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# Risk Factors of Non-Alcoholic Fatty Liver Disease

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**Abstract:**

An increasing number of people worldwide are suffering from non-alcoholic fatty liver disease (NAFLD), a condition characterized by fat buildup in the liver. Numerous categories can be used to group the risk factors for non-alcoholic fatty liver disease (NAFLD), including metabolic, genetic, epigenetic, demographic, and environmental factors. First, metabolic variables—obesity and insulin resistance in particular—are among the main risk factors for non-alcoholic fatty liver disease (NAFLD). The accumulation of fat in the liver is largely caused by obesity, and the disruption of normal fat metabolism caused by insulin resistance adds to the burden on the liver. Furthermore, there is a strong correlation between the onset of NAFLD and the existence of metabolic syndrome. Second, how susceptible a person is to NAFLD depends largely on hereditary factors. The start of the disease is also significantly influenced by epigenetic variables. Age, gender, and other demographic traits are linked to an increased risk of developing nonalcoholic fatty liver disease (NAFLD). In addition, smoking, leading a poor lifestyle, and being around pollutants can all increase the risk of developing the condition. In order to lower the incidence of NAFLD, effective prevention and intervention methods will be devised with the help of a thorough analysis of the interactions among these factors.

**Keywords:** Non-alcoholic fatty liver disease; risk factors; pathogenesis; treatment.

## 1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the hepatic component of a spectrum of diseases associated with metabolic dysfunction. Over 5% of hepatocytes have steatosis, which is its defining characteristic. It also occurs in the absence of other chronic liver illnesses or heavy alcohol consumption (≥30 g/day for males and ≥20 g/day for women), coupled with metabolic risk factors, including obesity and type 2 diabetes. With an estimated prevalence of about 25%, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver ailment worldwide in recent decades. This illness includes more severe non-alcoholic steatohepatitis (NASH) as well as benign non-alcoholic fatty liver (NAFL).

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NASH is a kind of NAFLD that progresses over time and is characterized by lobular inflammation, fibrosis, ballooning hepatocyte degeneration, and steatosis. The potential seriousness of NASH is highlighted by the fact that it can progress to cirrhosis and hepatocellular carcinoma (HCC) if left untreated. At the moment, NAFLD is the liver-related mortality cause with the fastest rate of growth in the globe. Furthermore, it is a major factor in cases of primary liver cancer, end-stage liver disease, and liver transplantation.

There are no approved medications or surgical treatments for NASH at this time. Hence, way of life adjustments stays basic treatment methodologies that principally center around dietary administration and customary actual work. Nonetheless, these mediations frequently face difficulties in accomplishing effective or practical execution among numerous patients. Subsequently, NAFLD represents a critical general wellbeing challenge. The fundamental components driving NAFLD are not yet completely comprehended. The goal of this article is to learn more about this problem and look into the risk factors for NAFLD.

## 2. Risk Factors of NAFLD

### 2.1 Metabolic Factors

Metabolic variables are the essential gamble supporters of NAFLD. Studies show that heftiness, diabetes, insulin obstruction, and metabolic disorder have a bidirectional relationship with NAFLD.

The connection among corpulence and NAFLD has been reliably approved. Obesity is one of the main causes of NAFLD and is currently recognized as a global epidemic. Due to the accumulation of hepatic triglycerides and insulin resistance, people with this condition typically have more liver fat. At the point when liver fat collection surpasses 5%, it shows liver steatosis [1]. Obesity caused by high-calorie diets and sedentary lifestyles is linked to liver fat accumulation. Weight frequently comes connected at the hip with persistent second rate irritation; Obese people have higher levels of cytokines that promote inflammation, like interleukin-6 and tumor necrosis factor alpha. These incendiary markers can hurt liver cells and add to the advancement of NAFLD. Besides, stoutness might upset ordinary lipid digestion by expanding fat combination in the liver while diminishing its oxidation, deteriorating NAFLD.

By causing the accumulation of free fatty acids within hepatocytes, insulin resistance plays a crucial role in the intricate pathogenesis of NAFLD. This condition is usually connected with type 2 diabetes; in this way, people experiencing type 2 diabetes face an uplifted gamble for creating NAFLD because of their insulin-safe state. Insulin opposition reduces how really the liver answers insulin, affecting glucose and lipid digestion inside the organ and advancing hepatic fat development. Moreover, hyperglycemia - a trademark component of type 2 diabetes - causes an expansion in glycogen and fat creation by the liver under high glucose conditions, further raising NAFLD risk. Besides, insulin opposition relates with more elevated levels of supportive of provocative cytokines that can set off fiery reactions inside the liver prompting extra cell harm.

Metabolic condition incorporates different metabolic aggravations including stomach corpulence, hypertension, raised glucose levels, and dyslipidemia. Patients encountering metabolic disorder might give indications like stoutness or hyperglycemia alongside insulin opposition - all expected antecedents for creating NAFLD as recently talked about. The hepatic fat content may rise as a direct result of metabolic syndrome's ability to disrupt lipid metabolism. Additionally, oxidative stress, which is frequently associated with metabolic syndrome, can damage liver cells and increase fatty acid oxidation, both of which contribute to liver fat accumulation.

### 2.2 Genetic Factors

Genetic abnormalities significantly increase the risk of non-alcoholic fatty liver disease (NAFLD) in addition to metabolic influences. Because it has been identified as a primary common genetic factor associated with NAFLD, the PNPLA3 variant is particularly noteworthy. Moreover, variations in TM6SF2 and GCKR with moderate impact sizes have likewise been viewed as significant [2]. Besides, atomic receptors assume a part in advancing the improvement of NAFLD.

The most unmistakable and reliably noticed hereditary change connected with NAFLD is the replacement of isoleucine for methionine at position 148 in PNPLA3 (rs738409 C>G), known as the PNPLA3 I148M variation [3]. Hydrolase activity is demonstrated toward triglycerides and retinyl esters by the wild-type PNPLA3 protein. Triglyceride hydrolysis, which can result in NAFLD, may be difficult for individuals deficient in PNPLA3.

Transmembrane 6 superfamily part 2 (TM6SF2) supports moving fatty substances to apolipoprotein B100 during extremely low-thickness lipoprotein discharge from liver cells. The rs58542926 C>T polymorphism makes an E K change at position 167, bringing about a deficiency of-capability that raises liver fatty oil levels while decreasing

coursing lipoproteins [4]. Ongoing examinations propose that TM6SF2 influences subjective parts of fatty substance improvement as well as assumes a part in lipid blend and quantitatively influences the quantity of emitted lipoprotein particles [5].

Hereditary varieties inside the glucokinase controller (GCKR) locus have been connected to NAFLD. GCKR directs once more lipogenesis by controlling glucose section into hepatocytes. A typical missense transformation prompting loss-of-capability in GCKR (rs1260326), which brings about the P446L variation, seems huge for hepatic fat gathering [6]. In particular, this P446L modification changes GCKR's capacity to adversely control glucokinase while answering fructose-6-phosphate, consequently persistently improving hepatic glucose take-up [7]. This cycle at last prompts lower fasting glucose and insulin levels while expanding malonyl-CoA creation — supporting hepatic fat development by filling in as a substrate for lipogenesis and repressing unsaturated fat oxidation.

The liver's lipid metabolism is essentially controlled by nuclear receptors; peroxisome proliferator-enacted atomic receptors (PPARs) are viewed as key focuses for tending to NAFLD. Actuation of PPAR-α energizes unsaturated fat breakdown through improved mitochondrial take-up and β-oxidation processes, while PPAR-γ offers insulin-sharpening impacts alongside calming properties. Besides, some examination features LPIN1 - a phospholipid phosphatase prevalently communicated in liver and fat tissues - which is engaged with blending phospholipids and fatty oils while working as an inducible transcriptional coactivator managing unsaturated fat digestion. The TT genotype at LPIN1 rs13412852 associates with expanded LIPIN1 articulation giving assurance against NAFLD [8].

## 2.3 Epigenetic Factors

There is proof proposing that epigenetic factors assume a critical part in the improvement of NAFLD. DNA methylation, a vital epigenetic administrative instrument, essentially happens at the 5-position carbon of cytosine. Irregularities in DNA methylation during NAFLD movement can impact the declaration of fundamental qualities connected with fat digestion, irritation, and fibrosis. Late examinations show that different qualities associated with lipid, energy, and vitamin D homeostasis are essentially impacted by changes in CpG site methylation related with NAFLD and its fibrosis [9]. These discoveries propose that the structure of lipoprotein particles might be impacted by the predominance and movement of NAFLD, giving further knowledge into the components behind lipid arrangement changes in this condition.

MicroRNAs (miRNAs) are fundamental in controlling essentially all organic cycles inside liver cell types. They have arisen as clever controllers and possible biomarkers with regards to NAFLD. Given their assorted jobs in different organic cycles, dysregulation of miRNAs essentially adds to the pathogenesis of NAFLD at various phases of illness improvement and movement. Some miRNAs are engaged with managing glucose and lipid digestion, while others are connected to pathways overseeing cell passing and endurance [10].

## 2.4 Demographic Factors

There are varying risk levels based on gender and age for NAFLD. The incidence of NAFLD among youngsters is on the rise, with males showing a higher prevalence than females.

There are 9% to 37% prevalence rates in the general population, according to narrative reviews on pediatric NAFLD. The average prevalence of NAFLD in children across general population studies stands at 7.6% (interquartile range: 5.5% to 10.3%), whereas studies focusing on childhood obesity clinics show a prevalence of 34.2% (interquartile range: 27.8% to 41.2% Furthermore, the prevalence of the illness tends to be higher among males and progresses with increasing body mass index. In obese individuals and males, NAFLD is notably prevalent [11].

The prevalence of NAFLD is associated with gender. The incidence of NAFLD is higher in men than women, according to longitudinal studies. Postmenopausal women had higher rates of NAFLD incidence than premenopausal women, according to one study. Additionally, other longitudinal studies have demonstrated that estrogen serves as a protective factor against the development of NAFLD. Furthermore, other longitudinal studies have demonstrated that estrogen serves as a protective factor against the development of NAFLD [12].

## 2.5 Environmental Factors

Environmental influences significantly impact the development of NAFLD. Recent research suggests that unhealthy dietary and lifestyle choices, persistent smoking, air pollution, and various natural and social environmental elements contribute to the onset of NAFLD, according to recent research.

Overeating is the primary cause of NAFLD, leading to the expansion of fat stores and sporadic fat accumulation. Poor diet and lifestyle choices are a major risk factor for NAFLD. Eating better and moving more can lower the risk of developing NAFLD, highlighting that poor nutri-

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tion and a lack of physical activity are, in fact, contributing factors to this condition.

A recent study found a link between current smoking and a higher risk of non-alcoholic fatty liver disease. The risk of NAFLD increases with the number of cigarettes smoked among current smokers. Cotinine-verified smoking and self-reported smoking are independent risk factors for NAFLD, but further longitudinal studies are needed to confirm these findings [13].

Over the past decade, increasing evidence has revealed the potential impact of environmental pollutants on liver health, particularly regarding the incidence of NAFLD. These pollutants have a significant capacity to promote fat accumulation, and they should be considered genuine risk factors for NAFLD. Long-term exposure to air pollution can allow particulate matter to reach the liver, which may be critical for the development of NAFLD [14]. Additionally, copper overload in the liver can lead to the onset and progression of steatosis, as this metal can disrupt lipid metabolism and induce oxidative stress, increasing the risk of NAFLD.

## 3. Conclusions

NAFLD is increasingly recognized as a significant health concern. The pathogenesis and risk factors associated with NAFLD continue to be subjects of ongoing research. This article primarily outlines the various known risk factors for NAFLD, which include metabolic factors (such as obesity, diabetes, insulin resistance, and metabolic syndrome), genetic factors (such as PNPLA3, TM6SF2, and GCKR), epigenetic factors (like DNA methylation and miRNAs), demographic factors (including age and gender), and environmental factors (such as diet, lifestyle, smoking, and air pollution). Awareness of these risk factors is crucial for the prevention and management of NAFLD. Moreover, while there has been steady progress in understanding the epidemiology, pathogenesis, and potential therapeutic targets for NAFLD, advancements in treatment options remain slow. There is an urgent need for effective therapeutic strategies. Currently, the primary approach to treating NAFLD emphasizes lifestyle modifications rather than halting disease progression, and this method has proven to be insufficiently effective. It is important to note that studies have clarified the roles of insulin sensitizers, thyroid hormone mimetics, antioxidants, cholesterol-lowering medications, intestinal insulinotropic agents, and cytokines as potential therapeutic targets for NASH; however, additional research is still required.

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