EPIDEMIOLOGICAL MODIFIERS OF NONALCOHOLIC FATTY LIVER DISEASE. FOCUS ON HIGH-RISK GROUPS

Running Title: NAFLD epidemiology: focus on high-risk groups

Authors: The NAFLD study group*. Dedicated to the memory of Professor Paola Loria

*Authors List: Amedeo Lonardo[1], Stefano Bellentani[1,2], Curtis K. Argo[3], Stefano Ballestri[4], Christopher D. Byrne[5], Stephen H. Caldwell[3], Helena Cortez-Pinto[6], Antonio Grieco[7], Mariana V. Machado[6], Luca Miele[7], Giovanni Targher[8]

[1]Internal Medicine and Outpatient Liver Clinic, NOCSAE Baggiovara, Azienda USL di Modena, Modena, Italy

[2] Department of Gastroenterology and Endoscopy, NOCSE Baggiovara, Azienda USL di Modena, Modena, Italy

[3]University of Virginia, Charlottesville, VA, USA

[4]Internal Medicine Pavullo Hospital Azienda USL di Modena, Modena, Italy

[5] Nutrition and Metabolism, University of Southampton, Southampton National Institute for Health Research Biomedical Research Centre, Southampton, UK

[6] Department of Gastroenterology, University Hospital of Santa Maria, Faculty of Medicine, Lisbon, Portugal

[7]Institute of Internal Medicine. Catholic University of Rome, Rome, Italy

[8] Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Verona and Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

Corresponding Author:

Amedeo Lonardo, M.D. Tel. +39(0)593961807; Fax +39(0)593961322; Postal Address: NOCSAE – Via Giardini 1355 Baggiovara, Modena 41126 Italy; E-mail address**:** a.lonardo@libero.it; a.lonardo@ausl.mo.it

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ABSTRACT

An improved understanding of nonalcoholic fatty liver disease epidemiology would lead to identifying those groups of individuals at high risk for developing chronic liver disease and extra-hepatic complications thus contributing to more effective case finding of nonalcoholic fatty liver disease among selected groups of individuals.

We aimed to illustrate the epidemiology of nonalcoholic fatty liver disease in high-risk groups, which were identified based on existing literature. To this end, PubMed was searched to retrieve original articles published through May 2015 using relevant and pertinent keywords “nonalcoholic fatty liver disease” and “diabetes”, “obesity”, “hyperlipidemia”, “familial heterozygous hypobelipoproteinemia”, “hypertension”, “metabolic syndrome”, “ethnicity”, “family history” or “genetic polymorphisms”.

We found that age, sex and ethnicity are major physiologic modifiers of the risk of nonalcoholic fatty liver disease, along with belonging to “nonalcoholic fatty liver disease families” and carrying risk alleles for selected genetic polymorphisms. Metabolic syndrome, diabetes, obesity, mixed hyperlipidaemia and hypocholesterolemia due to familial hypobetalipoproteinaemia are the major metabolic modifiers of nonalcoholic fatty liver disease risk. Compared to these metabolic conditions, however, arterial hypertension appears to carry a relatively more modest risk of nonalcoholic fatty liver disease.

A better understanding of the epidemiology of nonalcoholic fatty liver disease may result in a more liberal policy of case finding among high-risk groups.

Keywords: Dyslipidemia; Metabolic Syndrome; NAFLD; Obesity; Type 2 Diabetes mellitus

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the most common liver disease worldwide,[1]includes simple steatosis and non-alcoholic steatohepatitis (NASH) which associate with or precede the metabolic syndrome (MetS) and its individuals features.[2-6] NAFLD carries an increased risk of hepatic [*e.g.*, cirrhosis and hepatocellular carcinoma (HCC)] and extra-hepatic complications [*e.g.*, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), chronic kidney disease and cancer][7,8] and therefore tends to be associated with excess morbidity/mortality and health expenditure.[9-11]

Presently, the majority of hepatological scientific societies do not suggest a policy of case finding for NAFLD given that no specific drug treatment is available.[2,12] However, NAFLD care exceeds drug therapy and includes both diagnostic procedures and tailored follow-up schedules.[7,12] Clearly, the high prevalence of NAFLD worldwide[1] makes it illogical to propose any screening campaigns to identify cases of NAFLD in the general adult population. Therefore, we hypothesize that a better understanding of NAFLD epidemiology would improve characterization of those groups of individuals at high risk for developing chronic liver disease and extra-hepatic complications.

This clinical review aims to specifically illustrate the epidemiology of NAFLD in high-risk groups, which were identified according to literature data.[1,6,13,14] To this end, PubMed was searched for articles published between 1990 and May 2015 in peer-reviewed journals using pertinent keywords: “nonalcoholic fatty liver disease” or “fatty liver” AND “diabetes”, “obesity”, “dyslipidemia”, “hyperlipidemia”, “familial hypobelipoproteinemia”, “hypertension”, “metabolic syndrome”, “ethnicity”, “family history” or “genetic polymorphisms”.

Our findings identify both physiologic (*i.e.*, age, sex, ethnicity, families and genetics) and metabolic modifiers of NAFLD (*i.e.,*MetS and its individual features) which may change present clinical attitudes in the diagnosis and management of NAFLD.

2. AGE, SEX AND ETHNICITY

Age, sex and ethnicity modulate NAFLD risk in high-risk individuals and in the general population.[14,15]

NAFLD is more common in men, increases with age and shows sex-specific differences.[16-19] In men**,** NAFLD increases from younger to middle-ages and, describing an "inverted U shaped curve", starts declining after the age of 50-60 years.[16,19]Conversely, pre-menopausal women are relatively spared by NAFLD, but the prevalence of this condition rises after the age of 50, peaking at 60–69 years and declining after the 7th decade of life.[16,18,19] Accordingly, after the 5th decade, the prevalence of NAFLD is similar in both sexes or possibly lower in men.[16,20]

Most, though not all, studies have shown that advancing age and male sex affect the risk of NAFLD, independently of coexisting MetS features.[21-26] Other studies, although confirming that men are at higher risk of NAFLD, have shown an inverse association between NAFLD and age.[27-30] Conversely, in women, advancing age, menopausal status and MetS features are all independent predictors of NAFLD.[31,32] The lower prevalence of NAFLD which has been reported with advancing age in the elderly, [33] is potentially attributable to either selective mortality or development of cirrhosis (which generally loses steatosis). "Lean NAFLD" is associated with younger age, but findings regarding the role of sex are conflicting.[29,34]

Increasing age may also impact the risk of NASH and fibrosis, but data on sex are, again, inconsistent. Middle-aged and elderly individuals have a higher prevalence of fibrosing NASH.[35,36] Most studies,[20,32,37-39] except one,[40] have reported that NASH is histologically more severe in women than in men. However, a systematic review shows that only age and hepatic necro-inflammation are independent predictors for the development of advanced fibrosis in NASH patients, whilst MetS features and sex are not.[41] Finally, a recent study reports, men have a higher risk of more severe liver fibrosis compared to premenopausal women; however, post-menopausal women have a severity of liver fibrosis similar to men suggesting that estrogens may protect from fibrosis. [42]

Advancing age increases the risk of NAFLD hepatic and extra-hepatic complications,[43] it is, therefore, expected that older NAFLD patients will have a higher likelihood of overall and disease-specific mortality.[44-47] Whether sex affects NAFLD natural history and mortality is uncertain, although studies have suggested a worse outcome in men.[45,48,49]

The prevalence of NAFLD follows a gradient Hispanics >Whites-Caucasians >Afro-Americans[50-53] and ethnicity may modulate the association between NAFLD, sex and MetS features. For example, NAFLD is more common in men than in women among Whites, but not among Blacks or Hispanics.[50] Moreover, although they have the highest prevalence of obesity, a smaller percentage of obese/MetS Afro-Americans have NAFLD. In contrast, Hispanics have the highest prevalence of NAFLD, including the obese and MetS population.[53] Interestingly, among patients with NAFLD, African Americans have NASH less frequently than Hispanics.[54] Finally, the adverse effect of insulin resistance (IR) on NASH risk is worsened by non-Latino ethnicity.[38]

In summary **(Figure 1, panel A)**, age, sex and ethnicity produce complex and intertwined relationships among them and with MetS features which heavily affect the risk of NAFLD/NASH.

3. FAMILY STUDIES

Inheritable factors play a major role in the variety of presentations of NASH/NAFLD.[55] Family and twin studies have provided substantial support for this connection and the identification of high-risk genetic polymorphisms, such as patatin-like phospholipase domain-containing 3 (*PNPLA3*), may provide keys to uncovering a familial inheritance pattern. For example, familial patterns of NASH, frequently related to the recognition of cirrhosis in multiple generations, have been described. Differences in environmental exposure combined with genetic predisposition ("nature *plus* nurture") both likely contribute to the variance in phenotypic expression of NASH, although they can be difficult to separate due to the commonalities of both genetics and environment factors in families.

Several studies have established the presence of NASH and NAFLD of varying severity within kindreds. Struben *et al*. were first in reporting the clinical pattern of almost always histologically proven

NASH, usually associated with cirrhosis, within multiple generations of eight different kindreds.[56] Obesity and T2DM were common threads within the families and members of both sexes were affected. Analysis of 90 NASH patients allowed identification of nine kindreds with each index patient having at least one family member with NASH or cryptogenic cirrhosis.[57] Seven of the nine families had at least one affected member with cirrhosis, and several had experienced portal hypertension. Most patients showed bridging fibrosis or cirrhosis before age 60 years, with one cirrhotic patient as young as 14 years. Tokushige *et al.* detailed the clinical histories of three families with at least two members affected by NASH[58] and identified a different genetic polymorphism in each family.

Other family studies have focused on disorders commonly associated with NAFLD/NASH. A family study of 157 individuals with familial combined hyperlipidemia showed that both the presence of fatty liver and the levels of alanine aminotransferase (ALT) were increased both in index dyslipidemic patients and in normolipidemic family members.[59] A case-control family aggregation study of 20 NAFLD patients showed that IR occurs more commonly within families of NAFLD patients, with significantly higher risks of T2DM and IR and a strong trend for familial clustering of NAFLD or cryptogenic cirrhosis with maternal linkage.[60] Additionally, the degree of hepatic steatosis, as assessed by magnetic resonance imaging, has proven to occur significantly more frequently in family members of overweight and obese children with NAFLD.[61]

Twin studies have confirmed these findings, although most studies have used NAFLD surrogate markers [ALT and gamma-glutamyltransferase (GGT)] and not all studies have shown a strong connection. Serum ALT levels had strong heritability (up to 60%) in a Danish twin study and a Finnish study of both identical and fraternal twins.[62,63]Loomba *et al*. showed a strong genetic association between serum GGT levels, fatty liver/MetS features and beta-2-adrenergic receptor alleles in identical twins.[64] Other investigators confirmed these findings demonstrating co-aggregation of MetS features and NAFLD.[65] The support for this concept has not been universal, however, as even in the setting of increased CVD and MetS, a Hungarian twin study showed low heritability rates for NAFLD on ultrasonography.[66] Lastly, a recent monozygotic and dizygotic twin study of 40 twin-pairs demonstrated that heritable serum microRNA (miR)

levels, specifically miR-331-3p and miR-30c, may account for discordance of the presence or absence of NAFLD in twins.[67]

In summary, family studies indicate that there are some kindreds at high risk for NAFLD. However, the risk profiles (*e.g.,* sex distribution and MetS features) may be influenced by the possible effects of small numbers of cases and selection bias. It is conceivable that NAFLD in families is closely linked to genetic traits. However, there could be a strong environmental influence on lifestyles or epigenetic phenomena and, therefore, findings may be at variance with those from population-based and cohort-based studies. The existence of chronic liver disease or "cryptogenic" cirrhosis in the family history should heighten concern for an individual index patient.

4. MOLECULAR GENETICS

The natural history of NAFLD exhibits a great inter-individual variability and heritability may account for increased susceptibility to developing NASH. Hypothesis-driven candidate gene approaches have resulted in several genes being identified, which are potentially involved in NAFLD development and progression.

To understand the genetic variability that may explain the complex trait disease, the choice of candidate genes can be done with either a classic approach based on 'a priori hypothesis' or by the identification of a candidate gene on the basis of the product of the gene. This approach was overtaken by the genome wide association study (GWAS), which allows exploration of millions of single nucleotide polymorphism (SNP) thanks to the absence of the 'a priori hypothesis'. The GWAS approach allows one to explore the putative mechanisms and pathways of complex disease traits.

NAFLD and IR are closely associated and one large European study showed that genetic polymorphisms both in ectoenzyme nucleotide pyrophosphate phosphodiesterase-1 (*ENPP1-PC1*), *i.e.,* a candidate gene identified by GWAS associated with T2DM, and in insulin receptor substrate-1 (*IRS1*) were associated with hepatic fibrosis and IR in patients with biopsy-proven NAFLD.[55]

Using the GWAS approach, a SNP of the *PNPLA3* gene [rs738409 C>G encoding for isoleucine to methionine in position 148 (M148I)] was found to be significantly associated with intra-hepatic fat content and with more progressive NAFLD forms. Several variants have been explored for *PNPLA3*. The choice of the variant M148I (rs738409) was based on its being strongly associated with NAFLD histological severity independent of ethnicity, race, gender and age. The other genetic variants (rs738407 and rs2896019), were less predictive of progressive liver disease than the M148I variant. *PNPLA3* encodes for a lipase, which may regulate energy consumption/storage balance in the liver and adipose tissue.[68] The rs738409 polymorphism of this gene results in lipase hypo-activity and is invariably associated with increased hepatic steatosis, inflammation and fibrosis.[69-73] However, further studies are needed to better elucidate the physiologic function of PNPLA3 and its role in the pathogenesis of NAFLD.

The hepatic glucokinase regulatory protein(*GCKR*) gene encodes for a protein that modulates the activity of glucokinase, an enzyme implicated in hepatic glycogen synthesis and glycolysis. The rs780094 polymorphism of this gene is associated with an increased risk of NAFLD development and progression.[74,75]

Other genes have been identified by the GWAS approach. The neurocan (*NCAN*) gene encodes for a protein that is expressed mainly in the nervous system and seems to be involved in cell adhesion and migration. The rs2228603 polymorphism of this gene is associated with steatosis, lobular inflammation and fibrosis risk.[76,77]

Among the candidate genes identified by the 'a priori hypothesis', the pathways involved in the oxidative stress and immune response have been studied. For example, superoxide dismutase-2 enzyme (SOD2) has been extensively studied in NAFLD, owing to its anti-oxidant activity. A reduced SOD2 activity, by decreasing the liver's ability to detoxify mitochondrial superoxide anion, increases the susceptibility to oxidative stress, and NASH in obese children.[78]

The interleukin 28B(*IL28B*) gene stimulates the expression of multiple genes encoding pro-inflammatory cytokines. The rs12979860 polymorphism of IL28B gene is associated with the severity of lobular inflammation and fibrosis.[79]

With regards to the progression of hepatic fibrosis by a candidate gene approach, the Kruppel like factor-6 (KLF6) is a tumour suppressor gene that is ubiquitously expressed and promotes fibrogenesis via activation of hepatic stellate cells during inflammation, liver injury and oxidative stress. Variant 1 of the rs3750861 functional polymorphism (*KLF6-SV1*) of this gene is associated with more advanced stages of hepatic fibrosis and is an independent predictor of NASH.[80]

In the same region of NCAN the trans-membrane 6 superfamily member 2 (*TM6SF*) gene has been identified. *TM6SF* encodes for a trans-membrane protein, which seems to be involved in very-low density lipoprotein (VLDL) secretion; its malfunctioning predisposed to NAFLD in some studies. The rs58542926 (449 C>T, Glu167Lys)of this gene encodes for a hypo-functional protein, which has been associated to an increased NASH risk. [81]

The lipin-1 (*LPIN1*) gene encodes for the magnesium-dependent lipin, which is involved in triglyceride synthesis and is critical in regulating lipids flowing to the liver. The rs13412852 polymorphism of this gene is associated, in adults, with lower body mass index, and fasting insulin levels [82]and, in children, reduced triglycerides and NASH prevalence,[83] thus acting as a possible protective factor in both age groups.

Finally, familial hypobetalipoproteinemia, although a genetic form of NAFLD, will be discussed in the chapter 8, given that it, at variance with the others, can be suspected on clinical grounds.

In summary, although several genes modulate the risk of developing NAFLD/NASH, presently a genetic profiling is not widely available outside tertiary referral centres and no clear evidence supports its routine use in clinical practice. However, the possibility to further identify high-risk groups through a genetic fingerprint with specific genes (*e.g*., PNPLA3 and TM6SF2 gene variants) may soon add to clinical phenotyping NAFLD patients in the near future.

5. METABOLIC SYNDROME

Although the definition of the MetS remains controversial, increased arterial pressure is definitely one of its five established features together with IR, atherogenic dyslipidemia, and dysglycemia.[84] Since

Reaven's description,[85] the definition of MetS has evolved to place the major focus on visceral obesity with the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel guidelines in 2001.[86] The NCEP guidelines were refined in 2005, and in 2009 the essential pre-requisite of visceral obesity was removed from the definition.[84]

Regardless of how best to define the MetS, the field has moved on again since 2009 and it is now clear that NAFLD is not simply the "hepatic manifestation" but also a pathogenic determinant of the MetS.[8,87,88] NAFLD well illustrates the notion that ectopic fat deposition in a key visceral organ is not harmless and has the potential to trigger progressive hepatic and extra-hepatic diseases.[89,90]Indeed, NAFLD is strongly associated with the MetS which, in its turn, carries a higher risk of progressive NASH.[2,4-6,10-15,87,88] Moreover, as discussed below, visceral overweight/obesity, glucose intolerance/T2DM and hypertriglyceridemia are the individual MetS features that are more strongly associated with NAFLD development and progression.[2,4-6,10-15,87,88]

Although a strong and bidirectional association links NAFLD and T2DM as a key component feature of the MetS, to date there is less evidence for an association between NAFLD and hypertension. That said, hypertension has recently been shown to be a significant risk factor for the development of hepatic fibrosis in a meta-analysis of patients with simple steatosis or NASH at baseline[91]and, conversely, NAFLD may also be an independent risk factor for the development of hypertension. A recent retrospective cohort study conducted in 11,448 South Korean people without hypertension at baseline elegantly supports the notion that development of new or resolution of pre-existing fatty liver over 5 years strongly affects the risk of incident hypertension[92]. Another large prospective cohort study has shown that the risk of developing hypertension increased substantially in those with NAFLD and the risk, although attenuated, remained significant after adjustment for covariates[93]. Supporting a dose-response relationship, the investigators reported that hypertension was particularly common in those who had moderate-to-severe NAFLD at baseline.[93]

So closely are increased serum uric acid (SUA) levels associated with other features of the MetS [94-98] that they can be considered an additional feature of the MetS. There is a graded, positive association between SUA levels and NAFLD severity and elevated SUA levels predict NAFLD risk independently of coexisting MetS features in different ethnicities.[99-108] Accordingly, a large study found that increased SUA levels were associated with cirrhosis and elevated serum liver enzymes, independent of potential confounders, in 5,518 participants during a mean follow-up of 12.9 years.[96] Further studies are needed to ascertain whether reducing SUA levels would prevent NAFLD/NASH development and progression.

6. TYPE 2 DIABETES MELLITUS

Hepatic fat content is closely correlated with the number of the MetS features and serum aminotransferases levels.[109] However, T2DM patients have a hepatic fat content that is ~80% greater and their serum liver enzymes levels are less representative of the severity of hepatic steatosis than age-, sex- and body weight-matched non-diabetic controls.[110] Moreover NAFLD *per se* may hamper glycemic control in T2DM[4,89]. Indeed, hepatic fat content is the strongest determinant of the daily insulin dose needed to achieve good glycemic control in insulin-treated T2DM patients.[111]

Based on these findings, it is not surprising that the prevalence of NAFLD is remarkably increased in T2DM. As summarized in **Supplemental Table 1**, the prevalence of NAFLD in patients with T2DM ranges widely (from 45% to 75%) in large hospital-based studies and (from 30% to 70%) population-based studies reflecting demographic differences and diagnostic criteria. Most T2DM patients with NAFLD have normal serum liver enzymes, which is not reassuring given that NASH, advanced fibrosis and even cirrhosis may be found in such "normal" liver enzymes individuals.[4,89,112]Accordingly, NAFLD prevalence is much higher (76%) than previously believed in overweight/obese T2DM patients with normal serum aminotransferases, and that 56% of these patients had histologically-proven NASH.[113] Collectively, these studies imply that the "normal" range of serum liver enzymes needs to be lowered to capture more NAFLD cases.

T2DM patients are at a very high-risk of NASH, and a two-fold to four-fold increase in risk of developing liver-related complications.[4,92,114] These findings, together with the notion that they have an

increased mortality risk from cirrhosis of any aetiology[115-117] fully support screening for NAFLD and/or advanced fibrosis in T2DM patients. For example, Zoppini *et al*. recently reported that, compared to the age and sex-matched general population, T2DM patients had an approximately three-fold higher risk of dying of non-viral and non-alcoholic chronic liver disease, thus largely attributable to NAFLD.[118] In agreement, a study of 337 T2DM patients reported that NAFLD carried a two-fold increased risk of all-cause mortality (malignancy, CVD and liver-related complications) during a mean 11-year follow-up.[119]

Growing evidence suggests that NAFLD is associated not only with liver-related morbidity or mortality, but also with an increased risk of developing CVD, *i.e*., the most common cause of death in T2DM.[8,120,121]Emerging evidence also suggests that NAFLD is associated with increased risk of microvascular diabetic complications (*i.e*., chronic kidney disease and advanced diabetic retinopathy) in people with T2DM.[122-124] Overall, we believe that the strong link between T2DM and NAFLD supports more careful monitoring and evaluation of NAFLD among patients with T2DM.

7. VISCERAL OBESITY

Obesity is a major risk factor for NAFLD. The growing epidemic of obesity parallels the rising prevalence of NAFLD and its adverse outcomes. The prevalence of obesity almost doubled in the last 30 years worldwide. In 2008, 1.4 billion adults were overweight and half a billion obese, 35% and 11% of the population, respectively.[125] In the United States, two thirds of the population are overweight and one third obese, whereas in Europe up to one fourth is obese.[126,127] More recently, although the prevalence of obesity is stabilizing,[128] the average body weight of the population and severe obesity continue to increase.[128]

The majority of NAFLD patients are overweight or obese.[129] Roughly, NAFLD is two-fold more prevalent in overweight and four-fold in obese individuals.[130-132]Most patients with severe obesity have fatty liver and more than one third have NASH.[133] Weight gain is a strong predictor for the development of NAFLD and obesity associates with increased risk of NASH, fibrosis and HCC.[134-137] However, a recent meta-analysis of paired biopsies failed to show obesity as a risk factor for fibrosis progression.[91]

Type of fat and its distribution are more important than fat amount. Visceral obesity, as opposed to subcutaneous obesity, is metabolically more active and associated with IR, increased lipolysis and overflow of free fatty acids to the liver.[138] Moreover, visceral adipose tissue is a powerful endocrine organ which, when dysregulated, may release multiple pro-inflammatory and pro-fibrogenic mediators (*e.g*., tumor necrosis factor and leptin), and decreases expression of beneficial adipocytokines (*e.g*., adiponectin).[139] Indeed, visceral adipose tissue positively associates, whereas subcutaneous adipose tissue inversely associates with hepatic fat content,[140] suggesting that the subcutaneous compartment may function as a protective reservoir of inert and metabolically silent fat. Visceral adipose tissue is also an independent risk factor for hepatic necro-inflammation and fibrosis.[141] Ethnicity modulates obesity as a risk factor for NAFLD. For example, Asian populations tend to have more visceral adipose tissue, being more prone to having NAFLD with lower body mass index.[142]

NAFLD may be envisaged as a result of a systemic *"adiposopathy"* promoting multi-organ ectopic fat deposition, which occurs in the liver and in extra-hepatic organs. For example, epicardial fat thickness is associated with NAFLD and hepatic fibrosis severity, independent of visceral adiposity.[143-146] The same is true for dorso-cervical fat.[147] The association of NAFLD with other forms of ectopic fat deposition may not only translate into more serious *"adiposopathy",* but also contribute to the pathogenesis of liver disease. For example, epicardial fat associates with autonomic nervous system dysfunction, which may further promote NAFLD progression.[148]

Conversely, up to a quarter of patients with NAFLD are lean and not all patients with obesity have NAFLD.[149] Up to one quarter of obese individuals do not have MetS features[150] and are dubbed metabolically healthy obese, though it is still unclear if those individuals are also protected from CVD.[151] In fact, though the prevalence of NAFLD is lower in metabolically healthy obese patients than in dysmetabolic obese patients, it is still double than in lean healthy subjects.[92] On the opposite end of the spectrum, there are normal weight subjects who are, nevertheless, metabolically unhealthy (MONW – metabolically obese normal weight). MONW individuals, who sum up ~5% of Western populations and are even more common in Asian populations,[152,153]usually have a history of enlarged fat mass during adulthood and tend to be

sedentary, insulin resistant and at increased cardiovascular risk.[154,155] In these individuals, NAFLD is less common than in obese individuals with similar metabolic disturbances and as common as in those with metabolically healthy obesity.[92] Metabolic disturbances and fat overload/obesity may then be independent risk factors for NAFLD and CVD, acting synergistically.

8. HYPERLIPIDEMIA AND HYPOLIPIDEMIA

Recent studies on the association of hyperlipidemia, hypolipidemia and NAFLD are summarized in **Supplemental Table 2**.

Other conditions, which may mimic NAFLD, require a different and specific treatment. For instance, the common NASH phenotype exhibiting progressive liver damage, atherogenic dyslipidemia and premature atherosclerosis is virtually indistinguishable from that of late onset lysosomal acid lipase (LAL) deficiency, *i.e.,* a cholesteryl ester storage disease.[156,157] This uncommon disease occurs due to mutations of the LIPA gene encoding LAL enzyme which results in deficiency of LAL leading to accumulation of cholesterol esters and triglycerides in the lysosomes of liver cells.[156,157] At variance with NAFLD, which features increased intra-hepatic triglyceride content, LAL deficiency will lead to intrahepatic increases in both cholesteryl ester and triglyceride content.[156] Proton magnetic resonance spectroscopy may identify and quantify abnormal lipid content in these patients' livers so allowing the non-invasive monitoring of the effectiveness of enzyme replacement on steatosis.[156] Definite diagnosis of this lysosomal storage disease, which requires demonstration of a significantly deficient LAL activity followed by molecular sequencing of the LIPA gene,[157] has major clinical consequences given that enzyme replacement therapy with sebelipase alfa is safe and effective.[158,159]

Based on studies showing that hypertriglyceridemia is the most common feature and is an independent predictor of NAFLD,[160-164] we recommend that hypertriglyceridemic should invariably undergo liver ultrasonagraphy. In particular, mixed hyperlipidemia associated with raised ALT accurately predicts NAFLD.[50] NAFLD-associated mixed hyperlipidemia is a primary (often familial) hyperlipidemia. Alternatively, both hyperlipidemia (particularly hypertriglyceridemia) and NAFLD may result from underlying IR and

sedentary lifestyles,[164,165]and hypertriglyceridemia may worsen the natural course of NAFLD as elevated triglyceride levels are a significant predictor of incident cirrhosis.[166]

Studies have pinpointed the association between NASH and increased non-HDL cholesterol levels. [167,168] This finding may be of potential significance in differentiating simple steatosis from NASH[167]and suggests that most hyperlipidemic patients with increased non-HDL cholesterol levels are potential candidates to liver biopsy, given that they are more likely to develop NASH. Hepatic biosynthetic failure occurring in those developing cirrhosis will blunt the severity of the initial dyslipidemia [169-171] mirroring the disappearance of hepatic steatosis associated with the development of NASH-cirrhosis.[141]

Low high-density lipoprotein (HDL)-cholesterol concentrations are an established risk factor for CVD, whereas hypertriglyceridemia appears to be a more important marker of the MetS and physical inactivity.[165,172]Although an innovative view suggests that the hepatic histological changes, rather that plasma lipid phenotypes, are associated with an increased CVD risk,[171] the independent contribution of NAFLD to CVD risk prediction needs further evaluation.[173]

An otherwise unexplained hypolipidemia being associated with non-cirrhotic NAFLD may be a clue to the diagnosis of familial hypobetalipoproteinemia.[174]At variance with primary NAFLD and similar to other forms of hepatic steatosis due to genetic polymorphisms, familial hypobetalipoproteinemia is usually dissociated from systemic IR.[173] Given that the risk for these individuals to develop a progressive form of NAFLD remains still controversial,[175,176]it seems reasonable to submit them to liver biopsy at baseline and to non-invasive surveillance of liver fibrosis development with ultrasonography-based transient elastography.

Figure 1 (panel B) summarizes the chief findings on metabolic modifiers of NAFLD risk.

9. WILL TREATMENT OF METABOLIC MODIFIERS RESULT IN IMPROVEMENT/REVERSAL OF NAFLD?

Metabolic modifiers offer a clue to NAFLD case-finding. Moreover, the close inter-relationship between NAFLD and the MetS,[6] predicts that treatment of the individual MetS features will improve

NAFLD histology. Here we discuss to what extent this prediction is evidence-based. Systematic analysis of NAFLD treatment is further explored elsewhere.[2,4,5,12,15]

Presently, no treatment is specifically licensed for NAFLD and lifestyle interventions (weight loss and treatment of individual MetS features, possibly with interventions carrying beneficial liver effects) are the mainstay of NAFLD management. Weight loss obtained through low-calorie diet associated with physical exercise undoubtedly is the chief goal in NAFLD overweight or obese patients. Indeed, losing ~5% of body weight will decrease hepatic steatosis; however as much as ~10% weight loss is required to improve hepatic necro-inflammation and fibrosis.[134,177-179]Meta-analytical evidence has also shown that regular moderate exercise decreases steatosis.[180] However, NAFLD patients prefer diet to exercise.[181] Although weight reduction obtained through diet is generally of short duration, its beneficial metabolic effects may last for up to 2 years despite weight regain.[182] Finally, effective bariatric surgery will markedly improve/reverse all histologic features of NAFLD, notably including fibrosis, in severely obese patients.[183]

Most pharmacological options for NAFLD are commonly used for treating T2DM and indirectly improve NAFLD ameliorating IR and dysglycemia. Paradoxically, however, many therapeutic trials have excluded patients with T2DM, a surprising fact considering that NAFLD/NASH disproportionally affects these patients.

Metformin, the first-line oral antidiabetic agent, decreases aminotransferases and hepatic IR, without improving NAFLD histology.[89,184-186] and decreases HCC risk.[173] Pioglitazone is the most effective drug in patients with histologically proven NASH in the short-term.[89,187]However, the long-term cardiovascular and non-cardiovascular adverse effects of pioglitazione are a serious concern. Preliminary evidence also suggests some benefit of glucagon-like peptide-1 agonists (*e.g.*, exenatide and liraglutide) in ameliorating hepatic steatosis, although it is uncertain whether this benefit results from concurrent weight loss.[188]

Renin-angiotensin-aldosterone system inhibitors should be the first-line choice in the treatment of hypertensive patients with NAFLD given the potential anti-fibrogenic effect of these drugs in experimental

and human studies.[189]In particular, losartan improves various surrogate indices of NASH in humans,[190,191]whereas telmisartan may improve hepatic inflammation and fibrosis.[192]Finally, a cross-sectional study showing that renin-angiotensin-aldosterone system inhibitors use was associated with less advanced hepatic fibrosis,[189] suggests that the renin-angiotensin-aldosterone system is involved in NAFLD pathogenesis.

Treatment of hyperlipidemia likely decreases the NAFLD-related CVD risk. However it is uncertain if it may also improve the course of liver disease, given that hyperlipidemia typically interacts with other physiologic and metabolic modifiers of NAFLD risk. For example, resolution of NASH with either pioglitazone or vitamin E treatment is associated with improvements in serum triglyceride and HDL-cholesterol levels, but not in LDL-cholesterol and non-HDL-cholesterol levels.[168]

Treatment with high dose triglyceride-lowering omega-3 fatty acids significantly decreases steatosis without any improvement of liver fibrosis in NAFLD.[193,194] or has no effects on NASH istology.[195] Statins in primary CVD prevention markedly reduce all-cause mortality and CVD events.[196]Moreover, conflicting with a previous study, [197] recent research suggests that statins reduces the risk of NAFLD progression,[91] Emerging data suggest that statin use is associated with a reduced HCC risk, adding to the evidence that statins may beneficially affect the hepatic and extra-hepatic NAFLD natural course .[173] Ezetimibe, a lipid-lowering agent which reduces the intestinal uptake of cholesterol may improve NAFLD histology based on preliminary data.[198,199] Finally, the farnesoid X receptor agonist obeticholic acid (which regulates glucose and lipid metabolism) has recently been associated with improved liver histology in non-cirrhotic NASH patients, although its safety and long-term benefits need further clarification.[200]

Preliminary evidence also suggests some benefit of vitamin E in non-diabetic adults; however, data are insufficient to advocate its use in patients with non-cirrhotic NAFLD. Future studies should focus on innovative drugs or the combination of available drugs with better efficacy and safety.

10. CONCLUSIONS

We have identified groups of individuals in whom compared to the general adult population, so high is the risk of developing NAFLD and its hepatic and extra-hepatic complications as to support a more active policy in identifying NAFLD cases. Moreover, we have found that tailored interventions promise to improve the natural history of disease in at least a subset of such individuals.

In agreement with previous reports[201]and based on the findings discussed above (**Table 1**), screening and surveillance strategies in all individuals with either the MetS or its individual features may be proposed. NAFLD families and, in the future, individuals with specific genetic polymorphisms (*e.g.*, *PNPLA3* genotype) should also be cohorts in which case finding and surveillance of NAFLD should be liberally conducted. Metabolic and genetic factors tend to cluster and the more the features of the MetS in the same individual, the more stringent the need for hepatological evaluation based on additive risk of progressive NAFLD forms.

CONFLICTS OF INTEREST: nothing to declare.

FIGURE LEGEND

FIGURE 1 - Prevalence of non-alcoholic fatty liver disease in various high-risk groups compared to the general adult population. **Panel A)** Chief physiological modifiers (age, sex and ethnicity)

Data, which are extrapolated from papers quoted in the individual pertinent sections of the present review as well as in Supplementary Tables 1 and 2, illustrate the effect of gender (NAFLD is more common in men than in women), age (”inverted U pattern”) and ethnicity (gradient Hispanics >Whites-Caucasians >Afro-Americans) on NAFLD prevalence.

Abbreviations: AA= Afro-Americans; F= Female; H = Hispanics; M= Male; W= Whites-Caucasians

***Color Codes*:**

Gender: Pink = Women; Grey = Men; Age = Pink < 40 years; Light Pink 40-60 years; Green = 60-85 years; Violet = > 85 years; Ethnicity: Yellow = AA; Grey = Whites; Red = H.

FIGURE 1 - Prevalence of non-alcoholic fatty liver disease in various high-risk groups compared to the general adult population. **Panel B)** Effect of the metabolic syndrome and its individual features.

Data, which are extrapolated from papers quoted in the individual pertinent sections of the present review as well as in Supplementary Tables 1 and 2, demonstrate that type 2 diabetes seems to abrogate the sex differences in the susceptibility to NAFLD. Indeed, type 2 diabetic patients are equally affected by NAFLD irrespective of sex, which is at variance with what occurs in the general population (Figure 1 Panel A) wherein men tend to be more often affected than women.

Moreover, the metabolic syndrome seemingly adds little to the risk of developing NAFLD conveyed by most of its individual features, except for hypertension.

Among the various features of the metabolic syndrome there is a gradient of risk in the association with NAFLD: obesity > mixed dyslipidemia with raised serum alanine aminotransferase (ALT) levels >type 2 diabetes mellitus> hypertension.

Abbreviations: F= Female; M= Male; T2DM = Type 2 Diabetes; MetS = Metabolic Syndrome

***Color Codes*:**

- Dyslipidemia: Blue = Hypercholesterolemia; Yellow = Hypertriglyceridemia; Green = Mixed Hyperlipidemia; Orange = Mixed hyperlipidemia with raised serum ALT levels.
- T2DM: Red = Women; Blue = Men

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SUPPLEMENTARY TABLE S1 - Principal cross-sectional hospital and population-based studies of the prevalence of NAFLD (as diagnosed by imaging techniques or biopsy) in patients with type 2 diabetes mellitus, ordered by publication year.

Authors, year (ref.)	Study Design & Study Population	Diagnosis of NAFLD	Main Findings
Hospital-based study			
Targher G et al. 2007 [1]	Cross-sectional sample of 2,839 Italian type 2 diabetic outpatients (the Valpolicella Heart Diabetes Study). Mean age 63 years, mean BMI 27 kg/m^2	Ultrasonography	Prevalence of NAFLD was 69.5% and NAFLD was the most common cause (81%) of hepatic steatosis
Leite NC et al. 2009 [2]	Cross-sectional sample of 180 consecutive Brazilian type 2 diabetic outpatients without secondary causes of CLD. Mean age 55 years, mean BMI 30 kg/m^2	Ultrasonography	Prevalence of NAFLD was 69.4%
Leite NC et al. 2011 [3]	Cross-sectional sample of 96 Brazilian type 2 diabetic outpatients with ultrasonographic hepatic steatosis and raised serum liver enzymes (without known causes of CLD). Mean age 51 years, mean BMI 31 kg/m^2	Biopsy	NAFLD was histologically confirmed in 94% of these patients; NASH was present in 76% of cases
Williamson RM et al. 2011 [4]	Cross-sectional sample of 939 UK type 2 diabetic individuals (the Edimburgh T2D Study). Mean age 69 years, mean BMI 31 kg/m^2	Ultrasonography	Prevalence of NAFLD was 42.6% and NAFLD was the most common cause (76%) of hepatic steatosis
Lv WS et al. 2013 [5]	Cross-sectional sample of 1,217 Chinese type 2 diabetic inpatients. Mean age 59 years, mean BMI 32.8 kg/m^2	Ultrasonography	Prevalence of NAFLD was 61% among these hospitalized patients
Targher G et al. 2013 [6]	Cross-sectional sample of 702 Italian type 2 diabetic inpatients without known CLDs. Mean age 66 years, mean BMI 31 kg/m^2	Ultrasonography	Prevalence of NAFLD was 73% among these hospitalized patients
Kim SK et al. 2014 [7]	Cross-sectional sample of 4,437 Korean type 2 diabetic outpatients without cirrhosis. Mean age 57 years, mean BMI 24 kg/m^2	Ultrasonography	Prevalence of NAFLD was 72.7%
Portillo Sanchez P et al. 2014 [8]	Cross-sectional sample of 103 US overweight/obese type 2 patients with normal serum aminotransferases and without known liver diseases. Mean age 60 years, mean BMI 33 kg/m^2	Magnetic resonance spectroscopy and biopsy	Prevalence of NAFLD was 76% and NASH was present in 56% of cases

Kwok R et al. 2015 [9]	Cross-sectional sample of 1,918 Chinese type 2 outpatients without known liver diseases	Controlled attenuation parameter (CAP) and liver stiffness measurements (LSM) by FibroScan; biopsy in a subgroup	The prevalence of NAFLD and the proportion of patients with increased LSM were 72.8% and 17.7%, respectively. Ninety-four patients (80% had increased LSM) underwent liver biopsy: 56% had NASH and 50% had advanced fibrosis
Population-based study			
Browning JD et al. 2004 [10]	Cross-sectional multi-ethnic cohort of 2,287 US adult participants from the Dallas Heart Study. Mean age 45 years, mean BMI 30 kg/m^2 (whole cohort)	Magnetic resonance spectroscopy	Prevalence of NAFLD was 31% in the whole cohort, whereas prevalence of NAFLD was 42% in those with T2DM and/or impaired fasting glycaemia (combined population)
Volzke H et al. 2005 [11]	Cross-sectional cohort of 4,222 German adult participants from the Study of Health in Pomerania without chronic viral hepatitis or cirrhosis. Mean age 52 years, mean BMI 27 kg/m^2 (whole cohort)	Ultrasonography	Prevalence of NAFLD was 29.9% in the whole cohort, whereas the prevalence of NAFLD was 64% in those with T2DM (n=374)
Jimba S et al. 2005 [12]	Cross-sectional cohort of 1,950 healthy middle-aged Japanese subjects (health check-up examination). Mean age 49 years, mean BMI 24 kg/m^2 (whole cohort)	Ultrasonography	Prevalence of NAFLD was 62% in patients with newly-diagnosed T2D (n=45), 43% in those with impaired fasting glycaemia (n=107) and 27% in those with normal fasting glucose levels (n=1675)
Mohan V et al. 2009 [13]	Cross-sectional cohort of 541 Indian adult subjects with different degrees of glucose tolerance (Chennai Urban Rural Epidemiology Study). Mean age 51 years, mean BMI 25 kg/m^2 (diabetics)	Ultrasonography	Prevalence of NAFLD was 54.5% in patients with T2D (n=132), 33% in those with pre-diabetes (impaired fasting glycaemia or impaired glucose tolerance; n=80) and 22.5% in those with normal glucose tolerance (n=329)
Speliotes EK et al. 2010 [14]	Cross-sectional cohort of 2,589 white participants from the Framingham Heart Study. Mean age 51 years, mean BMI 27.6 kg/m^2 (whole cohort)	Multidetector computed tomography (using a liver phantom ratio >0.33)	Prevalence of NAFLD was 17% in the whole cohort, whereas the prevalence of NAFLD was 37% in those with established T2D (n=173)
Williams CD et al. 2011 [15]	Cross-sectional multi-ethnic cohort of 328 US adults without known liver diseases (Brooke Army Medical Center). Mean age 59 years, mean BMI 33 kg/m^2 (diabetics)	Ultrasonography and biopsy	Prevalence of NAFLD was 46% in the whole cohort. Prevalence of ultrasonographic NAFLD was 74%, whereas that of NASH was 22% in those with T2D (n=54)

Lazo M et al. 2013 [16]	Cross-sectional multi-ethnic cohort of 12,454 US adult participants from the Third National Health and Nutrition Examination Survey 1988–1994. Mean age 43 years, 80% had a BMI <30 kg/m^2 (whole cohort)	Ultrasonography (included only moderate or severe hepatic steatosis)	Prevalence of NAFLD was 19% in the whole cohort; the age-, sex- and race-adjusted prevalence ratio of NAFLD was 2.5 times higher in those with established diabetes than in those without diabetes (i.e. estimated prevalence of approximately 40%)
Zeb I et al. 2013 [17]	Cross-sectional multi-ethnic cohort of 4,140 US participants from the Multi-Ethnic Study of Atherosclerosis. Mean age 65 years, mean BMI 30.9 kg/m^2 (diabetics)	Computed tomography (using liver-to-spleen ratio <1 or liver attenuation)	Prevalence of NAFLD was 19% in the whole cohort, whereas the prevalence of NAFLD was 29% in those with T2D (n=554)

Abbreviations used (Table S-1)
BMI = Body Mass Index
CAP = Controlled attenuation parameter ()
NAFLD = Nonalcoholic Gatty Liver Disease
CLD = Chronic Liver Disease
LSM = liver stiffness measurement
T2DM = Type 2 Diabetes Mellitus

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SUPPLEMENTARY TABLE S2 – Principal observational studies that have assessed the association between hyperlipidemia/hypolipidemia and NAFLD, ordered by publication year.

Authors, year (ref.)	Study Design & Study Population	Findings	Comments
Hyperlipidaemia and NAFLD			
Fallo F et al. 2009 [1]	Cross-sectional study of 86 nonobese, nondiabetic patients with essential hypertension (48 with and 38 without NAFLD at ultrasonography)	Serum triglycerides were associated with NAFLD at univariate analysis, but this association disappeared after adjusting for HOMA-IR	These findings are compatible with the hypothesis that the association between NAFLD and hypertriglyceridemia is largely mediated by IR
Magosso E et al. 2010 [2]	Cross-sectional study of 180 untreated hypercholesterolemic volunteers. NAFLD was diagnosed by ultrasonography	NAFLD was diagnosed in 102 subjects (56.7%). Of these subjects, 80.4% were graded as mild, 16.7% as moderate and 2.9% as severe FL cases	NAFLD is fairly common in hypercholesterolemic volunteers
Riggio S et al. 2010 [3]	Cross-sectional study of 60 subjects with familial combined hyperlipidemia stratified by severity of NAFLD (by using ultrasonography and FibroScan)	NAFLD and liver stiffness were independently associated with HOMA-IR	In familial combined hyperlipidemia the development and progression of NAFLD are mainly dictated by IR
He S et al. 2011 [4]	3,850 subjects randomly selected out of a cohort of 6063 Chinese adults. NAFLD was diagnosed by ultrasonography	MetS-related hyperlipidemia was among the conditions significantly associated with NAFLD	It is unclear from this study whether NAFLD is associated with hyperlipidemia independently of MetS
Schult A et al. 2011 [5]	Prospective cohort of 855 Swedish adult men with a 40-year follow-up period. Incident cases of cirrhosis were identified by searching National Hospital Discharge and death certificates databases	Overweight and hypertriglyceridemia were independently associated with the risk of incident cirrhosis	Hypertriglyceridemia is a risk factor for the development of cirrhosis independently of BMI. This finding is compatible with both NAFLD and alcoholic FL disease
Zhang H et al. 2011 [6]	Population-based study of 3,791 Chinese adults. NAFLD was diagnosed by ultrasonography	Abnormal aminotransferases in patients with MetS and NAFLD were associated with increased triglycerides	A previous study reported that individuals with hypertriglyceridemia and elevated serum liver enzymes had a 83% chance of having steatosis at MR spectroscopy
Hou XH et al. 2011 [7]	Population-based study of 2,226 Chinese adults. NAFLD was diagnosed by ultrasonography	Higher ALT levels in NAFLD cases were associated with hypertriglyceridemia and hyperglycemia	See comment above

Cotrim HP et al. 2011 [8]	Cross-sectional sample of 1,280 patients with NAFLD from 16 Brazilian centers. Liver biopsy (performed in 437 cases) showed simple steatosis in 42%, NASH in 58%. Cirrhosis was observed in 15.4% and HCC in 0.7% of cases	Hyperlipidaemia was observed in 66.8% of cases, obesity in 44.7%, diabetes in 22.7%, and toxin exposure in 10%. MetS was found in 41.3% of cases	In this nation-wide study hyperlipidaemia appears to be the most common concurrent condition in NAFLD patients
Liao XH et al. 2013 [9]	Cross-sectional study of 430 out of 3433 patients retrospectively enrolled who had both NAFLD and complete information. NAFLD was diagnosed by ultrasonography	Among the 430 patients with NAFLD 30% had hypertriglyceridemia, 21% had mixed hyperlipidemia and 12% had hypercholesterolemia	This study confirms hypertriglyceridemia to be the most common type of hyperlipidemia in NAFLD
Männistö VT et al. 2014[10]	Cross-sectional study involving 76 out of 116 obese individuals with detailed liver histology. 32 had normal liver, 9 had simple steatosis and 25 had NASH	Simple steatosis was not associated with serum lipids. NASH was associated with VLDL and LDL cholesterol concentrations independently of hepatic steatosis and serum triglycerides. The VLDL and LDL lipid abnormalities that were associated with NASH decreased significantly after bariatric surgery	There is a strong link between VLDL and LDL cholesterol levels and NASH. This study agrees with previous findings that non-HDL cholesterol (VLDL+LDL) is a biomarker for NASH
Siddiqui S et al. 2014 [11]	Case-control study of 82 patients with biopsy-proven NAFLD and 162 age and sex–matched non-steatotic controls (81 obese and 81 lean)	Plasma lipoprotein abnormalities tend to resolve with progression of NASH to cirrhosis, supposedly as a result of increased hepatic IR and impending synthetic failure of the liver	It has long been known that cirrhosis is associated with hypolidemia
Corey KE et al. 2014 [12]	Post-hoc analysis of 222 NASH patients from the PIVENS trial (treated with either vitamin E or pioglitazone) with paired liver biopsies and fasting lipid levels	Pre-treatment, dyslipidemia was common in NASH: increased non-HDL-cholesterol in 73%; low HDL-cholesterol in 63%, hypertriglyceridemia in 46%; increased LDL-cholesterol in 16%. Post-treatment (irrespective of the drug used), HDL-cholesterol increased, triglycerides and TG/HDL-Cholesterol ratio decreased following NASH resolution. Non-HDL-cholesterol, and LDL-cholesterol did not change significantly as a result of NASH resolution.	This is an important proof-of concept study showing that hypertriglyceridemia and low HDL-cholesterol levels are specifically associated with NASH, given that they improve after NASH resolution. The finding that non-HDL cholesterol levels do not decrease after NASH resolution is the basis for the statin use in NASH
Hypolipidaemia and NAFLD			

Cefalù AB et al. 2013 [13]	This is a study of a single family with FHBL due to a non-sense variant, K2240X, attributable to an A>T mutation in of APOB (c.6718A>T) was identified. Genotypic 16 family members showed this mutation (rather than PNPLA3 I148M genotype) to co-segregate with hypocholesterolemia trait	The proband, a 25-year-old lady, had hypocholesterolemia associated with NAFLD. The same association was found in 10 additional family members (1 member had cirrhosis, and 4 more subjects died of primary liver cancer)	This study confirms that FHBL features the association of hypocholesterolemia and FL and that cirrhosis and primary liver cancers are part of the FHBL disease spectrum
Di Filippo M et al. 2014 [14]	This study includes a report of novel cases and a review of previously published ones. Genetic, clinical, histological and biological characteristics of 7 ABL and 7 Ho-FHBL new cases are compared to all published ABL and Ho-FHBL probands	Carriers of APOB mutations were more likely to be obese. Despite subtle differences in serum lipids, fatty liver, which was often associated with advanced fibrosis, was frequently observed in Ho-FHBL and ABL. Liver histologic changes observed in Ho-FHBL were independent of the size and concentrations of truncated apoB	This report challenges two common beliefs that the shorter the apoB truncated molecule the more severe the liver damage, and that FHBL is a non-progressive form of NAFLD

Abbreviations used (Table S-2)
ABL = Abetalipoproteinemia
APOB =Apolipoprotein B
BMI = Body Mass Index
FHBL =Familial hypobetalipoproteinemia
FL = Fatty Liver
HDL = High Density Lipoprotein
HCC = Hepatocellular Carcinoma
Ho =Homozygous
IR = Insulin Resistance
LDL = Low Density Lipoproteins
MetS = Metabolic Syndrome
NAFLD = Nonalcoholic Fatty Liver Disease
NASH = Nonalcoholic Steatohepatitis
TG = Triglycerides

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TABLE 1 - High-risk group patients for NAFLD or NASH at a glance.

Groups At Risk	Development of NAFLD	Progression of NAFLD	Will treatment of this condition benefit NAFLD histologically?
Age	Strong risk factor	Strong risk factor	Not evaluable
Sex	Strong risk factor	Uncertain	Not evaluable
Ethnicity	Strong risk factor	Strong risk factor	Not evaluable
Family history	Appears to impact risk	Probably influences progression whether by 'nature' or 'nurture'	Likely will influence the acceptable risk-benefit ratio in deciding more or less aggressive therapy
Genetics	Appears to impact risk	Appears to impact risk	Not evaluable
Hypertension	Uncertain	Probably influences progression	Renin-angiotensin system inhibitors may exert anti-fibrogenic activity and reduce the risk of developing cardiovascular events and chronic kidney disease
Metabolic syndrome	Strong risk factor	Strong risk factor	See its individual features
T2D	Strong risk factor	Strong risk factor	Diet and moderate physical activity are the cornerstone of treatment. Pioglitazone may improve histological features of NASH in the short-term. Metformin is associated with reduced risk of HCC. Promising data are observed with glucagon-like peptide-1 antagonists
Obesity	Strong risk factor	Strong cofactor	Weight loss >10% associated with improved hepatic steatosis, inflammation and fibrosis. Bariatric surgery significantly improves all histologic features of NAFLD
Hyperlipidemia	Strong risk factor, particularly hypertriglyceridaemia; mixed hyperlipidaemia with raised serum ALT	Strong risk factor	Statins remain uncertain but may prevent hepatic fibrosis progression and possibly HCC development; statins can effectively riduce risk of future cardiovascular morbidity and mortality
Hypolipidemia (FHBL)	Strong risk factor	Uncertain	Not available

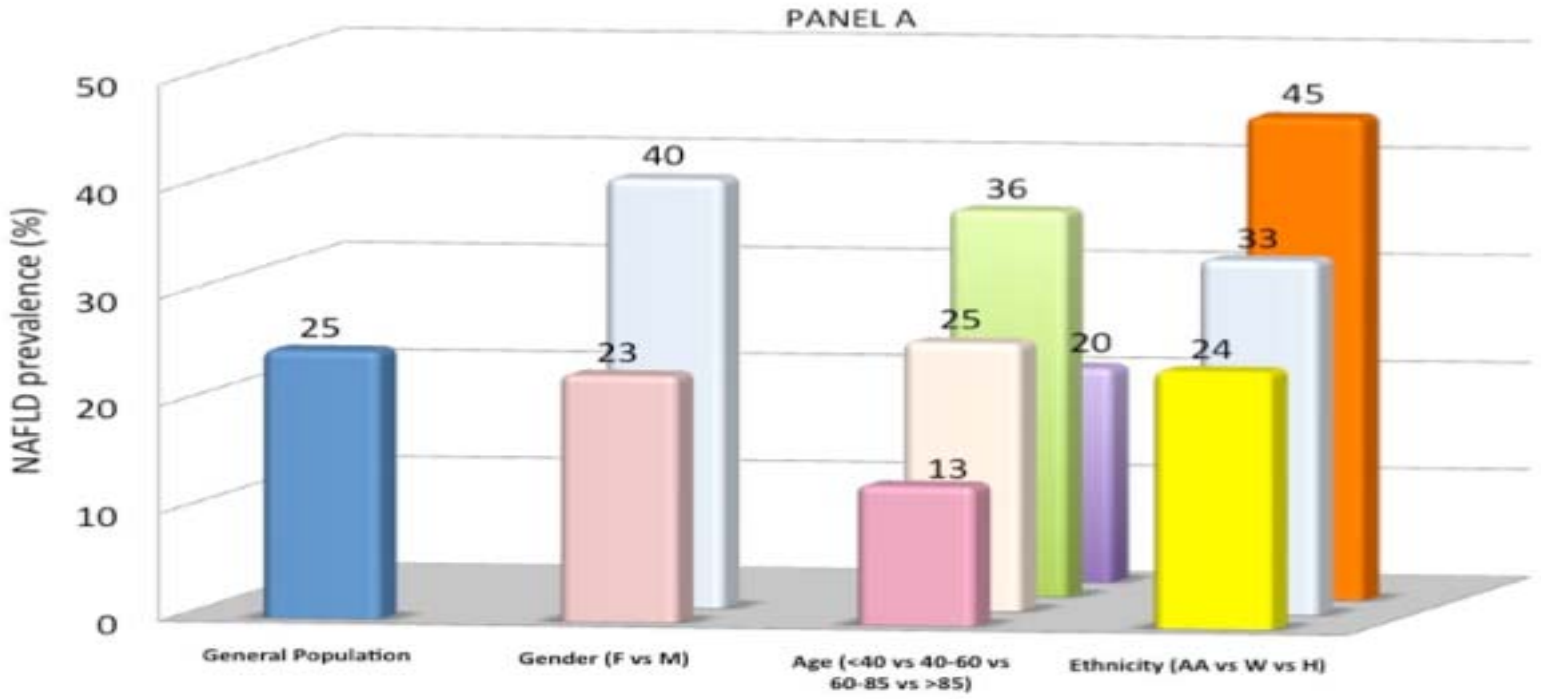
PANEL A
NAFLD prevalence (%)
50
40
30
20
10
0
25
40
23
36
25
13
20
45
33
24
General Population
Gender (F vs M)
Age (<40 vs 40-60 vs 60-85 vs >85)
Ethnicity (AA vs W vs H)

Figure 1A

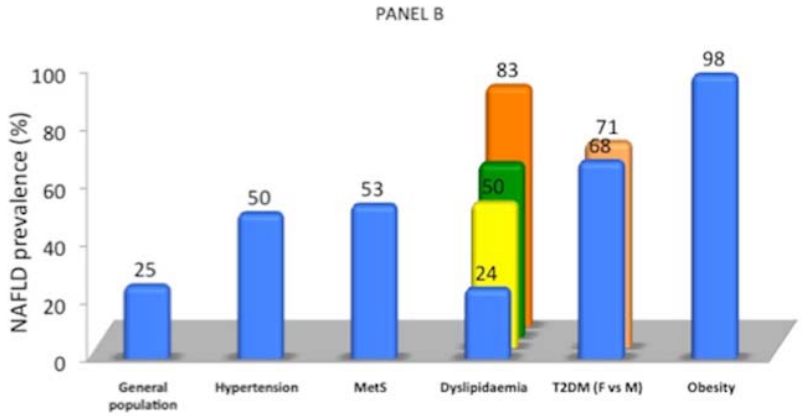
PANEL B
NAFLD prevalence (%)
100
80
60
40
20
0
25
50
53
24
50
83
68
71
98
General population
Hypertension
MetS
Dyslipidaemia
T2DM (F vs M)
Obesity

Figure 1B