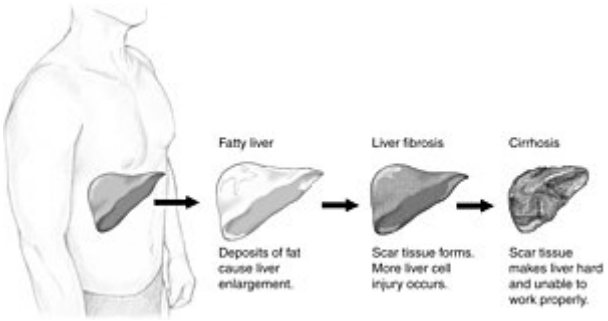
Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (**NAFLD**) is excessive fat build-up in the liver with insulin resistance due to causes other than alcohol use.[1][2] There are two types; **non-alcoholic fatty liver** (**NAFL**) and **non-alcoholic steatohepatitis** (**NASH**), with the latter also including liver inflammation.[2][3][5] Non-alcoholic fatty liver disease is a less serious than NASH, and usually does not progress to NASH or to liver cirrhosis. [2] When NAFLD does progress to NASH, it may eventually lead to complications such as cirrhosis, liver cancer, liver failure, or cardiovascular disease.[2][6]

Being overweight is the strongest risk factor of NAFLD.[4] Other risks include metabolic syndromes (diabetes, obesity, high blood pressure), a diet high in fructose, and older age.[5] NAFLD and alcoholic liver disease are types of fatty liver disease.[5] Diagnosis is by a liver biopsy after excluding other potential causes of fatty liver.[1][4][5]

Treatment for NAFLD is weight loss by dietary changes and exercise.[3][7][8] There is tentative evidence for pioglitazone and vitamin E.[2][9][10] Bariatric surgery can improve or resolve severe cases.[7][11] Those with NASH have a 2.6% increased risk of dying per year.[3]

NAFLD is the most common liver disorder in developed countries, affecting 75 to 100 million Americans in 2017.[12][13][14][15] Over 90% of obese, 60% of diabetic and up to 20% normal-weight people develop it.[16][17] It is estimated that 24% of the worldwide population is affected as of 2017.[16] NAFLD is the leading cause of chronic liver disease,[15][16] and the second most common reason for liver transplantation in USA and Europe as of 2017.[7] About 12 to 25% of people in USA have NAFLD[18] and 20 to 25% in Europe,[11] while NASH affects between 2 and 12% in USA.[18] The annual economic burden was estimated at US$103 billion in the US in 2016.[16]

Non-alcoholic fatty liver disease	
Other names	NAFLD
 Stages of non-alcoholic fatty liver disease, progressing from healthy, to steatosis (fat accumulation), inflammation, fibrosis and cirrhosis.	
Specialty	Hepatology
Symptoms	Asymptomatic, liver dysfunction
Complications	Cirrhosis, liver cancer, liver failure, cardiovascular disease[1][2]
Duration	Long term
Types	Non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH)[2][3]
Causes	Genetic, environmental
Risk factors	Metabolic syndrome, diabetes type 2, liver disease
Diagnostic method	Liver biopsy
Treatment	Weight loss (diet and exercise)[2][4]
Prognosis	Depends on type[5]
Frequency	24% in worldwide population, 80% in obese, 20% in normal-weight
Deaths	NASH: 2.6% risk of death per year[3]

Contents

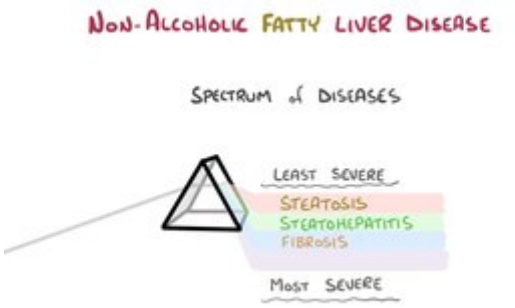
Definition

Non-alcoholic fatty liver disease (NAFLD) is characterized by an abnormal accumulation of fat in the liver related to insulin resistance, in the absence of significant alcohol use, according to ICD-11. NAFLD is a continuum of liver abnormalities, from non-alcoholic fatty liver (NAFL, simple steatosis) to non-alcoholic steatohepatitis (NASH). These diseases begin with fatty accumulation in the liver (hepatic steatosis). A liver can remain fatty without disturbing liver function (NAFL), but by various mechanisms

and possible insults to the liver, it may also progress into a non-alcoholic steatohepatitis (NASH), a state in which steatosis is combined with inflammation and sometimes fibrosis (steatohepatitis). NASH can then lead to complications such as cirrhosis and hepatocellular carcinoma.[1][3][19]

Signs and symptoms

People with NAFLD are likely to be asymptomatic − to have no noticeable symptoms − and often have normal laboratory profiles.[9][19]



Play media
Overview of non-alcoholic fatty liver disease

NAFLD can cause symptoms related to liver dysfunction. NAFLD can be diagnosed by performing a liver biopsy, and is often incidentally diagnosed following abnormal liver function tests during routine blood tests or after a hepatic steatosis is detected by biopsy. Indeed, in cases of symptoms or signs attributable to liver disease or when tests show abnormal liver chemistries, NAFLD should be suspected and investigated. However, when no symptoms or signs attributable to liver disease are reported or when the tests show normal liver chemistries, but a hepatic steatosis is detected, other metabolic risk factors (e.g., obesity, diabetes mellitus, dyslipidemia) and alternate causes such as alcohol should be investigated.[3]

People with NAFLD may complain of fatigue, malaise, and dull right-upper-quadrant abdominal discomfort. Mild jaundice may be noticed, although this is rare.[20]

Risk factors

Comorbidities

NAFLD is strongly associated with or caused by insulin resistance and metabolic syndromes (obesity, combined hyperlipidemia, diabetes mellitus (type II), and high blood pressure). It is also associated with hormonal disorders (panhypopituitarism, hypothyroidism, hypogonadism, polycystic ovary syndrome), persistently elevated transaminases, increasing age and BMI and hypoxia caused by obstructive sleep apnea, with some of them predicting disease progression.[1][4][6][10][12][16][21]

In particular, for a majority of non-obese people affected by NAFLD ("lean NAFLD"), they have been found to have impaired insulin sensitivity, to be frequently sedentary, to have increased cardiovascular risk and increased liver lipid levels, being the consequence of a decreased capacity for storing fat and reduced mitochondrial function in adipose tissue and increased hepatic de novo lipogenesis.[4][16]

NAFLD has been observed to be twice as prevalent in men compared to women,[3] which might be explained by estrogen deficiencies.[22]

Genetics

Genetic risk factors of NAFLD are also known. Two-thirds of families with a history of diabetes type 2 report more than one family member having NAFLD. There is a higher risk of fibrosis for family members where someone was diagnosed with NASH.[19] Asian populations are more susceptible to metabolic syndrome and NAFLD than their western counterparts.[4] Hispanic persons have higher prevalence of NAFLD than white individuals, whereas the lowest susceptibility is observed in black individuals.[16]

Two genetic mutations for NAFLD susceptibility have been identified and validated in large cohorts: the non-synonymous single-nucleotide polymorphisms (SNPs) in PNPLA3 and TM6SF2, as they have been shown to correlate with NAFLD presence and severity, but their roles for diagnosis remain unclear.[16][23]

Although NAFLD has a genetic component, the AASLD does not recommend screening family members as there is not enough confirmation of heritability,[3] although there is some evidence from familial aggregation and twin studies.[16]

Dysbiosis

Links between dysbiosis of the gut microbiota and liver diseases, in particular NAFLD, have been documented. Individuals with NASH can have increased levels of blood ethanol. Individuals with a more aggressive NAFLD were found to have a choline depletion linked to an increased choline metabolism.[24][25][26][27]

Diet

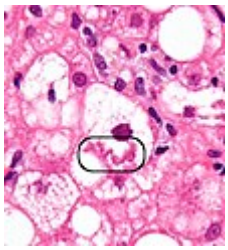
According to the Asia-Pacific Working Group on NAFLD, overnutrition is a major factor of NAFLD and NASH, particularly for lean NAFLD.[4] Diet composition and quantity, in particular omega-6 fatty acid lipids and fructose sugar, has an important role in disease progression from NAFL to NASH and fibrosis.[28][29] Choline deficiency can lead to the development of NAFLD.[30] There is indeed a complex interplay between the environment, particularly the diet, the genetics and gut microbiota dysbiosis that can impact the development and progression of NAFLD.[29]

Pathophysiology

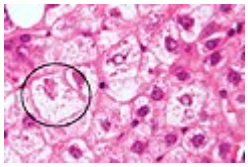
NAFLD can include either a steatosis alone; a steatosis concurrent with lobular or portal inflammation without ballooning; or a steatosis with ballooning but without inflammation. In NASH, other histological features can appear but are not necessary for diagnosis, such as portal inflammation, polymorphonuclear infiltrates, mallory bodies, apoptotic bodies, clear vacuolated nuclei, microvacuolar steatosis, megamitochondria, and perisinusoidal fibrosis.[11] Hepatocyte death via apoptosis or necroptosis is increased in NASH compared with simple steatosis, and inflammation is one of NASH hallmarks.[23]

One debated mechanism proposes a *second hit*, or further injury, enough to cause change that leads from hepatic steatosis to hepatic inflammation. Oxidative stress, hormonal imbalances, and mitochondrial abnormalities are potential causes for this "second hit" phenomenon.[19] A further nutrigenomics model named *multiple hit* extends the *second hit* model by integrating multiple disease biomarkers and factors such as genes and nutrition to predict the impact of lifestyle changes and genetics for the evolution of the NAFLD pathology.[31] Indeed, NAFLD can be considered a *multisystem* disease, as it impacts and is influenced by organs and regulatory pathways other than the liver.[32][33][34]

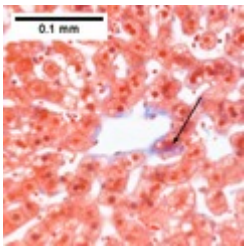
Non-alcoholic and alcoholic fatty liver disease share similar histological features, which suggests that they might share common pathogenic pathways. Indeed, people with NASH can have elevated levels of blood ethanol and proteobacteria (which produce alcohol), with dysbiosis proposed as a mechanism for this elevation.[24] Fructose can cause inflammation and addiction similarly to ethanol by using similar metabolic pathways, unlike glucose, which prompts some researchers to argue that non-alcoholic and alcoholic fatty liver diseases are more similar than previously thought.[28][35] Excessive macronutrients intake contributes to gut tissues inflammation and perturbation of homeostasis, and micronutrients may also be involved.[36] Lifestyle changes, in addition to reducing weight and risk factors, may prompt positive changes in the gut microbiota.[37] In particular, diet diversity may play a role that was overlooked in animal studies, since they often compare a "western" high fat diet but with low diversity, against a "chow" low fat diet but with a higher diversity.[38] The health benefits after bariatric surgery may also involve changes in the gut microbiota, by increasing gut permeability.[38]



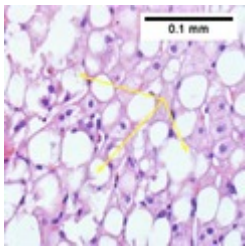
Mallory-Denk body



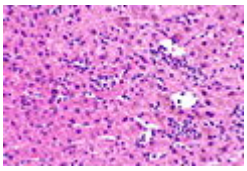
Ballooning degeneration



NASH (inflammation) and fibrosis stage 1



NASH (inflammation) and fibrosis stage 2

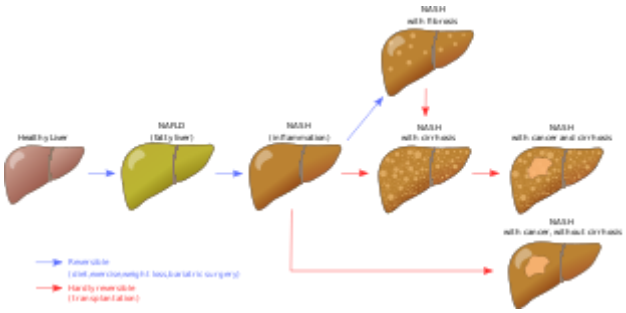


Lobular inflammation

Diagnosis

NAFLD is the evidence of fatty liver, and the absence of another factor that could explain the liver fat accumulation, such as excessive alcohol use (>21 standard drinks/week for men and >14 for women in USA; >30 g daily for men and >20 g for women in UK and EU, >140 g/week for men and >70 g/week for women in Asia-Pacific and most NIH clinical studies), drug-induced steatosis, chronic hepatitis C, heredity or by deficiencies in parenteral nutrition such as choline and endocrine conditions. If any of these factors is observed, alternative causes of fatty liver unrelated to NAFLD should be investigated instead. Past history of chronic alcohol usage should also be taken into account.[1][3][4][9][11]

The NAFLD can be separated into two histological categories: NAFL, and the more aggressive form NASH. Both NAFL and NASH are defined by the presence of at least 5% of fatty liver, but only NASH is characterized by the histological presence of substantial lobular inflammation and hepatocyte injury such as ballooning or Mallory hyaline. NASH is more likely to be associated with pericentral and perisinusoidal fibrosis for adults, and portal fibrosis sometimes for children. NASH is the clinical worsening of NAFL, associated with bad outcomes such as cardiovascular events, cirrhosis or hepatocellular carcinoma. The majority of NAFL cases show minimal or no inflammation.[1][3][4]



Stages of progression of non-alcoholic fatty liver disease

ICD-11 did not retain the term NAFL as it was deemed confusing with the family of disorders NAFLD. The preferred descriptions are instead: "NAFLD without NASH" or "simple steatosis", "NASH". In addition, the diagnosis can be completed with "with or without fibrosis or cirrhosis".[1][4]

Blood tests

Elevated liver enzymes are common. According to NICE guidelines, it is disadvised to test enzymes levels to rule out NAFLD, as they are often within the normal range even in advanced disease.[6][9][16]

Blood tests that are useful to confirm diagnosis or rule out others include erythrocyte sedimentation rate, glucose, albumin, and kidney function. Because the liver is important for making proteins used in blood clotting, coagulation-related studies are often carried out, especially the INR (international normalized ratio). In people with fatty liver with associated inflammatory injury (steatohepatitis) blood tests are usually used to rule out viral hepatitis (hepatitis A, B, C and herpesviruses such as Epstein-Barr virus or cytomegalovirus), rubella, and autoimmune diseases. Low thyroid activity is more prevalent in people with NASH, which would be detected by determining the thyroid-stimulating hormone.[39] Some biomarker-based blood tests have been developed and may be useful for diagnosis.[40]

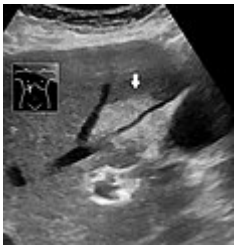
Although blood tests cannot diagnose NAFLD, circulating serum biomarkers of liver fibrosis can give moderate estimates in the diagnosis of liver fibrosis and cirrhosis, and AST platelet ratio index and Fibrotest are recommended as the preferred noninvasive tests for cirrhosis by the APASL.[41]

Imaging

A liver ultrasound scan or magnetic resonance imaging (MRI) can diagnose steatosis,[42] but not fibrosis, and early cirrhosis detection by ultrasound should be confirmed by other methods.[41] The EASL recommend screening for a steatosis whenever a NAFLD is suspected as this is a key predictor of the disease evolution and predicts future diabetes type II, cardiovascular events and hypertension.[11] These non-invasive methods can be used for NAFLD screening but is not accepted as a substitute for liver biopsy in NAFLD nor NASH clinical trials, as only a liver biopsy can define a liver pathology, according to the Asia-Pacific Work Party on NAFLD as of 2017.[4][7]

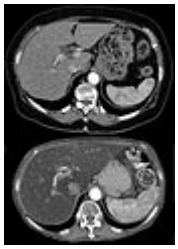
CT scans and MRI are more accurate in detecting cirrhosis than conventional ultrasound.[41] Transient elastography (FibroScan) is recommended for the initial assessment of liver fibrosis and cirrhosis, and it helps to predict complications and prognosis, but the interpretation of results should be carefully weighted in the presence of limitating factors, such as steatosis, high BMI, lower degrees of hepatic fibrosis and narrow intercostal spaces. However, transient elastography can fail for people with pre-hepatic portal hypertension. Transient elastography should not be considered as a replacement of liver biopsy.[41]

Magnetic resonance elastography (MRE) is an emerging method that can accurately assess hepatic fibrosis and is recommended by the APASL.[41] MRE possess a good sensitivity to quantify hepatic fat and excellent accuracy to detect fibrosis in NAFLD regardless of BMI and inflammation, and is suggested as a more reliable alternative to diagnose NAFLD and its progression to NASH compared to ultrasound and blood tests.[20][23][43][44]

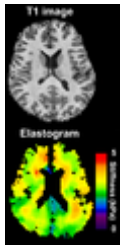


Abdominal ultrasonography of the liver of an 88-year-old woman, showing focal steatosis.

MRI of a healthy liver (top row) and one with severe steatosis (bottom row).



CT scan of a normal (top) and a liver with steatosis (bottom). The liver becomes darker as a result of the increased storage of low-radiopacity fat.

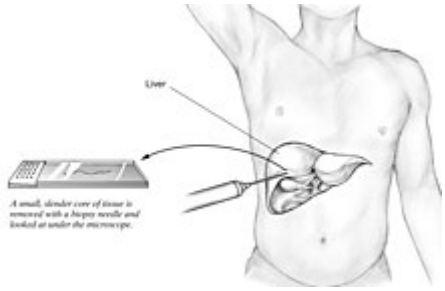


Magnetic resonance elastography of a brain, a non invasive way to visualize the tissues' stiffness. The same technic can be applied on the liver to detect regions of abnormal stiffness, indicating fat accumulation.

Liver biopsy

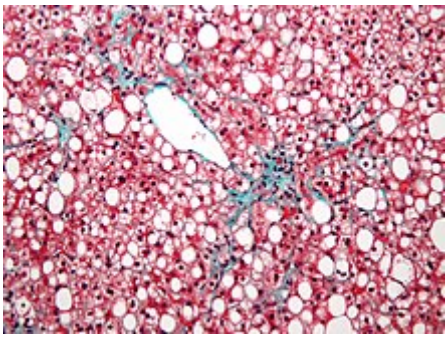
A liver biopsy (tissue examination) is the only test widely accepted (gold standard) as definitively diagnosing and distinguishing NAFLD (including NAFL and NASH) from other forms of liver disease and can be used to assess the severity of the inflammation and resultant fibrosis. However, since most people affected by NAFLD are likely to be asymptomatic, liver biopsy presents too high a risk for routine diagnosis, so other methods may be preferred, such as liver ultrasonography or liver MRI. For young people, liver ultrasonography is advised, but biopsy remain the best evidence.[3][4][9][20] Liver biopsy is also the gold standard to detect hepatic fibrosis and assess its progression.[41] Routine liver function blood tests are not sensitive enough to detect NAFLD, and biopsy is the only procedure that can reliably differentiate NAFL from NASH.[11]

Several liver biopsy techniques may be used to obtain liver tissue. Percutaneous liver biopsy remains the most common practice, but biopsies can also be performed via the transvenous route, either during surgery or by laparoscopy, especially for people with contraindications to a percutaneous approach. The liver biopsy can also be image-guided, in real-time or not, which is recommended for some clinical situations such as people with known intra-hepatic lesions, previous intra-abdominal surgery who may have adhesions, small liver difficult to percuss, obese people and people with evident ascites. Vital signs must be monitored frequently afterward (at least every 15 minutes in the hour following the biopsy).[41]



A small quantity of tissue is sampled from the liver when doing a biopsy, which is then examined under a microscope

According to AASLD guidelines, liver biopsy should be considered in people with NAFLD who are at increased risk of having steatohepatitis and/or advanced fibrosis, but only when all other competing chronic liver diseases are excluded (such as alcoholic liver disease). The presence of a metabolic syndrome, NAFLD Fibrosis Score (FIB-4), or liver stiffness (as measured by VCTE or MRE) may be used to identify the individuals who are at higher risk of steatohepatitis or advanced fibrosis.[3]


Micrograph of non-alcoholic fatty liver disease, demonstrating marked steatosis (fat in liver cells appears white; connective tissue, blue). Trichrome stain

The AASLD and ICD-11 consider that a clinically useful pathology reporting should distinguish "between NAFL (steatosis), NAFL with inflammation and NASH (steatosis with lobular and portal inflammation and hepatocellular ballooning)", with the presence or absence of fibrosis being described, and optionally a comment on severity.[3][4] The EASL recommend the FLIP algorithm to grade the ballooning, and the use of the NAFLD Activity Score (NAS) to grade the severity of NASH rather than for its diagnosis. They also consider the steatosis, activity and fibrosis (SAF) score to be an accurate and reproducible scoring system.[11] The AASLD recommends the use of the NAS and/or SAF scoring systems if deemed appropriate.[3] The Asia-Pacific Working Group on NAFLD disadvise the use of NAS, as it is considered uninformative for NAFLD and inappropriate to diagnose NASH.[7]

According to the Asia-Pacific Work Group on NAFLD, clinical outcome should be evaluated either on longevity or its only surrogate, improvement in liver fibrosis.[7]

For liver fibrosis assessment, percutaneous liver biopsy, with or without image guidance, should not be used in uncooperative people. Transjugular liver biopsy is indicated for people with a diffuse liver disease who need a biopsy but have a contra-indication to percutaneous biopsy or need a hemodynamic evaluation for diagnosis purposes. People with clinically evident ascites should have a transvenous liver biopsy instead of percutaneous, although percutaneous biopsy is acceptable after removal of ascites.[41]

Management

People with NAFLD (including those who are not overweight) should be considered for treatment.[4] NAFLD is a preventable cause of death.[15] Guidelines are available from the American Association for the Study of Liver Diseases (AASLD), American Association of Clinical Endocrinologists (AACE)

National Institute for Health and Care Excellence (NICE), the European Association for the Study of the Liver (EASL) and the Asia-Pacific Working Party on NAFLD.[3][4][7][9][11][45][46]

Lifestyle

Weight loss is the most effective treatment for NAFLD. A loss of 4% to 10% body weight is recommended, with 10% to 40% weight loss completely reversing NASH without cirrhosis. Offering people with NAFLD a structured weight loss program achieves greater weight loss compared with simple advice and this leads to demonstrable improvements in NAFLD measured using blood tests, ultrasound, imaging, or liver biopsies. Although fibrosis was shown to be improved by lifestyle interventions and weight loss, there is limited evidence for cirrhosis.[4][7][45][47]

A combination of improved diet and exercise, rather than either alone, appears to best help manage NAFLD and reduce insulin resistance.[3][8][11][48][49] Motivational support, such as with cognitive-behavioral therapy, is helpful, as most people with NAFLD do not perceive their condition as a disease, and thus have a low motivation to change.[3][6][9][11][50]

Higher-intensity behavioral weight loss therapies (diet plus exercise) may produce more weight loss than lower-intensity ones. Weight loss is associated with improvements in biomarkers, NAFLD grade and reduced chances of NASH, but their impact on long-term health is yet unknown. A 2019 systematic review thus suggest change of guidelines to recommend these therapies for NAFLD management.[51]

Diet

Treatment of NAFLD typically involves counseling to improve nutrition and calorie restriction.[6][45][52] People with NAFLD can benefit from a moderate to low-carbohydrate diet and low-fat diet.[6][53] The Mediterranean diet also showed promising results in a 6-week scheme in reduction of NASH induced inflammation and fibrosis, independently from weight loss.[6][11][49][54] Tentative evidence supports dietary interventions in individuals with fatty liver who are not overweight.[55]

The EASL recommend energy restriction of 500–1000 kcal/week less than the normal daily diet (a very-low-calorie diet), a target of 7–10% weight loss for obese/overweight NAFLD, a low- to moderate-fat, and moderate- to high-carbohydrate diet, or a low-carbohydrate ketogenic or high-protein diet such as the Mediterranean diet, and avoiding all beverages and food containing fructose.[11]

The NICE guidelines include recommendations for vitamin E, although it is not useful for all people with NAFLD.[6][9] The NICE does not recommend omega-3 fatty acid supplementation since randomized trials were inconclusive,[6][9] although previous systematic reviews found that omega-3 fatty acid supplementation in those with NAFLD/NASH using doses of 1 gram daily or more (median dose 4 grams/day with median treatment duration 6 months) has been associated with improvements in liver fat.[50][56] According to AASLD guidelines, "omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but they may be considered to treat hypertriglyceridemia for patients with NAFLD".[3]

Alcohol is an aggravating factor and should be avoided by people with NAFLD or NASH.[3][6][9][57] The EASL allow alcohol consumption below 30g/day for men and 20g/day for women.[11]

For the EASL, there are no liver-related limitations to the consumption of coffee.[11]

Herbal compounds such as silymarin, curcumin and green tea were shown to be effective for biomarkers enhancement and NAFLD grade reduction.[34] In particular, silymarin shown effective reduction of fibrosis in biopsy-proved NASH people.[7] Anthocyanins have also been looked at as a nutritional therapy.[58]

Physical activity

Weight loss may improve the process, and is recommended particularly for obese or overweight people.[59][60][61] Similar physical activities and diets are advisable for overweight people with NAFLD as for other obese and overweight people.[9][49] Although physical activity is less important for weight loss than dietary adaptations (to reduce caloric intake),[50] the NICE advises physical activity to reduce liver fat even if there is no overall body weight reduction.[6][9] Weight loss, through exercise or diet, was shown to be the most effective way to reduce liver fat and help NASH and fibrosis remission.[50] Exercise alone can prevent or reduce hepatic steatosis, but it remains unknown whether it can improve all other aspects of the liver, hence a combined approach with exercise and diet is advised.[3][8] Aerobic exercise may be more effective than resistance training, although there are contradictory results.[6][62] Vigorous training is preferable to moderate training, as only high intensity exercising was shown to reduce chances of NASH developing into a steatohepatitis or advanced fibrosis.[6][63] The EASL recommend between 150 and 200 min/week in 3 to 5 sessions of moderate intensity aerobic physical activity or resistance training. Since both effectively reduce liver fat, the choice of activity can be tailored to fit the individual's preferences with the goal of maintaining in the long-term: "any engagement in physical activity or increase over previous levels is however better than continuing inactivity".[11]

Medication

Medications should be primarily aimed at improving liver disease and should generally be limited to those with biopsy-proven NASH and fibrosis.[3][9][11]

No medicines specifically for NAFLD or NASH had received approval as of 2018 although antiglycemic drugs may help in liver fat loss. While many treatments appear to improve biochemical markers such as alanine transaminase levels, most have not been shown to reverse histological abnormalities or reduce clinical endpoints.[3][7][64]

Insulin sensitizers (metformin and thiazolidinediones, such as pioglitazone) and liraglutide are not specially recommended for NAFLD as they do not directly improve the liver condition, but they can be indicated for diabetic individuals, after a careful assessment of risks, to reduce insulin resistance and risks of complications.[3][7] Indeed, the side effects associated with these drugs, which include osteopenia, increased fracture risk, fluid retention, congestive heart failure, bladder cancer, and long-term weight gain, have limited their adoption.[6][65][66] Due to these side effects, AASLD recommend the use of pioglitazone only for individuals with biopsy-proven NASH, and the Asia-Pacific Work Group to only individuals with NAFLD with known diabetic issues. However, AASLD advise against the use of metformin as studies were inconclusive about the improvement of the liver histological condition, although there was an improvement in insulin resistance and serum aminotransferases, as this did not translate into NASH improvements.[3] NICE provides similar guidelines to AASLD regarding pioglitazone, which should be administered in secondary care to adults with advanced liver fibrosis, whether or not they have diabetes.[9]

Vitamin E is an effective treatment that can be administered for individuals with biopsy-proven NASH.[3][6][9] For the Asia-Pacific Work Group, Vitamin E may improve liver condition and aminotransferase levels, but only in non-cirrhotic non-diabetic NASH adults.[7]

Improvements in liver biochemistry and histology have been found in people with NAFLD through treatment with statins. Since people with NAFLD are at a higher risk of cardiovascular disease, statins treatment is indicated. People with NAFLD are not at higher risk for serious liver injury from statins according to AASLD and EASL. However, even if statins can be used to treat people with NASH cirrhosis, they should be avoided in case of decompensated cirrhosis.[3][11][67] Statins have also been recommended for use in treating dyslipidemia for people with NAFLD. According to NICE guidelines, statins can continue to be administered unless liver enzyme levels double within 3 months of starting statins.[9] Treatment with pentoxifylline is not recommended.[7]

Obeticholic acid and elafibranor might improve NASH but are not recommended as of 2018 by the AASLD nor the Asia-Pacific Work Group until phase 3 trials are completed as they produce inconsistent results and adverse effects.[3][7]

Synbiotics, combining both probiotics and prebiotics, can have favorable effects on inflammation and dysbiosis in people with NAFLD.[24][25][68]

Omega-3 fatty acid may reduce liver fat and improve blood lipid profile but does not seem to improve the liver histology (fibrosis, cirrhosis, cancer).[7]

Surgery

For severely obese individuals with NAFLD or NASH, bariatric surgery improves or cures the liver disease if there is no cirrhosis nor liver cancer.

Bariatric surgery is an effective method for obese and diabetic individuals with NAFLD to induce weight loss and reduce or resolve NASH inflammation, including fibrosis, and improve longevity.[6][7][11][50][69][70] For the AASLD, bariatric surgery can be considered only for NASH on a case-by-case basis by an experienced bariatric surgery program.[3] Indeed, some individuals might develop new or worsened features of NAFLD.[70]

About 92% of people with NAFLD saw an improvement in steatosis and 70% a complete resolution after a bariatric surgery.[71]

A preoperative diet such as a low-calorie diet or very-low-calorie diet is usually recommended to reduce liver volume by 16–20%, and preoperative weight loss is the only factor associated with postoperative weight loss.[72][73] Preoperative weight loss can reduce operative time and hospital stay.[72][74][75] although there is insufficient evidence whether preoperative weight loss may be beneficial to reduce long-term morbidity or complications.[75][76] Weight loss and decreases in liver size may be independent from the amount of calorie restriction.[73]

According to the Asia-Pacific Work Group on NAFLD, bariatric surgery should be limited to class II obesity (BMI >32.5 kg/m² for Asians, 35 kg/m² for Caucasians). They consider its effects on improving liver-related complications are unproven yet, but it effectively increases longevity by improving cardiovascular factors.[7]

Surgery carries more risks for individuals with NASH-caused cirrhosis, with a review estimating an overall morbidity of 21%. For people with NAFLD, in cases of cirrhosis, the cause should be elucidated, and hepatic function and presence of portal hypertension should be evaluated.[7]

Screening

The cardiovascular system screening is considered mandatory by the EASL, as NAFLD outcomes often result in cardiovascular complications[11] which can manifest as subclinical atherosclerosis, and being the cause of the majority of NAFLD-related deaths.[32][77] Indeed, people with NAFLD are at a high risk for cardiovascular morbidity and mortality, and "aggressive modification of cardiovascular disease risk factors should be considered in all patients with NAFLD" according to AASLD.[3]

The AASLD further recommends for people with a cirrhotic NASH to be systematically screened for gastric and esophageal varices and liver cancer. Routine screening of liver cancer and liver biopsy is not recommended for non-cirrhotic people with NASH, but it might be considered on a case-by-case basis.[3]

Also, people with NAFLD should be considered for screening for hepatocellular carcinoma (liver cancer) and gastroesophageal varices. The NICE advises regular screening of NAFLD for advanced liver fibrosis every three years to adults and every two years for children using the enhanced liver fibrosis (ELF) blood test.[9] Follow-up is recommended for people with obesity and insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR). People with NASH with fibrosis and hypertension should have closer monitoring as there is a higher risk of disease progression.[11]

Transplantation

NAFLD is the second most common indication for liver transplantation in USA and Europe as of 2017.[7] NAFLD/NASH is expected to become the leading cause of liver transplantation by 2020.[78]

For people with NASH and with an end-stage liver disease, liver failure or liver cancer, liver transplantation is an accepted procedure according to the EASL.[11] People with a cirrhotic NASH considered for a liver transplantation should be systematically examined for cardiovascular diseases (whether the symptoms are apparent or not).[3]

The overall survival is comparable to transplantation following other diseases,[7][11] but they are more likely to die post-transplant because of cardiovascular disease or chronic kidney disease, which is related to the fact that people with NASH are often older and thus more prone to these complications.[7] For this and other reasons, individuals with morbid obesity (BMI > 40 kg/m²) and NASH with cirrhosis may be considered unfit for liver transplantation until they follow lifestyle modifications to reduce body weight.[7] Diabetic people with poor glycemic control are at similar risks, and good glycemic control should be ensured before attempting transplantation.[7]

Lifestyle modifications should be offered both before and after transplantation to reduce potential surgery risks and to manage NAFLD afterwards.[7]

Simultaneous bariatric surgery and liver transplantation were performed in exceptional circumstances.[7]

After transplantation, liver biopsy is the best method to monitor the evolution of post-transplant fibrosis, with significant fibrosis or portal hypertension one year after transplantation predicting rapid progression and graft loss and indicating the need for an urgent intervention.[41]

Related complications

There is no special treatment for liver cancer associated with NAFLD/NASH, thus these should be treated according to general guidelines on liver cancers.[7]

Outcomes

The exact causes of the disease and mechanisms by which the disease progresses from one stage to the next are not fully understood, although findings provide new insights into the mechanisms. Indeed, NAFLD is a multisystem disease, impacting and being influenced by several other organs and pathways other than the liver.[32][50][79][80]

The progression rate of fibrosis in humans with NASH is estimated to be 7 years, compared to 14 years with NAFLD, and with a dynamically, exponentially increasing rate along as more stages are reached, but it is very variable with different clinical manifestations among individuals.[16][19][81] Fibrosis in humans with NASH progressed more rapidly than in humans with NAFLD.[6] Obesity predicts a worse long-term outcome than for lean individuals.[82][83] In the Asia-Pacific region, about 25% of NAFLDs progress to NASH under 3 years, but only a low proportion (3.7%) develop advanced liver fibrosis.[4] An international study showed that people with NAFLD had a 10-year survival rate of 81.5%.[3]

NAFLD is a risk factor for fibrosis, hypertension, chronic kidney disease, atrial fibrillation, myocardial infarction, ischaemic stroke and death from cardiovascular causes based on very low to low quality evidence from observational studies.[9][84][85]

NAFL and NASH increase the risk of liver cancer. Cirrhosis and liver cancer induced by NAFLD were the second cause of liver transplantation in the US in 2017. Liver cancer develops in NASH in the absence of cirrhosis in 45% in the cases,[86] and people with NASH cirrhosis have increased risk of liver cancer. Indeed, the rate of liver cancer associated with NASH increased fourfold between 2002 and 2012 in the US, which is more than any other cause of liver cancer. NAFLD constitutes the third most common risk factor for liver cancer.[87] NAFL and NASH were found to worsen with a cirrhosis in respectively 2–3% and 15–20% of the people over a 10–20 year period.[6] Cirrhosis is found in only about 50% of people with NAFLD and with liver cancer, so that liver cancer and cirrhosis are not always linked.[7]

NAFLD is also thought to be a precursor of metabolic syndrome, although a bidirectional influence is not excluded.[88][89][90]

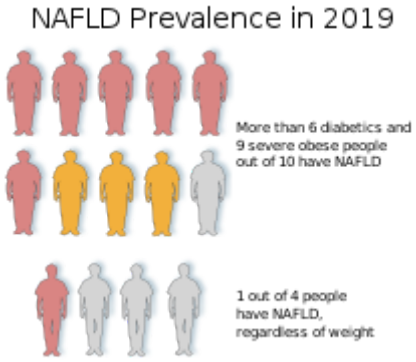
The presence and stage of fibrosis are the strongest prognostic factor for liver-related events and mortality, in particular for NAFLD.[16]

Although NAFLD can cause cirrhosis and liver failure and liver cancer, the majority of deaths among people with NAFLD is attributable to cardiovascular disease.[32] Indeed, according to a meta-analysis of 34,000 people with NAFLD over 7 years, they have 65% increased risk of developing fatal or nonfatal cardiovascular events.[19]

Epidemiology

NAFLD incidence is rapidly rising, in link with obesity and diabetes, and has become the most common cause of liver disease in developed countries, for adults, teenagers and children.[15][16]

The percentage of people with NAFLD ranges from 9 to 36.9% in different parts of the world.[91][92] For severely obese individuals, the prevalence of NAFLD rises over 90%, and for those with diabetes, over 60%, and up to 20% for normal-weight people.[16][17] However, studies based on elevated liver enzymes systematically underestimated the true prevalence worldwide, and ultrasonography and proton NMR spectroscopy studies suggest about 25% of the population seems to be affected by NAFLD or NASH.[4][16] Approximately 20% of the United States and 25% of the Asia-Pacific populations have non-alcoholic fatty liver.[4][13] Similar prevalence can be found in Europe countries although less data is available.[16] NAFLD is the most common in the Middle East (32%) and South America (30%) while Africa has the lowest rates (13%).[3][16] In children ages 1 to 19, prevalence was found to be approximately 8% in the general population up to 34% in studies with data from child obesity clinics.[93] Compared to the 2000s, NAFL and NASH respectively increased 2-fold and 2.5-fold in the 2010s in the USA.[94]



Non-alcoholic fatty liver disease prevalence in 2019

NAFLD and NASH are more prevalent in Hispanics - which can be attributed to high rates of obesity and type 2 diabetes in Hispanic populations -, intermediate in Whites and lowest in Blacks.[14][16][95]

NAFLD was observed to be twice as prevalent in men as women.[3]

Although the disease is commonly associated with obesity, a significant proportion of sufferers are normal weight or lean. Lean NAFLD affects between 10–20% of Americans and Europeans, and approximately 25% of the Asians, although some countries have a higher incidence (e.g., India has a very high proportion of lean NAFLD and almost no obese NAFLD). Lean NAFLD people are at the same or higher risks, with a poorer median survival rate (free of liver transplantation) than for obese NAFLD people, according to an international cohort study. PNPLA3 may be relevant for the progression of NAFLD in lean people. Thus, people suffering from NAFLD should be considered as a potential population for treatment regardless of obesity.[4][16][50][96]

In the study of Children of the 90s, 2.5% born in 1991 and 1992 were found by ultrasound at the age of 18 to have non-alcoholic fatty liver disease; five years later transient elastography (fibroscan) found over 20% to have the fatty deposits on the liver, indicating non-alcoholic fatty liver disease; half of those were classified as severe. The scans also found that 2.4% had the liver scarring, which can lead to cirrhosis.[97]

The majority of cryptogenic cirrhosis is believed to be due to NASH.[4]

NAFLD is present in 65% to 90% people that had bariatric surgery, and up to 75% of them have NASH.[7]

NAFLD prevalence is expected to increase steadily,[98] from 25% in 2018 to a projected 33.5% of people with NAFLD globally in 2030, and from 20% to a projected 27% of those with NAFLD will progress to NASH.[99]

History

The first acknowledged case of obesity-related non-alcoholic fatty liver was observed in 1952 by Samuel Zelman.[100][101] Zelman started investigating after observing a fatty liver in a hospital employee who drank more than twenty bottles of Coca-Cola a day. He then went on to design a trial during a year and half on 20 obese people who were not alcoholic, finding that about half of them had substantially fatty livers.[100] Fatty liver was, however, linked to diabetes, atherosclerosis and choline depletion since at least 1784[102] and sugar in 1949,[103] and was already recognized as a common occurrence in severe diabetes in the 1930s.[104]

The name "non-alcoholic steatohepatitis" (NASH) was later defined in 1980 by Jurgen Ludwig and his colleagues from the Mayo Clinic[105] in order to raise awareness on the existence of this pathology, as similar reports previously were dismissed as "patients' lies".[101] This paper was mostly ignored at the time but eventually came to be seen as a landmark paper, and starting in the mid-1990s the condition began to be intensively studied, with a series of international meetings being held on the topic since 1998.[106] The broader NAFLD term started to be used around 2002.[106][107] Diagnostic criteria began to be worked out, and in 2005 the Pathology Committee of the NIH NASH Clinical Research Network proposed the NAS scoring system.[106]

Society and culture

Political recommendations

EASL recommends Europe's public health authorities to "restrict advertising and marketing of sugar-sweetened beverages and industrially processed foods high in saturated fat, sugar and salt", as well as "fiscal measures to discourage the consumption of sugar-sweetened beverages and legislation to ensure that the food industry improves labelling and the composition of processed foods", as well as "public awareness campaigns on liver disease, highlighting that it is not only linked to excessive consumption of alcohol".[98]

Lobbying

In France, the French syndicate of non-alcoholic beverages "Boissons Rafraîchissantes de France" (that included soft drink producers such as Coca-Cola France, Orangina, PepsiCo France) was denounced by the French journal *fr:Canard Enchainé* for misleading consumers using a communication on their website titled "Better understanding the NASH pathology",[108] explaining that "NASH pathology is sometimes called the soda illness by language abuse or an unfortunate semantic shortcut, as it is not directly linked to the consumption of non-alcoholic beverages". This page and others on the same website such as one titled "Say no to disinformation" were since then removed.[109]

Children

Pediatric nonalcoholic fatty liver disease (NAFLD) was first reported in 1983.[110][111] It is the most common chronic liver disease among children and adolescents since at least 2007, affecting 10 to 20% of them in the US in 2016.[16][111][112] NAFLD has been associated with the metabolic syndrome, which is a cluster of risk factors that contribute to the development of cardiovascular disease and type 2 diabetes mellitus. Studies have demonstrated that abdominal obesity and insulin-resistance in particular are thought to be key contributors to the development of NAFLD.[113][114][115][116][117] Coexisting liver diseases, such as hepatitis C and cardiovascular diseases such as atherosclerosis are also associated with

an increased risk of NAFLD.[20][32] Some children were diagnosed as young as 2 years old, with a mean age of diagnosis between 11–13 years old.[111] The mean age is usually above 10 years, as children can also report non-specific symptoms and are thus difficult to diagnose for NAFLD.[111]

Boys are more likely to be diagnosed with NAFLD than girls.[20][93] Overweight, or even weight gain, in childhood and adolescence is associated with an increased risk of NAFLD later in life, with adult NAFLD predicted in a 31-year follow-up study by risk factors during childhood including BMI, plasma insulin levels, male sex, genetic background (PNPLA3 and TM6SF2 variants) and low birth weight, an emerging risk factor for adulthood NAFLD.[16][20] In a study, simple steatosis was observed in up to 45% in children with a clinical suspicion of NAFLD.[20] Children with a simple steatosis have a worse prognosis than adults, with significantly more of them progressing from NAFLD to NASH compared to adults. Indeed, 17-25% of children with NAFLD develop a NASH in general, and up to 83% for children with severe obesity (versus 29% for adults), further suggesting that hepatic fibrosis seem to follow a more aggressive clinical course in children compared to adults.[111]

Early diagnosis of NAFLD in children may help prevent the development of liver disease during adulthood.[115][118] This is challenging as most children with NAFLD are asymptomatic with only 42-59% showing abdominal pain.[20][118] Other symptoms might be present, such as right upper quadrant pain or acanthosis nigricans, the latter being frequently observed in children with NASH, or hepatomegaly found in 30–40% of children with NAFLD.[20]

Liver biopsies for diagnosis in children should be done when the diagnosis is unclear or before starting a potentially hepatotoxic medical therapy according to AASLD.[3] The EASL suggest using fibrosis tests such as elastography, acoustic radiation force impulse imaging and serum biomarkers in order to reduce the number of biopsies.[11] In followup, children should be offered a regular NAFLD screening for advanced liver fibrosis every two years using the enhanced liver fibrosis (ELF) blood test according to NICE.[9] Several studies also suggest magnetic resonance elastography as an alternative to the less reliable ultrasonography.[20]

Intensive lifestyle modifications, including physical activity and dietary changes, should be the first line of treatment according to AASLD and EASL as it improves the liver histology and aminotransferases levels. In terms of pharmacological treatment, metformin should be avoided but Vitamin E may improve liver health for some children.[3][11] The NICE advises the use of Vitamin E for children with advanced liver fibrosis, whether they have diabetes or not.[9] The only treatment shown to be truly effective in childhood NAFLD is weight loss.[119]

There is some evidence that maternal undernutrition or overnutrition increases the susceptibility to NASH in childhood and hastens its progression over lifespan.[120]

Research

Diagnosis and biomarkers

Because diagnosis based on a liver biopsy is invasive and makes it difficult to estimate epidemiology, accurate and inexpensive and noninvasive methods of diagnosing and monitoring NAFLD disease progression are a research priority.[23][121] Search for these biomarkers of NAFLD, NAFL and NASH is involving lipidomics, medical imaging, proteomics, blood test and scoring systems.[23]

According to a 2018 Nature Review, proton density fat fraction estimation by magnetic resonance imaging (MRI-PDFF) should be considered the most accurate and even gold standard test to quantify hepatic steatosis. They recommend ultrasound-based transient elastography (FibroScan) to accurately diagnose both fibrosis and cirrhosis in a routine clinical setting, with more objectivity than ultrasonography but with a lower accuracy than magnetic resonance elastography; and plasma cytokeratin 18 (CK18) fragment levels to be a moderately accurate biomarker of steatohepatitis.[23] However, transient elastography can fail for people with pre-hepatic portal hypertension.[41]

Drug development

Drug development for NASH is very active and advancing rapidly. New drugs are being designed to target various intrahepatic sites, from regulating lipids and glucose homeostasis, to oxidant stress and mitochondrial targets in hepatocytes, inflammatory signals on hepatocytes and intracellular targets related to stellate cell activation and fibrogenesis.[19] As of 2018, clinical trials are underway for cenicriviroc, elafibranor, obeticholic acid and selonsertib in phase 3, and several others in phase 2.[6][3][19][122] Since NAFLD is a complex disease that involves several organs and tissues, combination therapies (combining compounds) and conjugate therapies (combining drugs and non-pharmacological therapies such as behavioral therapies or lifestyle changes) are investigated as a way to increase drugs efficiencies.[19][34] However, most trials were relatively short, from 3 to 18 months, whereas real-world use will involve administration in the long-term.[19]

See also

- Foie gras, fatty liver induced in poultry, with pathophysiology homologous to that of NAFLD in humans

References

1. "DB92 Non-alcoholic fatty liver disease" (https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1912806631). *WHO*. WHO. 18 June 2018. Retrieved 2 October 2019.
2. "Nonalcoholic Fatty Liver Disease & NASH" (https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/all-content). *National Institute of Diabetes and Digestive and Kidney Diseases*. November 2016. Retrieved 7 November 2018.
3. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ (January 2018). "The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases" (https://scholarworks.iupui.edu/bitstream/1805/14037/1/chalasani_2017_diagnosis.pdf) (PDF). *Hepatology* (Professional society guidelines). **67** (1): 328–357. doi:10.1002/hep.29367 (https://doi.org/10.1002%2Fhep.29367). hdl:1805/14037 (https://hdl.handle.net/1805%2F14037). PMID 28714183 (https://pubmed.ncbi.nlm.nih.gov/28714183).
4. Wong, Vincent Wai-Sun; Chan, Wah-Kheong; Chitturi, Shiv; Chawla, Yogesh; Dan, Yock Young; Duseja, Ajay; Fan, Jiangao; Goh, Khean-Lee; Hamaguchi, Masahide; Hashimoto, Etsuko; Kim, Seung Up (2018-07-03). "Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment". *Journal of Gastroenterology and Hepatology* (Professional society guidelines). **33** (1): 70–85. doi:10.1111/jgh.13857 (https://doi.org/10.1111%2Fjgh.13857). ISSN 1440-1746 (https://www.worldcat.org/issn/1440-1746). PMID 28670712 (https://pubmed.ncbi.nlm.nih.gov/28670712).

5. Iser D, Ryan M (July 2013). "Fatty liver disease--a practical guide for GPs". *Australian Family Physician*. **42** (7): 444–7. PMID 23826593 (https://pubmed.ncbi.nlm.nih.gov/23826593).
6. Rinella ME, Sanyal AJ (April 2016). "Management of NAFLD: a stage-based approach". *Nature Reviews. Gastroenterology & Hepatology*. **13** (4): 196–205. doi:10.1038/nrgastro.2016.3 (https://doi.org/10.1038%2Fnrgastro.2016.3). PMID 26907882 (https://pubmed.ncbi.nlm.nih.gov/26907882).
7. Chitturi, Shiv; Wong, Vincent Wai-Sun; Chan, Wah-Kheong; Wong, Grace Lai-Hung; Wong, Simon Kin-Hung; Sollano, Jose; Ni, Yen-Hsuan; Liu, Chun-Jen; Lin, Yu-Cheng; Lesmana, Laurentius Adrianto; Kim, Seung Up (2018-07-10). "The Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 2: Management and special groups". *Journal of Gastroenterology and Hepatology* (Professional society guidelines). **33** (1): 86–98. doi:10.1111/jgh.13856 (https://doi.org/10.1111%2Fjgh.13856). ISSN 1440-1746 (https://www.worldcat.org/issn/1440-1746). PMID 28692197 (https://pubmed.ncbi.nlm.nih.gov/28692197).
8. Kenneally S, Sier JH, Moore JB (1 June 2017). "Efficacy of dietary and physical activity intervention in non-alcoholic fatty liver disease: a systematic review" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5508801). *BMJ Open Gastroenterology*. **4** (1): e000139. doi:10.1136/bmjgast-2017-000139 (https://doi.org/10.1136%2Fbmjgast-2017-000139). PMC 5508801 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5508801). PMID 28761689 (https://pubmed.ncbi.nlm.nih.gov/28761689).
9. "NG49: Non-alcoholic fatty liver disease (NAFLD): assessment and management | Guidance and guidelines" (https://www.nice.org.uk/guidance/ng49). NICE. July 2016. Glen J, Floros L, Day C, Pryke R (September 2016). "Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance". *BMJ* (National guidelines). **354**: i4428. doi:10.1136/bmj.i4428 (https://doi.org/10.1136%2Fbmj.i4428). PMID 27605111 (https://pubmed.ncbi.nlm.nih.gov/27605111).
10. Tilg H, Moschen AR, Roden M (January 2017). "NAFLD and diabetes mellitus". *Nature Reviews. Gastroenterology & Hepatology*. **14** (1): 32–42. doi:10.1038/nrgastro.2016.147 (https://doi.org/10.1038%2Fnrgastro.2016.147). PMID 27729660 (https://pubmed.ncbi.nlm.nih.gov/27729660).
11. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO) (June 2016). "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease". *Journal of Hepatology* (Professional society guidelines). **64** (6): 1388–402. doi:10.1016/j.jhep.2015.11.004 (https://doi.org/10.1016%2Fj.jhep.2015.11.004). PMID 27062661 (https://pubmed.ncbi.nlm.nih.gov/27062661). Lay summary (https://www.revmed.ch/RMS/2017/RMS-N-547/La-steatopathie-non-alcoolique).
12. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M (July 2016). "Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes". *Hepatology*. **64** (1): 73–84. doi:10.1002/hep.28431 (https://doi.org/10.1002%2Fhep.28431). PMID 26707365 (https://pubmed.ncbi.nlm.nih.gov/26707365).
13. Rinella ME (June 2015). "Nonalcoholic fatty liver disease: a systematic review". *JAMA* (Systematic review). **313** (22): 2263–73. doi:10.1001/jama.2015.5370 (https://doi.org/10.1001%2Fjama.2015.5370). hdl:2318/1636665 (https://hdl.handle.net/2318%2F1636665). PMID 26057287 (https://pubmed.ncbi.nlm.nih.gov/26057287).
14. Rich NE, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, Mayo H, Singal AG (February 2018). "Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5794571). *Clinical Gastroenterology and Hepatology*. **16** (2): 198–210.e2. doi:10.1016/j.cgh.2017.09.041 (https://doi.org/10.1016%2Fj.cgh.2017.09.041). PMC 5794571 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5794571). PMID 28970148 (https://pubmed.ncbi.nlm.nih.gov/28970148).

15. "Obesity epidemic results in Non-Alcoholic Fatty Liver Disease (NAFLD) becoming the most common cause of liver disease in Europe" (https://web.archive.org/web/20191005233915/https://easl.eu/press-release/easl-nafld-obesity-epidemic-europe/). *EASL-The Home of Hepatology*. 25 September 2019. Archived from the original (https://easl.eu/press-release/easl-nafld-obesity-epidemic-europe/) on 5 October 2019. Retrieved 5 October 2019.
16. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E (January 2018). "Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention". *Nature Reviews. Gastroenterology & Hepatology*. **15** (1): 11–20. doi:10.1038/nrgastro.2017.109 (https://doi.org/10.1038%2Fnrgastro.2017.109). hdl:2318/1659230 (https://hdl.handle.net/2318%2F1659230). PMID 28930295 (https://pubmed.ncbi.nlm.nih.gov/28930295).
17. Younossi, ZM (March 2019). "Non-alcoholic fatty liver disease - A global public health perspective". *Journal of Hepatology*. **3** (70): 531–544. doi:10.1016/j.jhep.2018.10.033 (https://doi.org/10.1016%2Fj.jhep.2018.10.033). PMID 30414863 (https://pubmed.ncbi.nlm.nih.gov/30414863).
18. "Fatty Liver Disease (Nonalcoholic Steatohepatitis)" (https://www.niddk.nih.gov/health-information/health-topics/liver-disease/nonalcoholic-steatohepatitis/pages/facts.aspx). *NIDDK*. May 2014. Retrieved 10 November 2016.
19. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ (July 2018). "Mechanisms of NAFLD development and therapeutic strategies" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6553468). *Nature Medicine*. **24** (7): 908–922. doi:10.1038/s41591-018-0104-9 (https://doi.org/10.1038%2Fs41591-018-0104-9). PMC 6553468 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6553468). PMID 29967350 (https://pubmed.ncbi.nlm.nih.gov/29967350).
20. AlKhater SA (May 2015). "Paediatric non-alcoholic fatty liver disease: an overview". *Obesity Reviews*. **16** (5): 393–405. doi:10.1111/obr.12271 (https://doi.org/10.1111%2Fobr.12271). PMID 25753407 (https://pubmed.ncbi.nlm.nih.gov/25753407).
21. Musso G, Cassader M, Olivetti C, Rosina F, Carbone G, Gambino R (May 2013). "Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis". *Obesity Reviews*. **14** (5): 417–31. doi:10.1111/obr.12020 (https://doi.org/10.1111%2Fobr.12020). hdl:2318/127880 (https://hdl.handle.net/2318%2F127880). PMID 23387384 (https://pubmed.ncbi.nlm.nih.gov/23387384).
22. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A (June 2017). "NAFLD as a Sexual Dimorphic Disease: Role of Gender and Reproductive Status in the Development and Progression of Nonalcoholic Fatty Liver Disease and Inherent Cardiovascular Risk" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5487879). *Advances in Therapy*. **34** (6): 1291–1326. doi:10.1007/s12325-017-0556-1 (https://doi.org/10.1007%2Fs12325-017-0556-1). PMC 5487879 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5487879). PMID 28526997 (https://pubmed.ncbi.nlm.nih.gov/28526997).
23. Wong VW, Adams LA, de Lédinghen V, Wong GL, Sookoian S (August 2018). "Noninvasive biomarkers in NAFLD and NASH - current progress and future promise". *Nature Reviews. Gastroenterology & Hepatology*. **15** (8): 461–478. doi:10.1038/s41575-018-0014-9 (https://doi.org/10.1038%2Fs41575-018-0014-9). PMID 29844588 (https://pubmed.ncbi.nlm.nih.gov/29844588).
24. Leung C, Rivera L, Furness JB, Angus PW (July 2016). "The role of the gut microbiota in NAFLD". *Nature Reviews. Gastroenterology & Hepatology*. **13** (7): 412–25. doi:10.1038/nrgastro.2016.85 (https://doi.org/10.1038%2Fnrgastro.2016.85). PMID 27273168 (https://pubmed.ncbi.nlm.nih.gov/27273168).
25. Mehal WZ (November 2013). "The Gordian Knot of dysbiosis, obesity and NAFLD". *Nature Reviews. Gastroenterology & Hepatology*. **10** (11): 637–44. doi:10.1038/nrgastro.2013.146 (https://doi.org/10.1038%2Fnrgastro.2013.146). PMID 23958600 (https://pubmed.ncbi.nlm.nih.gov/23958600).

26. Wieland A, Frank DN, Harnke B, Bambha K (November 2015). "Systematic review: microbial dysbiosis and nonalcoholic fatty liver disease". *Alimentary Pharmacology & Therapeutics*. **42** (9): 1051–63. doi:10.1111/apt.13376 (https://doi.org/10.1111%2Fapt.13376). PMID 26304302 (https://pubmed.ncbi.nlm.nih.gov/26304302).
27. Sharpton SR, Ajmera V, Loomba R (September 2018). "Emerging Role of the Gut Microbiome in Nonalcoholic Fatty Liver Disease: From Composition to Function" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6314895). *Clinical Gastroenterology and Hepatology*. **17** (2): 296–306. doi:10.1016/j.cgh.2018.08.065 (https://doi.org/10.1016%2Fj.cgh.2018.08.065). PMC 6314895 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6314895). PMID 30196156 (https://pubmed.ncbi.nlm.nih.gov/30196156).
28. Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH (May 2010). "The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome". *Nature Reviews. Gastroenterology & Hepatology*. **7** (5): 251–64. doi:10.1038/nrgastro.2010.41 (https://doi.org/10.1038%2Fnrgastro.2010.41). PMID 20368739 (https://pubmed.ncbi.nlm.nih.gov/20368739).
29. Wree A, Broderick L, Canbay A, Hoffman HM, Feldstein AE (November 2013). "From NAFLD to NASH to cirrhosis-new insights into disease mechanisms". *Nature Reviews. Gastroenterology & Hepatology*. **10** (11): 627–36. doi:10.1038/nrgastro.2013.149 (https://doi.org/10.1038%2Fnrgastro.2013.149). PMID 23958599 (https://pubmed.ncbi.nlm.nih.gov/23958599).
30. Leermakers ET, Moreira EM, Kiefte-de Jong JC, Darweesh SK, Visser T, Voortman T, Bautista PK, Chowdhury R, Gorman D, Bramer WM, Felix JF, Franco OH (August 2015). "Effects of choline on health across the life course: a systematic review". *Nutrition Reviews*. **73** (8): 500–22. doi:10.1093/nutrit/nuv010 (https://doi.org/10.1093%2Fnutrit%2Fnuv010). PMID 26108618 (https://pubmed.ncbi.nlm.nih.gov/26108618).
31. Della Pepa G, Vetrani C, Lombardi G, Bozzetto L, Annuzzi G, Rivellese AA (September 2017). "Isocaloric Dietary Changes and Non-Alcoholic Fatty Liver Disease in High Cardiometabolic Risk Individuals" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5691682). *Nutrients*. **9** (10): 1065. doi:10.3390/nu9101065 (https://doi.org/10.3390%2Fnu9101065). PMC 5691682 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5691682). PMID 28954437 (https://pubmed.ncbi.nlm.nih.gov/28954437).
32. Byrne CD, Targher G (April 2015). "NAFLD: a multisystem disease". *Journal of Hepatology*. **62** (1 Suppl): S47–64. doi:10.1016/j.jhep.2014.12.012 (https://doi.org/10.1016%2Fj.jhep.2014.12.012). PMID 25920090 (https://pubmed.ncbi.nlm.nih.gov/25920090).
33. Zhang X, Ji X, Wang Q, Li JZ (February 2018). "New insight into inter-organ crosstalk contributing to the pathogenesis of non-alcoholic fatty liver disease (NAFLD)" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818366). *Protein & Cell*. **9** (2): 164–177. doi:10.1007/s13238-017-0436-0 (https://doi.org/10.1007%2Fs13238-017-0436-0). PMC 5818366 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818366). PMID 28643267 (https://pubmed.ncbi.nlm.nih.gov/28643267).
34. Bagherniya M, Nobili V, Blesso CN, Sahebkar A (April 2018). "Medicinal plants and bioactive natural compounds in the treatment of non-alcoholic fatty liver disease: A clinical review". *Pharmacological Research*. **130**: 213–240. doi:10.1016/j.phrs.2017.12.020 (https://doi.org/10.1016%2Fj.phrs.2017.12.020). PMID 29287685 (https://pubmed.ncbi.nlm.nih.gov/29287685).
35. Lustig RH (September 2010). "Fructose: metabolic, hedonic, and societal parallels with ethanol". *Journal of the American Dietetic Association*. **110** (9): 1307–21. doi:10.1016/j.jada.2010.06.008 (https://doi.org/10.1016%2Fj.jada.2010.06.008). PMID 20800122 (https://pubmed.ncbi.nlm.nih.gov/20800122).

36. Pickett-Blakely O, Young K, Carr RM (2018). "Micronutrients in Nonalcoholic Fatty Liver Disease Pathogenesis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6170520). *Cellular and Molecular Gastroenterology and Hepatology*. **6** (4): 451–462. doi:10.1016/j.jcmgh.2018.07.004 (https://doi.org/10.1016%2Fj.jcmgh.2018.07.004). PMC 6170520 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6170520). PMID 30294653 (https://pubmed.ncbi.nlm.nih.gov/30294653).
37. Panasevich MR, Peppler WT, Oerther DB, Wright DC, Rector RS (August 2017). "Microbiome and NAFLD: potential influence of aerobic fitness and lifestyle modification". *Physiological Genomics*. **49** (8): 385–399. doi:10.1152/physiolgenomics.00012.2017 (https://doi.org/10.1152%2Fphysiolgenomics.00012.2017). PMID 28600319 (https://pubmed.ncbi.nlm.nih.gov/28600319).
38. Heiman, ML; Greenway, FL (May 2016). "A healthy gastrointestinal microbiome is dependent on dietary diversity" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837298). *Molecular Metabolism* (Review). **5** (5): 317–320. doi:10.1016/j.molmet.2016.02.005 (https://doi.org/10.1016%2Fj.molmet.2016.02.005). PMC 4837298 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837298). PMID 27110483 (https://pubmed.ncbi.nlm.nih.gov/27110483). "Stable, diverse and healthy GI microbial ecosystems are an important component to consider when using diet to perturb physiological systems in animal models of disease, and it is an aspect often overlooked. A common model to study obesity and insulin resistance is one in which the diet is switched from a basic chow diet to a “Western” or “high fat” diet with a predominance of fat and sugar."
39. Liangpunsakul S, Chalasani N (October 2003). "Is hypothyroidism a risk factor for non-alcoholic steatohepatitis?". *Journal of Clinical Gastroenterology*. **37** (4): 340–3. doi:10.1097/00004836-200310000-00014 (https://doi.org/10.1097%2F00004836-200310000-00014). PMID 14506393 (https://pubmed.ncbi.nlm.nih.gov/14506393).
40. Musso G, Gambino R, Cassader M, Pagano G (December 2011). "Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity". *Annals of Medicine*. **43** (8): 617–49. doi:10.3109/07853890.2010.518623 (https://doi.org/10.3109%2F07853890.2010.518623). PMID 21039302 (https://pubmed.ncbi.nlm.nih.gov/21039302).
41. Shiha, G; Ibrahim, A; Helmy, A; Sarin, SK; Omata, M; Kumar, A; Bernstien, D; Maruyama, H; Saraswat, V; Chawla, Y; Hamid, S; Abbas, Z; Bedossa, P; Sakhuja, P; Elmahatab, M; Lim, SG; Lesmana, L; Sollano, J; Jia, JD; Abbas, B; Omar, A; Sharma, B; Payawal, D; Abdallah, A; Serwah, A; Hamed, A; Elsayed, A; AbdelMaqsod, A; Hassanein, T; Ihab, A; GHaziuan, H; Zein, N; Kumar, M (January 2017). "Asian-Pacific Association for the Study of the Liver (APASL) consensus guidelines on invasive and non-invasive assessment of hepatic fibrosis: a 2016 update". *Hepatology International* (Professional society guidelines). **11** (1): 1–30. doi:10.1007/s12072-016-9760-3 (https://doi.org/10.1007%2Fs12072-016-9760-3). PMID 27714681 (https://pubmed.ncbi.nlm.nih.gov/27714681).
42. Vilgrain, V; Ronot, M; Abdel-Rehim, M; Zappa, M; d'Assignies, G; Bruno, O; Vullierme, MP (2012). "Hepatic steatosis: a major trap in liver imaging". *Diagnostic and Interventional Imaging* (Tutorial). **94** (7–8): 713–27. doi:10.1016/j.diii.2013.03.010 (https://doi.org/10.1016%2Fj.diii.2013.03.010). PMID 23751229 (https://pubmed.ncbi.nlm.nih.gov/23751229).
43. Singh S, Venkatesh SK, Loomba R, Wang Z, Sirlin C, Chen J, Yin M, Miller FH, Low RN, Hassanein T, Godfrey EM, Asbach P, Murad MH, Lomas DJ, Talwalkar JA, Ehman RL (May 2016). "Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5051267). *European Radiology* (Systematic review). **26** (5): 1431–40. doi:10.1007/s00330-015-3949-z (https://doi.org/10.1007%2Fs00330-015-3949-z). PMC 5051267 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5051267). PMID 26314479 (https://pubmed.ncbi.nlm.nih.gov/26314479).

44. Srinivasa Babu, A; Wells, ML; Teytelboym, OM; Mackey, JE; Miller, FH; Yeh, BM; Ehman, RL; Venkatesh, SK (2015). "Elastography in Chronic Liver Disease: Modalities, Techniques, Limitations, and Future Directions" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5584553). *Radiographics* (Review). **36** (7): 1987–2006. doi:10.1148/rg.2016160042 (https://doi.org/10.1148%2Frg.2016160042). PMC 5584553 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5584553). PMID 27689833 (https://pubmed.ncbi.nlm.nih.gov/27689833).
45. Garvey, WT; Mechanick, JI; Brett, EM; Garber, AJ; Hurley, DL; Jastreboff, AM; Nadolsky, K; Pessah-Pollack, R; Plodkowski, R; Reviewers of the AACE/ACE Obesity Clinical Practice, Guidelines. (July 2016). "American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity". *Endocrine Practice* (Professional society guidelines). 22 Suppl 3: 1–203. doi:10.4158/EP161365.GL (https://doi.org/10.4158%2FEP161365.GL). PMID 27219496 (https://pubmed.ncbi.nlm.nih.gov/27219496).
46. Lonardo A, Nascimbeni F, Targher G, Bernardi M, Bonino F, Bugianesi E, Casini A, Gastaldelli A, Marchesini G, Marra F, Miele L, Morisco F, Petta S, Piscaglia F, Svegliati-Baroni G, Valenti L, Bellentani S (May 2017). "AISF position paper on nonalcoholic fatty liver disease (NAFLD): Updates and future directions". *Digestive and Liver Disease* (Professional society guidelines). **49** (5): 471–483. doi:10.1016/j.dld.2017.01.147 (https://doi.org/10.1016%2Fj.dld.2017.01.147). hdl:2318/1636507 (https://hdl.handle.net/2318%2F1636507). PMID 28215516 (https://pubmed.ncbi.nlm.nih.gov/28215516).
47. Koutoukidis DA, Astbury NM, Tudor KE, Morris E, Henry JA, Noreik M, Jebb SA, Aveyard P (2019-07-01). "Association of Weight Loss Interventions With Changes in Biomarkers of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6604126). *JAMA Internal Medicine*. **179**: 1262. doi:10.1001/jamainternmed.2019.2248 (https://doi.org/10.1001%2Fjamainternmed.2019.2248). PMC 6604126 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6604126). PMID 31260026 (https://pubmed.ncbi.nlm.nih.gov/31260026).
48. Paris T, George ES, Roberts SK, Tierney AC (August 2017). "The effects of diet and lifestyle interventions on insulin resistance in patients with nonalcoholic fatty liver disease: a systematic review". *European Journal of Gastroenterology & Hepatology*. **29** (8): 867–878. doi:10.1097/MEG.0000000000000890 (https://doi.org/10.1097%2FMEG.0000000000000890). PMID 28471823 (https://pubmed.ncbi.nlm.nih.gov/28471823).
49. Romero-Gómez M, Zelber-Sagi S, Trenell M (October 2017). "Treatment of NAFLD with diet, physical activity and exercise". *Journal of Hepatology*. **67** (4): 829–846. doi:10.1016/j.jhep.2017.05.016 (https://doi.org/10.1016%2Fj.jhep.2017.05.016). PMID 28545937 (https://pubmed.ncbi.nlm.nih.gov/28545937).
50. Marchesini G, Petta S, Dalle Grave R (June 2016). "Diet, weight loss, and liver health in nonalcoholic fatty liver disease: Pathophysiology, evidence, and practice". *Hepatology*. **63** (6): 2032–43. doi:10.1002/hep.28392 (https://doi.org/10.1002%2Fhep.28392). PMID 26663351 (https://pubmed.ncbi.nlm.nih.gov/26663351).
51. Koutoukidis, DA; Astbury, NM; Tudor, KE; Morris, E; Henry, JA; Noreik, M; Jebb, SA; Aveyard, P (1 July 2019). "Association of Weight Loss Interventions With Changes in Biomarkers of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6604126). *JAMA Internal Medicine*. **179**: 1262. doi:10.1001/jamainternmed.2019.2248 (https://doi.org/10.1001%2Fjamainternmed.2019.2248). PMC 6604126 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6604126). PMID 31260026 (https://pubmed.ncbi.nlm.nih.gov/31260026).
52. Rusu E, Enache G, Jinga M, Dragut R, Nan R, Popescu H, Parpala C, Homentcovschi C, Nitescu M, Stoian M, Costache A, Posea M, Rusu F, Jinga V, Mischianu D, Radulian G (2014). "Medical nutrition therapy in non-alcoholic fatty liver disease--a review of literature" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4556902). *Journal of Medicine and Life*. **8** (3): 258–62. PMC 4556902 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4556902). PMID 26351523 (https://pubmed.ncbi.nlm.nih.gov/26351523).

53. Hsu CC, Ness E, Kowdley KV (March 2017). "Nutritional Approaches to Achieve Weight Loss in Nonalcoholic Fatty Liver Disease" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5347099). *Advances in Nutrition*. **8** (2): 253–265. doi:10.3945/an.116.013730 (https://doi.org/10.3945%2Fan.116.013730). PMC 5347099 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5347099). PMID 28298270 (https://pubmed.ncbi.nlm.nih.gov/28298270).
54. Zelber-Sagi S, Salomone F, Mlynarsky L (July 2017). "The Mediterranean dietary pattern as the diet of choice for non-alcoholic fatty liver disease: Evidence and plausible mechanisms". *Liver International*. **37** (7): 936–949. doi:10.1111/liv.13435 (https://doi.org/10.1111%2Fliv.13435). PMID 28371239 (https://pubmed.ncbi.nlm.nih.gov/28371239).
55. Merchant, Hamid A. (2017-09-19). "Can Diet Help Non-Obese Individuals with Non-Alcoholic Fatty Liver Disease (NAFLD)?" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5615281). *Journal of Clinical Medicine*. **6** (9): 88. doi:10.3390/jcm6090088 (https://doi.org/10.3390%2Fjcm6090088). ISSN 2077-0383 (https://www.worldcat.org/issn/2077-0383). PMC 5615281 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5615281). PMID 28925934 (https://pubmed.ncbi.nlm.nih.gov/28925934).
56. Parker HM, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J (April 2012). "Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis" (http://www.journal-of-hepatology.eu/article/S0168-8278(11)00740-9/pdf). *Journal of Hepatology* (Systematic review and meta-analysis). **56** (4): 944–51. doi:10.1016/j.jhep.2011.08.018 (https://doi.org/10.1016%2Fj.jhep.2011.08.018). PMID 22023985 (https://pubmed.ncbi.nlm.nih.gov/22023985).
57. Veena J, Muragundla A, Sidgiddi S, Subramaniam S (December 2014). "Non-alcoholic fatty liver disease: need for a balanced nutritional source". *The British Journal of Nutrition*. **112** (11): 1858–72. doi:10.1017/S0007114514002591 (https://doi.org/10.1017%2FS0007114514002591). PMID 25274101 (https://pubmed.ncbi.nlm.nih.gov/25274101).
58. Valenti, L.; Riso, P.; Mazzocchi, A.; Porrini, M.; Fargion, S.; Agostoni, C. (2013). "Dietary Anthocyanins as Nutritional Therapy for Nonalcoholic Fatty Liver Disease" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3824564). *Oxidative Medicine and Cellular Longevity*. **2013**: 145421. doi:10.1155/2013/145421 (https://doi.org/10.1155%2F2013%2F145421). PMC 3824564 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3824564). PMID 24282628 (https://pubmed.ncbi.nlm.nih.gov/24282628).
59. US Department of Health and Human Services. (2017). "2015–2020 Dietary Guidelines for Americans - health.gov" (https://health.gov/dietaryguidelines/2015/). *health.gov*. Skyhorse Publishing Inc. Retrieved 30 September 2019.
60. Arnett, Donna K.; Blumenthal, Roger S.; Albert, Michelle A.; Buroker, Andrew B.; Goldberger, Zachary D.; Hahn, Ellen J.; Himmelfarb, Cheryl D.; Khera, Amit; Lloyd-Jones, Donald; McEvoy, J. William; Michos, Erin D.; Miedema, Michael D.; Muñoz, Daniel; Smith, Sidney C.; Virani, Salim S.; Williams, Kim A.; Yeboah, Joseph; Ziaeian, Boback (17 March 2019). "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease". *Circulation*. **140** (11): e596–e646. doi:10.1161/CIR.0000000000000678 (https://doi.org/10.1161%2FCIR.0000000000000678). PMID 30879355 (https://pubmed.ncbi.nlm.nih.gov/30879355).

61. Jensen, MD; Ryan, DH; Apovian, CM; Ard, JD; Comuzzie, AG; Donato, KA; Hu, FB; Hubbard, VS; Jakicic, JM; Kushner, RF; Loria, CM; Millen, BE; Nonas, CA; Pi-Sunyer, FX; Stevens, J; Stevens, VJ; Wadden, TA; Wolfe, BM; Yanovski, SZ; Jordan, HS; Kendall, KA; Lux, LJ; Mentor-Marcel, R; Morgan, LC; Trisolini, MG; Wnek, J; Anderson, JL; Halperin, JL; Albert, NM; Bozkurt, B; Brindis, RG; Curtis, LH; DeMets, D; Hochman, JS; Kovacs, RJ; Ohman, EM; Pressler, SJ; Sellke, FW; Shen, WK; Smith SC, Jr; Tomaselli, GF; American College of Cardiology/American Heart Association Task Force on Practice, Guidelines.; Obesity, Society. (24 June 2014). "2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5819889). *Circulation*. **129** (25 Suppl 2): S102-38. doi:10.1161/01.cir.0000437739.71477.ee (https://doi.org/10.1161%2F01.cir.0000437739.71477.ee). PMC 5819889 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5819889). PMID 24222017 (https://pubmed.ncbi.nlm.nih.gov/24222017).
62. Hashida R, Kawaguchi T, Bekki M, Omoto M, Matsuse H, Nago T, Takano Y, Ueno T, Koga H, George J, Shiba N, Torimura T (January 2017). "Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review". *Journal of Hepatology*. **66** (1): 142–152. doi:10.1016/j.jhep.2016.08.023 (https://doi.org/10.1016%2Fj.jhep.2016.08.023). PMID 27639843 (https://pubmed.ncbi.nlm.nih.gov/27639843).
63. Ratziu V (January 2017). "Non-pharmacological interventions in non-alcoholic fatty liver disease patients". *Liver International*. 37 Suppl 1: 90–96. doi:10.1111/liv.13311 (https://doi.org/10.1111%2Fliv.13311). PMID 28052636 (https://pubmed.ncbi.nlm.nih.gov/28052636).
64. Ratziu V, Goodman Z, Sanyal A (April 2015). "Current efforts and trends in the treatment of NASH". *Journal of Hepatology*. **62** (1 Suppl): S65–75. doi:10.1016/j.jhep.2015.02.041 (https://doi.org/10.1016%2Fj.jhep.2015.02.041). PMID 25920092 (https://pubmed.ncbi.nlm.nih.gov/25920092).
65. Raziel A, Sakran N, Szold A, Goitein D (April 2015). "Current solutions for obesity-related liver disorders: non-alcoholic fatty liver disease and non-alcoholic steatohepatitis" (http://www.ima.org.il/FilesUpload/IMAJ/0/142/71367.pdf) (PDF). *The Israel Medical Association Journal*. **17** (4): 234–8. PMID 26040050 (https://pubmed.ncbi.nlm.nih.gov/26040050).
66. "Pour mieux soigner : des médicaments à écarter - actualisation 2018" (http://www.prescrire.org/fr/3/31/53765/0/NewsDetails.aspx). *www.prescrire.org*. Prescrire. 2018-01-25.
67. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ (June 2012). "The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology". *Gastroenterology*. **142** (7): 1592–609. doi:10.1053/j.gastro.2012.04.001 (https://doi.org/10.1053%2Fj.gastro.2012.04.001). PMID 22656328 (https://pubmed.ncbi.nlm.nih.gov/22656328).
68. Hadi A, Mohammadi H, Miraghajani M, Ghaedi E (March 2018). "Efficacy of synbiotic supplementation in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis of clinical trials: Synbiotic supplementation and NAFLD". *Critical Reviews in Food Science and Nutrition*. **59** (15): 2494–2505. doi:10.1080/10408398.2018.1458021 (https://doi.org/10.1080%2F10408398.2018.1458021). PMID 29584449 (https://pubmed.ncbi.nlm.nih.gov/29584449).
69. Lee, Y; Doumouras, AG; Yu, J; Brar, K; Banfield, L; Gmora, S; Anvari, M; Hong, D (May 2019). "Complete Resolution of Nonalcoholic Fatty Liver Disease After Bariatric Surgery: A Systematic Review and Meta-analysis". *Clinical Gastroenterology and Hepatology*. **17** (6): 1040–1060.e11. doi:10.1016/j.cgh.2018.10.017 (https://doi.org/10.1016%2Fj.cgh.2018.10.017). PMID 30326299 (https://pubmed.ncbi.nlm.nih.gov/30326299).

70. Fakhry, TK; Mhaskar, R; Schwitalla, T; Muradova, E; Gonzalvo, JP; Murr, MM (March 2019). "Bariatric surgery improves nonalcoholic fatty liver disease: a contemporary systematic review and meta-analysis". *Surgery for Obesity and Related Diseases*. **15** (3): 502–511. doi:10.1016/j.soard.2018.12.002 (https://doi.org/10.1016%2Fj.soard.2018.12.002). PMID 30683512 (https://pubmed.ncbi.nlm.nih.gov/30683512).
71. Mummadi RR, Kasturi KS, Chennareddygari S, Sood GK (December 2008). "Effect of bariatric surgery on nonalcoholic fatty liver disease: systematic review and meta-analysis". *Clinical Gastroenterology and Hepatology*. **6** (12): 1396–402. doi:10.1016/j.cgh.2008.08.012 (https://doi.org/10.1016%2Fj.cgh.2008.08.012). PMID 18986848 (https://pubmed.ncbi.nlm.nih.gov/18986848).
72. Thorell, A; MacCormick, AD; Awad, S; Reynolds, N; Roulin, D; Demartines, N; Vignaud, M; Alvarez, A; Singh, PM; Lobo, DN (September 2016). "Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations". *World Journal of Surgery* (Professional society guidelines). **40** (9): 2065–83. doi:10.1007/s00268-016-3492-3 (https://doi.org/10.1007%2Fs00268-016-3492-3). PMID 26943657 (https://pubmed.ncbi.nlm.nih.gov/26943657).
73. Holderbaum, M; Casagrande, DS; Sussenbach, S; Buss, C (February 2018). "Effects of very low calorie diets on liver size and weight loss in the preoperative period of bariatric surgery: a systematic review". *Surgery for Obesity and Related Diseases* (Systematic review). **14** (2): 237–244. doi:10.1016/j.soard.2017.09.531 (https://doi.org/10.1016%2Fj.soard.2017.09.531). PMID 29239795 (https://pubmed.ncbi.nlm.nih.gov/29239795).
74. Livhits, M; Mercado, C; Yermilov, I; Parikh, JA; Dutson, E; Mehran, A; Ko, CY; Gibbons, MM (2008). "Does weight loss immediately before bariatric surgery improve outcomes: a systematic review". *Surgery for Obesity and Related Diseases*. **5** (6): 713–21. doi:10.1016/j.soard.2009.08.014 (https://doi.org/10.1016%2Fj.soard.2009.08.014). PMID 19879814 (https://pubmed.ncbi.nlm.nih.gov/19879814).
75. Roman, M; Monaghan, A; Serraino, GF; Miller, D; Pathak, S; Lai, F; Zaccardi, F; Ghanchi, A; Khunti, K; Davies, MJ; Murphy, GJ (February 2019). "Meta-analysis of the influence of lifestyle changes for preoperative weight loss on surgical outcomes". *The British Journal of Surgery* (Meta-analysis). **106** (3): 181–189. doi:10.1002/bjs.11001 (https://doi.org/10.1002%2Fbjs.11001). hdl:2381/43636 (https://hdl.handle.net/2381%2F43636). PMID 30328098 (https://pubmed.ncbi.nlm.nih.gov/30328098).
76. Cassie, S; Menezes, C; Birch, DW; Shi, X; Karmali, S (2010). "Effect of preoperative weight loss in bariatric surgical patients: a systematic review". *Surgery for Obesity and Related Diseases* (Systematic review). **7** (6): 760–7, discussion 767. doi:10.1016/j.soard.2011.08.011 (https://doi.org/10.1016%2Fj.soard.2011.08.011). PMID 21978748 (https://pubmed.ncbi.nlm.nih.gov/21978748).
77. Zhou, Yaoyao; Fu, Shenwen (October 2017). "GW28-e0325 Association of non-alcoholic fatty liver disease and subclinical atherosclerosis: a systematic review and meta-analysis". *Journal of the American College of Cardiology*. **70** (16): C81. doi:10.1016/j.jacc.2017.07.284 (https://doi.org/10.1016%2Fj.jacc.2017.07.284).
78. Mahady SE, George J (August 2012). "Management of nonalcoholic steatohepatitis: an evidence-based approach". *Clinics in Liver Disease*. **16** (3): 631–45. doi:10.1016/j.cld.2012.05.003 (https://doi.org/10.1016%2Fj.cld.2012.05.003). PMID 22824485 (https://pubmed.ncbi.nlm.nih.gov/22824485).
79. Khan RS, Newsome PN (February 2018). "NAFLD in 2017: Novel insights into mechanisms of disease progression". *Nature Reviews. Gastroenterology & Hepatology*. **15** (2): 71–72. doi:10.1038/nrgastro.2017.181 (https://doi.org/10.1038%2Fnrgastro.2017.181). PMID 29300050 (https://pubmed.ncbi.nlm.nih.gov/29300050).

80. Neuschwander-Tetri BA (February 2017). "Non-alcoholic fatty liver disease" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5330146). *BMC Medicine*. **15** (1): 45. doi:10.1186/s12916-017-0806-8 (https://doi.org/10.1186%2Fs12916-017-0806-8). PMC 5330146 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5330146). PMID 28241825 (https://pubmed.ncbi.nlm.nih.gov/28241825).
81. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R (April 2015). "Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4208976). *Clinical Gastroenterology and Hepatology*. **13** (4): 643–54.e1–9, quiz e39–40. doi:10.1016/j.cgh.2014.04.014 (https://doi.org/10.1016%2Fj.cgh.2014.04.014). PMC 4208976 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4208976). PMID 24768810 (https://pubmed.ncbi.nlm.nih.gov/24768810).
82. Lu, Feng-Bin; Hu, En-De; Xu, Lan-Man; Chen, Lu; Wu, Jin-Lu; Li, Hui; Chen, Da-Zhi; Chen, Yong-Ping (2018-05-21). "The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis". *Expert Review of Gastroenterology & Hepatology*. **12** (5): 491–502. doi:10.1080/17474124.2018.1460202 (https://doi.org/10.1080%2F17474124.2018.1460202). ISSN 1747-4132 (https://www.worldcat.org/issn/1747-4132). PMID 29609501 (https://pubmed.ncbi.nlm.nih.gov/29609501).
83. Sookoian, S.; Pirola, C. J. (2018-10-30). "Systematic review with meta-analysis: the significance of histological disease severity in lean patients with nonalcoholic fatty liver disease". *Alimentary Pharmacology & Therapeutics*. **47** (1): 16–25. doi:10.1111/apt.14401 (https://doi.org/10.1111%2Fapt.14401). ISSN 1365-2036 (https://www.worldcat.org/issn/1365-2036). PMID 29083036 (https://pubmed.ncbi.nlm.nih.gov/29083036).
84. Minhas AM, Usman MS, Khan MS, Fatima K, Mangi MA, Illovsky MA (April 2017). "Link Between Non-Alcoholic Fatty Liver Disease and Atrial Fibrillation: A Systematic Review and Meta-Analysis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5419817). *Cureus*. **9** (4): e1142. doi:10.7759/cureus.1142 (https://doi.org/10.7759%2Fcureus.1142). PMC 5419817 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5419817). PMID 28484681 (https://pubmed.ncbi.nlm.nih.gov/28484681).
85. Usman MS, Siddiqi TJ (October 2017). "Emerging evidence for the association between non-alcoholic fatty liver disease and cardiac arrhythmias". *Digestive and Liver Disease*. **49** (10): 1166. doi:10.1016/j.dld.2017.07.013 (https://doi.org/10.1016%2Fj.dld.2017.07.013). PMID 28822729 (https://pubmed.ncbi.nlm.nih.gov/28822729).
86. Bellentani S (January 2017). "The epidemiology of non-alcoholic fatty liver disease". *Liver International*. 37 Suppl 1: 81–84. doi:10.1111/liv.13299 (https://doi.org/10.1111%2Fliv.13299). PMID 28052624 (https://pubmed.ncbi.nlm.nih.gov/28052624).
87. Marengo A, Rosso C, Bugianesi E (14 January 2016). "Liver Cancer: Connections with Obesity, Fatty Liver, and Cirrhosis". *Annual Review of Medicine*. **67** (1): 103–17. doi:10.1146/annurev-med-090514-013832 (https://doi.org/10.1146%2Fannurev-med-090514-013832). hdl:2318/1636160 (https://hdl.handle.net/2318%2F1636160). PMID 26473416 (https://pubmed.ncbi.nlm.nih.gov/26473416).
88. Lonardo A, Ballestri S, Marchesini G, Angulo P, Loria P (March 2015). "Nonalcoholic fatty liver disease: a precursor of the metabolic syndrome". *Digestive and Liver Disease*. **47** (3): 181–90. doi:10.1016/j.dld.2014.09.020 (https://doi.org/10.1016%2Fj.dld.2014.09.020). PMID 25739820 (https://pubmed.ncbi.nlm.nih.gov/25739820).
89. Yki-Järvinen H (November 2014). "Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome". *The Lancet. Diabetes & Endocrinology*. **2** (11): 901–10. doi:10.1016/S2213-8587(14)70032-4 (https://doi.org/10.1016%2FS2213-8587%2814%2970032-4). PMID 24731669 (https://pubmed.ncbi.nlm.nih.gov/24731669).

90. Katsiki, Niki; Perez-Martinez, Pablo; Anagnostis, Panagiotis; Mikhailidis, Dimitri P.; Karagiannis, Asterios (2018). "Is Nonalcoholic Fatty Liver Disease Indeed the Hepatic Manifestation of Metabolic Syndrome?". *Current Vascular Pharmacology*. **16** (3): 219–227. doi:10.2174/1570161115666170621075619 (https://doi.org/10.2174%2F1570161115666170621075619). ISSN 1875-6212 (https://www.worldcat.org/issn/1875-6212). PMID 28669328 (https://pubmed.ncbi.nlm.nih.gov/28669328).
91. Omagari K, Kadokawa Y, Masuda J, Egawa I, Sawa T, Hazama H, Ohba K, Isomoto H, Mizuta Y, Hayashida K, Murase K, Kadota T, Murata I, Kohno S (October 2002). "Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics". *Journal of Gastroenterology and Hepatology*. **17** (10): 1098–105. doi:10.1046/j.1440-1746.2002.02846.x (https://doi.org/10.1046%2Fj.1440-1746.2002.02846.x). PMID 12201871 (https://pubmed.ncbi.nlm.nih.gov/12201871).
92. Hilden M, Christoffersen P, Juhl E, Dalgaard JB (1977). "Liver histology in a 'normal' population--examinations of 503 consecutive fatal traffic casualties". *Scandinavian Journal of Gastroenterology*. **12** (5): 593–7. doi:10.3109/00365527709181339 (https://doi.org/10.3109%2F00365527709181339). PMID 918553 (https://pubmed.ncbi.nlm.nih.gov/918553).
93. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A (29 October 2015). "The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4626023). *PLOS ONE*. **10** (10): e0140908. Bibcode:2015PLoSO..1040908A (https://ui.adsabs.harvard.edu/abs/2015PLoSO..1040908A). doi:10.1371/journal.pone.0140908 (https://doi.org/10.1371%2Fjournal.pone.0140908). PMC 4626023 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4626023). PMID 26512983 (https://pubmed.ncbi.nlm.nih.gov/26512983).
94. Kabbany MN, Conjeevaram Selvakumar PK, Watt K, Lopez R, Akras Z, Zein N, Carey W, Alkhouri N (April 2017). "Prevalence of Nonalcoholic Steatohepatitis-Associated Cirrhosis in the United States: An Analysis of National Health and Nutrition Examination Survey Data". *The American Journal of Gastroenterology*. **112** (4): 581–587. doi:10.1038/ajg.2017.5 (https://doi.org/10.1038%2Fajg.2017.5). PMID 28195177 (https://pubmed.ncbi.nlm.nih.gov/28195177).
95. Flegal KM, Carroll MD, Ogden CL, Johnson CL (October 2002). "Prevalence and trends in obesity among US adults, 1999-2000". *JAMA*. **288** (14): 1723–7. doi:10.1001/jama.288.14.1723 (https://doi.org/10.1001%2Fjama.288.14.1723). PMID 12365955 (https://pubmed.ncbi.nlm.nih.gov/12365955).
96. Lu FB, Hu ED, Xu LM, Chen L, Wu JL, Li H, Chen DZ, Chen YP (May 2018). "The relationship between obesity and the severity of non-alcoholic fatty liver disease: systematic review and meta-analysis". *Expert Review of Gastroenterology & Hepatology*. **12** (5): 491–502. doi:10.1080/17474124.2018.1460202 (https://doi.org/10.1080%2F17474124.2018.1460202). PMID 29609501 (https://pubmed.ncbi.nlm.nih.gov/29609501).
97. Sarah Boseley (12 April 2019). "Experts warn of fatty liver disease 'epidemic' in young people" (https://www.theguardian.com/society/2019/apr/12/experts-warn-of-fatty-liver-disease-epidemic-in-young-people). *The Guardian*.
98. EASL (April 2019). "Policy Statement - Obesity is feeding the rise in Non-Alcoholic Fatty Liver Disease (NAFLD) across Europe" (https://web.archive.org/web/20191007160746/https://easl.eu/wp-content/uploads/2019/04/EASL-POLICY-Obesity-and-NAFLD-FINAL.pdf) (PDF). Archived from the original (https://easl.eu/wp-content/uploads/2019/04/EASL-POLICY-Obesity-and-NAFLD-FINAL.pdf) (PDF) on 2019-10-07.
99. Estes, C; Razavi, H; Loomba, R; Younossi, Z; Sanyal, AJ (January 2018). "Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5767767). *Hepatology*. **1** (67): 123–133. doi:10.1002/hep.29466 (https://doi.org/10.1002%2Fhep.29466). PMC 5767767 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5767767). PMID 28802062 (https://pubmed.ncbi.nlm.nih.gov/28802062).

100. Zelman S (August 1952). "The liver in obesity". *Archives of Internal Medicine*. **90** (2): 141–56. doi:10.1001/archinte.1952.00240080007002 (https://doi.org/10.1001%2Farchinte.1952.00240080007002). PMID 14943295 (https://pubmed.ncbi.nlm.nih.gov/14943295).
101. Ludwig J, McGill DB, Lindor KD (May 1997). "Review: nonalcoholic steatohepatitis". *Journal of Gastroenterology and Hepatology*. **12** (5): 398–403. doi:10.1111/j.1440-1746.1997.tb00450.x (https://doi.org/10.1111%2Fj.1440-1746.1997.tb00450.x). PMID 9195388 (https://pubmed.ncbi.nlm.nih.gov/9195388).
102. Rabinowitch IM (June 1948). "Relationship between impairment of liver function and premature development of arteriosclerosis in diabetes mellitus" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1590957). *Canadian Medical Association Journal*. **58** (6): 547–56. PMC 1590957 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1590957). PMID 18862251 (https://pubmed.ncbi.nlm.nih.gov/18862251).
103. Best CH, Hartroft WS (November 1949). "Liver damage produced by feeding alcohol or sugar and its prevention by choline" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2051633). *British Medical Journal*. **2** (4635): 1002–6, pl. doi:10.1136/bmj.2.4635.1001 (https://doi.org/10.1136%2Fbmj.2.4635.1001). PMC 2051633 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2051633). PMID 15393035 (https://pubmed.ncbi.nlm.nih.gov/15393035).
104. HANSSEN, PER (14 March 1936). "Enlargement of the Liver in Diabetes Mellitus". *Journal of the American Medical Association*. **106** (11): 914. doi:10.1001/jama.1936.02770110030011 (https://doi.org/10.1001%2Fjama.1936.02770110030011).
105. Ludwig J, Viggiano TR, McGill DB, Oh BJ (July 1980). "Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease". *Mayo Clinic Proceedings*. **55** (7): 434–8. PMID 7382552 (https://pubmed.ncbi.nlm.nih.gov/7382552).
106. Farrell GC, Larter CZ (February 2006). "Nonalcoholic fatty liver disease: from steatosis to cirrhosis". *Hepatology*. **43** (2 Suppl 1): S99–S112. doi:10.1002/hep.20973 (https://doi.org/10.1002%2Fhep.20973). PMID 16447287 (https://pubmed.ncbi.nlm.nih.gov/16447287).
107. Drew L (October 2017). "Fatty liver disease: turning the tide". *Nature*. **550** (7675): S101. doi:10.1038/550S101a (https://doi.org/10.1038%2F550S101a). PMID 29019967 (https://pubmed.ncbi.nlm.nih.gov/29019967).
108. "Consommation et Nutrition - Boissons Rafraichissantes de France" (https://web.archive.org/web/20180425032329/http://www.boissonsrafraichissantes.com/consommation-et-nutrition/).
109. "Il était un foie le soda" (5102). Le Canard Enchaîné. August 2018.
110. Moran JR, Ghishan FK, Halter SA, Greene HL (June 1983). "Steatohepatitis in obese children: a cause of chronic liver dysfunction". *The American Journal of Gastroenterology*. **78** (6): 374–7. PMID 6859017 (https://pubmed.ncbi.nlm.nih.gov/6859017).
111. Temple JL, Cordero P, Li J, Nguyen V, Oben JA (June 2016). "A Guide to Non-Alcoholic Fatty Liver Disease in Childhood and Adolescence" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4926480). *International Journal of Molecular Sciences*. **17** (6): 947. doi:10.3390/ijms17060947 (https://doi.org/10.3390%2Fijms17060947). PMC 4926480 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4926480). PMID 27314342 (https://pubmed.ncbi.nlm.nih.gov/27314342).
112. Papandreou D, Rousso I, Mavromichalis I (2007). "Update on non-alcoholic fatty liver disease in children". *Clinical Nutrition*. **16** (4): 409–415. doi:10.1016/j.clnu.2007.02.002 (https://doi.org/10.1016%2Fj.clnu.2007.02.002). PMID 17449148 (https://pubmed.ncbi.nlm.nih.gov/17449148).
113. Cortez-Pinto H, Camilo ME, Baptista A, et al. (1999). "Nonalcoholic fatty liver: another feature of the metabolic syndrome?". *Clinical Nutrition*. **18** (6): 353–8. doi:10.1016/S0261-5614(99)80015-6 (https://doi.org/10.1016%2FS0261-5614%2899%2980015-6). PMID 10634920 (https://pubmed.ncbi.nlm.nih.gov/10634920).

114. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N (August 2001). "Nonalcoholic fatty liver disease: a feature of the metabolic syndrome". *Diabetes*. **50** (8): 1844–50. doi:10.2337/diabetes.50.8.1844 (https://doi.org/10.2337%2Fdiabetes.50.8.1844). PMID 11473047 (https://pubmed.ncbi.nlm.nih.gov/11473047).
115. Nobili V, Marcellini M, Devito R, Ciampalini P, Piemonte F, Comparcola D, Sartorelli MR, Angulo P (August 2006). "NAFLD in children: a prospective clinical-pathological study and effect of lifestyle advice". *Hepatology*. **44** (2): 458–65. doi:10.1002/hep.21262 (https://doi.org/10.1002%2Fhep.21262). PMID 16871574 (https://pubmed.ncbi.nlm.nih.gov/16871574).
116. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, Cassader M, David E, Cavallo-Perin P, Rizzetto M (February 2002). "Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association". *Hepatology*. **35** (2): 367–72. doi:10.1053/jhep.2002.30690 (https://doi.org/10.1053%2Fjhep.2002.30690). PMID 11826410 (https://pubmed.ncbi.nlm.nih.gov/11826410).
117. Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S (July 2008). "Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996820). *Circulation*. **118** (3): 277–83. doi:10.1161/CIRCULATIONAHA.107.739920 (https://doi.org/10.1161%2FCIRCULATIONAHA.107.739920). PMC 2996820 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996820). PMID 18591439 (https://pubmed.ncbi.nlm.nih.gov/18591439).
118. Roberts EA (June 2007). "Pediatric nonalcoholic fatty liver disease (NAFLD): a "growing" problem?". *Journal of Hepatology*. **46** (6): 1133–42. doi:10.1016/j.jhep.2007.03.003 (https://doi.org/10.1016%2Fj.jhep.2007.03.003). PMID 17445934 (https://pubmed.ncbi.nlm.nih.gov/17445934).
119. Gibson PS, Lang S, Dhawan A, Fitzpatrick E, Blumfield ML, Truby H, Hart KH, Moore JB (August 2017). "Systematic Review: Nutrition and Physical Activity in the Management of Paediatric Nonalcoholic Fatty Liver Disease" (http://eprints.whiterose.ac.uk/116076/3/Gibson_Manuscript_080517_symplectic.pdf) (PDF). *Journal of Pediatric Gastroenterology and Nutrition*. **65** (2): 141–149. doi:10.1097/MPG.0000000000001624 (https://doi.org/10.1097%2FMPG.0000000000001624). PMID 28737568 (https://pubmed.ncbi.nlm.nih.gov/28737568).
120. Wesolowski SR, Kasmi KC, Jonscher KR, Friedman JE (February 2017). "Developmental origins of NAFLD: a womb with a clue" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5725959). *Nature Reviews. Gastroenterology & Hepatology*. **14** (2): 81–96. doi:10.1038/nrgastro.2016.160 (https://doi.org/10.1038%2Fnrgastro.2016.160). PMC 5725959 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5725959). PMID 27780972 (https://pubmed.ncbi.nlm.nih.gov/27780972).
121. Araújo AR, Rosso N, Bedogni G, Tiribelli C, Bellentani S (February 2018). "Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: What we need in the future". *Liver International*. 38 Suppl 1: 47–51. doi:10.1111/liv.13643 (https://doi.org/10.1111%2Fliv.13643). PMID 29427488 (https://pubmed.ncbi.nlm.nih.gov/29427488).
122. Liyanagedera S, Williams RP, Veraldi S, Nobili V, Mann JP (November 2017). "The pharmacological management of NAFLD in children and adolescents" (https://www.repository.cam.ac.uk/handle/1810/287322). *Expert Review of Clinical Pharmacology*. **10** (11): 1225–1237. doi:10.1080/17512433.2017.1365599 (https://doi.org/10.1080%2F17512433.2017.1365599). PMID 28803504 (https://pubmed.ncbi.nlm.nih.gov/28803504).

External links

- NIH (http://digestive.niddk.nih.gov/ddiseases/pubs/nash/) page on non-alcoholic steatohepatitis

Classification	**ICD-10**: K75.8 (htt D p://apps.who.int/cla ssifications/icd10/br

- Mayo Clinic (https://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/symptoms-causes/syc-20354567) page on NAFLD

	owse/2016/en#/K75.8), K76.0 (http://apps.who.int/classifications/icd10/browse/2016/en#/K76.0) · **ICD-10-CM**: K75.81 (https://icdcodelookup.com/icd-10/codes/K75.81), K76.0 (https://icdcodelookup.com/icd-10/codes/K76.0) · **ICD-9-CM**: 571.8 (http://www.icd9data.com/getICD9Code.ashx?icd9=571.8) · **MeSH**: D065626 (https://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?field=uid&term=D065626) · **DiseasesDB**: 29786 (http://www.diseasesdatabase.com/ddb29786.htm)
External resources	**eMedicine**: med/775 (https://emedicine.medscape.com/med/775-overview)