Comparison between obese and non-obese NAFLD

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Abstract

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver conditions that are characterized by excess accumulation of fat in the liver and is diagnosed following exclusion of significant alcohol intake and other causes of chronic liver disease. In the majority of cases, it is associated with overnutrition and obesity, although it may also be found in lean or non-obese persons. It has been estimated that 19.2% of NAFLD patients are lean and 40.8% are non-obese. The proportion of patients with more severe liver disease and the incidence of all-cause mortality, liver-related mortality and cardiovascular mortality among non-obese and obese NAFLD patients varies across studies and may be confounded by selection bias, underestimation of alcohol intake and unaccounted weight changes over time. Genetic factors may have a greater effect towards the development of NAFLD in lean or non-obese individuals, but the effect may be less pronounced in the presence of strong environmental factors, such as poor dietary choices and a sedentary lifestyle, as body mass increases and in the obese state. Overall, non-invasive tests, such as Fibrosis-4 index, NAFLD fibrosis score and liver stiffness measurement, perform better in lean or non-obese compared with obese NAFLD patients. Lifestyle intervention works in non-obese NAFLD patients and less amount of weight loss may be required to achieve similar results compared with obese NAFLD patients. Pharmacological therapy in non-obese NAFLD patients may require special consideration and a different approach compared with obese NAFLD patients.
Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver conditions that are characterized by excess accumulation of fat in the liver. The diagnosis is made following exclusion of significant alcohol intake and other causes of chronic liver disease.\(^{(1, 2)}\) In the majority of cases, it is associated with overnutrition and obesity, although it may also be found in non-obese persons. The condition is closely associated with the metabolic syndrome, which is a constellation of risk factors for cardiovascular disease.\(^{(3)}\) The prevalence of NAFLD has been increasing and it is recognized as the most common cause of chronic liver disease worldwide.\(^{(4, 5)}\) In 2020, an international panel of experts has proposed a new term, metabolic dysfunction-associated fatty liver disease (MAFLD), which is diagnosed in persons with fatty liver in the presence of overweight or obesity, type 2 diabetes mellitus or at least two metabolic risk abnormalities.\(^{(6)}\) This review focuses primarily on the comparison between obese and non-obese NAFLD, for which there is a richer body of literature given that the term NAFLD has been in existence for a much longer period of time. However, the literature on MAFLD is rapidly expanding, and a similar review on MAFLD in due time would be of great interest. In general, a body mass index (BMI) cut-off of 25 and 30 kg per m\(^2\) is used for the definition of obesity for Asian and Caucasian populations, respectively. In studies using the term lean NAFLD, the non-lean group includes patients who are overweight or obese, defined by a BMI of $\geq23$ and $\geq25$ kg per m\(^2\) for Asian and Caucasian populations, respectively.

Epidemiology and natural history of non-obese NAFLD

Initial recognition and increasing interest
One of the earliest reports on non-obese NAFLD came from India. In a study on 1911 subjects from the rural administrative unit of West Bengal that was published in 2013, Das and colleagues found the prevalence of NAFLD to be 8.7%. While this was relatively low compared with studies from other parts of India, the prevalence was considerably high given that the majority of subjects were young, physically active, less affluent and non-obese. The term “third-world NAFLD” was used to describe this phenotype, where instead of overt obesity, subtle measures of increased adiposity predisposed to NAFLD. (7) The interest in non-obese NAFLD sky-rocketed following an abstract presented at the Digestive Disease Week the following year. In a study on 1090 biopsy-proven NAFLD patients who were followed for 133 months, Dela Cruz and colleagues found that lean NAFLD patients had a significantly shorter survival compared with non-lean NAFLD patients. (8) Subsequently, a population-based study on 911 subjects using proton-magnetic resonance spectroscopy and transient elastography in Hong Kong found non-obese NAFLD patients to have less severe liver disease based on significantly lower serum cytokeratin-18 level and liver stiffness measurement. (9) Furthermore, in another study on 307 biopsy-proven NAFLD patients, non-obese NAFLD patients had significantly lower serum cytokeratin-18 level, liver stiffness measurement and histological fibrosis stage. During follow-up, six patients died, two developed hepatocellular carcinoma and one had liver failure, all of whom were in the obese group. (10)

Possible reasons for disparities in data

Several other longitudinal studies have shown conflicting results (see Table 1). A study in Sweden found that patients with lean NAFLD were paradoxically more likely to develop more severe liver disease despite having less severe liver disease.
at baseline compared with their non-lean counterparts. Further studies are warranted to understand the reasons behind these inconsistent findings. One possible explanation is that the lean NAFLD patients in the study had more severe liver disease that would be expected compared with the general population, which is expected given that the patients were seen in a secondary or tertiary care setting and underwent liver biopsy. This is evident from the high proportion of lean patients with NASH and advanced liver fibrosis at 50% and 9.8%, respectively. Furthermore, important confounding factors such as changes in alcohol intake and body weight over time were not taken into account. Alcohol intake is an important confounding factor and may not be adequately captured due to under-reporting. In a study on 184 patients, repeated moderate to excessive alcohol intake was detected in 28.6% of patients with presumed NAFLD, and patients with repeated moderate to excessive alcohol intake had significantly lower BMI. This may partly contribute to the high proportion of lean or non-obese NAFLD patients with more severe liver disease. Assessment of alcohol intake by ethylglucuronide in hair had an area under curve of 0.93 for the detection of repeated moderate to excessive alcohol consumption, which may be useful to more accurately classify patients with fatty liver as NAFLD or not.

**Epidemiology and clinical characteristics**

A systematic review and meta-analysis estimated the prevalence of lean NAFLD and non-obese NAFLD in the general population to be 5.1% (95% CI 3.7% - 7.0%) and 12.1% (95% CI 9.3% - 15.6%), respectively. Among NAFLD patients, an estimated 19.2% (95% CI 15.9% - 23.0%) were lean and 40.8% (36.6% - 45.1%) were non-obese. Among patients with non-obese or lean NAFLD, 39.0% (95% CI 24.1% - 56.3%) had non-alcoholic steatohepatitis (NASH), 29.2% (95% CI
21.9% - 37.9%) had significant fibrosis and 3.2% (1.5% - 5.7%) had cirrhosis. The corresponding rates among obese NAFLD were 52.9% (38.3% - 67.0%), 38.3% (30.6% - 46.6%) and 2.0% (0.4% - 5.7%). In the largest multicentre biopsy-proven NAFLD registry in Asia to date consisting of 1812 patients, 21.6% of patients were non-obese. The proportion of patients with NASH and advanced liver fibrosis among non-obese NAFLD patients were 50.5% and 14%, respectively, while the corresponding rates among obese NAFLD patients were 56.5% and 18.7%, respectively.(13)

Natural history and prognosis

The incidence of all-cause mortality, liver-related mortality and cardiovascular-related mortality among patients with lean or non-obese NAFLD was found to be 12.1 (95% CI 0.5 – 38.8), 4.1 (95% CI 1.9 – 7.1) and 4.0 (95% CI 0.1 – 14.9) per 1000 person-years, respectively. The corresponding rates among obese NAFLD patients were 7.5 (95% CI 0 – 33.6), 2.4 (95% CI 1.0 – 4.4) and 2.4 (95% 0 – 13.3) per 1000 person-years, respectively (see Figure 1).(14) Although it appeared that lean or non-obese NAFLD patients have higher all-cause mortality, liver-related mortality and cardiovascular mortality, the results should be interpreted with caution due to the small number of studies. The authors have cautioned that further research is needed before any conclusions are made on this due to the scarcity of data for obese and non-obese populations.(14) The results on all-cause mortality, liver-related mortality and cardiovascular mortality were based on only three studies. Furthermore, only one study provided all-cause mortality, cardiovascular mortality and liver-related mortality for lean and non-lean NAFLD patients;(11) another study provided all-cause mortality and cardiovascular mortality for obese and non-obese
NAFLD patients; (15) a third study provided all-cause mortality and cardiovascular mortality only for non-obese NAFLD patients. (16)

Pathophysiology of non-obese NAFLD

The role of obesity and lipotoxicity in the development of NAFLD and NASH has been well described. (17) Briefly, obesity and insulin resistance leads to excess free fatty acids and increased de novo lipogenesis in the liver. Free fatty acids are either stored as triglyceride, exported from the liver, or undergo oxidation. The excess in free fatty acids causes oxidative stress, liver cell injury and death, inflammation and eventually fibrosis. On the other hand, the pathophysiology of lean or non-obese NAFLD is not completely understood. Despite having a normal or lower BMI, lean or non-obese NAFLD patients have excess visceral adiposity. Lean or non-obese NAFLD patients share common altered metabolic and cardiovascular profile as their non-lean or obese counterparts, although the alterations are generally less severe. (18) While it is reasonable to think that lean or non-obese NAFLD is the early phase of NAFLD or the less severe end of the NAFLD spectrum, evidence suggests that there may be more to it.

Ethnic differences in body fat distribution and genetic factors

It is well-known that different ethnic groups have different tendency to accumulate visceral and liver fat and to develop the metabolic syndrome. Ethnic difference in the prevalence of hepatic steatosis was first pointed out in the landmark paper by Browning and colleagues in 2004, where Hispanics were found to have the highest prevalence of hepatic steatosis, while the prevalence was significantly lower among Blacks despite an equally high prevalence of obesity and insulin resistance. (19) In a subsequent multi-ethnic cohort study on 1794 subjects of
African, European, Japanese, Latino or Native Hawaiian ancestry in the United States, the mean visceral and liver fat were greatest among the Japanese Americans, which jointly accounted for a statistically significant fraction of the difference in metabolic syndrome prevalence compared with other ethnic groups independently of total fat mass. (20) Studies on multi-ethnic Malaysians have also consistently found the prevalence of NAFLD to be higher among the Indians and Malays compared with the Chinese, (21, 22) with the ethnic predilection seen as early as young adulthood. (23) Consistent with this is the greater prevalence of metabolic syndrome among the Indians and Malays compared with the Chinese. (24) The difference in tendency for visceral adiposity, NAFLD and the metabolic syndrome between the different ethnic groups may be explained by genetic differences. A single nucleotide polymorphism in the patatin-like phospholipase domain-containing-3 (PNPLA3) gene, the rs738409C > G variant, which results in substitution of isoleucine by methionine at position 148 (I148M), was found to be associated with increased liver fat in a genome-wide association study, and the risk allele was found to be highest among Hispanics and lowest among Blacks, (25) providing an explanation to the initial observation by Browning and colleagues. Genetic polymorphisms in the PNPLA3 gene have subsequently been recognised as a major genetic determinant of NAFLD and its severity. (26) The PNPLA3 protein has lipase activity in hepatocytes and I148M leads to loss of function that promotes accumulation of triglycerides in liver cells. (27) Interestingly, a population-based study in Hong Kong found that the PNPLA3 gene polymorphism had greater effect on liver fat in lean individuals compared with overweight and obese individuals. Furthermore, lean individuals were significantly more likely to carry the risk allele compared with overweight and obese individuals. (28) Therefore, genetic factors may have a greater
effect towards the development of NAFLD in lean or non-obese individuals, but the effect may be less pronounced in the presence of strong environmental factors, such as poor dietary choices and a sedentary lifestyle, with increasing body mass index and in the obese state (see Figure 1). The findings were somewhat different in a study in the Western population, which found that the effect of the risk allele was amplified by increasing adiposity. (29) The inconsistent findings may be due to other genetic determinants at play, environmental factors such as diet, or difference in the metabolic profile of the study populations. A difference in the effect of genetic polymorphisms in the PNPLA3 gene on NAFLD has been observed among different ethnic groups, with the effect lowest among the Chinese compared with the Indians and Malays. (30) In a subsequent study, the HSD17B13 rs72613567 and rs6834314 variants were found to be associated with lower odds of NASH and adverse liver-related outcomes among the Chinese but not the Indians and Malays, supporting the role of polygenic determinants in the disease phenotype. (31) The transmembrane 6 superfamily member 2 (TM6SF2) encodes a membrane protein required for normal very low density lipoprotein secretion. The rs58542926C > T variant, which results in substitution of glutamate by lysine at position 167 (E167K), was found to be associated with higher circulating levels of serum alanine aminotransferase, a marker of liver injury, but lower level of serum low density lipoprotein cholesterol and triglycerides. (32) In a retrospective cohort study on 669 consecutive patients with biopsy-proven NAFLD in Italy, a significantly greater proportion of patients with lean NAFLD had E167K compared with their non-lean counterparts. In the same study, I148M was the only independent factor found to be associated with NASH and significant fibrosis among lean patients. (33) Additionally, lean NAFLD may also be
driven by other rare genetic disorder, such as familial hypobetalipoproteinemia and cholesteryl ester storage disease. (34, 35)

More severe liver disease in some non-obese NAFLD patients

Even among lean or non-obese NAFLD patients, varying proportions of more severe liver disease has been observed. As elucidated earlier, this may be due to under-reporting of alcohol intake, particularly in populations with high alcohol consumption, as well as genetic factors. For example, in a study on an outpatient population in the United States, the ethic differences in prevalence of cryptogenic cirrhosis mirrored the prevalence of hepatic steatosis and the frequency of I148M among the different ethnic groups. (25) Another point for consideration is the loss of weight from poorly controlled diabetes mellitus and the loss of muscle mass associated with more advanced chronic liver disease in patients with long-standing history of obesity, NAFLD and diabetes mellitus. The inclusion of these patient as lean or non-obese NAFLD will paradoxically enrich the population with patients who are worse metabolically and have more severe liver disease with resultant poorer outcomes. The gut microbiome may play a role in the pathogenesis of NAFLD, (36) but this remains unclear and deserves further studies, especially in non-obese NAFLD.

Non-invasive tests in non-obese NAFLD

It is well recognized that fibrosis stage is the single most important predictor for overall and liver-related mortality in patients with NAFLD. (37) The same has been observed for the subpopulation of lean or non-obese NAFLD patients. (11) Because of the high prevalence of NAFLD in the general population and only a small yet significant proportion of patients have advanced liver fibrosis, (38) a simple
assessment and referral pathway is needed to identify patients who are more likely to have more severe liver disease for specialist care and to limit unnecessary referrals. (39) Although liver biopsy is considered the reference standard for fibrosis assessment and required for the diagnosis of NASH, it is not routinely performed because it is invasive and associated with a small risk of serious complications. 

Since the initial description and following refinement and validation, sequential testing with simple fibrosis score followed by liver stiffness measurement has become the backbone for fibrosis assessment in patients with NAFLD. (39-42) In a multicentre study in France, Malaysia and Hong Kong, all non-invasive tests that were tested, including fibrosis-4 index, the NAFLD fibrosis score and liver stiffness measurement, performed equally well in non-obese compared with obese patients, and the same cut-offs can be used with similar or higher sensitivities and specificities. Furthermore, the negative predictive value of every non-invasive test was found to be higher due to the lower prevalence of advanced fibrosis among non-obese compared with obese patients. (43) A subsequent individual patient data meta-analysis evaluating non-invasive tests against liver histology using data from 5705 patients (15.2% of patients had a BMI of <25 kg per m²) found that non-invasive tests, namely fibrosis-4 index, the NAFLD fibrosis score and liver stiffness measurement, performed better in patients with lower BMI. (44) The area under the curve of some of the most commonly used non-invasive tests among non-obese patients compared with obese patients are summarized in Table 2.

**Lifestyle intervention and pharmacological treatment in non-obese NAFLD**

Lifestyle intervention is the cornerstone for the management of NAFLD. A landmark study on comprehensive lifestyle program for patients with biopsy-proven NASH has shown that weight loss of ≥10% can result in NASH resolution and
fibrosis improvement in 90% and 45%, respectively. In a randomized controlled trial of a 12-month lifestyle intervention program, a significantly greater proportion of patients in the intervention group achieved remission of NAFLD based on proton-magnetic resonance spectroscopy compared with the control group (64% vs. 20%, p<0.001) with 97% of patients with ≥10% weight loss achieving remission of NAFLD. More importantly, a secondary analysis found similar beneficial effect of lifestyle intervention program regardless of baseline BMI. The proportion of patients achieving remission of NALFD was 67% in the intervention group vs 18% in the control group among non-obese patients. The corresponding rates among obese patients were 61% and 21%, respectively. Furthermore, 50% of non-obese patients achieved remission of NAFLD with 3-5% weight loss, while the same could only be achieved with 7-10% weight loss among obese patients.

To date, there are no pharmacological therapy approved for NAFLD. However, multiple drugs targeting obesity and the metabolic syndrome have shown promising results. In a multicentre, randomized, double-blind, placebo-controlled trial on biopsy-proven NASH patients, liraglutide 1.8 mg daily for 48 weeks resulted in significantly greater resolution of definite NASH compared with placebo. In another study, semaglutide at increasing dosages resulted in significantly greater NASH resolution without worsening fibrosis compared with placebo, but not fibrosis improvement without worsening NASH. However, these studies enrolled only overweight patients with BMI ≥25 kg per m². Whether glucagon-like peptide-1 receptor agonists will be beneficial over standard of care and have acceptable side effect profile in lean NAFLD patients is not clear. Another concern related to marked weight loss, although desirable for the underlying NAFLD, is whether it comes with an associated loss of muscle mass. Sarcopenia is a common and important
complication of chronic liver disease, including NAFLD, and has been associated with poorer outcome.(50) However, post-hoc analysis of the STEP 1 trial, which was a trial evaluating semaglutide 2.4 mg once-weekly for adult patients with BMI ≥27 kg per m² with ≥1 weight-related comorbidity or BMI ≥30 kg per m², without diabetes, found semaglutide to be associated with reduced total fat mass and regional visceral fat mass, and an increased proportion of lean body mass. Although the total lean body mass decreased from baseline (-9.7%), the proportion relative to total body mass increased by 3.0% with improvement in lean body mass to fat mass ratio.(51) Another study found that semaglutide resulted in significant decline in fat mass index and visceral adipose tissue, but not skeletal mass index, fat free mass index and muscle strength.(52) However, further studies are needed on the use of these emerging novel therapies in lean or non-obese NAFLD patients.(53)

Conclusion

Lean or non-obese NAFLD is a common entity and may be more than just the early phase or the less severe end of the NAFLD spectrum. While confounding factors such as alcohol intake and weight loss following disease progression could explain more severe liver disease and a worse outcome in some patients with lean or non-obese NAFLD, genetic factors are increasingly recognized to have an important role. Further studies to understand these genetic determinants in lean or non-obese NAFLD patients may open the door to better diagnostics and therapeutics that may have the potential to be expanded to obese NAFLD patients. Overall, non-invasive tests perform better in lean or non-obese NAFLD patients than their obese counterparts. Lifestyle intervention works for lean or non-obese NAFLD patients and less amount of weight loss may be required to achieve similar results compared with
obese NAFLD patients. The role of emerging therapeutics in lean or non-obese NAFLD patients is unclear and further studies are warranted.

Conflicts of interest

WKC has served as a consultant for Abbvie, Boehringer Ingelheim and Novo Nordisk; and a speaker for Viatris and Hisky Medical.

Abbreviations

BMI body mass index
E167K substitution of glutamate by lysine at position 167
I148M substitution of isoleucine by methionine at position 148
MAFLD metabolic dysfunction-associated fatty liver disease
NAFLD non-alcoholic fatty liver disease
PNPLA3 patatin-like phospholipase domain-containing-3
TM6SF2 transmembrane 6 superfamily member 2

References


of Lean Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2014;146:S909.


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disease severity in non-alcoholic fatty liver disease. Hum Genet 2012;131:1145-1152.


53. Patoulias D, Doumas M. Lean non-alcoholic fatty liver disease: Is there a place for novel antidiabetics in the therapeutic management of this underappreciated "enemy"? Clin Mol Hepatol 2020;26:582-583.


<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>Proportion of patients with lean and/or non-obese NAFLD</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| Leung JCF, et al. (2017) (10) | 342 biopsy-proven NAFLD patients in Hong Kong | 23.5% were non-obese. | 1. Non-obese NAFLD patients had lower NAFLD activity score, histological fibrosis stage, serum cytokeratin-18 levels and liver stiffness measurement by transient elastography.  
2. During median follow-up of 49 months, 6 patients died, 2 developed hepatocellular carcinoma and 1 had liver failure, all of whom were in the obese group. |
| Hagstrom H, et al. (2017) (11) | 646 biopsy-proven NAFLD patients in Sweden | 19% were lean. | 1. Lean patients had less severe liver disease. |
NASH: 50% among lean vs. 64.6% among overweight patients and 79.8% among obese patients, p<0.001.
Advanced fibrosis: 9.8% vs. 10.8% and 15.9%.
2. During mean follow-up of 19.9 years, compared with patients who were overweight, patients with lean NAFLD had no increased risk for overall mortality (hazard ratio 1.06, p=0.73) but has increased risk for developing more severe liver disease (hazard ratio 2.69, p=0.007).

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Prevalence of NAFLD</th>
<th>Liver-related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang Y, et al. (2019) (15)</td>
<td>437,828 Korean adults</td>
<td>Prevalence of NAFLD was 20.9%. Among individuals with NAFLD, 61.7% were obese.</td>
<td>Compared with individuals without fatty liver, the liver-related mortality was higher among non-obese NAFLD individuals (hazard ratio 2.12, 95% CI 1.12 – 4.02) than among obese NAFLD individuals (hazard ratio 0.54, 95% CI 0.25 –</td>
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</table>
1.14). The liver-related mortality increased with increasing fibrosis-4 index category, especially in non-obese NAFLD patients.

<table>
<thead>
<tr>
<th>Golabi P, et al. (2019) (16)</th>
<th>5375 lean participants from the third National Health and Nutrition Survey (NHANES) in the United States</th>
<th>Prevalence of NAFLD was 10.8%.</th>
<th>The presence of NAFLD in lean individuals was independently associated with increased all-cause and cardiovascular mortality.</th>
</tr>
</thead>
</table>
| Zou B, et al. (2020) (54)   | 21,827 participants from the 1999 – 2016 NHANES in the Unites States | Prevalence of NAFLD was 32.3%. Among individuals with NAFLD, 29.7% were non-obese, 13.6% were lean. | 1. Greater proportion of non-obese NAFLD individuals had elevated fibrosis-4 index (41.4%) than obese NAFLD individuals (29.9%) and non-NAFLD individuals (27.1%) (p <0.001).
2. Non-obese NAFLD individuals had higher 15-year cumulative all-cause mortality (51.7%) than obese NAFLD individuals |
<table>
<thead>
<tr>
<th>Younes R, et al. (2022) (55)</th>
<th>1352 biopsy-proven NAFLD patients in Italy, United Kingdom, Spain and Australia</th>
<th>14.4% were lean.</th>
<th>(27.2%) and non-NAFLD individuals (20.7%) (p &lt;0.001).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Lean patients had less severe liver disease. NASH: 54.1% among lean vs. 71.2% among non-lean patients, p&lt;0.001. Advanced fibrosis: 10.1% vs. 25.2%, p&lt;0.001. <strong>2.</strong> During median follow-up of 94 months, 4.7% of lean patients had liver-related events compared with 7.7% among non-lean patients, p=0.37. Overall survival was not significantly different when comparing lean to overweight and obese patients (p=0.069), but was significantly better when comparing non-obese to obese patients (p=0.021).</td>
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</table>
Table 2 The area under the curve for some of the most commonly used non-invasive tests for non-alcoholic fatty liver disease (NAFLD) according to body mass index (BMI) category based on a multicentre study and an individual patient data meta-analysis.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Non-invasive test</th>
<th>BMI &lt;25 kg per m²</th>
<th>BMI ≥25 kg per m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu C, et al. (2020) (43)</td>
<td>Fibrosis-4 index</td>
<td>0.86 (0.75 – 0.98)</td>
<td>0.73 (0.69 – 0.77)</td>
</tr>
<tr>
<td></td>
<td>NAFLD fibrosis score</td>
<td>0.85 (0.73 – 0.96)</td>
<td>0.69 (0.64 – 0.73)</td>
</tr>
<tr>
<td></td>
<td>Liver stiffness measurement</td>
<td>0.93 (0.87 – 0.98)</td>
<td>0.83 (0.80 – 0.87)</td>
</tr>
<tr>
<td>Mozes FE, et al. (2022) (44)</td>
<td>Fibrosis-4 index</td>
<td>0.81 (0.78 – 0.84)</td>
<td>0.77 (0.75 – 0.80)</td>
</tr>
<tr>
<td></td>
<td>NAFLD fibrosis score</td>
<td>0.76 (0.71 – 0.81)</td>
<td>0.74 (0.71 – 0.77)</td>
</tr>
<tr>
<td></td>
<td>Liver stiffness measurement</td>
<td>0.91 (0.89 – 0.94)</td>
<td>0.87 (0.85 – 0.89)</td>
</tr>
</tbody>
</table>
Figure 1 The effect of genetic, environmental and confounding factors in the severity of liver disease and outcomes of lean or non-obese compared with obese NAFLD patients

Genetic factors may have a more pronounced effect towards development of NAFLD in lean or non-obese individuals, but the effect may appear less pronounced in the presence of strong environmental factors, such as poor dietary choices and a sedentary lifestyle, in the obese state. Selection bias, underestimation of alcohol intake and unaccounted weight loss over time from poorly controlled diabetes mellitus and/or loss of muscle mass from advanced liver disease are important confounding factors for varying severity of liver disease and outcomes in lean or non-obese NAFLD patients compared with obese NAFLD patients, although genetic factors may play a role.

*NASH, non-alcoholic steatohepatitis*
+, Relative frequency of the corresponding variable when comparing between lean or non-obese NAFLD and obese NAFLD