabolic risk conditions according to sex and age percentiles such as hypertension, increased waist circumference, hypertriglyceridemia, low serum HDL cholesterol levels, triglyceride-to-HDL ratio ≥ 2.25, and impaired fasting glucose)[75].

Contrary to the adult findings, the natural history of fatty liver in children is still not fully understood but its increase has been mainly linked to obesity[75]. Pediatric fatty liver usually does not occur in children < 3 years and is rare in those aged < 10 years. To date, it has been demonstrated that the entire spectrum of liver disease severity (from simple steatosis to steatohepatitis, fibrosis, and end-stage cirrhosis) might occur also in pediatric patients diagnosed with fatty liver, and that the progression is strongly related to IR severity[75]. As a consequence, the occurrence of severe complications (including liver transplantation) at this early age has also been reported. The pivotal role of primary care for early detection of pediatric fatty liver is widely recognized, and lifestyle modifications are the only valid treatment for the disease[75]. Therefore, redefinition of pediatric MAFLD represents a crucial step for global management improvement, including risk stratification and multidisciplinary care.

**MAFLD: NEW INSIGHTS AND FUTURE DIRECTIONS**

The tangled and multifactorial physiopathology of MAFLD (including inflammation, sex, age, ethnicity, diet and microbiota, hormones, and genetics) is still poorly defined. Despite the centrality of metabolic dysfunction, diagnosing fatty liver is also essential for MAFLD definition. Liver biopsy represents the common diagnostic gold standard for hepatic fat content assessment, but its invasiveness has limited its clinical utility in children[76,77]. A growing number of studies has evaluated different noninvasive biomarkers for MAFLD diagnosis, by identifying novel attractive therapeutic options for the management of the disease[78-81]. In this context, investigation of the gut–liver axis has attracted scientific attention[81-84]. Considering the relevance of the intestinal barrier in multiple biological mechanisms and the crucial influence of the immune system (located in the liver, intestine and adipose tissue)[84], this term strengthens the association of the liver with the gut barrier.

The association of gut–liver axis changes with MAFLD pathophysiology have recently been explored[78], by pointing out the role of inflammation and release of chemokines and cytokines by liver-infiltrating macrophages as key factors for progressive forms of fatty liver[78].

Dysbiosis and gut barrier changes have both been linked to inflammation and metabolic abnormalities in MAFLD. Remarkably, a peculiar association of microbiome alterations with carbohydrates, lipids and amino acids metabolism in MAFLD has also been described[81], but no consensus has been reached in this field. Nevertheless, promising preclinical studies[81] have enriched the spectrum of potential MAFLD therapeutic tools such as fecal microbiota transplantation[82-84]. A similar study on MAFLD adults[84] investigated microbiota-derived metabolites as potential noninvasive biomarkers for MAFLD, by identifying certain metabolites [*e.g.,* phosphatidylcholine (PC), lysoPC, plasma eicosanoic acid or fatty acid 20:1 (FA20:1), PCaaC24:0, xanthine, and triglycerides] as early microbiota-related products involved in liver disease progression[84]. In addition, a significant association of the *PNPLA3* gene with plasma monounsaturated fatty acid FA(20:1) or eicosanoic acid was also demonstrated.

Notably, serum mi-RNA-122 (as the major hepatic mi-RNA involved in metabolic diseases) is significantly related to MAFLD progression in subjects with obesity and MAFLD[80]; therefore suggesting their potential prognostic utility for liver disease progression[80].

Although preliminary, some promising evidence supports the identification of novel potential therapeutic targets for MAFLD[85-88]. In particular, a significant decrease in MAFLD prevalence has been reported in normal-weight adolescents treated with a low-dose combination of spironolactone, pioglitazone and metformin (SPIOMET)[86-90] than those with classical hormone therapy, by underlining the role of SPIOMET treatment as a promising new pathophysiological approach in MAFLD patients[88]. Due to the relevant cardiometabolic burden of MAFLD and the absence of effective pharmacological agents both in children and adults, further studies are needed to identify specific noninvasive markers able to improve the management of MAFLD patients[75]. Several novel therapeutic targets based on molecular pathways are under investigation[78,84], but there are no current licensed MAFLD treatments[75].

**CONCLUSIONS**

The natural history of pediatric MAFLD remains to be defined, but mounting evidence from adults supports a significant increased cardiovascular risk in view of the concomitant occurrence of metabolic impairments with liver disease. Therefore, better knowledge of the intricate MAFLD pathophysiology might pave the way for new therapeutic approaches to improve the management of these patients at greater cardiometabolic risk.

**REFERENCES**

1 **Eslam M**, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbæk H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020; **73**: 202-209 [PMID: 32278004 DOI: 10.1016/j.jhep.2020.03.039]

2 **Morandi A**, Di Sessa A, Zusi C, Umano GR, El Mazloum D, Fornari E, Miraglia Del Giudice E, Targher G, Maffeis C. Nonalcoholic Fatty Liver Disease and Estimated Insulin Resistance in Obese Youth: A Mendelian Randomization Analysis. *J Clin Endocrinol Metab* 2020; **105** [PMID: 32841326 DOI: 10.1210/clinem/dgaa583]

3 **Manco M**. Insulin Resistance and NAFLD: A Dangerous Liaison beyond the Genetics. *Children (Basel)* 2017; **4** [PMID: 28805745 DOI: 10.3390/children4080074]

4 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: 32044314 DOI: 10.1053/j.gastro.2019.11.312]

5 **Kuchay MS**, Misra A. From non-alcoholic fatty liver disease (NAFLD) to metabolic-associated fatty liver disease (MAFLD): A journey over 40 years. *Diabetes Metab Syndr* 2020; **14**: 695-696 [PMID: 32442920 DOI: 10.1016/j.dsx.2020.05.019]

6 **Tilg H**, Effenberger M. From NAFLD to MAFLD: when pathophysiology succeeds. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 387-388 [PMID: 32461575 DOI: 10.1038/s41575-020-0316-6]

7 **Utzschneider KM**, Kahn SE. Review: The role of insulin resistance in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* 2006; **91**: 4753-4761 [PMID: 16968800 DOI: 10.1210/jc.2006-0587]

8 **Di Bonito P**, Valerio G, Licenziati MR, Miraglia Del Giudice E, Baroni MG, Morandi A, Maffeis C, Campana G, Spreghini MR, Di Sessa A, Morino G, Crinò A, Chiesa C, Pacifico L, Manco M. High uric acid, reduced glomerular filtration rate and non-alcoholic fatty liver in young people with obesity. *J Endocrinol Invest* 2020; **43**: 461-468 [PMID: 31637675 DOI: 10.1007/s40618-019-01130-6]

9 **Targher G**, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010; **363**: 1341-1350 [PMID: 20879883 DOI: 10.1056/NEJMra0912063]

10 **Targher G**. What's Past Is Prologue: History of Nonalcoholic Fatty Liver Disease. *Metabolites* 2020; **10** [PMID: 33049948 DOI: 10.3390/metabo10100397]

11 **Mantovani A**, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut* 2021; **70**: 962-969 [PMID: 32938692 DOI: 10.1136/gutjnl-2020-322572]

12 **Xian YX**, Weng JP, Xu F. MAFLD vs. NAFLD: shared features and potential changes in epidemiology, pathophysiology, diagnosis, and pharmacotherapy. *Chin Med J (Engl)* 2020; **134**: 8-19 [PMID: 33323806 DOI: 10.1097/CM9.0000000000001263]

13 **Cox AJ**, West NP, Cripps AW. Obesity, inflammation, and the gut microbiota. *Lancet Diabetes Endocrinol* 2015; **3**: 207-215 [PMID: 25066177 DOI: 10.1016/S2213-8587(14)70134-2]

14 **Esser N**, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract* 2014; **105**: 141-150 [PMID: 24798950 DOI: 10.1016/j.diabres.2014.04.006]

15 **Saltiel AR**, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. *J Clin Invest* 2017; **127**: 1-4 [PMID: 28045402 DOI: 10.1172/JCI92035]

16 **Alberti KG**, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; **23**: 469-480 [PMID: 16681555 DOI: 10.1111/j.1464-5491.2006.01858.x]

17 **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults**. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486-2497 [PMID: 11368702 DOI: 10.1001/jama.285.19.2486]

18 **Zimmet P**, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S; International Diabetes Federation Task Force on Epidemiology and Prevention of Diabetes. The metabolic syndrome in children and adolescents. *Lancet* 2007; **369**: 2059-2061 [PMID: 17586288 DOI: 10.1016/S0140-6736(07)60958-1]

19 **Chiarelli F**, Mohn A. Early diagnosis of metabolic syndrome in children. *Lancet Child Adolesc Health* 2017; **1**: 86-88 [PMID: 30169210 DOI: 10.1016/S2352-4642(17)30043-3]

20 **Ahrens W**, Moreno LA, Mårild S, Molnár D, Siani A, De Henauw S, Böhmann J, Günther K, Hadjigeorgiou C, Iacoviello L, Lissner L, Veidebaum T, Pohlabeln H, Pigeot I; IDEFICS consortium. Metabolic syndrome in young children: definitions and results of the IDEFICS study. *Int J Obes (Lond)* 2014; **38 Suppl 2**: S4-14 [PMID: 25376220 DOI: 10.1038/ijo.2014.130]

21 **Di Sessa A**, Guarino S, Umano GR, Arenella M, Alfiero S, Quaranta G, Miraglia Del Giudice E, Marzuillo P. MAFLD in Obese Children: A Challenging Definition. *Children (Basel)* 2021; **8** [PMID: 33806784 DOI: 10.3390/children8030247]

22 **Genovesi S**, Antolini L, Orlando A, Gilardini L, Bertoli S, Giussani M, Invitti C, Nava E, Battaglino MG, Leone A, Valsecchi MG, Parati G. Cardiovascular Risk Factors Associated With the Metabolically Healthy Obese (MHO) Phenotype Compared to the Metabolically Unhealthy Obese (MUO) Phenotype in Children. *Front Endocrinol (Lausanne)* 2020; **11**: 27 [PMID: 32117055 DOI: 10.3389/fendo.2020.00027]

23 **Di Bonito P**, Miraglia Del Giudice E, Chiesa C, Licenziati MR, Manco M, Franco F, Tornese G, Baroni MG, Morandi A, Maffeis C, Pacifico L, Valerio G; CARITALY Study on the behalf of the Childhood Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Preclinical signs of liver and cardiac damage in youth with metabolically healthy obese phenotype. *Nutr Metab Cardiovasc Dis* 2018; **28**: 1230-1236 [PMID: 30355472 DOI: 10.1016/j.numecd.2018.08.007]

24 **Chiesa C**, Pacifico L, Xi B, Cadenas-Sanchez C. Editorial: Metabolically Healthy and Unhealthy Obese Children and Adolescents. *Front Endocrinol (Lausanne)* 2020; **11**: 613703 [PMID: 33250860 DOI: 10.3389/fendo.2020.613703]

25 **Eckel N**, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol* 2018; **6**: 714-724 [PMID: 29859908 DOI: 10.1016/S2213-8587(18)30137-2]

26 **Caleyachetty R**, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, Nirantharakumar K. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. *J Am Coll Cardiol* 2017; **70**: 1429-1437 [PMID: 28911506 DOI: 10.1016/j.jacc.2017.07.763]

27 **Lassale C**, Tzoulaki I, Moons KGM, Sweeting M, Boer J, Johnson L, Huerta JM, Agnoli C, Freisling H, Weiderpass E, Wennberg P, van der A DL, Arriola L, Benetou V, Boeing H, Bonnet F, Colorado-Yohar SM, Engström G, Eriksen AK, Ferrari P, Grioni S, Johansson M, Kaaks R, Katsoulis M, Katzke V, Key TJ, Matullo G, Melander O, Molina-Portillo E, Moreno-Iribas C, Norberg M, Overvad K, Panico S, Quirós JR, Saieva C, Skeie G, Steffen A, Stepien M, Tjønneland A, Trichopoulou A, Tumino R, van der Schouw YT, Verschuren WMM, Langenberg C, Di Angelantonio E, Riboli E, Wareham NJ, Danesh J, Butterworth AS. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. *Eur Heart J* 2018; **39**: 397-406 [PMID: 29020414 DOI: 10.1093/eurheartj/ehx448]

28 **Tarantino G**. NAFLD or MAFLD: That is the conundrum. *Hepatobiliary Pancreat Dis Int* 2022 [PMID: 35125337 DOI: 10.1016/j.hbpd.2022.01.008]

29 **Brunt EM**, Wong VW, Nobili V, Day CP, Sookoian S, Maher JJ, Bugianesi E, Sirlin CB, Neuschwander-Tetri BA, Rinella ME. Nonalcoholic fatty liver disease. *Nat Rev Dis Primers* 2015; **1**: 15080 [PMID: 27188459 DOI: 10.1038/nrdp.2015.80]

30 **Dongiovanni P**, Donati B, Fares R, Lombardi R, Mancina RM, Romeo S, Valenti L. PNPLA3 I148M polymorphism and progressive liver disease. *World J Gastroenterol* 2013; **19**: 6969-6978 [PMID: 24222941 DOI: 10.3748/wjg.v19.i41.6969]

31 **Romeo S**, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; **40**: 1461-1465 [PMID: 18820647 DOI: 10.1038/ng.257]

32 **Tang S**, Zhang J, Mei TT, Guo HQ, Wei XH, Zhang WY, Liu YL, Liang S, Fan ZP, Ma LX, Lin W, Liu YR, Qiu LX, Yu HB. Association of PNPLA3 rs738409 G/C gene polymorphism with nonalcoholic fatty liver disease in children: a meta-analysis. *BMC Med Genet* 2020; **21**: 163 [PMID: 32811452 DOI: 10.1186/s12881-020-01098-8]

33 **Kozlitina J**, Smagris E, Stender S, Nordestgaard BG, Zhou HH, Tybjærg-Hansen A, Vogt TF, Hobbs HH, Cohen JC. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2014; **46**: 352-356 [PMID: 24531328 DOI: 10.1038/ng.2901]

34 **Mancina RM**, Dongiovanni P, Petta S, Pingitore P, Meroni M, Rametta R, Borén J, Montalcini T, Pujia A, Wiklund O, Hindy G, Spagnuolo R, Motta BM, Pipitone RM, Craxì A, Fargion S, Nobili V, Käkelä P, Kärjä V, Männistö V, Pihlajamäki J, Reilly DF, Castro-Perez J, Kozlitina J, Valenti L, Romeo S. The MBOAT7-TMC4 Variant rs641738 Increases Risk of Nonalcoholic Fatty Liver Disease in Individuals of European Descent. *Gastroenterology* 2016; **150**: 1219-1230.e6 [PMID: 26850495 DOI: 10.1053/j.gastro.2016.01.032]

35 **Di Sessa A**, Umano GR, Cirillo G, Del Prete A, Iacomino R, Marzuillo P, Del Giudice EM. The Membrane-bound O-Acyltransferase7 rs641738 Variant in Pediatric Nonalcoholic Fatty Liver Disease. *J Pediatr Gastroenterol Nutr* 2018; **67**: 69-74 [PMID: 29601441 DOI: 10.1097/MPG.0000000000001979]

36 **Umano GR**, Caprio S, Di Sessa A, Chalasani N, Dykas DJ, Pierpont B, Bale AE, Santoro N. The rs626283 Variant in the MBOAT7 Gene is Associated with Insulin Resistance and Fatty Liver in Caucasian Obese Youth. *Am J Gastroenterol* 2018; **113**: 376-383 [PMID: 29485130 DOI: 10.1038/ajg.2018.1]

37 **Su W**, Mao Z, Liu Y, Zhang X, Zhang W, Gustafsson JA, Guan Y. Role of HSD17B13 in the liver physiology and pathophysiology. *Mol Cell Endocrinol* 2019; **489**: 119-125 [PMID: 30365983 DOI: 10.1016/j.mce.2018.10.014]

38 **Abul-Husn NS**, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, Liu Y, Kozlitina J, Stender S, Wood GC, Stepanchick AN, Still MD, McCarthy S, O'Dushlaine C, Packer JS, Balasubramanian S, Gosalia N, Esopi D, Kim SY, Mukherjee S, Lopez AE, Fuller ED, Penn J, Chu X, Luo JZ, Mirshahi UL, Carey DJ, Still CD, Feldman MD, Small A, Damrauer SM, Rader DJ, Zambrowicz B, Olson W, Murphy AJ, Borecki IB, Shuldiner AR, Reid JG, Overton JD, Yancopoulos GD, Hobbs HH, Cohen JC, Gottesman O, Teslovich TM, Baras A, Mirshahi T, Gromada J, Dewey FE. A Protein-Truncating HSD17B13 Variant and Protection from Chronic Liver Disease. *N Engl J Med* 2018; **378**: 1096-1106 [PMID: 29562163 DOI: 10.1056/NEJMoa1712191]

39 **Anstee QM**, Darlay R, Cockell S, Meroni M, Govaere O, Tiniakos D, Burt AD, Bedossa P, Palmer J, Liu YL, Aithal GP, Allison M, Yki-Järvinen H, Vacca M, Dufour JF, Invernizzi P, Prati D, Ekstedt M, Kechagias S, Francque S, Petta S, Bugianesi E, Clement K, Ratziu V, Schattenberg JM, Valenti L, Day CP, Cordell HJ, Daly AK; EPoS Consortium Investigators. Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort☆. *J Hepatol* 2020; **73**: 505-515 [PMID: 32298765 DOI: 10.1016/j.jhep.2020.04.003]

40 **Ma Y**, Karki S, Brown PM, Lin DD, Podszun MC, Zhou W, Belyaeva OV, Kedishvili NY, Rotman Y. Characterization of essential domains in HSD17B13 for cellular localization and enzymatic activity. *J Lipid Res* 2020; **61**: 1400-1409 [PMID: 32973038 DOI: 10.1194/jlr.RA120000907]

41 **Dong XC**. A closer look at the mysterious HSD17B13. *J Lipid Res* 2020; **61**: 1361-1362 [PMID: 33008926 DOI: 10.1194/jlr.C120001160]

42 **Tang S**, Zhang J, Mei TT, Zhang WY, Zheng SJ, Yu HB. Association of HSD17B13 rs72613567: TA allelic variant with liver disease: review and meta-analysis. *BMC Gastroenterol* 2021; **21**: 490 [PMID: 34930143 DOI: 10.1186/s12876-021-02067-y]

43 **Krawczyk M**, Rau M, Schattenberg JM, Bantel H, Pathil A, Demir M, Kluwe J, Boettler T, Lammert F, Geier A; NAFLD Clinical Study Group. Combined effects of the PNPLA3 rs738409, TM6SF2 rs58542926, and MBOAT7 rs641738 variants on NAFLD severity: a multicenter biopsy-based study. *J Lipid Res* 2017; **58**: 247-255 [PMID: 27836992 DOI: 10.1194/jlr.P067454]

44 **Cobbina E**, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug Metab Rev* 2017; **49**: 197-211 [PMID: 28303724 DOI: 10.1080/03602532.2017.1293683]

45 **Lin YC**, Wu CC, Ni YH. New Perspectives on Genetic Prediction for Pediatric Metabolic Associated Fatty Liver Disease. *Front Pediatr* 2020; **8**: 603654 [PMID: 33363067 DOI: 10.3389/fped.2020.603654]

46 **Xue WY**, Zhang L, Liu CM, Gao Y, Li SJ, Huai ZY, Dai J, Wang YY. Research progress on the relationship between TM6SF2 rs58542926 polymorphism and non-alcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol* 2022; **16**: 97-107 [PMID: 35057689 DOI: 10.1080/17474124.2022.2032661]

47 **Dongiovanni P**, Petta S, Maglio C, Fracanzani AL, Pipitone R, Mozzi E, Motta BM, Kaminska D, Rametta R, Grimaudo S, Pelusi S, Montalcini T, Alisi A, Maggioni M, Kärjä V, Borén J, Käkelä P, Di Marco V, Xing C, Nobili V, Dallapiccola B, Craxi A, Pihlajamäki J, Fargion S, Sjöström L, Carlsson LM, Romeo S, Valenti L. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. *Hepatology* 2015; **61**: 506-514 [PMID: 25251399 DOI: 10.1002/hep.27490]

48 **Liu YL**, Reeves HL, Burt AD, Tiniakos D, McPherson S, Leathart JB, Allison ME, Alexander GJ, Piguet AC, Anty R, Donaldson P, Aithal GP, Francque S, Van Gaal L, Clement K, Ratziu V, Dufour JF, Day CP, Daly AK, Anstee QM. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. *Nat Commun* 2014; **5**: 4309 [PMID: 24978903 DOI: 10.1038/ncomms5309]

49 **Marzuillo P**, Di Sessa A, Cirillo G, Umano GR, Pedullà M, La Manna A, Guarino S, Miraglia Del Giudice E. Transmembrane 6 superfamily member 2 167K allele improves renal function in children with obesity. *Pediatr Res* 2020; **88**: 300-304 [PMID: 31923913 DOI: 10.1038/s41390-020-0753-5]

50 **Targher G**, Mantovani A, Alisi A, Mosca A, Panera N, Byrne CD, Nobili V. Relationship Between PNPLA3 rs738409 Polymorphism and Decreased Kidney Function in Children With NAFLD. *Hepatology* 2019; **70**: 142-153 [PMID: 30912854 DOI: 10.1002/hep.30625]

51 **Mantovani A**, Taliento A, Zusi C, Baselli G, Prati D, Granata S, Zaza G, Colecchia A, Maffeis C, Byrne CD, Valenti L, Targher G. PNPLA3 I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: Clinical and experimental findings. *Liver Int* 2020; **40**: 1130-1141 [PMID: 32125756 DOI: 10.1111/liv.14419]

52 **Meroni M**, Longo M, Fracanzani AL, Dongiovanni P. MBOAT7 down-regulation by genetic and environmental factors predisposes to MAFLD. *EBioMedicine* 2020; **57**: 102866 [PMID: 32629394 DOI: 10.1016/j.ebiom.2020.102866]

53 **Ismaiel A**, Dumitrascu DL. Genetic predisposition in metabolic-dysfunction-associated fatty liver disease and cardiovascular outcomes-Systematic review. *Eur J Clin Invest* 2020; **50**: e13331 [PMID: 32589269 DOI: 10.1111/eci.13331]

54 **Vilar-Gomez E**, Pirola CJ, Sookoian S, Wilson LA, Liang T, Chalasani N. The Protection Conferred by HSD17B13 rs72613567 Polymorphism on Risk of Steatohepatitis and Fibrosis May Be Limited to Selected Subgroups of Patients With NAFLD. *Clin Transl Gastroenterol* 2021; **12**: e00400 [PMID: 34506332 DOI: 10.14309/ctg.0000000000000400]

55 **Zhang HB**, Su W, Xu H, Zhang XY, Guan YF. HSD17B13: A Potential Therapeutic Target for NAFLD. *Front Mol Biosci* 2021; **8**: 824776 [PMID: 35071330 DOI: 10.3389/fmolb.2021.824776]

56 **Di Sessa A**, Umano GR, Cirillo G, Passaro AP, Verde V, Cozzolino D, Guarino S, Marzuillo P, Miraglia Del Giudice E. Pediatric non-alcoholic fatty liver disease and kidney function: Effect of *HSD17B13* variant. *World J Gastroenterol* 2020; **26**: 5474-5483 [PMID: 33024398 DOI: 10.3748/wjg.v26.i36.5474]

57 **Panera N**, Meroni M, Longo M, Crudele A, Valenti L, Bellacchio E, Miele L, D'Oria V, Paolini E, Maggioni M, Fracanzani AL, Alisi A, Dongiovanni P. The KLB rs17618244 gene variant is associated with fibrosing MAFLD by promoting hepatic stellate cell activation. *EBioMedicine* 2021; **65**: 103249 [PMID: 33640795 DOI: 10.1016/j.ebiom.2021.103249]

58 **Wang P**, Wu CX, Li Y, Shen N. HSD17B13 rs72613567 protects against liver diseases and histological progression of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2020; **24**: 8997-9007 [PMID: 32964989 DOI: 10.26355/eurrev\_202009\_22842]

59 **Liu WY**, Eslam M, Zheng KI, Ma HL, Rios RS, Lv MZ, Li G, Tang LJ, Zhu PW, Wang XD, Byrne CD, Targher G, George J, Zheng MH. Associations of Hydroxysteroid 17-beta Dehydrogenase 13 Variants with Liver Histology in Chinese Patients with Metabolic-associated Fatty Liver Disease. *J Clin Transl Hepatol* 2021; **9**: 194-202 [PMID: 34007801 DOI: 10.14218/JCTH.2020.00151]

60 **Lin S**, Huang J, Wang M, Kumar R, Liu Y, Liu S, Wu Y, Wang X, Zhu Y. Comparison of MAFLD and NAFLD diagnostic criteria in real world. *Liver Int* 2020; **40**: 2082-2089 [PMID: 32478487 DOI: 10.1111/liv.14548]

61 **Alharthi J**, Gastaldelli A, Cua IH, Ghazinian H, Eslam M. Metabolic dysfunction-associated fatty liver disease: a year in review. *Curr Opin Gastroenterol* 2022 [PMID: 35143431 DOI: 10.1097/MOG.0000000000000823]

62 **Devi J**, Raees A, Butt AS. Redefining non-alcoholic fatty liver disease to metabolic associated fatty liver disease: Is this plausible? *World J Hepatol* 2022; **14**: 158-167 [PMID: 35126845 DOI: 10.4254/wjh.v14.i1.158]

63 **Kang SH**, Cho Y, Jeong SW, Kim SU, Lee JW; Korean NAFLD Study Group. From nonalcoholic fatty liver disease to metabolic-associated fatty liver disease: Big wave or ripple? *Clin Mol Hepatol* 2021; **27**: 257-269 [PMID: 33751877 DOI: 10.3350/cmh.2021.0067]

64 **Kawaguchi T**, Tsutsumi T, Nakano D, Torimura T. MAFLD: Renovation of clinical practice and disease awareness of fatty liver. *Hepatol Res* 2021 [PMID: 34472683 DOI: 10.1111/hepr.13706]

65 **Sun DQ**, Jin Y, Wang TY, Zheng KI, Rios RS, Zhang HY, Targher G, Byrne CD, Yuan WJ, Zheng MH. MAFLD and risk of CKD. *Metabolism* 2021; **115**: 154433 [PMID: 33212070 DOI: 10.1016/j.metabol.2020.154433]

66 **Rispo A**, Imperatore N, Guarino M, Tortora R, Alisi A, Cossiga V, Testa A, Ricciolino S, Fiorentino A, Morisco F. Metabolic-associated fatty liver disease (MAFLD) in coeliac disease. *Liver Int* 2021; **41**: 788-798 [PMID: 33319459 DOI: 10.1111/liv.14767]

67 **Qu W**, Ma T, Cai J, Zhang X, Zhang P, She Z, Wan F, Li H. Liver Fibrosis and MAFLD: From Molecular Aspects to Novel Pharmacological Strategies. *Front Med (Lausanne)* 2021; **8**: 761538 [PMID: 34746195 DOI: 10.3389/fmed.2021.761538]

68 **Lee H**, Lee YH, Kim SU, Kim HC. Metabolic Dysfunction-Associated Fatty Liver Disease and Incident Cardiovascular Disease Risk: A Nationwide Cohort Study. *Clin Gastroenterol Hepatol* 2021; **19**: 2138-2147.e10 [PMID: 33348045 DOI: 10.1016/j.cgh.2020.12.022]

69 **Ramírez-Mejía MM**, Díaz-Orozco LE, Barranco-Fragoso B, Méndez-Sánchez N. A Review of the Increasing Prevalence of Metabolic-Associated Fatty Liver Disease (MAFLD) in Children and Adolescents Worldwide and in Mexico and the Implications for Public Health. *Med Sci Monit* 2021; **27**: e934134 [PMID: 34456329 DOI: 10.12659/MSM.934134]

70 **Flisiak-Jackiewicz M**, Bobrus-Chociej A, Wasilewska N, Lebensztejn DM. From Nonalcoholic Fatty Liver Disease (NAFLD) to Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)-New Terminology in Pediatric Patients as a Step in Good Scientific Direction? *J Clin Med* 2021; **10** [PMID: 33804296 DOI: 10.3390/jcm10050924]

71 **Zimmet P**, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, Wong G, Bennett P, Shaw J, Caprio S; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatr Diabetes* 2007; **8**: 299-306 [PMID: 17850473 DOI: 10.1111/j.1399-5448.2007.00271.x]

72 **Yıldız Y**, Sivri HS. Inborn errors of metabolism in the differential diagnosis of fatty liver disease. *Turk J Gastroenterol* 2020; **31**: 3-16 [PMID: 32009609 DOI: 10.5152/tjg.2019.19367]

73 **Yodoshi T**, Orkin S, Arce-Clachar AC, Bramlage K, Xanthakos SA, Valentino PL, Mouzaki M. Alternative Etiologies of Liver Disease in Children With Suspected NAFLD. *Pediatrics* 2021; **147** [PMID: 33785637 DOI: 10.1542/peds.2020-009829]

74 **Marzuillo P**, Di Sessa A, Guarino S, Capalbo D, Umano GR, Pedullà M, La Manna A, Cirillo G, Miraglia Del Giudice E. Nonalcoholic fatty liver disease and eGFR levels could be linked by the PNPLA3 I148M polymorphism in children with obesity. *Pediatr Obes* 2019; **14**: e12539 [PMID: 31184438 DOI: 10.1111/ijpo.12539]

75 **Eslam M**, Alkhouri N, Vajro P, Baumann U, Weiss R, Socha P, Marcus C, Lee WS, Kelly D, Porta G, El-Guindi MA, Alisi A, Mann JP, Mouane N, Baur LA, Dhawan A, George J. Defining paediatric metabolic (dysfunction)-associated fatty liver disease: an international expert consensus statement. *Lancet Gastroenterol Hepatol* 2021; **6**: 864-873 [PMID: 34364544 DOI: 10.1016/S2468-1253(21)00183-7]

76 **Hashimoto E**, Taniai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. *J Gastroenterol Hepatol* 2013; **28 Suppl 4**: 64-70 [PMID: 24251707 DOI: 10.1111/jgh.12271]

77 **Sumida Y**, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol* 2014; **20**: 475-485 [PMID: 24574716 DOI: 10.3748/wjg.v20.i2.475]

78 **Martín-Mateos R**, Albillos A. The Role of the Gut-Liver Axis in Metabolic Dysfunction-Associated Fatty Liver Disease. *Front Immunol* 2021; **12**: 660179 [PMID: 33936094 DOI: 10.3389/fimmu.2021.660179]

79 **Sharpton SR**, Schnabl B, Knight R, Loomba R. Current Concepts, Opportunities, and Challenges of Gut Microbiome-Based Personalized Medicine in Nonalcoholic Fatty Liver Disease. *Cell Metab* 2021; **33**: 21-32 [PMID: 33296678 DOI: 10.1016/j.cmet.2020.11.010]

80 **Hegazy MA**, Abd ALgwad I, Abuel Fadl S, Sayed Hassan M, Ahmed Rashed L, Hussein MA. Serum Micro-RNA-122 Level as a Simple Noninvasive Marker of MAFLD Severity. *Diabetes Metab Syndr Obes* 2021; **14**: 2247-2254 [PMID: 34040409 DOI: 10.2147/DMSO.S291595]

81 **Duan Y**, Llorente C, Lang S, Brandl K, Chu H, Jiang L, White RC, Clarke TH, Nguyen K, Torralba M, Shao Y, Liu J, Hernandez-Morales A, Lessor L, Rahman IR, Miyamoto Y, Ly M, Gao B, Sun W, Kiesel R, Hutmacher F, Lee S, Ventura-Cots M, Bosques-Padilla F, Verna EC, Abraldes JG, Brown RS Jr, Vargas V, Altamirano J, Caballería J, Shawcross DL, Ho SB, Louvet A, Lucey MR, Mathurin P, Garcia-Tsao G, Bataller R, Tu XM, Eckmann L, van der Donk WA, Young R, Lawley TD, Stärkel P, Pride D, Fouts DE, Schnabl B. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. *Nature* 2019; **575**: 505-511 [PMID: 31723265 DOI: 10.1038/s41586-019-1742-x]

82 **Sabino J**, Hirten RP, Colombel JF. Review article: bacteriophages in gastroenterology-from biology to clinical applications. *Aliment Pharmacol Ther* 2020; **51**: 53-63 [PMID: 31696976 DOI: 10.1111/apt.15557]

83 **Hsu BB**, Gibson TE, Yeliseyev V, Liu Q, Lyon L, Bry L, Silver PA, Gerber GK. Dynamic Modulation of the Gut Microbiota and Metabolome by Bacteriophages in a Mouse Model. *Cell Host Microbe* 2019; **25**: 803-814.e5 [PMID: 31175044 DOI: 10.1016/j.chom.2019.05.001]

84 **Mazzini FN**, Cook F, Gounarides J, Marciano S, Haddad L, Tamaroff AJ, Casciato P, Narvaez A, Mascardi MF, Anders M, Orozco F, Quiróz N, Risk M, Gutt S, Gadano A, Méndez García C, Marro ML, Penas-Steinhardt A, Trinks J. Plasma and stool metabolomics to identify microbiota derived-biomarkers of metabolic dysfunction-associated fatty liver disease: effect of PNPLA3 genotype. *Metabolomics* 2021; **17**: 58 [PMID: 34137937 DOI: 10.1007/s11306-021-01810-6]

85 **DiVall S**, Merjaneh L. Adolescent Polycystic Ovary Syndrome: An Update. *Pediatr Ann* 2019; **48**: e304-e310 [PMID: 31426098 DOI: 10.3928/19382359-20190729-01]

86 **Ibáñez L**, Oberfield SE, Witchel S, Auchus RJ, Chang RJ, Codner E, Dabadghao P, Darendeliler F, Elbarbary NS, Gambineri A, Garcia Rudaz C, Hoeger KM, López-Bermejo A, Ong K, Peña AS, Reinehr T, Santoro N, Tena-Sempere M, Tao R, Yildiz BO, Alkhayyat H, Deeb A, Joel D, Horikawa R, de Zegher F, Lee PA. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. *Horm Res Paediatr* 2017; **88**: 371-395 [PMID: 29156452 DOI: 10.1159/000479371]

87 **Legro RS**, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, Welt CK; Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2013; **98**: 4565-4592 [PMID: 24151290 DOI: 10.1210/jc.2013-2350]

88 **de Zegher F**, López-Bermejo A, Ibáñez L. Central Obesity, Faster Maturation, and 'PCOS' in Girls. *Trends Endocrinol Metab* 2018; **29**: 815-818 [PMID: 30297320 DOI: 10.1016/j.tem.2018.09.005]

89 **Ibáñez L**, Díaz M, García-Beltrán C, Malpique R, Garde E, López-Bermejo A, de Zegher F. Toward a Treatment Normalizing Ovulation Rate in Adolescent Girls With Polycystic Ovary Syndrome. *J Endocr Soc* 2020; **4**: bvaa032 [PMID: 32342022 DOI: 10.1210/jendso/bvaa032]

90 **de Zegher F**, Diaz M, Ibañez L. From adolescent PCOS to adult MAFLD: opposing effects of randomised interventions. *BMJ Open Gastroenterol* 2021; **8** [PMID: 34011622 DOI: 10.1136/bmjgast-2020-000574]

**Footnotes**

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/Licenses/by-nc/4.0/>

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** October 18, 2021

**First decision:** December 3, 2021

**Article in press:** April 25, 2022

**Specialty type:** Pediatrics

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C, C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Chen GX, China; Chen F, China; Gao Y, China; Ulasoglu C, Turkey; Zhang LL, China **S-Editor:** Ma YJ **L-Editor:** Kerr C **P-Editor:** Ma YJ

**Table 1 Comparison between MAFLD and NAFLD diagnostic criteria**

|  |  |
| --- | --- |
| **MAFLD criteria**[1] | **NAFLD criteria**[62] |
| Histological (biopsy), imaging or blood biomarker evidence of hepatic steatosis and the presence of one of these criteria: | Presence of steatosis in > 5% of hepatocytes detected by biopsy |
| (1) Overweight/obesity |
| (2) Diabetes mellitus |
| (3) Evidence of metabolic dysregulation defined as the presence of ≥ 2 of the following conditions: (a) waist circumference ≥ 102 cm in Caucasian men and 88 cm in women (or ≥ 90/80 cm in Asian men and women); (b) blood pressure ≥ 130/85 mmHg or specific drug treatment; (c) triglyceride ≥ 1.70 mmol/L or specific drug treatment; (d) high-density lipoprotein cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women; (e) prediabetes (*i.e.,* fasting glucose levels 5.6–6.9 mmol/L, or 2-h postload glucose levels 7.8–11.0 mmol/L or hemoglobin A1c 5.7%–6.4%; (f) homeostasis model assessment-insulin resistance score ≥ 2.5; and (g) high sensitive C-reactive protein > 2 mg/L | -The proton density fat fraction (providing a rough estimation of the volume fraction of fatty material in the liver) > 5.6% assessed by proton magnetic resonance spectroscopy |
|  | -Quantitative fat/water selective magnetic resonance imaging |
|  | Exclusion of both secondary causes and a daily alcohol consumption ≥ 30 g for men and 20 g for women |

MAFLD: Metabolic associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease.

**Table 2 Main findings of the studies on MAFLD genetics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Gene** | **Study design** | **Population** | **Gene pathophysiology** | **Main findings** |
| *b-Klotho (KLB) gene* | Panera *et al*[57], Hospital-based retrospective cohort study | 1111 adult Italian MAFLD patients from the Metabolic Liver Diseases outpatient service at Fondazione IRCCS Ca’Granda of Milan between January 1999 and December 2019. Patients were stratified according to obesity status: | The *rs17618244 G>A* variant in the *b-Klotho (KLB)* gene encodes for a transmembrane protein which complexes with Fibroblast Growth Factor Receptors to bind the hormones FGF21 and FGF19. Both genes play an important role in lipid and glucose metabolism and in obesity | *KLB rs17618244* variant was linked to hepatic fibrosis;  KLB A allele was associated with lobular inflammation and cirrhosis in patients stratified for obesity status; Hepatic KLB mut expression seemed to be linked to proliferative rate improvement and pro-fibrogenic genes induction |
| -BMI > 35: 708 subjects; |
| -BMI ≤ 35: 403 subjects; |
| Inclusion criteria were liver biopsy or severe obesity and availability of DNA samples |
| *Hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13)* gene | Liu *et al*[59], Cross-sectional analysis | 427 Han Chinese from the PERSONS cohort with biopsy confirmed MAFLD; | *Hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13)* gene encodes a hepatic lipid droplet protein | Data confirmed that the *HSD17B13* region is a susceptibility locus for MAFLD-related fibrosis; |
| Aged ≥ 18 yr |
| An effect of modulated PNPLA*3* rs738409 on hepatic steatosis was reported; |
| Significant differences in levels of fasting glucose, triglycerides, and high-density lipoprotein cholesterol among subject with *HSD17B13-* rs72613567 (TA allele) genotypes were observed, but no differences in biochemical parameters among the rs6531975 (A allele) genotypes were found; The minor TA allele was linked to an increased risk of fibrosis, while the minor A allele had a protective effect against liver damage |
| Membrane-bound O-acyltransferase domain-containing protein 7 (MBOAT7) | (1) Meroni *et al*[52], Review: 21 studies: -6 case control studies; -10 case only; -2 metanalysis; -2 GWAS; -1 cohort studies | (1) Age: -4 pediatric studies; -17 adult studies; Ethnicity: -14 Caucasian; -5 multiethnic; -2 Asian | The MBOAT7 codifies for an enzyme highly expressed in hepatocytes, hepatic stellate cells and hepatic sinusoidal cells; It has been involved in fatty acid metabolism and in hepatic both inflammation and fibrosis | (1) In patients with MAFLD, MBOAT7 might affect liver damage |
| Downregulation of liver expression of MBOAT7 induces changes in phosphoinositide composition pattern with subsequent modified membrane lipid composition and lipid mediator profiles |
| Hyperinsulinemia, is a cofactor for MBOAT impairment; MBOAT7 dysfunction may influence liver disease progression to steatohepatitis and fibrosis and chronic hyperinsulinemia to steatosis development |
| (2) Except for Asian population, studies on European, Hispanic, and African American adults with MAFLD evaluating the *rs641738* variant reported a downregulation of the MBOAT7 expression, which increased MAFLD severity, liver fat, NASH progression, advanced fibrosis, and HCC |
| (2) Ismaiel *et al*[53], Review: 22 studies: -7 case control studies; -3 case only; -5 metanalysis; -7 cohort studies | (2) A total of 22 studies: -4 pediatric studies with ultrasound (US) diagnosis of fatty liver; -18 adult studies: 17 with fatty liver diagnosis with liver biopsy/ imaging and 1 with US | No association with coronary artery disease was found. In children with obesity this variant was associated with increased plasma ALT levels |

MAFLD: Metabolic associated fatty liver disease; FGFR: Fibroblast growth factor receptor; ALT: Alanine transaminase; MBOAT7: Membrane-bound O-acetyltransferase domain-containing protein 7; US: Ultrasound; GWAS: genome-wide association study.

**Table 3 Metabolic syndrome criteria in adults and children**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Abdominal obesity** | **Hypertension** | **Dyslipidemia** | **Fasting glucose** |
| IDF central obesity + 2 of 4 criteria in adult patients and children aged >10 yr[87-89] | 10–15 yr old waist circumference (WC) ≥ 90th percentile for age and sex | Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg | TG ≥ 150 mg/dL or specific treatment HDL < 40 mg/dL (male), HDL < 50 mg/dL (female) | ≥ 100 mg/dL or diagnosis of type 2 diabetes mellitus |
|  | >15 yr old WC ≥ 94 cm (male) b WC ≥ 80 cm (female) | | | |
| Panel: IDEFICS definition of metabolic syndrome in children aged 2–11 yr[90]1 | 10–15 yr old WC ≥ 90th percentile for age and sex | Blood pressure: systolic ≥ 90th percentile or diastolic ≥ 90th percentile | TG: ≥ 90th percentile or HDL cholesterol: ≤ 10th percentile | Insulin ≥ 90th percentile or fasting glucose ≥ 90th percentile |
|  | > 15 yr old adults criteria | | | |

1Children would require close monitoring if three or more of these risk factors exceed the 90th percentile (or ≤ 10th percentile for HDL cholesterol), and an intervention if three or more of these risk factors exceed the 95th percentile (or ≤ 5th percentile for HDL cholesterol).

BP: Blood pressure; HDL:High-density lipoprotein; IDEFICS: Identification and prevention of dietary- and lifestyle-induced health effects in children and infants; IDF: International diabetes federation; TG: triglycerides; WC: waist circumference.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**